NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 416

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *o*-NITROANISOLE

(CAS NO. 91-23-6)

IN F344 RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

FOREWORD

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

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

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

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

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF *o*-NITROANISOLE

(CAS NO. 91-23-6)

IN F344 RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

May 1993

NTP TR 416

NIH Publication No. 93-3147

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

CONTRIBUTORS

National Toxicology Program

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

Hazleton Raltech, Inc.

Conducted 14-day and 13-week studies, evaluated pathology findings

K.M. MacKenzie, Ph.D., Principal Investigator
B.G. Boysen, D.V.M., M.Sc.
T.A. Jackson, D.V.M., Ph.D.
P.S. MacWilliams, D.V.M., Ph.D.

Southern Research Institute

Conducted 2-year studies, evaluated pathology findings

J.D. Prejean, Ph.D., Principal Investigator
D.R. Farnell, D.V.M., Ph.D.
C.H. Farr, Ph.D.
H.D. Giles, D.V.M., Ph.D.
J.E. Heath, D.V.M.
R.B. Thompson, D.V.M., Ph.D.

Experimental Pathology Laboratories, Inc.

Provided pathology quality assurance

J.F. Hardisty, D.V.M., Principal Investigator
B.F. Hamilton, D.V.M., Ph.D.
K. Yoshitomi, D.V.M., Ph.D.

Integrated Laboratory Systems

Prepared quality assurance audits

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

NTP Pathology Working Group

Evaluated slides, prepared pathology report on rats (28 August 1990)

A. Pinter, M.D., Ph.D., Chair
National Institute of Hygiene, Hungary
S.L. Eustis, D.V.M., Ph.D.
National Toxicology Program
J.R. Hailey, D.V.M.
National Toxicology Program
B.F. Hamilton, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
S. Imoto, D.V.M., Ph.D.
Shin Nippon Biomedical Laboratories, Japan
M.P. Jokinen, D.V.M.
National Toxicology Program
M.M. McDonald, D.V.M., Ph.D.
National Toxicology Program

Evaluated slides, prepared pathology report on mice (25 July 1990)

R.M. Kovatch, D.V.M., Chair
Pathology Associates, Inc.
M.P. Jokinen, D.V.M.
National Toxicology Program
M.M. McDonald, D.V.M., Ph.D.
National Toxicology Program
A. Pinter, M.D., Ph.D.
National Institute of Hygiene, Hungary
B.P. Stuart, D.V.M., Ph.D.
Mobay Chemical Corporation
K. Yoshitomi, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.

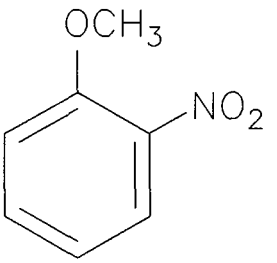
Biotechnical Services, Inc.

Prepared Technical Report

D.D. Lambright, Ph.D., Principal Investigator
P. Chaffin, M.S.
G.F. Corley, D.V.M.
C.J. Fitz, M.A.

CONTENTS

ABSTRACT



o-NITROANISOLE

CAS No. 91-23-6

Chemical Formula: $C_7H_7NO_3$ Molecular Weight: 153.13

Synonyms: Methoxynitrobenzene, nitrophenyl methyl ether

o-Nitroanisole is used as an intermediate for the preparation of *o*-anisidine and in the manufacture of azo dyes. Toxicology and carcinogenesis studies were conducted by administering *o*-nitroanisole (>99% pure) in the diet to groups of male and female F344 rats and B6C3F$_1$ mice for 14 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, Chinese hamster ovary cells, and mouse lymphoma cells.

14-Day Studies

Groups of five male and five female F344 rats received diets containing 0, 583, 1,166, 2,332, 4,665, or 9,330 ppm *o*-nitroanisole. Mean body weight gains and final mean body weights of males in the 4,665 and 9,330 ppm groups were lower than those of the controls. Absolute liver weights were significantly increased in males receiving 1,166 ppm or more and in females receiving 583 ppm or more.

Groups of five male and five female B6C3F$_1$ mice received diets containing 0, 250, 500, 1,000, 2,000, or 4,000 ppm *o*-nitroanisole. Mean body weight gains and final mean body weights of males that received 250 ppm and females that received 4,000 ppm were significantly lower than those of the controls. No other chemical-associated effects were observed.

13-Week Studies

Groups of 10 male and 10 female F344 rats received diets containing 0, 200, 600, 2,000, 6,000, or 18,000 ppm *o*-nitroanisole. Final mean body weights and feed consumption by male and female rats receiving 6,000 and 18,000 ppm were lower than those of the controls. Hemoglobin and hematocrit values were significantly lower and methemoglobin levels significantly higher in males in the 6,000 and 18,000 ppm groups than in controls. Absolute liver weights were significantly increased in females that received 200, 600, 2,000, and 6,000 ppm, absolute kidney weights were significantly increased in males that received 600, 2,000, and 6,000 ppm, and absolute spleen weights were significantly increased in males and females that received 6,000 and 18,000 ppm.

Groups of 10 male and 10 female B6C3F$_1$ mice received diets containing 0, 60, 200, 600, 2,000, or 6,000 ppm *o*-nitroanisole. Final mean body weight gains, final mean body weights, and feed consumption by male and female mice receiving 6,000 ppm were lower than those of the controls. Hemoglobin and hematocrit values in males and females that received 2,000 or 6,000 ppm were significantly lower than those in the controls. The absolute and relative liver weights of females in the 600 ppm group and relative liver weights of males and females in the 2,000 and

6,000 ppm groups were significantly greater than those of controls.

Lesions associated with exposure to *o*-nitroanisole were present in the urinary bladder, spleen, kidney, liver, testis, and uterus of rats. Diffuse hyperplasia of the transitional epithelium of the urinary bladder occurred in all male and female rats that received 6,000 and 18,000 ppm. A transitional cell papilloma occurred in one male and transitional cell carcinomas occurred in two males and three females receiving 18,000 ppm. Congestion of the red pulp and capsular hyperplasia of the spleen and hepatocellular hypertrophy of the liver were present in males and females from the 18,000 ppm groups. Multifocal degeneration and necrosis of the renal tubule epithelium with infiltration of mononuclear inflammatory cells were present in male rats that received 600, 2,000, and 6,000 ppm. At the 18,000 ppm level, degeneration of the seminiferous epithelium accompanied by loss of spermatogenic cells and decreased numbers of spermatozoa were observed in the testes of male rats, while uterine atrophy was observed in female rats.

Hepatocyte hypertrophy of the centrilobular and midzonal regions of liver lobules was present in mice that received 200 ppm and increased in severity at higher exposure levels.

2-YEAR STUDIES

The doses selected for the 2-year study of *o*-nitroanisole in rats were based on lower mean body weights, reduced feed consumption, and increased severity of regenerative anemia in male and female rats receiving 6,000 and 18,000 ppm during the 13-week study. Groups of 60 male and 60 female F344 rats received diets containing 0, 222, 666, or 2,000 ppm *o*-nitroanisole. Groups of 60 male and 60 female B6C3F$_1$ mice received diets containing 0, 666, 2,000, or 6,000 ppm *o*-nitroanisole. After 15 months, up to 10 animals from each group were evaluated for chemical-related lesions.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Survival of male rats receiving 2,000 ppm was significantly lower than that of the controls due to increased severity of nephropathy. Survival of 222 and 666 ppm male rats and all exposed female rats was similar to that of the controls. Survival of groups of exposed male and female mice was similar to that of the controls. The final mean body weight of male rats receiving 2,000 ppm was lower than that of the controls. Final mean body weights of male and female mice that received 2,000 and 6,000 ppm were lower than those of the controls. Feed consumption by male and female rats was similar to that by the controls. The only clinical finding in male or female mice attributable to chemical administration was discolored urine.

Neoplasms and Nonneoplastic Lesions

The incidence of mononuclear cell leukemia was significantly increased in male rats that received 666 and 2,000 ppm and in female rats that received 2,000 ppm (males: 0 ppm, 26/50; 222 ppm, 25/50; 666 ppm, 42/50; 2,000 ppm, 34/50; females: 14/50, 11/50, 14/50, 26/50). Nephropathy occurred in all male rats; the severity increased with exposure level. Focal hyperplasia of the renal tubule epithelium was present in three males receiving 222 ppm and two males receiving 2,000 ppm. Renal tubule adenomas occurred in one male from each of the 222, 666, and 2,000 ppm groups, and renal tubule carcinomas occurred in two males from the 2,000 ppm group. Focal hyperplasia of the transitional epithelium of the urinary bladder was present in one female rat that received 222 ppm and two male rats and six female rats that received 2,000 ppm. A transitional cell papilloma occurred in the urinary bladder of one female rat from the 2,000 ppm group, and a transitional cell carcinoma occurred in another female from the 2,000 ppm group. The incidence of forestomach ulcers increased in male rats that received 2,000 ppm, and the incidence of focal hyperplasia of the forestomach increased with exposure level in male and female rats. In addition, squamous cell papillomas of the forestomach were present in one female receiving 222 ppm, one male receiving 666 ppm, and one male and one female receiving 2,000 ppm, while squamous cell carcinomas were present in one male receiving 666 ppm and one male and one female receiving 2,000 ppm. The incidences of pituitary gland adenomas in male rats and mammary gland fibroadenomas in female rats decreased with exposure level.

The incidence of cellular alteration in the liver was significantly increased in exposed groups of male and female mice. The incidences of hepatocellular adenoma, hepatocellular adenoma or carcinoma (combined), and hepatocellular carcinoma or hepatoblastoma (combined) were significantly

increased in male mice receiving 2,000 and 6,000 ppm. The incidences of hepatocellular adenoma or carcinoma were significantly increased in female mice that received 2,000 ppm.

Stop-Exposure Study

Groups of 60 male and 60 female F344 rats received diets containing 0, 6,000, or 18,000 ppm *o*-nitroanisole for 27 weeks and were then maintained on control feed without further chemical exposure for up to an additional 77 weeks. Up to 10 rats from each group were evaluated for the presence of chemical-related lesions at 3, 6, 9, and 15 months.

Survival and Body Weights

Survival of exposed male and female rats was significantly lower than that of the controls as a result of moribund deaths associated with significantly increased incidences of urinary bladder neoplasms, primarily transitional cell carcinomas. All male rats that received 18,000 ppm were dead by week 48 and all females that received 18,000 ppm were dead by week 61. Mean body weights of exposed male and female rats were lower than those of the controls throughout the study.

Neoplasms and Nonneoplastic Lesions

Hyperplasia of the transitional epithelium of the urinary bladder was present in nearly all exposed male and female rats examined at the interim evaluations. A transitional cell carcinoma was first observed at the 3-month interim evaluation in a male rat that received 18,000 ppm. At the 6- and 9-month interim evaluations, transitional cell papillomas or carcinomas were observed in both exposed groups of male rats. Transitional cell carcinomas were observed at the 6-month interim evaluation in females receiving 18,000 ppm and at the 9-month interim evaluation in females receiving 6,000 and 18,000 ppm.

Adenomatous polyps of the large intestine were observed in a small number of exposed rats at the 6-, 9-, and 15-month interim evaluations. At the end of the study, the incidence of adenomatous polyps of the large intestine was significantly increased in all exposed groups and carcinomas of the large intestine were present in four males and two females from the 18,000 ppm groups. The incidence of hyperplasia of the transitional epithelium of the kidney pelvis was significantly increased in exposed male and female rats and transitional cell papillomas were present in three males and one female that received 18,000 ppm. Transitional cell carcinomas of the kidney were present in one male receiving 6,000 ppm and six males and one female receiving 18,000 ppm. Transitional cell carcinomas of the urinary bladder were seen in nearly all exposed male and female rats. Of the males and females receiving 6,000 ppm which were without carcinomas, three males and one female had transitional cell papillomas.

Generalized centrilobular hypertrophy, focal hepatocellular necrosis, multifocal hepatocellular cytoplasmic vacuolation, and Kupffer cell pigmentation were observed in the livers of male and female rats at the 3- and 6-month interim evaluations; however, only Kupffer cell pigmentation was observed at the end of the study. Congestion of the red pulp of the spleen was observed in nearly all exposed male and female rats at the 3-, 6-, and 9-month interim evaluations but the incidence was only slightly increased in the 18,000 ppm groups at the end of the study. Degeneration and atrophy of the seminiferous tubule epithelium of the testes were observed at the 3- and 6-month interim evaluations in all male rats receiving 18,000 ppm.

Genetic Toxicology

o-Nitroanisole was tested in two laboratories for mutagenicity in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 with and without exogenous metabolic activation (S9). Positive responses were observed at both laboratories in TA100 with and without S9 activation. One laboratory found no increase in mutations, while the second laboratory detected a weakly positive response in TA1535 without S9. No mutagenic activity was observed in the other tester strains. *o*-Nitroanisole was positive in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y cells without S9 activation. In cytogenetic tests with Chinese hamster ovary cells, *o*-nitroanisole induced a significant increase in chromosomal aberrations at the highest dose tested in the presence of S9 activation; sister chromatid exchanges were induced both with and without S9.

CONCLUSIONS

Under the conditions of these feed studies there was *clear evidence of carcinogenic activity** of *o*-nitroanisole in male and female F344 rats that received diets containing 6,000 or 18,000 ppm for 6 months based on overall increased incidences of benign and malignant neoplasms of the urinary bladder, transitional cell neoplasms of the kidney, and benign and malignant neoplasms of the large intestine. There was a chemical-related increased incidence of mononuclear cell leukemia in male and female rats receiving diets containing 222, 666, or 2,000 ppm *o*-nitroanisole for 2 years. Marginally increased incidences of uncommon renal tubule neoplasms in male rats and forestomach neoplasms in male and female rats were considered uncertain findings. There was *clear evidence of carcinogenic activity* of *o*-nitroanisole in male $B6C3F_1$ mice based on increased incidences of benign and malignant hepatocellular neoplasms. There was *some evidence of carcinogenic activity* of *o*-nitroanisole in female $B6C3F_1$ mice based on increased incidences of hepatocellular adenomas.

Increased severity of nephropathy in male rats, and increased incidences of focal hyperplasia of the renal tubule epithelium and forestomach ulcers in male rats, and of transitional cell hyperplasia of the urinary bladder, focal hyperplasia of the forestomach, and hyperplasia of transitional epithelium of the kidney pelvis in male and female rats were associated with exposure to *o*-nitroanisole.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 12. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appear on page 14.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of *o*-Nitroanisole

	Male F344 Rats		Female F344 Rats	
	2-Year Study	Stop-Exposure Study[a]	2-Year Study	Stop-Exposure Study[a]
Doses	0, 222, 666, or 2,000 ppm in feed	0, 6,000, or 18,000 ppm in feed	0, 222, 666, or 2,000 ppm in feed	0, 6,000, or 18,000 ppm in feed
Body weights	High-dose group lower than controls	Exposed groups lower than controls	Exposed groups similar to controls	Exposed groups lower than controls
2-Year survival rates	32/50, 34/50, 24/50, 9/50	13/20, 1/20, 0/20	33/50, 41/50, 26/50, 33/50	14/20, 4/20, 0/20
Nonneoplastic effects	Forestomach: focal hyperplasia (3/50, 16/50, 25/50, 32/50); ulcers (3/50, 3/50, 8/50, 16/50) Kidney: renal tubule focal hyperplasia (0/49, 3/50, 0/50, 2/49); nephropathy severity (2.2, 2.4, 2.6, 3.2)	Urinary bladder: transitional cell hyperplasia (0/59, 38/59, 11/60) Kidney: transitional epithelium hyperplasia (5/60, 34/60, 27/60)	Forestomach: focal hyperplasia (8/50, 8/50, 13/50, 28/50)	Urinary bladder: transitional cell hyperplasia (0/58, 34/59, 11/60) Kidney: transitional epithelium hyperplasia (0/60, 6/60, 19/60)
Neoplastic effects	All organs: mononuclear cell leukemia (26/50, 25/50, 42/50, 34/50)	Urinary bladder: transitional epithelium papilloma (0/59, 9/59, 1/60); transitional epithelium carcinoma (0/59, 27/59, 50/60); squamous cell papilloma (0/59, 0/59, 4/60); squamous cell carcinoma (0/59, 0/59, 6/60); sarcoma (0/59, 2/59, 9/60) Large intestine: adenomatous polyp (0/60, 26/60, 30/60); carcinoma (0/60, 0/60, 5/60) Kidney: transitional epithelium papilloma (0/60, 0/60, 4/60); transitional epithelium carcinoma (0/60, 1/60, 8/60)	All organs: mononuclear cell leukemia (14/50, 11/50, 14/50, 26/50)	Urinary bladder: transitional epithelium papilloma (0/58, 2/59, 1/60); transitional epithelium carcinoma (0/58, 28/59, 48/60); sarcoma (0/58, 2/59, 14/60); squamous cell papilloma (0/58, 0/59, 4/60); squamous cell carcinoma (0/58, 0/59, 1/60) Large intestine: adenomatous polyp (0/60, 8/60, 18/60); carcinoma (0/60, 0/60, 2/60) Kidney: transitional epithelium papilloma (0/60, 0/60, 1/60); transitional epithelium carcinoma (0/60, 0/60, 1/60)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of *o*-Nitroanisole (continued)

	Male F344 Rats		Female F344 Rats	
	2-Year Study	Stop-Exposure Study	2-Year Study	Stop-Exposure Study
Uncertain findings	Kidney: renal tubule adenoma (0/49, 1/50, 1/50, 1/49); renal tubule carcinoma (0/49, 0/50, 0/50, 2/49) Forestomach: squamous cell papilloma (0/50, 0/50, 1/50, 1/50); squamous cell carcinoma (0/50, 0/50, 1/50, 1/50)	None	Forestomach: squamous cell papilloma (0/50, 1/50, 0/50, 1/50); squamous cell carcinoma (0/50, 0/50, 0/50, 1/50)	None
Level of evidence of carcinogenic activity	Clear evidence		Clear evidence	

	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 666, 2,000, or 6,000 ppm in feed	0, 666, 2,000, or 6,000 ppm in feed
Body weights	Exposed groups lower than controls	Exposed groups lower than controls
2-Year survival rates	35/50, 43/50, 39/50, 40/50	38/50, 26/50, 33/50, 45/50
Nonneoplastic effects	None	None
Neoplastic effects	Liver: hepatocellular adenoma (14/50, 26/50, 41/50, 29/50); carcinoma (7/50, 12/50, 11/50, 7/50); hepatoblastoma (0/50, 3/50, 17/50, 9/50)	Liver: hepatocellular adenoma (14/50, 20/50, 36/50, 18/50)
Uncertain findings	None	None
Level of evidence of carcinogenic activity	Clear evidence	Some evidence

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of *o*-Nitroanisole (continued)

Genetic toxicology	
Salmonella typhimurium gene mutation	Positive with or without S9 in strain TA100; positive without S9 in strain TA1535; negative with or without S9 in strains TA97, TA98, and TA1537
Mouse lymphoma gene mutations	Positive without S9
Sister chromatid exchanges	
Chinese hamster ovary cells *in vivo*:	Positive with or without S9
Chromosomal aberrations	
Chinese hamster ovary cells *in vitro*:	Weakly positive with S9; negative without S9

[a] Denominators of lesions reflect overall rates

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 chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement 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 *o*-nitroanisole on November 21, 1991, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing 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.

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

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

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

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

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

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

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

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

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

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

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

Lauren Zeise, Ph.D.
California Department of Health Services/RCHAS
Berkeley, CA

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On November 21, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of *o*-nitroanisole received public review by the National Toxicology Program 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. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of *o*-nitroanisole by discussing the rationale for study, describing the experimental design including additional 2-year stop-exposure studies in rats, reporting on survival and body weight effects, and commenting on compound-related neoplasms in rats and mice and nonneoplastic lesions in rats. The proposed conclusions were *clear evidence of carcinogenic activity* in male and female F344 rats that received diets containing 6,000 or 18,000 ppm for 6 months, *clear evidence of carcinogenic activity* in male $B6C3F_1$ mice, and *some evidence of carcinogenic activity* in female $B6C3F_1$ mice.

Dr. Hayden, a principal reviewer, agreed with the conclusions. He thought the rationale for study could be strengthened by adding a statement on consumer exposure as well as occupational exposure, and by noting that several aromatic amines have been identified as human bladder carcinogens. Dr. Irwin said there were no data on human exposure including the NIOSH National Occupational Exposure Survey.

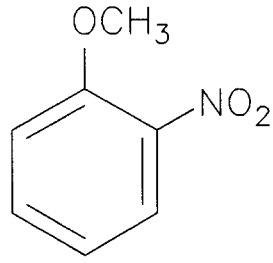
Dr. McKnight, the second principal reviewer, agreed with the conclusions. She said the rationale section should also include mention of why the stop-exposure studies were performed. Dr. Irwin said this would be added. Further, since the conclusions in rats rest heavily on the results of the stop-exposure studies, Dr. McKnight suggested that the appendixes should contain the same level of detail of reporting on individual animal results as that given the usual 2-year studies (Tables E2 and F2).

Dr. Garman, the third principal reviewer, agreed with the conclusions. He said that a statement that absence of renal tubule epithelial cell degeneration in male rats in the high-dose group of the stop-exposure study may have been due to marked reduction in feed consumption should be better elaborated. Dr. Irwin responded that the reduction in feed consumption and body weight was such that the physiology of the animal was altered, leading to an interpretation of an association with diminished renal pathology.

Noting that this was one of the first reports to be considered by the Subcommittee that had both conventional 2-year and stop-exposure study designs, Dr. Klaassen asked for discussion about presentation of design information and results. Dr. Goodman and Mr. Beliczky stated that the results should be considered and reported separately, while Dr. Garman thought they should not be separated, as the stop-exposure study serves to more or less support or confirm the chronic study. Dr. Irwin observed that the stop-exposure study is usually chosen based on the incidence of a lesion with questionable biological behavior at a higher dose level in prechronic studies. In this case, the data from the stop and chronic studies were treated as part of a dose-response and, thus, it was considered appropriate to combine the findings. Dr. S. Eustis, NIEHS, agreed and said that the NTP would prefer not to draw separate conclusions. Dr. Davidson pointed out that the level of evidence in rats would have been less clearcut without the results from the stop-exposure studies. Dr. Goodman said that separation of the statement about mononuclear cell leukemias in rats was appropriate, as the incidences of leukemia in male rats were supportive of *some evidence* and in female rats were supportive of *equivocal evidence*. Dr. Hayden commented that the evidence was supportive of a positive finding for leukemia in both male and female rats but perhaps not as part of *clear evidence*. Dr. Klaassen concluded that there was not a consensus on this issue.

Dr. Hayden moved that the Technical Report on *o*-nitroanisole be accepted with the revisions discussed and with the conclusions as written for male and female rats and male mice, *clear evidence of carcinogenic activity*, and for female mice, *some evidence of carcinogenic activity*. Dr. Garman seconded the motion. Dr. McKnight offered an amendment that mononuclear cell leukemia be listed in the first sentence as part of *clear evidence* in male and female rats. The amendment was tabled for lack of a second. Dr. Hayden's motion was then accepted unanimously with 10 votes.

INTRODUCTION



o-NITROANISOLE

CAS No. 91-23-6

Chemical Formula: $C_7H_7NO_3$ Molecular Weight: 153.13

Synonyms: Methoxynitrobenzene, nitrophenyl methyl ether

PHYSICAL AND CHEMICAL PROPERTIES, PRODUCTION, AND USE

o-Nitroanisole is a colorless to slightly yellow liquid with a boiling point of 277° C, a melting point of 9° to 10° C, and a specific gravity of 1.254. *o*-Nitroanisole is insoluble in water but is soluble in most organic solvents (*Merck Index*, 1983). Two general methods exist for the preparation of *o*-nitroanisole: methylation of *o*-nitrophenol or displacement of chloride from *o*-nitrochlorobenzene by the methoxide ion (NaOH/methanol). *o*-Nitroanisole is used primarily as a precursor to *o*-anisidine which is prepared by direct nitro-reduction. *o*-Anisidine is used extensively in the synthesis of azo dyes either directly after being converted to a diazonium salt or as a precursor for the preparation of dianisidine which is diazotized and coupled. Directly or indirectly, *o*-anisidine is used in the manufacture of over 100 azo dyes.

PHARMACOKINETICS AND METABOLISM

The pharmacokinetics and metabolism of *o*-nitroanisole have been examined in male F344 rats (Miller *et al.*, 1985). Following an intravenous dose of 25 mg/kg, ^{14}C derived from *o*-nitroanisole was rapidly distributed to tissues with the maximum tissue concentrations being reached within 15 minutes after administration. Elimination of ^{14}C from tissues was also rapid and followed a two-component decay. The initial elimination phase was rapid in all tissues and was characterized by a half-life of 1 to 2 hours; however, the terminal elimination phase was slower and varied considerably from tissue to tissue. In plasma, liver, brain, lung, small intestine, and kidney, the terminal elimination half-life was 2.5 days, while that from muscle, blood, spleen, and testes was 4.0, 4.5, 5.2, and 6.2 days, respectively. Elimination of the parent compound (nonradioactive) from the blood was also biphasic with half-lives of 30 minutes and 2.2 hours, while elimination of the parent compound from liver, kidney, and small intestine was monophasic.

Within 24 hours after oral administration of a 5 or 50 mg/kg dose of ^{14}C *o*-nitroanisole, 73% of the 5 mg/kg dose and 69% of the 50 mg/kg dose had been excreted in the urine. Within 7 days after administration, 71% to 78% of the label had been excreted in the urine and 7% in feces. Moreover, the quantity of radioactivity excreted in the bile was similar to the amount found in the feces, indicating that little if any enterohepatic recirculation was occurring. Examination of the urinary metabolites indicated that 63% of the administered dose was present as *o*-nitrophenyl sulfate, 11% as *o*-nitrophenyl glucuronide, 1.5% as *o*-nitrophenol, and 0.6% as *o*-anisidine. This suggests the metabolic

scheme shown in Figure 1, in which *o*-demethylation is the major pathway to form *o*-nitrophenol followed by sulfate or glucuronide conjugation.

Nitroreduction to *o*-anisidine was quantitatively a minor pathway; *o*-anisidine was found only in the liver, and the concentration decayed rapidly and was below the limit of detection within 2 hours after dosing.

CARCINOGENICITY

There are no published studies that have examined the toxicity or carcinogenicity of *o*-nitroanisole. However, *o*-anisidine has been evaluated for carcinogenic potential by the NTP (NCI, 1978b). Groups of 55 F344/N rats received diets containing 5,000 or 10,000 ppm and groups of 55 $B6C3F_1$ mice received diets containing 2,500 or 5,000 ppm *o*-anisidine for 103 weeks. The incidences of transitional cell papillomas or carcinomas of the urinary bladder were significantly increased in all groups of dosed rats (males: 0/51, 52/54, 52/52; females: 0/49, 46/49, 50/51) and in high-dose mice (males: 0/48, 2/55, 22/53; females: 0/50, 1/51, 22/50).

GENETIC TOXICITY

o-Nitroanisole was positive for induction of DNA damage in *Bacillus subtilis* in the absence of S9 (Shimizu and Yano, 1986) and induction of gene mutations in *Salmonella typhimurium* strain TA100, with and without S9 (Table G1; Chiu *et al.*, 1978; Tokiwa *et al.*, 1981; Haworth *et al.*, 1983). It was also reported to be mutagenic in *S. typhimurium* strains TA98 and TA1538 without S9 (Chiu *et al.*, 1978; Shimizu and Yano, 1986). In Chinese hamster ovary cell cultures, *o*-nitroanisole induced sister chromatid exchanges with and without S9 and chromosomal aberrations in the presence of S9 (Tables G3 and G4; Galloway *et al.*, 1987).

Mutagenicity data are available for two metabolites of *o*-nitroanisole, *o*-nitrophenol and *o*-anisidine. *o*-Nitrophenol did not induce gene mutations in *S. typhimurium*, with or without S9 (Chiu *et al.*, 1978; Haworth *et al.*, 1983; Suzuki *et al.*, 1983; Shimizu and Yano, 1986), did not induce DNA damage in *B. subtilis* (Natake *et al.*, 1979; Shimizu and Yano, 1986), and did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* (NTP, unpublished data).

o-Anisidine, the second metabolite, was genotoxic. It induced gene mutations in *S. typhimurium* in the presence, but not the absence, of S9 (Zeiger *et al.*, 1992), and was mutagenic with and without S9 in mouse lymphoma L5178Y cells (Wangenheim and Bolcsfoldi, 1988). It did not induce sex-linked recessive lethal mutations in *D. melanogaster* (Yoon *et al.*, 1985). Induction of DNA strand breaks was reported in mouse lymphoma L5178Y cells treated with *o*-anisidine in the presence of S9 (Garberg *et al.*, 1988), but tests for induction of DNA repair conducted in male rat hepatocytes without S9 were negative (Yoshimi *et al.*, 1988). *o*-Anisidine induced both sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells with and without S9 (Galloway *et al.*, 1987).

STUDY RATIONALE

o-Nitroanisole was evaluated for carcinogenic potential because of its structural similarity to *o*-anisidine and because human exposure might be associated with its widespread use in the manufacture of azo dyes.

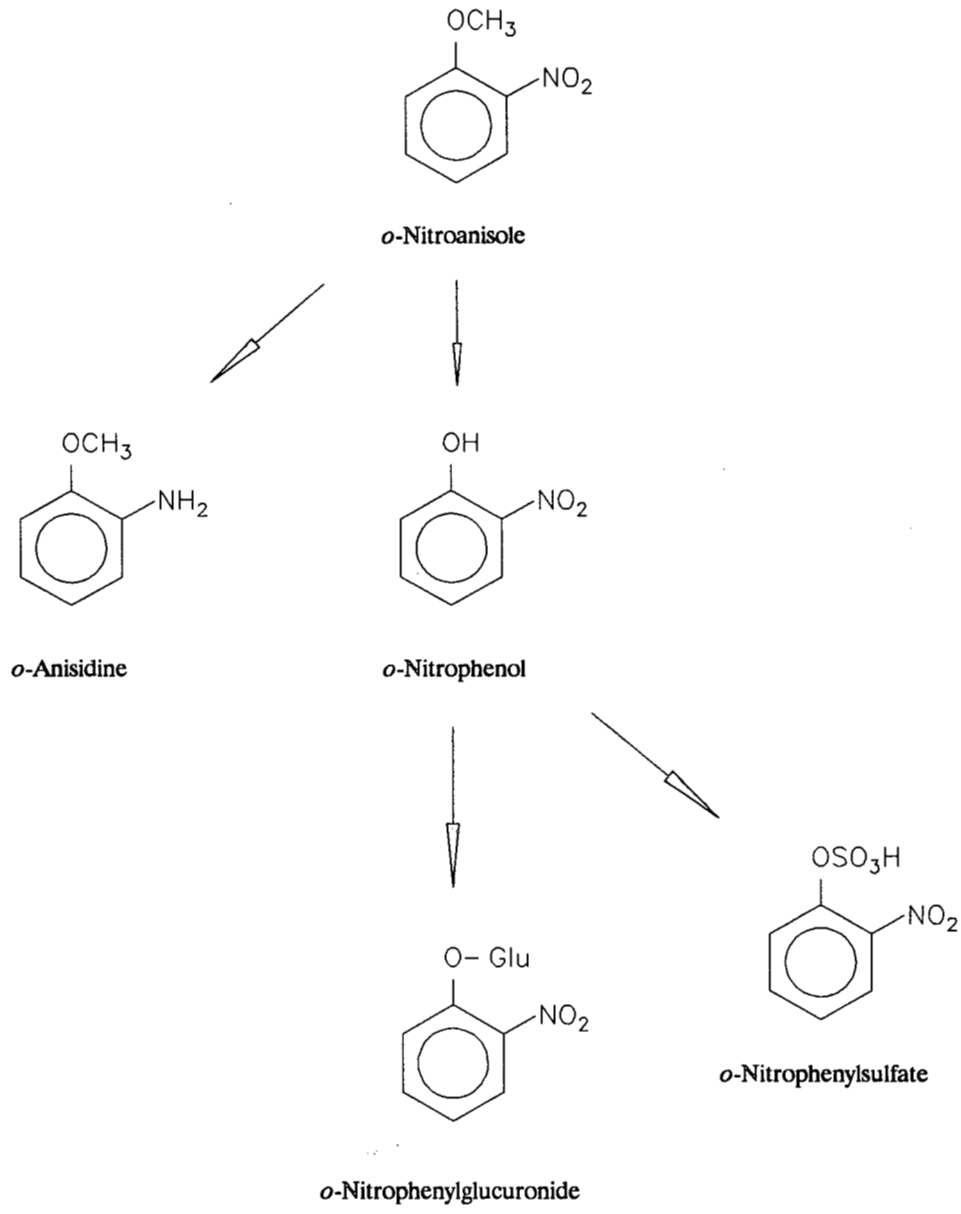


FIGURE 1
The Metabolic Pathway of *o*-Nitroanisole (Miller *et al.*, 1985)

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *o*-NITROANISOLE

o-Nitroanisole was obtained from the Aldrich Chemical Company (Milwaukee, WI) in three lots (lots TE061197, 2712DL, and 1517AM). Lot TE061197 was used throughout the 14-day and 13-week studies in rats and mice and in portions of the 2-year and stop-exposure studies in rats. Lot 2712DL was used in a portion of the stop-exposure study in rats and portions of the 2-year studies in rats and mice; lot 1517AM was used in a portion of the 2-year studies in rats and mice. Identity, purity, and stability analyses were performed by the analytical chemistry laboratory, Midwest Research Institute (MRI; Kansas City, MO), and confirmed by the study laboratory (Appendix J).

All three lots of the study chemical, a clear yellow liquid, were identified as *o*-nitroanisole by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of the lots was found to be greater than 99% by Karl Fischer water analysis, elemental analyses, titration of the nitro group, thin-layer chromatography, and gas chromatography. Stability studies performed at the analytical chemistry laboratory indicated that *o*-nitroanisole was stable as a bulk chemical for 2 weeks at temperatures up to 60° C when stored protected from light. The stability of the bulk chemical was monitored periodically at the study laboratory using infrared and ultraviolet spectroscopy and gas chromatography methods. No change in purity was observed.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing *o*-nitroanisole and feed in a blender (Table J1). Studies to determine homogeneity and stability of the dosed feed preparations were conducted by the analytical chemistry laboratory. Homogeneity was confirmed using ultraviolet spectroscopy methods for sample analysis. The stability studies of the dose formulations were performed using high performance liquid chromatography (HPLC) methods. These studies indicated that the dose formulations were stable for at least 3 weeks at room temperature and 1 week when stored under simulated animal cage conditions.

Periodic analyses of the dose formulations of *o*-nitroanisole were conducted at the study laboratory and the analytical chemistry laboratory using either ultraviolet spectroscopy or HPLC methods. During the 14-day studies, the dose formulations were analyzed at the beginning of the studies (Table J2). During the 13-week studies, the dose formulations were analyzed at the initiation, midpoint, and end of the studies (Table J3). During the 2-year studies, the dose formulations were analyzed at least once every 8 weeks (Table J4). In the 2-year and stop-exposure studies, 85% (141/166) of the dose formulations were within 10% of the target concentrations. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in good agreement with the results obtained by the study laboratory (Table J5).

14-DAY STUDIES

Male and female F344 rats and B6C3F$_1$ mice were obtained from the Charles River Breeding Facility (Kingston, NY). At receipt, the rats were 4 to 5 weeks old and the mice were 5 to 6 weeks old. The animals were quarantined for 21 days before exposure began. Before the beginning of the studies, five animals of each species and sex were randomly selected for parasite evaluation and gross observation for evidence of disease.

Groups of five male and five female rats were fed diets containing 0, 583, 1,166, 2,332, 4,665, or 9,330 ppm *o*-nitroanisole; groups of five male and five female mice were fed diets containing 0, 250, 500, 1,000, 2,000, or 4,000 ppm *o*-nitroanisole. The appropriate feed was supplied weekly and was available *ad libitum*. Animals were housed five per cage and water was available *ad libitum*. Clinical findings were recorded twice daily. Feed consumption was recorded weekly by cage. The animals were weighed at study initiation, at day 7,

and at the end of the studies. Details of study design and animal maintenance are summarized in Table 1.

At the end of the 14-day studies, blood and urine were collected from all male rats for clinical pathology analyses. The clinical pathology parameters measured are listed in Table 1. A gross necropsy was performed on all rats and mice. The brain, heart, right kidney, liver, lungs, right testis, thymus, and trachea were weighed from rats and mice. Histopathologic examinations were not conducted.

13-Week Studies

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to *o*-nitroanisole and to determine the appropriate doses to be used in the 2-year studies.

Male and female F344 rats and B6C3F$_1$ mice were obtained from the Charles River Breeding Facility (Portage, MI). Upon receipt, the rats were 4 to 5 weeks old and the mice were 5 to 6 weeks old. The animals were quarantined for 9 days before exposure began. Before the beginning of the studies, five animals of each species and sex were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five control animals of each species and sex using the protocols of the NTP Sentinel Animal Program (Appendix M).

Groups of 10 male and 10 female rats were fed diets containing 0, 200, 600, 2,000, 6,000, or 18,000 ppm *o*-nitroanisole; groups of 10 male and 10 female mice were fed diets containing 0, 60, 200, 600, 2,000, or 6,000 ppm *o*-nitroanisole. The appropriate feed was supplied weekly and was available *ad libitum*. Animals were housed five per cage; water was available *ad libitum*. Clinical findings were recorded twice daily. Feed consumption was recorded weekly by cage. The animals were weighed at the beginning of the studies and weekly thereafter. Further details of study design and animal maintenance are summarized in Table 1.

At the end of the 13-week studies, blood and urine were collected from all animals for clinical pathology analyses. The clinical pathology parameters measured are listed in Table 1. A necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, spleen, right testis, and thymus were weighed. Tissues for microscopic examination were embedded in paraffin, sectioned to a thickness of 4 to 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all control animals, all animals that received 6,000 ppm, and all animals dying early. The epididymis, kidney, liver, spleen, testis, and urinary bladder of all exposed rats were examined microscopically. Table 1 lists the tissues and organs routinely examined microscopically.

2-Year Studies

Study Design

In the core study, groups of 60 male and 60 female rats were fed diets containing 0, 222, 666, or 2,000 ppm *o*-nitroanisole; groups of 60 male and 60 female mice were fed diets containing 0, 666, 2,000, or 6,000 ppm *o*-nitroanisole for 103 weeks. Up to 10 rats and mice per group were designated for interim evaluations after 15 months of chemical administration.

The stop-exposure study consisted of groups of 60 male and 60 female rats fed diets of 0, 6,000, or 18,000 ppm *o*-nitroanisole for 27 weeks and then held up to an additional 77 weeks without further treatment. Ten rats per group were scheduled for interim evaluations after 3, 6, 9, and 15 months.

Source and Specification of Animals

Male and female F344 rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA) for use in the 2-year studies. Rats were quarantined for 11 days, and mice were quarantined for 10 days before the beginning of the studies. Five rats and five mice of each sex were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats and mice in the 2-year studies were approximately 40 days old at the beginning of the studies; rats in the stop-exposure study were approximately 41 days old at the beginning of the study. The health of the animals was monitored during the studies according to the NTP Sentinel Animal Program (Appendix M).

Animal Maintenance

Rats were housed five per cage; mice were housed individually. Feed and water were available *ad libitum*. Cages were rotated every 2 weeks during the studies. Further details of animal maintenance

are given in Table 1. Information on feed composition is provided in Appendix L.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded weekly for the first 13 weeks, and monthly thereafter. Animals were weighed at study initiation, weekly for the first 13 weeks, and monthly thereafter. Up to 10 rats and mice were selected from each group in the 2-year studies for interim evaluations at 15 months. During the stop-exposure study, up to 10 rats from each group were selected for interim evaluations after 3, 6, 9, and 15 months. All animals received a complete gross examination. The brain, right kidney, liver, spleen, and right testis were weighed at the 15-month interim evaluations in the 2-year studies.

Animals found in a moribund state or surviving to the end of the 2-year studies received a complete necropsy. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathologic examinations were performed on all tissues with grossly visible lesions. Tissues examined are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist and the pathology data were entered into the Toxicology Data Management System. The microscopic 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, slide and tissue counts were verified, and histotechnique was evaluated. For the 2-year studies in rats, a quality assessment pathologist reviewed the forestomach, kidney, large intestine (stop-exposure study), liver, pancreas (male), spleen, uterus (stop-exposure study), and urinary bladder for accuracy and consistency of diagnosis. In the 2-year study in mice, a quality assessment pathologist reviewed the liver, nose, lung, and lymphoid tissues.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the selected tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnosis between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chair to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined tissues without knowledge of exposure group or previously rendered diagnoses. When the consensus opinion of the PWG differed from that of the laboratory pathologist, the final diagnosis was changed. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

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 were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for 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 analysis are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, D5, E1, E4, F1, and F4 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, D3, E3, and F3) and all nonneoplastic lesions are given as the ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin or mammary

gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., mononuclear cell leukemia), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidence

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was logistic regression analysis, which assumed that the diagnosed neoplasms were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, neoplasm prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The neoplasm incidences of exposed and control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When neoplasms are incidental, this comparison of the time-specific neoplasm prevalences also provides a comparison of the time-specific neoplasm incidences (McKnight and Crowley, 1984).

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal neoplasms, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of neoplasm-bearing animals.

Tests of significance include pairwise comparisons of each exposed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, see Haseman (1984).

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of neoplasm incidence. Consequently, control neoplasm incidences from the NTP historical control database (Haseman *et al.*, 1984, 1985) are included in the NTP reports for neoplasms appearing to show compound-related effects.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Williams (1971, 1972) and Dunnett (1955). Hematology, clinical chemistry, and urinalysis data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-response trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-response trend (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Quality Assurance Methods

The 13-week and 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, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. 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 so all had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of *o*-nitroanisole was assessed by testing its ability to induce mutations in *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, and trifluorothymidine resistance in mouse L5178Y lymphoma cells. The protocols and results of these studies are given in Appendix G.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *o*-Nitroanisole

14-Day Studies	13-Week Studies	Stop-Exposure Study	2-Year Studies
Study Laboratory			
Hazleton Raltech, Inc. (Madison, WI)	Hazleton Raltech, Inc. (Madison, WI)	Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)
Strain and Species			
Rats: F344 Mice: $B6C3F_1$	Rats: F344 Mice: $B6C3F_1$	Rats: F344	Rats: F344 Mice: $B6C3F_1$
Animal Source			
Charles River Breeding Facility (Kingston, NY)	Charles River Breeding Facility (Portage, MI)	Simonsen Laboratories (Gilroy, CA)	Simonsen Laboratories (Gilroy, CA)
Time Held Before Studies			
21 days	9 days	11 days	Rats: 11 days Mice: 10 days
Average Age When Studies Began			
Rats: 7-8 weeks Mice: 8-9 weeks	Rats: 5-6 weeks Mice: 6-7 weeks	41 days	40 days
Date of First Dose			
31 March 1982	14 May 1982	18 September 1984	Rats: 11 September 1984 Mice: 23 October 1984
Duration of Dosing			
Rats: 14 days Mice: 15 days	Rats: 90 days (males) 91 days (females) Mice: 94 days (males) 95 days (females)	27 weeks	103 weeks
Date of Last Dose			
Rats: 14 April 1982 Mice: 15 April 1982	Rats: 13 August 1982 Mice: 17 August 1982	25 March 1985	Rats: 1 September 1986 Mice: 13 October 1986
Necropsy Dates			
Rats: 14 April 1982 Mice: 15 April 1982	Rats: 13 August 1982 Mice: 17 August 1982	3-Month interim: 13-14 December 1984 6-Month interim: 26-27 March 1985 9-Month interim: 18-19 June 1985 15-Month interim: 16-17 December 1985 Terminal: 15-16 September 1986	Rats – 15-Month interim: 10-12 December 1985 Terminal: 8-15 September 1986 Mice – 15-Month interim: 20-22 January 1986 Terminal: 20-27 October 1986

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *o*-Nitroanisole (continued)

14-Day Studies	13-Week Studies	Stop-Exposure Study	2-Year Studies
Average Age at Necropsy			
Rats: 9-10 weeks Mice: 10-11 weeks	Rats: 19-20 weeks Mice: 21-22 weeks	3-Month interim: 128 days 6-Month interim: 231 days 9-Month interim: 315 days 15-Month interim: 496 days Terminal: 769 days	15-Month interim: 496 days (rats) 495 days (mice) Terminal: 771 days
Size of Study Groups			
5 males and 5 females	10 males and 10 females	60 males and 60 females	60 males and 60 females
Method of Distribution			
Animals were grouped by weight intervals. Animals were assigned to cages, then the cages were assigned to dose groups using an appropriate table of random numbers.	Same as 14-day studies	Same as 14-day studies	Same as 14-day studies
Animals per Cage			
5	5	5	Rats: 5 Mice: 1
Method of Animal Identification			
Metal tags	Same as 14-day studies	Toe clip	Same as stop-exposure study
Diet			
NIH-07 open formula rat and mouse diet (Teklad Test Diets, Winfield, IA), available *ad libitum*	Same as 14-day studies	NIH-07 open formula mash diet, (Zeigler Brothers, Gardners, PA), available *ad libitum*	Same as stop-exposure study
Maximum Storage Time for Feed			
Not available	Not available	120 days from milling	120 days from milling
Water			
Automatic watering system (Systems Engineering, Palo Alto, CA), available *ad libitum*	Same as 14-day studies	Automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*	Same as stop-exposure study
Cages			
Polycarbonate, changed twice weekly	Same as 14-day studies	Polycarbonate (Lab Products, Inc., Garfield, NJ), changed twice weekly	Same as stop-exposure study, but changed twice weekly for rats and once weekly for mice

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *o*-Nitroanisole (continued)

14-Day Studies	13-Week Studies	Stop-Exposure Study	2-Year Studies
Bedding			
BetaChips hardwood laboratory bedding (Northeastern Products, Warrensburg, NY), changed twice weekly	Same as 14-day studies	Same as 14-day studies	Same as 14-day studies, but changed twice weekly (rats) and once weekly (mice)
Cage Filters			
Nonwoven polyester	Same as 14-day studies	Reemay spun-bonded polyester (Snow Filtration, Cincinnati, OH, or Andico, Birmingham, AL), changed once every 2 weeks	Same as stop-exposure study
Racks			
Stainless steel	Same as 14-day studies	Stainless steel (Lab Products, Inc., Maywood, NJ), changed once every 2 weeks	Stainless steel (Lab Products, Inc., Garfield, NJ), changed once every 2 weeks
Animal Room Environment			
Temperature: 22° ± 1° C Relative humidity: 50% ± 10% Fluorescent light: 12 hours/day Room air: 10-15 changes/hour	Temperature: 22° ± 2° C Relative humidity: 50% ± 20% Fluorescent light: 12 hours/day Room air: 10-15 changes/hour	Temperature: 19°-27° C (9/17/84-3/30/86); 20°-24° C (4/1/86-9/16/86) Relative humidity: 25%-65% (9/17/84-3/30/86); 18%-58% (4/1/86-9/16/86) Fluorescent light: 12 hours/day Room air: minimum of 15 changes/hour	Rats – Temperature: 19°-27° C (8/30/84-3/30/86); 15°-26° C (4/1/86-9/15/86) Relative humidity: 27%-61% (8/30/84-3/30/86); 23%-69% (4/1/86-9/15/86) Fluorescent light: 12 hours/day Room air: minimum of 15 changes/hour Mice – Temperature: 18°-26° C (10/12/84-3/30/86); 19°-25° C (4/1/86-10/27/86) Relative humidity: 24%-70% (10/12/84-3/30/86); 21%-73% (4/1/86-10/27/86) Fluorescent light: 12 hours/day Room air changes: minimum of 15 changes/hour

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *o*-Nitroanisole (continued)

14-Day Studies	13-Week Studies	Stop-Exposure Study	2-Year Studies
Doses			
Rats: 0, 583, 1,116, 2,332, 4,665, or 9,330 ppm in feed, available *ad libitum* Mice: 0, 250, 500, 1,000, 2,000, or 4,000 ppm in feed, available *ad libitum*	Rats: 0, 200, 600, 2,000, 6,000, or 18,000 ppm in feed, available *ad libitum* Mice: 0, 60, 200, 600, 2,000, or 6,000 ppm in feed, available *ad libitum*	0, 6,000, or 18,000 ppm in feed, available *ad libitum*	Rats: 0, 222, 666, or 2,000 ppm in feed, available *ad libitum* Mice: 0, 666, 2,000, or 6,000 ppm in feed, available *ad libitum*
Type and Frequency of Observation			
Observed twice daily; animals weighed initially, at day 7, and at end of studies; clinical observations recorded twice daily; feed consumption recorded by cage weekly.	Observed twice daily; animals weighed initially, weekly, and at end of studies; clinical observations recorded twice daily; feed consumption recorded by cage weekly.	Observed twice daily; animal weights and clinical findings recorded weekly through week 13, monthly thereafter, and at interim evaluations or death; feed consumption measured daily per cage for 1 week each month.	Observed twice daily; animal weights and clinical findings recorded weekly through week 13, monthly thereafter, and at interim evaluations or death; feed consumption measured daily per cage for 1 week each month.
Method of Sacrifice			
Not available	Not available	Thoracotomy under ether anesthesia at the 3-, 6-, and 9-month interim evaluations. Carbon dioxide asphyxiation at the 15-month interim evaluation and the end of the study.	Thoracotomy under ether anesthesia at the interim evaluations. Carbon dioxide asphyxiation at the end of the studies.
Necropsy			
Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lungs, right testis, thymus, and trachea.	Necropsy performed on all animals. Organs weighed were brain, heart, right kidney, liver, lungs, spleen, right testis, and thymus.	All animals necropsied; organs weighed at 3-, 6-, and 9-month interim evaluations were right kidney, liver, spleen, right testis, urinary bladder, and uterus. Organs weighed at the 15-month interim evaluation were right kidney, liver, spleen, right testis, urinary bladder, and uterus.	All animals necropsied. Organs weighed at the interim evaluations were brain, right kidney, liver, spleen, and right testis.
Clinical Pathology			
Blood and urine samples were collected from all male rats. *Hematology:* hematocrit, hemoglobin, erythrocytes, reticulocytes, total leukocyte count and differential, nucleated erythrocytes, and total bone marrow cellularity	Blood and urine samples were collected from all animals. *Hematology:* hematocrit, hemoglobin, erythrocytes, reticulocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte	Blood was collected twice at the 3- and 6-month interim evaluations for hematology and clinical chemistry determinations. Blood was collected once at the 9-month interim evaluation for hematology and clinical chemistry determinations.	None

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *o*-Nitroanisole (continued)

14-Day Studies	13-Week Studies	Stop-Exposure Study	2-Year Studies
Clinical Pathology (continued)			
Clinical chemistry: methemoglobin ***Urinalysis:*** specific gravity	***Hematology*** (continued): hemoglobin concentration, leucocyte count and differential, and nucleated erythrocytes ***Clinical chemistry:*** methemoglobin ***Urinalysis:*** specific gravity	***Hematology:*** hematocrit, hemoglobin, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, platelets, reticulocytes, total leukocyte count and differential, and nucleated erythrocytes ***Clinical chemistry:*** methemoglobin	
Histopathology			
None	Complete histopathologic examinations were performed on all control rats and mice, all rats and mice that received 6,000 ppm, and all rats and mice that died early. In addition to tissue masses, gross lesions, and associated lymph nodes, the tissues examined included: adrenal gland, colon (rats), clitoral gland (rats), epididymis, eye, heart (rats), kidney, liver, lung and mainstem bronchi, mammary gland (mice), mandibular lymph node (rats), nose (rats), ovary, parathyroid gland, pituitary gland (rats), preputial gland (rats), rectum (rats), salivary gland, seminal vesicle, skin (mice), spleen (rats), testis, thymus, thyroid gland, trachea (rats), urinary bladder, uterus (rats), and vagina (mice). In addition, the epididymis, kidney, liver, spleen, testis, and urinary bladder of all exposed rats were examined microscopically.	At the interim evaluations and the terminal sacrifice, kidney, liver, spleen, testis (including epididymis), urinary bladder, ureter, uterus, and gross lesions were examined microscopically in all exposed groups.	Complete histopathologic examinations were performed on all control, high-dose, and early death rats, all mice, and all rats and mice at the 15-month interim evaluations. In addition to tissue masses, gross lesions, and associated lymph nodes, the tissues examined included: adrenal gland, bone (including marrow), brain, clitoral gland, coagulating gland, ear (male rats), epididymis, esophagus, eye, gallbladder (mice), harderian gland, heart, kidney, lacrimal gland (female rats), large intestine (cecum, colon, rectum), liver, lung, lymph node (mandibular and mesenteric), mammary gland, mesentery, nose, ovary, pancreas, parathyroid gland, penis (mice), pharynx (rats), pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, skeletal muscle, skin, small intestine (duodenum, jejunum, ileum), spleen,

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *o*-Nitroanisole (continued)

14-Day Studies	13-Week Studies	Stop-Exposure Study	2-Year Studies
Histopathology (continued)			
			stomach (forestomach and glandular), testis, thymus, thyroid gland, tongue (females), tooth (mice and male rats), trachea, urinary bladder, uterus, vagina, and Zymbal's gland (female rats). The clitoral gland, epididymis, kidney, liver, preputial gland, spleen, testis, urinary bladder, and uterus of all rats receiving 222 and 666 ppm were examined microscopically.

RESULTS

Rats

14-Day Study

All rats survived until the end of the study (Table 2). The mean body weight gains of males receiving 4,665 and 9,330 ppm and the final mean body weight of males receiving 9,330 ppm were significantly lower than those of the controls. Mean body weight gains and final mean body weights of all exposed females were similar to those of the controls. Feed consumption by male and female rats administered *o*-nitroanisole was similar to that by the controls. Dietary levels of 583, 1,166, 2,332, 4,665, and 9,330 ppm resulted in average daily consumption levels of 48, 106, 209, 435, and 881 mg/kg for males and 48, 93, 197, 387, and 787 mg/kg for females.

Erythrocyte counts, hematocrit values, and hemoglobin concentrations in all exposed male groups were significantly lower than those in controls (Table I1). Reticulocyte counts and methemoglobin concentrations were significantly increased in males receiving 1,166 ppm or more, and Heinz bodies were present in erythrocytes from 9,330 ppm males.

At the end of the study, the relative brain, kidney, liver, and testis weights of males and the relative kidney and liver weights of females in the 9,330 ppm groups were significantly greater than those of the controls (Table H1). Because the absolute brain, kidney, and testis weights were not significantly increased in exposed groups, the increased relative organ weights were attributed primarily to the lower final mean body weights of the 9,330 ppm groups. However, the significantly increased absolute liver weights of males that received 1,166 ppm and of females that received 583 ppm or more *o*-nitroanisole were considered related to chemical administration.

TABLE 2
Survival, Mean Body Weights, and Feed Consumption of Rats in the 14-Day Feed Study of *o*-Nitroanisole

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Feed Consumption[c]	
		Initial	Final	Change		Week 1	Week 2
Male							
0	5/5	165 ± 2	237 ± 3	72 ± 2		15.7	18.7
583	5/5	169 ± 1	243 ± 3	73 ± 3	102	16.6	17.1
1,166	5/5	164 ± 2	243 ± 5	79 ± 3	102	16.5	19.7
2,332	5/5	166 ± 2	240 ± 4	74 ± 3	101	16.6	19.2
4,665	5/5	166 ± 3	229 ± 5	63 ± 2*	97	17.5	18.9
9,330	5/5	162 ± 2	212 ± 2**	51 ± 1**	90	15.0	19.3
Female							
0	5/5	121 ± 2	151 ± 1	30 ± 2		11.3	10.7
583	5/5	120 ± 3	154 ± 2	34 ± 1	102	11.2	11.1
1,166	5/5	117 ± 2	152 ± 2	35 ± 3	101	11.0	10.7
2,332	5/5	118 ± 2	150 ± 2	32 ± 2	99	12.0	10.7
4,665	5/5	118 ± 1	145 ± 1	26 ± 1	96	11.5	10.7
9,330	5/5	119 ± 2	148 ± 2	29 ± 1	98	10.5	11.5

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving at 14 days/number initially in group
[b] Weights given as mean ± standard error.
[c] Feed consumption is expressed as grams/animal per day.

13-WEEK STUDY

All rats survived until the end of the study, except one female receiving 2,000 ppm that died during week 5 (Table 3). Mean body weight gains and final mean body weights of males and females receiving 6,000 and 18,000 ppm were significantly lower than those of controls. The final mean body weight of 18,000 ppm males was 52% lower than that of the controls, while the final mean body weight of 18,000 ppm females was 36% lower than that of the controls. Final mean body weights of males and females receiving 6,000 ppm were 14% lower than those of the controls. Feed consumption by rats receiving 18,000 ppm was substantially less than that by controls throughout the study, whereas feed consumption by the 6,000 ppm groups was only slightly less than that by controls (Table 4). The reduced feed consumption may have been due to decreased palatability. Dietary levels of 200, 600, 2,000, 6,000, and 18,000 ppm resulted in average daily consumption levels of 10, 30, 100, 300, and 720 mg/kg for males and females.

Hemoglobin and hematocrit values in male and female rats receiving 2,000, 6,000, and 18,000 ppm were significantly lower than those in controls (Table I2). Erythrocyte counts were significantly lower primarily in males and females receiving 6,000 and 18,000 ppm. These differences were accompanied by increases in the mean values for nucleated erythrocytes, reticulocytes, methemoglobin, and total leukocyte counts. Heinz bodies were observed frequently in the erythrocytes of all rats receiving 18,000 ppm and in some rats receiving 6,000 ppm. These findings are consistent with a mild, regenerative anemia resulting from an increased formation of methemoglobin. Methemoglobin is formed by the oxidation of bound iron in hemoglobin from the Fe^{2+} to the Fe^{3+} oxidation state followed by irreversible denaturation of the globin portion of hemoglobin eventually leading to the formation of Heinz bodies, which are aggregates of denatured hemoglobin. Heinz body formation is often associated with premature erythrocyte destruction due to extravascular or intravascular hemolysis.

TABLE 3
Survival and Mean Body Weights of Rats in the 13-Week Feed Study of o-Nitroanisole

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	143 ± 6	360 ± 13	217 ± 14	
200	10/10	150 ± 5	373 ± 7	223 ± 5	104
600	10/10	153 ± 5	380 ± 7	226 ± 7	105
2,000	10/10	147 ± 6	363 ± 4	217 ± 8	101
6,000	10/10	142 ± 6	311 ± 5**	169 ± 5*	86
18,000	10/10	158 ± 4	173 ± 7**	15 ± 7**	48
Female					
0	10/10	116 ± 3	213 ± 3	97 ± 3	
200	10/10	113 ± 4	217 ± 3	104 ± 4	102
600	10/10	117 ± 3	211 ± 2	94 ± 3	99
2,000	9/10[c]	114 ± 2	208 ± 3	95 ± 3	98
6,000	10/10	115 ± 1	183 ± 2**	68 ± 2**	86
18,000	10/10	113 ± 2	137 ± 2**	24 ± 2**	64

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of death: 5

TABLE 4
Feed Consumption by Rats in the 13-Week Feed Study of *o*-Nitroanisole[a]

Week of Study	0 ppm	200 ppm	600 ppm	2,000 ppm	6,000 ppm	18,000 ppm
Male						
1	14.7	16.1	15.9	15.5	12.2	5.8
2	18.7	15.9	15.8	16.1	15.0	8.1
3	16.2	19.1	18.3	18.0	15.5	9.4
4	14.8	15.5	15.2	15.2	14.9	10.1
5	15.0	15.2	15.7	15.0	15.0	10.0
6	15.6	14.9	15.4	15.4	15.2	9.2
7	15.7	15.5	16.6	16.5	15.1	6.0
8	16.9	16.6	20.2	17.6	16.6	8.2
9	17.1	16.1	16.9	17.1	15.6	8.7
10	15.9	16.5	16.4	16.5	15.1	9.2
11	15.3	13.8	16.8	15.9	14.2	9.6
12	14.4	16.2	16.2	15.7	14.7	9.4
13	13.5	13.7	15.4	14.2	13.3	7.7
Female						
1	10.3	11.0	10.1	10.2	8.2	3.7
2	10.3	10.5	10.1	9.6	9.3	5.7
3	10.6	12.3	9.8	10.7	9.6	6.7
4	10.2	10.6	10.0	9.7	9.3	6.6
5	10.5	10.4	10.2	9.9	9.0	6.8
6	10.5	10.4	9.6	8.9	9.2	6.8
7	9.6	10.7	10.5	10.2	9.3	6.8
8	12.4	11.2	10.5	11.4	9.2	6.7
9	11.7	10.8	10.7	10.5	9.0	6.8
10	10.6	10.5	10.7	10.7	9.3	7.0
11	10.4	11.0	10.7	10.0	9.1	7.1
12	9.6	9.9	9.8	9.9	9.1	7.3
13	10.5	10.7	9.8	10.4	9.3	7.3

[a] Feed consumption is expressed as grams/animal per day.

Urine samples collected from rats receiving 2,000 ppm or more were dark yellow or amber-colored, whereas those of control rats were light yellow or straw-colored. The slightly darker color of the urine from exposed rats is probably due to increased excretion of hemoglobin or bilirubin metabolites rather than increased urine concentration since the specific gravity of urine from exposed animals was similar to that of the controls (Table I2).

The absolute and relative liver weights of all exposed male and female rat groups were significantly greater than those of the controls, with the exception of the absolute liver weight of 18,000 ppm males (Table H2). The absolute and relative kidney weights of males receiving 600, 2,000, and 6,000 ppm and the relative kidney weight of males receiving 18,000 ppm were significantly greater than those of the controls. In females, the relative kidney weights were significantly increased in the 6,000 and 18,000 ppm groups, but the absolute kidney weights of exposed female groups and controls were similar. The increases in absolute and relative liver and kidney weights were attributed to *o*-nitroanisole.

The absolute and relative spleen weights of male and female rats receiving 6,000 and 18,000 ppm were also significantly increased, which is consistent with the histologic lesions observed in the spleen. The absolute and relative thymus weights of female rats and the absolute thymus weight of male rats that received 18,000 ppm were significantly decreased. It is uncertain if this finding is due to a direct effect of *o*-nitroanisole on the thymus, or if the thymus is more sensitive than other organs to the nutritional effects associated with decreased feed consumption. The thymus is particularly sensitive to the effects of stress and debilitation associated with a variety of causes and becomes atrophic. Differences in the absolute or relative testis, heart, and lung weights of rats receiving 6,000 and 18,000 ppm were associated with the lower final mean body weights and are not believed to be the result of specific organ toxicity.

The principal lesions associated with the administration of *o*-nitroanisole to rats for 13 weeks were observed in the urinary bladder, spleen, kidney, liver, testis, and uterus as described below.

Urinary bladder: Diffuse hyperplasia of the transitional epithelium of the urinary bladder was seen in all rats receiving 6,000 and 18,000 ppm (Table 5). The hyperplasia generally was more severe in females than in males and more severe in the 18,000 ppm groups than in the 6,000 ppm groups. Focal squamous metaplasia frequently accompanied the hyperplasia, particularly in females. The transitional epithelium of exposed rats was thickened and formed rugose or papillary folds. In rats that received 18,000 ppm, the transitional epithelium was often greater than 30 cell layers thick, whereas that of controls was usually less than five cell layers thick. The foci of squamous metaplasia consisted of moderate to well-differentiated squamous epithelium with abundant eosinophilic cytoplasm, prominent intercellular bridges, and an overlying layer of keratin.

A transitional cell papilloma of the urinary bladder was seen in one male, transitional cell carcinomas were seen in two males and three females, and a squamous cell carcinoma was seen in one female, all in the 18,000 ppm groups. The neoplasms were seen in areas of diffuse hyperplasia. The papilloma consisted of thick branching folds of transitional epithelium, and differed from the more severe hyperplastic lesions primarily by the extent and complexity of branching. The transitional cell carcinomas were also exophytic nodular or rugose masses, but the markedly thickened epithelium consisted of anaplastic, pleomorphic cells. The squamous cell carcinoma consisted of an area of squamous differentiation with interconnecting cords and small clusters of pleomorphic squamous cells infiltrating the submucosa.

Spleen: The splenic red pulp of many males in the 18,000 ppm group and females in the 6,000 and 18,000 ppm groups contained increased numbers of erythrocytes (congestion), which probably accounts for the significantly increased absolute and relative spleen weights of these groups (Table 5). The congestion was associated with increased numbers of macrophages containing hemosiderin pigment. All rats receiving 18,000 ppm and several receiving 6,000 ppm had foci of capsular fibrosis with infiltrations of erythrocytes, hematopoietic cells, and mononuclear inflammatory cells which were diagnosed as capsular hyperplasia (Plate 1). In addition, all rats that received 18,000 ppm had mild to moderate depletion of lymphocytes from the periarteriolar lymphocytic sheaths and lymphoid follicles.

Since the spleen is a major site for the removal of senescent or damaged erythrocytes from the circulation, the congestion and accumulation of hemosiderin-laden macrophages in the spleen are frequently associated with hemolytic anemia and methemoglobinemia. The capsular hyperplasia is frequently seen in enlarged spleens due to a variety of causes, and may be the result of small ruptures in the delicate capsular connective tissue. The precise cause of the lymphoid depletion in the spleen is uncertain, but lymphoid depletion at various sites such as the thymus, lymph nodes, and spleen often accompanies reductions in body weight, and thus may not be a direct effect of *o*-nitroanisole.

Liver: Generalized centrilobular and midzonal hepatocyte hypertrophy was seen in all rats receiving 18,000 ppm. The affected hepatocytes were enlarged and had more homogeneous, eosinophilic cytoplasm than did unaffected cells in the centrilobular region. The livers of all rats that received 18,000 ppm also had scattered Kupffer cells filled with a granular, golden brown pigment, believed to be hemosiderin.

TABLE 5
Incidences of Selected Lesions in Rats in the 13-Week Feed Study of *o*-Nitroanisole

Dose (ppm)	0	200	600	2,000	6,000	18,000
Male						
n[a]	10	10	10	10	10	10
Urinary bladder						
Hyperplasia[b]	0	0	0	0	10**(2.3)[c]	10**(3.6)
Squamous metaplasia	0	0	0	0	0	2 (4.5)
Transitional cell papilloma	0	0	0	0	0	1
Transitional cell carcinoma	0	0	0	0	0	2
Squamous cell carcinoma	0	0	0	0	0	0
Spleen						
Congestion	0	0	0	0	0	7**(2.9)
Pigment (hemosiderin)	0	0	0	0	10**(3.2)	10**(2.6)
Lymphoid depletion	0	0	0	0	0	10**(3.1)
Capsule, hyperplasia	0	0	0	0	2 (3.0)	10**(2.7)
Kidney						
Degeneration/necrosis	0	0	10**(2.0)	10**(2.0)	10**(3.0)	0
Protein casts	0	0	0	3 (2.0)	10**(2.5)	0
Mononuclear cell infiltrate	0	0	2 (3.5)	4*(2.0)	7**(2.7)	0
Pigment (hemosiderin)	0	0	0	0	0	9**(3.1)
Liver						
Hepatocyte hypertrophy	0	0	0	0	0	10**(2.5)
Pigment (hemosiderin)	0	0	0	0	0	10**(2.1)
Testes						
Degeneration	0	0	0	0	0	10**(3.9)
Female						
n	10	10	10	10	10	10
Urinary bladder						
Hyperplasia	0	0	0	0	10**(3.0)	10**(4.2)
Squamous metaplasia	0	0	0	0	0	10**(3.5)
Transitional cell papilloma	0	0	0	0	0	0
Transitional cell carcinoma	0	0	0	0	0	3
Squamous cell carcinoma	0	0	0	0	0	1
Spleen						
Congestion	0	0	0	0	5*(2.2)	10**(3.3)
Pigment (hemosiderin)	0	0	0	0	10**(3.0)	1 (2.0)
Lymphoid depletion	0	0	0	0	0	10**(3.0)
Capsule, hyperplasia	0	0	0	0	3 (2.0)	10**(2.5)

(continued)

TABLE 5
Incidences of Selected Lesions in Rats in the 13-Week Feed Study of *o*-Nitroanisole (continued)

Dose (ppm)	0	200	600	2,000	6,000	18,000
Female (continued)						
Kidney						
Pigment (hemosiderin)	0	0	0	0	10**(2.3)	10**(3.5)
Liver						
Hepatocyte hypertrophy	0	0	0	0	0	10**(2.4)
Pigment (hemosiderin)	0	0	0	0	0	10**(2.3)
Uterus						
Atrophy	0	0	0	2 (3.0)	1 (3.0)	10**(4.0)

* Significantly different (P≤0.05) from the control group by the Fisher exact test
** P≤0.01
[a] Number of animals necropsied
[b] Number of animals with lesions
[c] Average severity grade of lesions in affected animals: 1 = slight, 2 = minimal, 3 = mild, 4 = moderate, 5 = severe.

Kidney: Multifocal degeneration, necrosis, or both, of the renal tubule epithelium with infiltration of mononuclear inflammatory cells and formation of tubular casts occurred in male rats receiving 600, 2,000, and 6,000 ppm (Plates 2 and 3), but not in those receiving 18,000 ppm or in exposed female rats (Table 5). The reduced nutrient and chemical intake associated with the lower feed consumption may account for the absence of these lesions in the 18,000 ppm group. Granular, golden brown pigment, believed to be hemosiderin, was observed in scattered epithelial cells in the proximal convoluted tubules of males receiving 18,000 ppm and females receiving 6,000 and 18,000 ppm.

Testis: All male rats that received 18,000 ppm exhibited degeneration of the seminiferous epithelium characterized by necrosis and loss of spermatogenic cells, decreased numbers of spermatozoa, and accumulations of necrotic debris and multinucleated cells in the seminiferous tubules (Table 5).

Uterus: Uterine atrophy was observed in all female rats receiving 18,000 ppm and in a few females receiving 2,000 and 6,000 ppm (Table 5). The affected uteri were smaller than those of the controls and the endometrial and myometrial cells had less abundant cytoplasm.

Dose selection rationale: The lower final mean body weights and reduced feed consumption observed in males and females that received diets containing 6,000 and 18,000 ppm *o*-nitroanisole suggest poor feed palatability. In addition, the severity of regenerative anemia associated with methemoglobin formation was significantly increased in males and females receiving 6,000 and 18,000 ppm. Consequently, these concentrations were considered too high for continuous dietary administration in a 2-year study. At 2,000 ppm, final mean body weights and feed consumption were similar to controls and the anemia was minimal. Therefore, 2,000 ppm was considered an acceptable high concentration for the 2-year study. The remaining concentrations selected were 222 and 666 ppm, since 222 ppm was a no-effect level and at 666 ppm only minimal signs of anemia were present.

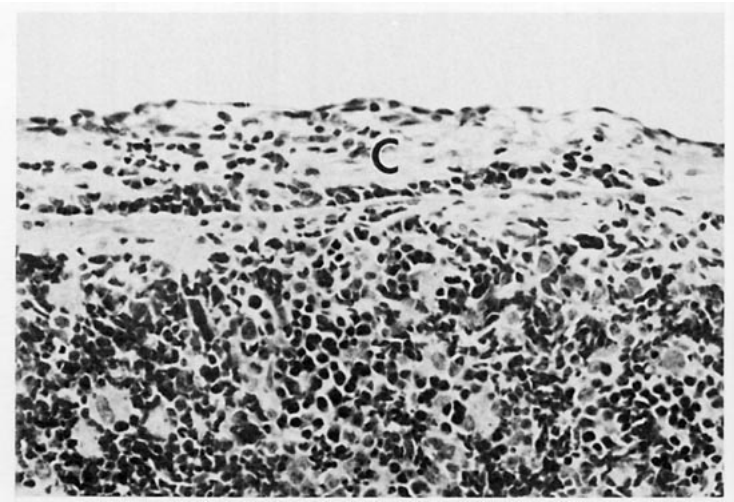


PLATE 1
Spleen: The splenic capsule (C) is thickened by accumulated mononuclear cells and delicate fibrous tissue. Male rat given 18,000 ppm *o*-nitroanisole in the 13-week feed study. H&E ×100

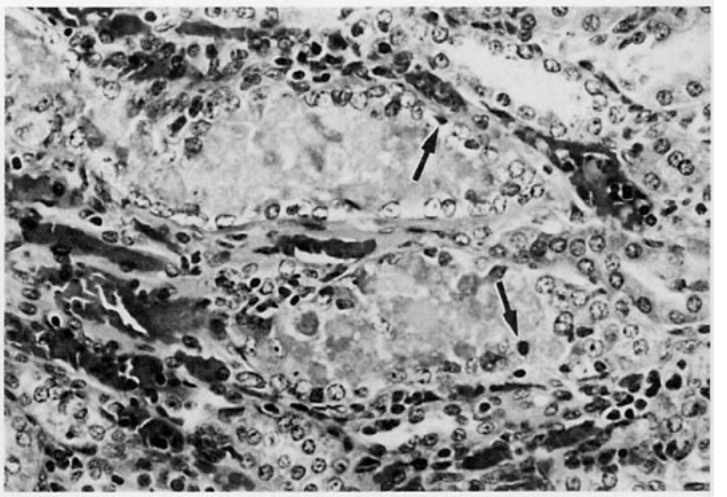


PLATE 2
Kidney: Note the renal tubule distended with cellular debris, the attenuated epithelium, and the occasional necrotic epithelial cells with pyknotic nuclei (arrows). Male rat given 6,000 ppm *o*-nitroanisole in the 13-week feed study. H&E ×100

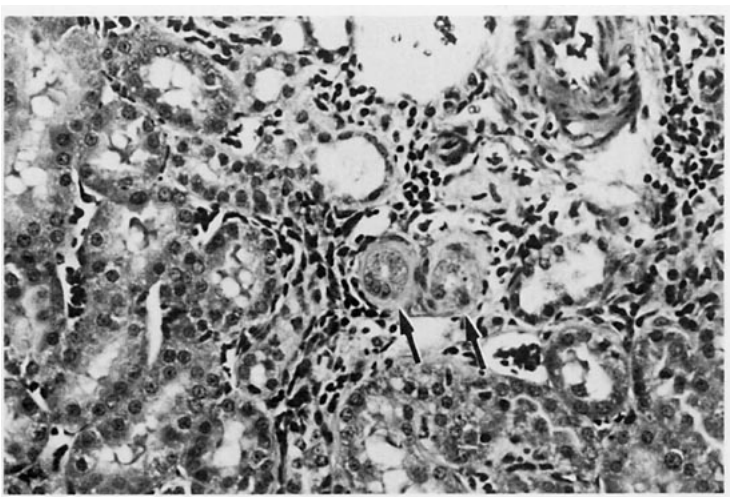


PLATE 3
Kidney: Mild nephropathy. Note the interstitial mononuclear cell infiltrate, tubules with thickened basement membrane (arrows), and slightly dilated tubules lined by attenuated epithelium. Male rat given 6,000 ppm *o*-nitroanisole in the 13-week feed study. H&E ×80

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female rats are shown in Table 6 and in the Kaplan-Meier curves in Figure 2. Survival of 2,000 ppm male rats was significantly lower than that of the controls. Survival of 666 ppm males was slightly lower than that of the controls, but the difference was not significant by the life table analysis. The reduced survival of 666 and 2,000 ppm males was primarily attributed to the increased numbers of animals with severe renal disease (nephropathy) and associated secondary hyperparathyroidism. Survival of males receiving 222 ppm and of all exposed females was similar to the controls.

TABLE 6
Survival of Rats in the 2-Year Feed Study of *o*-Nitroanisole

	0 ppm	222 ppm	666 ppm	2,000 ppm
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	9
Natural deaths	2	3	2	6
Moribund kills	16	13	24	36
Animals surviving to study termination	32	34	24	9[b]
Percent probability of survival at end of study[c]	64	69	48	18
Mean survival (days)[d]	655	644	647	603
Survival analysis[e]	P<0.001	P=0.892N	P=0.172	P<0.001
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	9
Natural deaths	0	2	6	3
Moribund kills	17	7	18	15
Animals surviving to study termination	33	41	26	33
Percent probability of survival at end of study	66	83	52	65
Mean survival (days)	655	664	631	648
Survival analysis	P=0.385	P=0.108N	P=0.149	P=0.904

[a] Censored from survival analyses
[b] Includes one animal that died during the last week of the study
[c] Kaplan-Meier determinations
[d] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[e] 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 dosed columns. A lower mortality in a dose group is indicated by N.

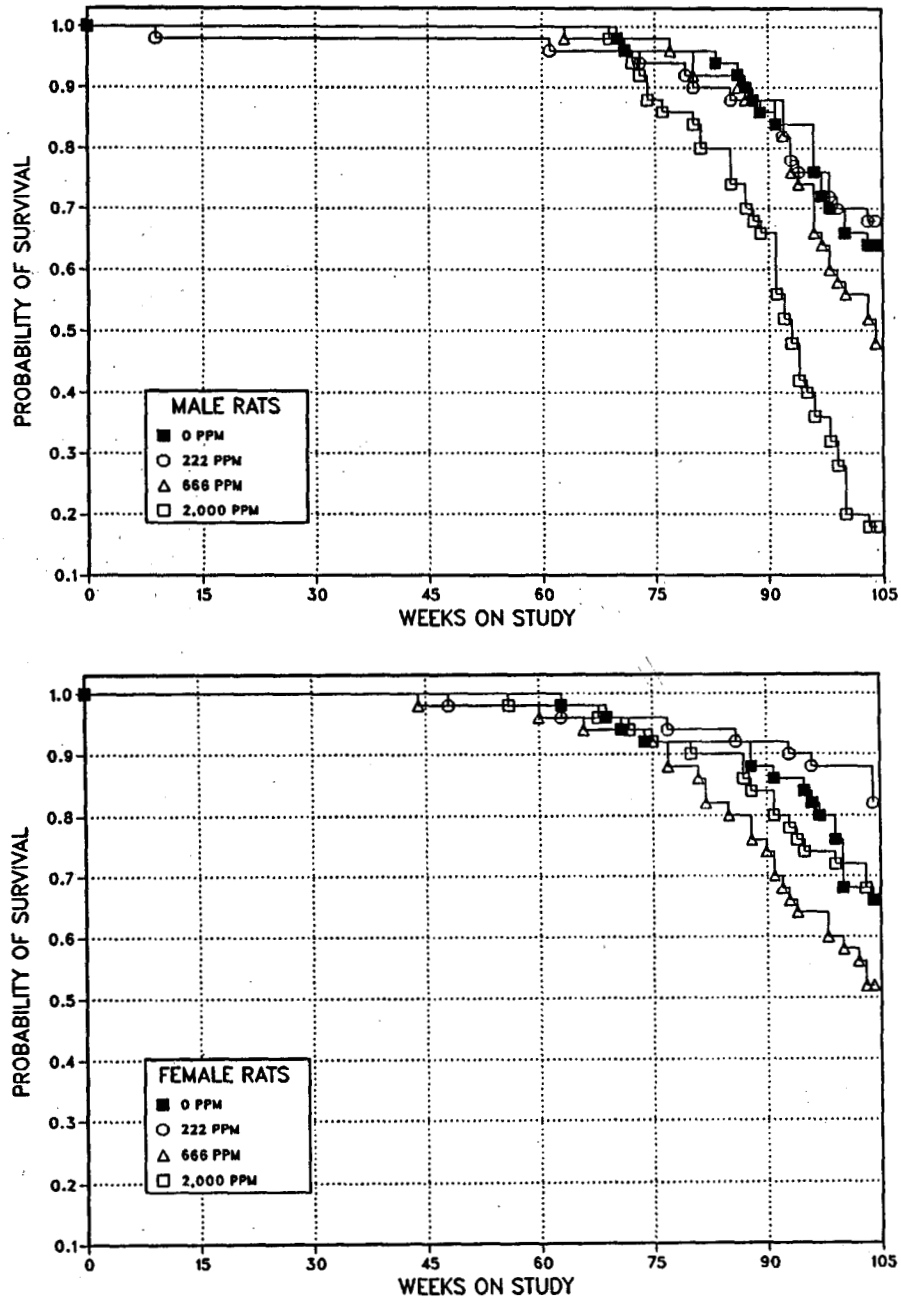


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female Rats Administered *o*-Nitroanisole in Feed for 2 Years

Body Weights, Feed Consumption, and Clinical Findings

Mean body weights of male and female rats that received 2,000 ppm were lower than those of controls (Tables 7 and 8). The mean body weights of 2,000 ppm male rats were within 5% of the controls until week 72 (Table 7 and Figure 3). Thereafter, the difference in mean body weight between males receiving 2,000 ppm and the controls gradually increased; the final mean body weight of males receiving 2,000 ppm was 16% lower than that of the controls. The mean body weights of 2,000 ppm female rats were within 5% of the controls until week 48, but the difference gradually increased; the final mean body weight of 2,000 ppm females was 9% lower than that of the controls (Table 8 and Figure 3). The mean body weights of male and female rats that received 222 and 666 ppm were within 5% of the controls throughout the 2-year study. Feed consumption by exposed male and female rats was similar to that by the controls throughout the study (Tables K1 and K2). Dietary levels of 222, 666, and 2,000 ppm resulted in average daily consumption levels of 10, 30, and 80 mg/kg for males and 10, 30, and 90 mg/kg for females. There were no clinical findings associated with *o*-nitroanisole administration.

Pathology and Statistical Analyses of Results

Summaries of the incidences of nonneoplastic lesions and neoplasms, the individual animal tumor diagnoses, the statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one group, and historical control incidences for the biologically significant neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Hematopoietic system: The incidences of mononuclear cell leukemia in males receiving 666 or 2,000 ppm and females receiving 2,000 ppm were significantly increased (Tables 9, A3, and B3). However, the incidence of mononuclear cell leukemia in 2,000 ppm males was slightly lower than in 666 ppm males, possibly due to the reduced survival in the 2,000 ppm group. The incidences of mononuclear cell leukemia in males receiving 666 or 2,000 ppm and females receiving 2,000 ppm also exceed the range for NTP historical controls (males: 32%-62%; females: 14%-36%; Tables A4a and B4a). Although incidences of mononuclear cell leukemia were increased, the mean time to observation (neoplasm latency) was not substantially reduced in the exposed groups (males: 0 ppm, 694 days; 222 ppm, 695 days; 666 ppm, 688 days; and 2,000 ppm, 638 days; females: 685, 701, 650, and 686 days).

Mononuclear cell leukemia was characterized by the proliferation of polymorphic mononuclear cells with hyperchromatic nuclei in the splenic sinusoids. In more advanced stages, this leukemia involved the interfollicular red pulp completely. As the disease progressed, infiltrates of mononuclear leukemia cells occurred in the liver, lung, kidney, lymph nodes, and other organs. In male rats with mononuclear cell leukemia, organs other than the spleen and liver were more frequently affected in the 666 and 2,000 ppm groups than in the control group. In female rats, the disease was generally limited to the spleen and liver.

Kidney: The relative kidney weight of males that received 2,000 ppm was significantly greater than that of the controls at the 15-month interim evaluation (Table H3). There was a corresponding slight increase in the absolute kidney weight of this group, even though the mean body weight of the 2,000 ppm group was substantially lower than that of the controls. Chronic nephropathy occurred in all male rats, and the severity of the disease increased in a dose-related manner at the 15-month interim evaluation and at the end of the 2-year study (Tables 10 and A5). In female rats, there was little evidence of a chemical-related effect on the kidney. Absolute and relative kidney weights of exposed female groups were similar to those of controls at the 15-month interim evaluation (Table H3). Although the incidences of nephropathy were marginally increased in the exposed female groups, the increased incidences were not significant and were not dose related (Tables 10 and B5). However, the proportion of female rats with moderate nephropathy was greater in the 2,000 ppm group than in the controls.

Nephropathy in rats was characterized by a spectrum of degenerative and inflammatory changes including degeneration and atrophy of the tubule epithelium with the formation of granular and hyaline casts in the tubule lumens, regeneration of the tubule epithelium, thickening of the glomerulus and tubule basement membranes, interstitial fibrosis, and infiltrates of mononuclear inflammatory cells. The severity of nephropathy was graded based on the extent of involvement as follows: minimal, less than 25%; mild, 25% to 50%; moderate, 50% to 75%; and marked, greater than 75%.

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of o-Nitroanisole

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	222 ppm Av. Wt. (g)	222 ppm Wt. (% of controls)	222 ppm No. of Survivors	666 ppm Av. Wt. (g)	666 ppm Wt. (% of controls)	666 ppm No. of Survivors	2,000 ppm Av. Wt. (g)	2,000 ppm Wt. (% of controls)	2,000 ppm No. of Survivors
1	127	60	126	99	60	123	97	60	125	99	60
2	183	60	182	100	60	180	99	60	187	102	60
3	213	60	216	102	60	210	99	60	211	99	60
4	236	60	240	101	60	236	100	60	241	102	60
5	245	60	258	106	60	255	104	60	259	106	60
6	271	60	273	100	60	270	99	60	273	101	60
7	282	60	287	102	60	282	100	60	283	100	60
8	289	60	295	102	60	289	100	60	293	101	60
9	302	60	302	100	60	301	100	60	301	100	60
10	316	60	313	99	59	310	98	60	312	99	60
11	324	60	322	99	59	319	98	60	318	98	60
12	331	60	326	99	59	324	98	60	324	98	60
16	364	60	360	99	59	357	98	60	353	97	59
21	380	60	375	99	59	373	98	60	371	98	59
24	403	60	389	96	59	392	97	60	391	97	59
28	408	60	401	98	59	400	98	60	399	98	59
32	421	60	413	98	59	413	98	60	412	98	59
36	428	60	420	98	59	421	98	60	421	98	59
40	438	60	424	97	59	432	99	60	429	98	59
44	444	60	437	98	59	438	99	60	435	98	59
48	450	60	439	98	59	440	98	60	438	97	59
52	441	60	437	99	59	440	100	60	437	99	59
56	447	60	441	99	59	441	99	60	435	97	59
60	445	60	437	98	59	441	99	60	436	98	59
64	447	60	438	98	58	442	99	59	430	96	59
68[a]	446	50	435	97	48	441	99	49	427	96	50
72	443	48	436	98	48	443	100	49	420	95	47
76	441	48	433	98	47	438	99	49	415	94	43
80	440	48	434	99	45	439	100	46	411	94	42
84	435	47	427	98	45	430	99	46	389	89	40
88	430	44	426	99	44	430	100	44	395	92	34
92	428	42	419	98	41	415	97	41	378	88	26
96	418	38	411	98	38	412	99	33	368	88	18
100	417	33	407	98	35	402	96	28	351	84	10
Terminal sacrifice		32			34			24			9
Mean for weeks											
1-13	260		262	101		258	99		261	100	
14-52	418		410	98		411	98		409	98	
53-101	436		429	98		431	99		405	93	

[a] Interim evaluation occurred during week 66.

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

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	222 ppm Av. Wt. (g)	222 ppm Wt. (% of controls)	222 ppm No. of Survivors	666 ppm Av. Wt. (g)	666 ppm Wt. (% of controls)	666 ppm No. of Survivors	2,000 ppm Av. Wt. (g)	2,000 ppm Wt. (% of controls)	2,000 ppm No. of Survivors
1	102	60	100	98	60	100	98	60	103	101	60
2	128	60	130	102	60	129	101	60	130	102	60
3	142	60	140	99	60	140	99	60	143	101	60
4	151	60	151	100	60	153	102	60	154	102	60
5	143	60	160	112	60	160	112	60	152	107	60
6	165	60	164	100	60	167	101	60	165	100	60
7	169	60	170	101	60	170	101	60	168	100	60
8	169	60	172	102	60	170	101	60	170	101	60
9	175	60	174	99	60	172	98	60	174	99	60
10	179	60	177	99	60	176	98	60	177	99	60
11	182	60	178	98	60	177	97	60	179	98	60
12	184	60	179	98	60	179	98	60	179	98	60
16	196	60	190	97	60	191	97	60	190	97	60
21	201	60	196	98	60	197	98	60	194	97	60
24	203	60	200	99	60	201	99	60	200	99	60
28	211	60	207	98	60	207	98	60	204	96	60
32	217	60	213	98	60	214	99	60	209	96	60
36	221	60	217	98	60	218	99	60	216	98	60
40	232	60	226	97	60	228	98	60	221	95	60
44	238	60	233	98	60	234	98	59	227	96	60
48	246	60	240	98	59	242	98	59	234	95	60
52	255	60	245	96	59	249	98	59	240	94	60
56	261	60	253	97	59	259	99	59	248	95	59
60	268	60	262	98	59	266	99	58	256	95	58
64	275	59	266	97	58	273	99	58	262	96	58
68[a]	282	49	272	97	48	279	99	47	266	94	48
72	289	47	279	97	48	284	98	47	273	95	47
76	298	46	284	96	48	289	97	46	279	94	46
80	304	46	293	96	47	294	97	44	285	94	45
84	306	46	294	96	47	294	96	41	286	93	45
88	313	44	309	99	46	302	96	38	295	94	42
92	316	43	305	97	46	305	97	34	293	93	40
96	315	41	308	98	44	304	96	32	291	92	37
100	317	34	304	96	44	304	96	29	289	91	36
Terminal sacrifice		33			41			26			33
Mean for weeks											
1-13	157		158	101		158	101		158	101	
14-52	222		217	98		218	98		214	96	
53-101	295		286	97		288	98		277	94	

[a] Interim evaluation occurred during week 66.

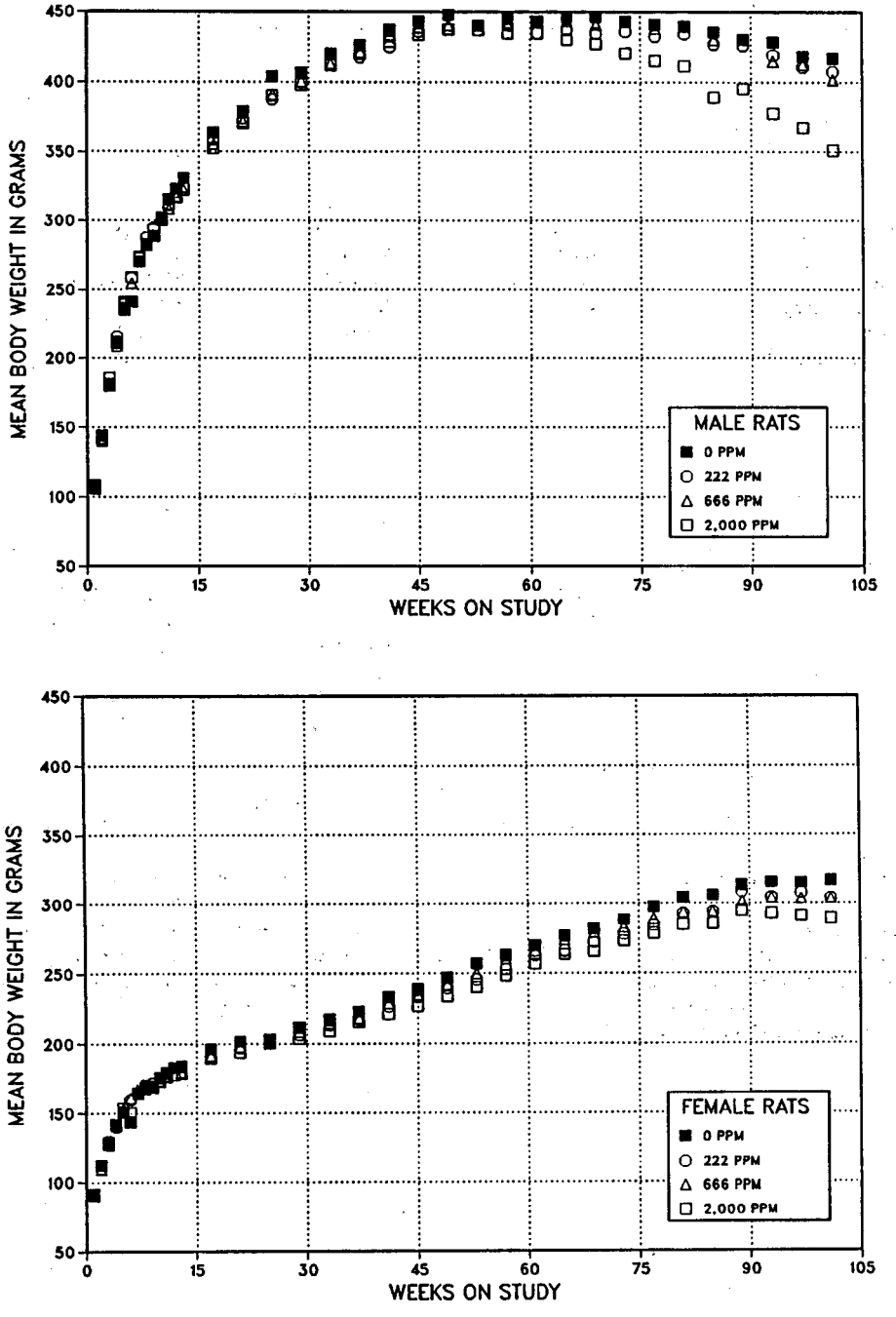


FIGURE 3
Growth Curves for Male and Female Rats Administered *o*-Nitroanisole in Feed for 2 Years

TABLE 9
Incidences of Mononuclear Cell Leukemia in Rats in the 2-Year Feed Study of *o*-Nitroanisole

Dose (ppm)	0	222	666	2,000
Male				
15-Month Interim Evaluation				
Overall rate[a]	0/10	1/10	0/10	2/9
2-Year Study[b]				
Overall rate	26/50 (52%)	25/50 (50%)	42/50 (84%)	34/50 (68%)
Adjusted rate[c]	60.9%	60.2%	91.2%	89.0%
Terminal rate[d]	16/32 (50%)	18/34 (53%)	20/24 (83%)	6/9 (67%)
First incidence (days)	496	423	437	491
Life table test[e]	P<0.001	P=0.445N	P<0.001	P<0.001
Logistic regression test[e]	P=0.033	P=0.515N	P<0.001	P=0.114
Female				
15-Month Interim Evaluation				
Overall rate	0/10	0/10	1/10	0/9
2-Year Study[f]				
Overall rate	14/50 (28%)	11/50 (22%)	14/50 (28%)	26/50 (52%)
Adjusted rate	32.7%	24.6%	37.3%	58.5%
Terminal rate	6/33 (18%)	8/41 (20%)	5/26 (19%)	15/33 (45%)
First incidence (days)	494	533	302	500
Life table test	P=0.001	P=0.204N	P=0.351	P=0.024
Logistic regression test	P<0.001	P=0.339N	P=0.523N	P=0.013

[a] Number of neoplasm-bearing animals/number of animals examined microscopically
[b] 2-Year historical incidence for control groups in NTP feed study (mean ± standard deviation): 385/800 (48.1% ± 7.7%); range 32%-62%
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table analysis regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression tests regard these lesions as nonfatal. For both tests, a lower incidence in a dose group is indicated by N.
[f] Historical incidence: 213/800 (26.6% ± 8.8%); range 14%-36%

TABLE 10
Incidence and Severity of Chronic Nephropathy in Rats in the 2-Year Feed Study of o-Nitroanisole[a]

Dose (ppm)	0	222	666	2,000
Male				
15-Month Interim Evaluation				
Nephropathy	10/10	10/10	10/10	9/9
Minimal	9	8	4	0
Mild	1	2	4	5
Moderate	0	0	2	4
Mean severity grade[b]	1.1 ± 0.1	1.2 ± 0.1	1.8 ± 0.2*	2.4 ± 0.2**
2-Year Study				
Nephropathy	49/49	50/50	50/50	49/49
Minimal	7	6	3	2
Mild	25	19	20	10
Moderate	17	23	22	15
Marked	0	2	5	22
Mean severity grade	2.2 ± 0.1	2.4 ± 0.1	2.6 ± 0.1*	3.2 ± 0.1**
Female				
15-Month Interim Evaluation				
Nephropathy	3/10	9/10	5/10	4/9
None	7	1	5	5
Minimal	2	6	3	1
Mild	1	3	2	3
Mean severity grade	0.4 ± 0.2	1.2 ± 0.2	0.7 ± 0.3	0.8 ± 0.3
2-Year Study				
Nephropathy	39/50	46/50	46/50	44/50
None	11	4	4	6
Minimal	0	6	1	0
Mild	34	37	37	26
Moderate	5	2	8	17
Marked	0	1	0	1
Mean severity grade	1.7 ± 0.1	1.8 ± 0.1	2.0 ± 0.1	2.1 ± 0.1**

* Significantly different (P≤0.05) from the control group by Mann-Whitney U test
** P≤0.01
[a] Number of lesion-bearing animals/number of animals examined microscopically
[b] Group mean severity ± standard error. None = 0; minimal = 1; mild = 2; moderate = 3; marked = 4.

Focal hyperplasia of the renal tubule was seen in three males receiving 222 ppm and two males receiving 2,000 ppm, but not in male rats receiving 666 ppm or in the controls (Table A5). Renal tubule adenomas were also seen in one male each from the 222, 666, and 2,000 ppm groups, and renal tubule carcinomas occurred in two additional males that received 2,000 ppm (Table A1). The incidence of adenoma or carcinoma (combined) occurred with a significant positive trend in male rats, and the incidence in the 2,000 ppm group was significantly greater than that in the controls (Table A3). The incidence of renal tubule neoplasms in NTP historical control male rats is 11 of 798 (1%) with a range of 0% to 6% (Table A4d). Thus, it is uncertain if the small number of renal tubule neoplasms in the exposed groups is related to *o*-nitroanisole exposure.

Focal hyperplasia, adenoma, and carcinoma of the renal tubule epithelium constitute a morphological continuum. Focal hyperplasia was considered a preneoplastic lesion and was differentiated from the epithelial regeneration which commonly accompanies nephropathy. It was characterized by one or several cross sections of a single tubule with two or more layers of epithelial cells partially or completely filling the tubule lumen. The adenomas were circumscribed solid masses, generally larger than five tubule diameters, consisting of polygonal epithelial cells with mild atypia. The carcinomas were substantially larger than the adenomas and exhibited heterogenous growth patterns, cellular pleomorphism, and cytologic atypia.

Liver: The absolute liver weights of males receiving 2,000 ppm and females receiving 666 and 2,000 ppm were significantly greater than those of the controls at the 15-month evaluation (Table H3). The chemical-related increase in absolute liver weights was accompanied by significant increases in relative liver weights of male and female rats that received 666 and 2,000 ppm. Despite the increased liver weights, there were no lesions of the liver that occurred more frequently in exposed rats than in controls at the 15-month interim evaluation (Tables 11, A5, and B5). However, the incidences of basophilic foci in males and females receiving 2,000 ppm and of clear cell foci in males receiving 2,000 ppm were lower than those in controls.

In the 2-year study, several nonneoplastic lesions occurred more frequently in exposed rats than in controls (Tables 11, A5, and B5). The incidence of focal cystic degeneration, also called spongiosis hepatis, was significantly increased in males that received 2,000 ppm. The lesion was characterized by small multilocular spaces distorting the hepatic cords and containing finely granular or flocculent material and occasional erythrocytes. The lesion is believed to constitute a degenerative process involving the fat storing cell (Ito cell). The incidence of eosinophilic foci occurred with a significant positive trend in exposed male rats and the incidences in all exposed groups were significantly greater than that in the controls. An eosinophilic focus is one of several different forms of cellular alteration occurring in the liver and is characterized by changes in staining quality of the hepatocyte cytoplasm. Eosinophilic foci were well circumscribed and slightly compressed the surrounding parenchyma. There was some irregularity of the hepatic cords, but they blended in with normal hepatic cords at the periphery. The cells were often slightly enlarged and the cytoplasm was homogeneous and eosinophilic. The incidence of focal hyperplasia of the bile ducts in the portal areas of the liver lobules was significantly increased in female rats receiving 2,000 ppm. The incidence of nodular hyperplasia was significantly increased in males that received 666 and 2,000 ppm and in females that received 2,000 ppm. Nodular hyperplasia generally occurred in the liver of rats with mononuclear cell leukemia and consisted of poorly circumscribed foci of hypertrophic hepatocytes. Nodular hyperplasia was considered to represent a regenerative response to the degenerative changes in the liver that commonly accompany mononuclear cell leukemia.

The incidences of basophilic foci in the 666 and 2,000 ppm groups of males and the 2,000 ppm group of females were significantly lower than those in controls. Similarly the incidences of clear cell foci in males receiving 666 and 2,000 ppm were significantly lower than that in controls. Basophilic focus is the most common spontaneously occurring form of cellular alteration in the liver of F344 rats, whereas clear cell focus occurs much less frequently. It is uncertain to what extent the decreased incidences of basophilic

TABLE 11
Incidences of Selected Liver Lesions in Rats in the 2-Year Feed Study of *o*-Nitroanisole

Dose (ppm)	0	222	666	2,000
Males				
15-Month Interim Evaluation				
n[a]	10	10	10	9
Degeneration, cystic[b]	1	0	0	0
Eosinophilic focus	0	2	3	0
Hyperplasia, nodular	0	0	0	0
Basophilic focus	5	1	0	1
Clear cell focus	5	1	1	1
2-Year Study				
n	50	50	50	50
Degeneration, cystic	10	10	14	24**
Eosinophilic focus	8	18*	21**	27**
Hyperplasia, nodular	7	2	18**	14
Basophilic focus	32	29	13**	7**
Clear cell focus	13	10	5*	5*
Females				
15-Month Interim Evaluation				
n	10	10	10	9
Degeneration, cystic	0	0	0	0
Eosinophilic focus	0	0	1	0
Bile duct hyperplasia	3	1	4	4
Hyperplasia, nodular	0	0	0	0
Basophilic focus	9	9	9	3
Clear cell focus	0	1	0	0
2-Year Study				
n	50	50	50	50
Degeneration, cystic	0	0	0	0
Eosinophilic focus	8	10	8	14
Bile duct hyperplasia	29	30	34	43**
Hyperplasia, nodular	4	1	3	14**
Basophilic focus	39	41	38	29*
Clear cell focus	6	1	3	5

* Significantly different (P≤0.05) from the control group by logistic regression test
** P≤0.01
[a] Number of animals with liver examined microscopically
[b] Number of animals with lesion

and clear cell foci are directly related to the ingestion of *o*-nitroanisole or to the increased incidences of mononuclear cell leukemia in the exposed groups. The leukemic infiltrates produce substantial degenerative changes in the liver which might obscure or affect the occurrence of spontaneous foci of cellular alteration.

Hepatocellular adenomas occurred in three males receiving 222 ppm, one male receiving 666 ppm, and two males and three females receiving 2,000 ppm (Tables A1 and B1). A hepatocellular carcinoma was seen in one additional male that received 222 ppm. Although no hepatocellular neoplasms were seen in control males, the incidences in the exposed males did not increase with dose and were not significantly increased (Table A3). The incidence of hepatocellular adenoma in female rats occurred with a significant positive trend, but the incidence in the 2,000 ppm group was not significantly greater than that in the controls (Table B3). In NTP historical controls, hepatocellular neoplasms have occurred in 24 of 799 (3%) male and 4 of 800 (0.5%) female rats (Tables A4b and B4b). The few hepatocellular neoplasms in exposed rats are not believed to be chemical related.

Urinary bladder: Focal hyperplasia of the transitional epithelium of the urinary bladder occurred in one female that received 222 ppm and two males and six females that received 2,000 ppm (Tables A5 and B5). Moreover, a transitional cell papilloma was seen in one female from the 2,000 ppm group and a transitional cell carcinoma was seen in another female from the same group (Table B1). Transitional cell neoplasms of the urinary bladder are rare spontaneous neoplasms and have occurred in 2 of 790 historical control female F344/N rats. These neoplasms are described further in the results of the stop-exposure study.

Stomach: The incidence of ulcers of the forestomach mucosa was significantly increased in male rats receiving 2,000 ppm (Tables 12 and A5). There were corresponding increased incidences of edema and chronic inflammation that were associated with the ulcers. There was a slightly but not significantly increased incidence of ulcers in females that received 2,000 ppm (Tables 12 and B5). The incidence of focal hyperplasia of the forestomach epithelium increased with exposure level in male and female rats, and the incidences in all exposed male groups and in females from the 2,000 ppm group were significantly increased. Squamous cell papillomas or carcinomas occurred in several groups of exposed males and females, but none were observed in controls (Tables A1 and B1). Squamous cell papillomas were seen in one female receiving 222 ppm, one male receiving 666 ppm, and one male and one female receiving 2,000 ppm. Squamous cell carcinomas were seen in one male receiving 666 ppm and one male and one female receiving 2,000 ppm. Although these neoplasms occurred at very low incidences, they are rare spontaneous neoplasms in F344 rats. In NTP historical controls, squamous cell papillomas have occurred in 2 of 800 males and 1 of 800 females; squamous cell carcinomas have occurred in 1 of 800 males and none have occurred in females (Tables A4c and B4c).

Focal hyperplasia and papillomas of the forestomach squamous epithelium constitute a morphological continuum. Focal hyperplasia was characterized by increased cellularity and thickening of the epithelium with the formation of rugose folds and simple blunt papillae. The papillomas were distinguished from hyperplasia on the basis of complexity of structure. The squamous cell papillomas were short stalks with branching papillae consisting of well-differentiated stratified epithelium overlying a delicate fibrovascular stroma. The squamous cell carcinomas invaded the forestomach mucosa with cords and clusters of anaplastic cells.

Lung: Hyperplasia of the alveolar epithelium occurred at a low incidence in all exposed female groups, but did not occur in controls (Table B5). In addition, alveolar/bronchiolar adenomas were seen in two females that received 666 ppm and three females that received 2,000 ppm, and a squamous cell carcinoma of the lung was seen in another female that received 2,000 ppm (Table B1). Alveolar/bronchiolar neoplasms have occurred in 17 of 800 (2%, range 0%-10%) historical control females. Because of the small number of pulmonary neoplasms, they are not believed to be chemical related. In male rats the incidences of alveolar/bronchiolar neoplasms were similar in control and exposed groups (Table A1).

Pituitary gland: At the 15-month interim evaluation, adenomas of the pars distalis were seen in three

TABLE 12
Selected Forestomach Lesions of Rats in the 2-Year Feed Study of o-Nitroanisole

Dose (ppm)	0	222	666	2,000
Male				
15-Month Interim Evaluation				
n[a]	10	0[c]	1	9
Ulcer[b]	0		0	0
Edema	0		0	0
Chronic inflammation	0		0	0
Focal hyperplasia	0		1	1
2-Year Study				
n	50	50	50	50
Ulcer	3	3	8	16**
Edema	3	3	5	11*
Chronic inflammation	2	2	1	12**
Focal hyperplasia	3	16**	25**	32**
Squamous cell papilloma	0	0	1	1
Squamous cell carcinoma	0	0	1	1
Female				
15-Month Interim Evaluation				
n	10	1	0[b]	9
Ulcer	0	0		0
Edema	0	0		0
Chronic inflammation	0	0		0
Focal hyperplasia	0	1		1
2-Year Study				
n	50	50	50	50
Ulcer	3	1	4	7
Edema	4	1	5	5
Chronic inflammation	4	2	2	6
Focal hyperplasia	8	8	13	28**
Squamous cell papilloma	0	1	0	1
Squamous cell carcinoma	0	0	0	1

* Significantly different (P≤0.05) from the control group by logistic regression
** P≤0.01
[a] Number of animals with forestomach examined microscopically
[b] Number of animals with lesions
[c] Forestomach not examined in this dose group

control males and one male receiving 222 ppm; none were observed in males receiving 2,000 ppm (Table A1). At the end of the 2-year study, the incidence of adenomas of the pars distalis occurred with a significant negative trend in exposed male rats, and the incidence in the 2,000 ppm group was significantly decreased (14/50, 11/50, 9/49, 4/49; Table A3). Carcinomas occurred in one control male and one male that received 666 ppm (Table A1). The incidence of focal hyperplasia of the pars distalis in males did not decrease with dose and was highest in the 666 ppm group (3/50, 9/50, 11/49, 5/49; Table A5).

Mammary gland: The incidence of fibroadenoma of the mammary gland was marginally decreased in females receiving 2,000 ppm (17/50, 18/50, 15/50, 9/50; Table B3). Although the trend test was signifi cant, the incidence of fibroadenoma in the 2,000 ppm group was not significantly lower than that in the control. Thus, the marginal decrease was not considered chemical related.

STOP-EXPOSURE STUDY

Survival

Estimates of survival probabilities for male and female rats are shown in Table 13 and in the Kaplan-Meier curves in Figure 4. Four males and four females in the 18,000 ppm groups scheduled for evaluation at 9 months, all males and females in the 18,000 ppm groups scheduled for evaluation at 15 months, and seven males in the 6,000 ppm group scheduled for evaluation at 15 months died before the evaluation periods. One male and two females in the control groups scheduled for evaluation at 15 months also died early. All early death animals were included with the core study animals for evaluation. In the stop-exposure core study, all males and females receiving 18,000 ppm had died or were killed moribund by week 48 (males) or week 61 (females). In the 6,000 ppm groups, all but one male and four females died or were killed moribund before the end of the study. Nearly all exposed rats that died early had urinary bladder neoplasms, which presumably was the major contributing cause of death.

Body Weights, Feed Consumption, and Clinical Findings

The final mean body weights of exposed male and female rats were significantly lower than those of the controls (Tables 14 and 15, and Figure 5). Feed consumption by exposed males and females was lower than that by the controls for the first year of the study (Tables K3 and K4). However, by the end of the study feed consumption by male and female exposed groups was similar to that by the controls. Dietary levels of 6,000 and 18,000 ppm resulted in average daily consumption levels of 340 and 1,100 mg/kg for males and females. The only clinical finding related to chemical administration in male and female rats was the presence of discolored urine.

Pathology and Statistical Analyses of Results

Summaries of the incidences of nonneoplastic lesions and neoplasms, the individual animal tumor diagnoses, and the statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one group are presented in Appendix E for male rats and Appendix F for female rats. Because of the extensive mortality in the exposed groups, logistic regression analyses had greatly reduced power and are not included here.

Urinary bladder: The urinary bladder was the primary organ in which neoplasms developed in rats following the ingestion of *o*-nitroanisole at dietary concentrations of 6,000 or 18,000 ppm for up to 6 months followed by a normal diet. At the 3-, 6-, and 9-month interim evaluations the absolute and relative urinary bladder weights of male and female rats receiving 18,000 ppm were significantly greater than those of the controls (Tables H4, H5, and H6).

At the 3-month interim evaluation, the principal lesions observed in the urinary bladder were similar to those observed at the same dietary concentrations in the 13-week study (Tables 16, E4, and F4). Diffuse hyperplasia of the transitional epithelium was seen in nearly all male and female rats that received 18,000 ppm and in 8 of 10 female rats that received 6,000 ppm. The transitional epithelium was irregularly thickened with many folds and blunt papillae separated by extensions of the basement membrane. Although the epithelium of controls was approximately 3 to 10 cell layers thick depending on the degree of bladder contraction (Plates 4 and 5), the epithelium of rats receiving 18,000 ppm was generally more than 30 cell layers thick (Plates 6 and 7). The size and staining properties of the epithelial cells in each bladder varied from populations of small basophilic cells to populations of larger, more typical transitional cells with eosinophilic cytoplasm. Focal or multifocal squamous metaplasia was also seen in all males and females in the 18,000 ppm groups. The squamous cells were well differentiated with prominent keratin layers on the surface (Plate 8). In one male receiving 18,000 ppm, the markedly thickened transitional epithelium exhibited sufficient focal cellular pleomorphism and atypia to be diagnosed as a carcinoma (Table 16). Subacute inflammation and proliferation of connective tissue in the lamina propria accompanied the epithelial changes described above in most males and females that received 18,000 ppm (Plate 9). They were characterized by scattered inflammatory cells, principally neutrophils and macrophages, and increased numbers of fibroblasts with immature collagen.

By 6 months, transitional cell carcinomas were present in all rats receiving 18,000 ppm (Tables 16, E1, and F1). The proliferation of the transitional epithelium in these rats was extensive enough to form exophytic nodular masses with heterogeneous growth

TABLE 13
Survival of Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole

	0 ppm	6,000 ppm	18,000 ppm
Male			
Animals initially in study	60	60	60
3-Month interim evaluation[a]	10	10	10
6-Month interim evaluation[a]	10	10	10
9-Month interim evaluation[a]	10	10	6
15-Month interim evaluation[a]	9	3	0
Natural deaths	1	0	11
Moribund kills	7	26	23
Animals surviving to study termination	13	1	0
Percent probability of survival at end of study[b]	63	4	0
Mean survival (days)[c]	399	332	218
Survival analysis[d]	P<0.001	P<0.001	P<0.001
Female			
Animals initially in study	60	60	60
3-Month interim evaluation[a]	10	10	10
6-Month interim evaluation[a]	10	10	10
9-Month interim evaluation[a]	10	10	6
15-Month interim evaluation[a]	8	10	0
Natural deaths	2	4	9
Moribund kills	6	12	25
Animals surviving to study termination	14	4	0
Percent probability of survival at end of study	68	23	0
Mean survival (days)	388	354	235
Survival analysis	P<0.001	P=0.012	P<0.001

[a] Censored from survival analyses
[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 dosed columns.

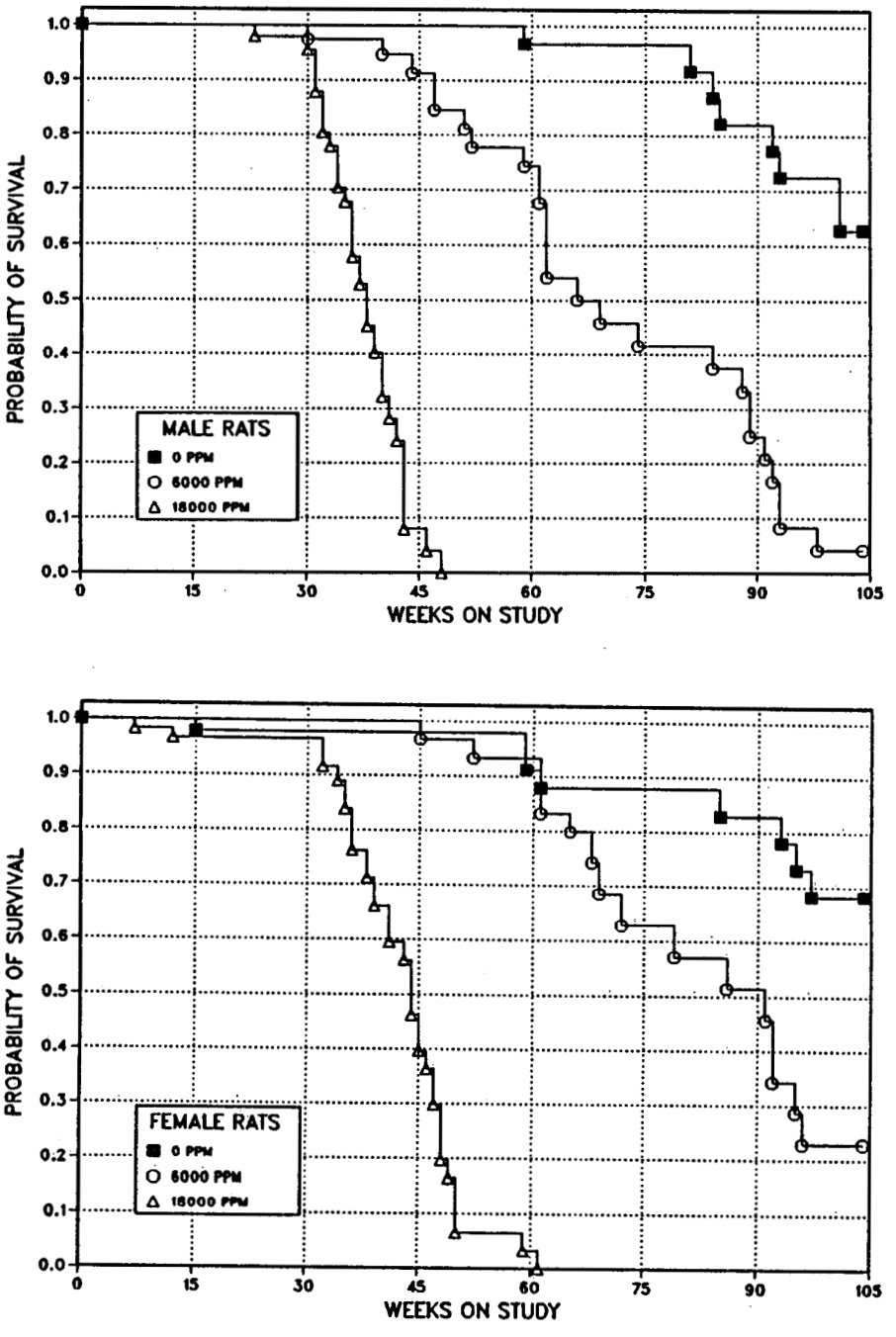


FIGURE 4
Kaplan-Meier Survival Curves for Male and Female Rats Administered *o*-Nitroanisole in Feed in the Stop-Exposure Study

TABLE 14
Mean Body Weights and Survival of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole

Week on Study	0 ppm		6,000 ppm			18,000 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
1	116	20	111	96	20	100	87	20
2	157	20	149	95	20	103	65	20
3	189	20	178	94	20	112	59	20
4	219	20	200	92	20	123	56	20
5	245	20	215	88	20	131	54	20
6	264	20	232	88	20	136	52	20
7	274	20	241	88	20	141	51	20
8	285	20	244	86	20	148	52	20
9	299	20	245	82	20	148	50	20
10	314	20	235	75	20	153	49	20
11	320	20	255	80	20	154	48	20
12	330	20	266	81	20	156	47	20
13	335	20	273	81	20	162	48	20
17	368	20	297	81	20	166	45	20
21	380	20	308	81	20	175	46	20
25	396	20	319	81	20	180	45	19
29	409	20	344	84	20	221	54	19
33	418	20	366	88	19	259	62	15
37	436	20	388	89	19	268	61	10
41	441	20	397	90	18	280	64	5
45	448	20	406	91	18	269	60	1
49	451	20	411	91	18			
53	447	20	407	91	17			
57	447	20	415	93	17			
61	447	20	413	93	15			
65	440	20	398	90	13			
69	452	20	403	89	12			
73	444	20	398	90	11			
77	444	20	402	91	10			
81	435	20	390	90	10			
85	439	17	369	84	9			
89	436	17	369	85	6			
93	427	16	381	89	3			
97	420	15	296	71	2			
101	404	14	354	88	1			
Terminal sacrifice		13			1			0
Mean for weeks								
1-13	257		219	85		136	53	
14-52	416		360	87		227	55	
53-101	437		384	88				

TABLE 15
Mean Body Weights and Survival of Female Rats in the Stop-Exposure Feed Study of o-Nitroanisole

Week on Study	0 ppm		6,000 ppm			18,000 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
1	97	20	94	97	20	87	90	20
2	119	20	113	94	20	85	71	20
3	137	20	125	92	20	89	65	20
4	143	20	134	94	20	96	67	20
5	153	20	142	93	20	98	64	20
6	162	20	150	93	20	99	61	20
7	166	20	153	93	20	100	61	20
8	170	20	155	91	20	105	62	19
9	173	20	157	91	20	106	61	19
10	178	20	154	87	20	109	61	19
11	181	20	162	89	20	109	60	19
12	183	20	165	90	20	111	61	19
13	182	20	167	91	20	113	62	19
17	198	19	180	91	20	119	60	19
21	203	19	176	87	20	122	60	19
25	208	19	180	87	20	124	60	19
29	212	19	193	91	20	148	70	19
33	217	19	196	90	20	162	75	17
37	230	19	205	89	20	171	74	14
41	235	19	207	88	20	172	73	12
45	245	19	215	88	19	181	74	7
49	253	19	219	87	19	185	73	3
53	259	19	224	86	18	187	72	2
57	270	19	231	85	18	192	71	2
61	278	18	233	84	16	167	60	1
65	288	18	235	82	15			
69	294	18	246	84	12			
73	299	18	249	83	11			
77	305	18	252	83	11			
81	307	18	253	83	10			
85	317	17	254	80	10			
89	320	17	258	81	9			
93	321	17	271	84	6			
97	321	15	268	83	4			
101	324	14	269	83	4			
Terminal sacrifice		14			4			0
Mean for weeks								
1-13	157		144	92		101	64	
14-52	222		197	89		154	69	
53-101	300		249	83		182	61	

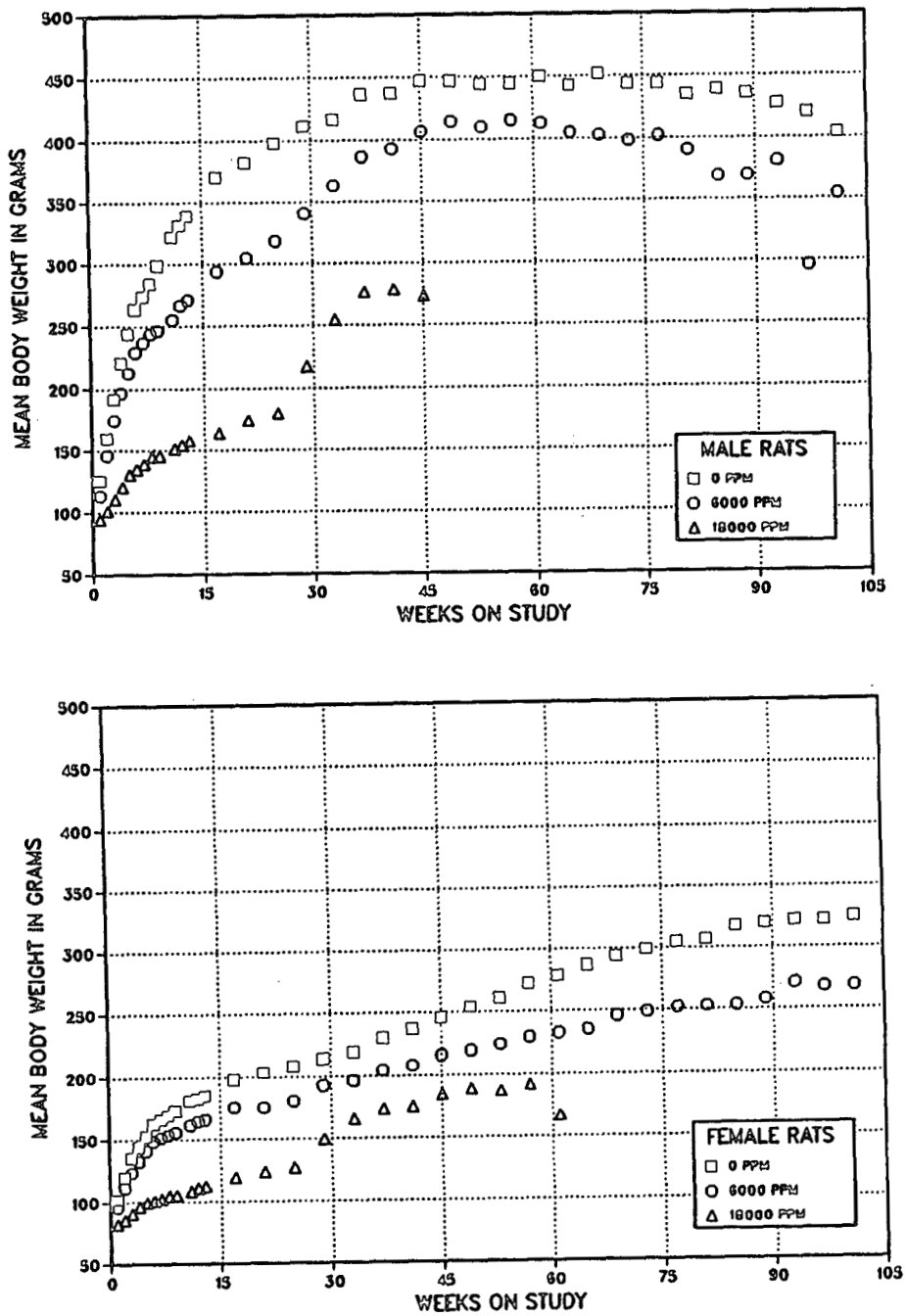


FIGURE 5
Growth Curves for Male and Female Rats Administered *o*-Nitroanisole in Feed in the Stop-Exposure Study

TABLE 16
Incidences of Selected Lesions of the Urinary Bladder of Rats in the Stop-Exposure Feed Study of o-Nitroanisole

	Male			Female		
	0 ppm	6,000 ppm	18,000 ppm	0 ppm	6,000 ppm	18,000 ppm
3-Month Interim Evaluation						
n[a]	9	9	10	10	10	10
Proliferation, connective tissue[b]	0	0	10**(2.1)[c]	0	0	6**(2.2)
Squamous metaplasia	0	0	10**(3.4)	0	0	10**(2.9)
Transitional cell hyperplasia	0	0	9**(3.8)	0	8**(1.0)	10**(3.7)
Transitional cell carcinoma	0	0	1	0	0	0
6-Month Interim Evaluation						
n	10	10	10	10	10	10
Proliferation, connective tissue	0	1 (1.0)	9**(3.4)	0	2 (1.5)	10**(2.6)
Squamous metaplasia	0	0	10**(3.6)	0	1 (2.0)	10**(3.7)
Transitional cell hyperplasia	0	10**(2.6)	0	0	10**(2.7)	0
Transitional cell papilloma	0	2	0	0	0	0
Transitional cell carcinoma	0	0	10**	0	0	10**
Sarcoma	0	0	2	0	0	0
9-Month Interim Evaluation						
n	10	10	6	10	9	6
Proliferation, connective tissue	0	0	4**(3.3)	0	1 (1.0)	4**(2.5)
Squamous metaplasia	0	0	4**(2.5)	0	0	4**(2.5)
Transitional cell hyperplasia	0	9**(2.4)	0	0	9**(2.2)	0
Transitional cell papilloma	0	2	0	0	0	0
Transitional cell carcinoma	0	3	6**	0	1	6**
Squamous cell carcinoma	0	0	1	0	0	0
Sarcoma	0	0	0	0	0	2
15-Month Interim Evaluation						
n	9	3	–[d]	8	10	–
Proliferation, connective tissue	0	1 (3.0)	–	0	6**(2.5)	–
Squamous metaplasia	0	0	–	0	2 (2.0)	–
Transitional cell hyperplasia	0	1 (2.0)	–	0	3 (3.0)	–
Transitional cell papilloma	0	2	–	0	1	–
Transitional cell carcinoma	0	1	–	0	9**	–
Sarcoma	0	1	–	0	0	–

(continued)

TABLE 16
Incidences of Selected Lesions of the Urinary Bladder of Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	Male			Female		
	0 ppm	6,000 ppm	18,000 ppm	0 ppm	6,000 ppm	18,000 ppm
2-Year Study						
n	21	27	34	20	20	34
Proliferation, connective tissue	0	1 (4.0)	24°°(3.0)	0	11°°(3.2)	20°°(3.2)
Squamous metaplasia	0	3 (3.0)	30°°(3.3)	0	6°(3.2)	25°°(3.2)
Transitional cell hyperplasia	0	9°°(2.4)	2 (3.0)	0	4 (3.0)	1 (2.0)
Transitional cell papilloma	0	3	1	0	1	1
Transitional cell carcinoma	0	23°°	33°°	0	18°°	32°°
Squamous cell papilloma	0	0	4	0	0	4
Squamous cell carcinoma	0	0	5	0	0	1
Sarcoma[e]	0	1	7°	0	2	12°°
Overall Rates						
n	59	59	60	58	59	60
Transitional cell papilloma	0	9°°	1	0	2	1
Transitional cell carcinoma	0	27°°	50°°	0	28°°	48°°
Squamous cell papilloma	0	0	4	0	0	4
Squamous cell carcinoma	0	0	6°	0	0	1
Sarcoma	0	2	9°°	0	2	14°°

° Significantly different ($P \leq 0.05$) from the control group by Fisher exact test
°° $P \leq 0.01$
[a] Number of animals with urinary bladder examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
[d] All males and females receiving 18,000 ppm died before the 15-month interim evaluation.
[e] Includes a leiomyosarcoma in one 6,000 ppm and two 18,000 ppm females and a fibrosarcoma in one 18,000 ppm female.

patterns and pleomorphic cell populations (Plates 10, 11, and 12). Foci of squamous differentiation were observed in all neoplasms. Diffuse hyperplasia of the transitional epithelium was present in all males and females that received 6,000 ppm, and papillomas were observed in two males that received 6,000 ppm.

Malignant mesenchymal neoplasms (sarcomas) were present in two males receiving 18,000 ppm. The sarcomas appeared to originate in the lamina propria and were characterized by the proliferation of anaplastic fusiform cells with elongated oval nuclei and scant cytoplasm. In contrast to the connective tissue proliferation seen in most males and females in the 18,000 ppm groups and some rats in the 6,000 ppm groups, the sarcomas were more localized and extensive and consisted of undifferentiated cells with little collagen production. Subacute inflammation was also observed in exposed rats.

At 9 months, only six males and six females in the 18,000 ppm groups were still alive; all had transitional cell carcinomas, one male had a squamous cell carcinoma (Plate 13), and two females had sarcomas (Table 16 and Plate 14). Hyperplasia was seen in nearly all males and females receiving 6,000 ppm. Transitional cell carcinomas were seen in three males and two females, and transitional cell papillomas were present in two males from the 6,000 ppm groups.

By 15 months, all males and females that received 18,000 ppm and 7 of 10 males that received 6,000 ppm had died. Transitional cell carcinomas were seen in 9 of 10 females receiving 6,000 ppm and a papilloma was seen in the other female from this group (Table 16).

Of the core group rats in the stop-exposure study, transitional cell carcinomas were seen in nearly all exposed male and female rats (Table 16). Of the males and females receiving 6,000 ppm that were without carcinomas, three males and one female had transitional cell papillomas. Moreover, squamous cell carcinomas were seen in five males and one female that received 18,000 ppm and squamous cell papillomas were seen in four males and four females that received 18,000 ppm. Sarcomas were seen in 7 males and 12 females receiving 18,000 ppm and in 1 male and 2 females receiving 6,000 ppm. Neoplasms arising from the urinary bladder epithelium were not observed in control rats. Inflammation and connective tissue proliferation in the lamina propria, similar to those seen at the interim evaluations, were also observed in many exposed rats. Two females from the 18,000 ppm group and three females from the 6,000 ppm group also exhibited focal proliferation of well-differentiated lipocytes (adipocytes or fat cells) in the lamina propria (Table F4). Since fat cells are not normally found in the lamina propria, the formation of these cells was considered a metaplastic process.

Large intestine: In the stop-exposure study, the intestines were examined at necropsy. Histologic sections were prepared and examined microscopically only when a lesion or mass was observed. Neoplasms of the large intestine, principally adenomatous polyps, were observed in small numbers of exposed rats at the 6-, 9-, and 15-month interim evaluations (Tables 17, E1, and F1). At the end of the stop-exposure study, however, the incidences of adenomatous polyps in exposed groups of males and females were significantly increased. In addition, four males and two females receiving 18,000 ppm had carcinomas of the large intestine. The neoplasms were polypoid masses in the colon, cecum, or rectum, and multiple neoplasms were observed in some animals. The adenomatous polyps consisted of a moderately well-differentiated columnar epithelium forming coiled tubular glands which were separated by a delicate fibrovascular stroma (Plate 15). The few carcinomas exhibited invasion of the stalk by anaplastic epithelial cells (Plate 16) with an accompanying proliferation of fibrous connective tissue (scirrhous reaction).

Kidney: Any potential chemical-related effect on absolute kidney weights was obscured by the more overt changes associated with the body weight differences between control and exposed groups. Relative kidney weights of most males and females receiving 6,000 and 18,000 ppm were significantly greater than those of the controls at the 3-, 6-, 9-, and 15-month interim evaluations (Tables H4, H5, H6, and H7). Absolute kidney weights of males and females that received 18,000 ppm were significantly lower than those of the controls at 3 and 6 months.

Hydronephrosis (dilatation of the renal pelvis) was observed in two exposed male rats at the 9-month interim evaluation and in many exposed male and female rats at the end of the stop-exposure study (Tables 18, E4, and F4). This was observed in rats

TABLE 17
Incidences of Neoplasms of the Large Intestine in Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole

	Male			Female		
	0 ppm	6,000 ppm	18,000 ppm	0 ppm	6,000 ppm	18,000 ppm
3-Month Interim Evaluation						
n[a]	10	10	10	10	10	10
Adenomatous polyp[b]	0	0	0	0	0	0
6-Month Interim Evaluation						
n	10	10	10	10	10	10
Adenomatous polyp	0	0	2	0	1	0
9-Month Interim Evaluation						
n	10	10	6	10	10	6
Adenomatous polyp	0	2	4**	0	0	1
Carcinoma	0	0	1	0	0	0
15-Month Interim Evaluation						
n	9	3	0	8	10	0
Adenomatous polyp	0	3**	–[c]	0	2	–
2-Year Study						
n	21	27	34	22	20	34
Adenomatous polyp	0	21**	24**	0	5*	17**
Carcinoma	0	0	4	0	0	2
Overall Rates						
n	60	60	60	60	60	60
Adenomatous polyp	0	26**	30**	0	8**	18**
Carcinoma	0	0	5*	0	0	2
Adenomatous polyp or carcinoma	0	26**	31**	0	8**	18**

* Significantly different ($P \leq 0.05$) from the control group by Fisher exact test
** $P \leq 0.01$
[a] Number of animals necropsied
[b] Number of animals with lesions
[c] All males and females receiving 18,000 ppm died before the 15-month interim evaluation.

TABLE 18
Incidences of Selected Kidney Lesions in Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole

	Male			Female		
	0 ppm	6,000 ppm	18,000 ppm	0 ppm	6,000 ppm	18,000 ppm
3-Month Interim Evaluation						
n[a]	10	10	10	10	10	10
Nephropathy[b]	4 (1.0)[c]	10**(1.9)	7 (1.7)	0	0	0
Pigmentation	0	9**(1.7)	10**(3.3)	0	10**(1.9)	10**(3.2)
6-Month Interim Evaluation						
n	10	10	10	10	10	10
Nephropathy	4 (1.0)	10**(2.3)	10**(1.8)	0	0	0
Transitional cell hyperplasia	0	0	5*(2.0)	0	0	2 (3.0)
Pigmentation	2 (1.5)	10**(2.6)	9**(3.0)	0	10**(2.0)	10**(3.3)
9-Month Interim Evaluation						
n	10	10	6	10	10	6
Nephropathy	10 (1.5)	10 (2.4)	6 (1.8)	5 (1.0)	3 (1.7)	3 (1.0)
Transitional cell hyperplasia	0	7**(1.9)	3*(2.3)	0	1 (2.0)	1 (2.0)
Pigmentation	10 (1.1)	10 (1.0)	6 (1.8)	6 (1.0)	10*(1.3)	6 (2.0)
Hydronephrosis	0	0	2 (4.0)	0	0	0
Transitional cell papilloma	0	0	1	0	0	0
Transitional cell carcinoma	0	0	2	0	0	0
15-Month Interim Evaluation						
n	9	3	–[d]	8	10	–
Nephropathy	9 (1.6)	3 (3.0)	–	5 (1.0)	5 (1.2)	–
Transitional cell hyperplasia	0	3 (2.3)	–	0	0	–
Pigmentation	9 (1.0)	3 (1.3)	–	7 (1.0)	10 (1.0)	–
2-Year Study						
n	21	27	34	22	20	34
Nephropathy	21 (3.0)	27 (2.9)	24 (1.7)	19 (1.6)	12 (1.7)	3 (1.7)
Transitional cell hyperplasia	5 (1.6)	24**(2.0)	19*(2.2)	0	5*(1.6)	16**(2.3)
Pigmentation	20 (1.1)	26 (1.4)	34 (2.3)	20 (1.1)	20 (1.1)	34 (2.1)
Hydronephrosis	0	2 (3.0)	11**(3.6)	0	3 (4.0)	15**(3.0)
Transitional cell papilloma	0	0	3	0	0	1
Transitional cell carcinoma	0	1	6*	0	0	1
Overall Rates						
n	60	60	60	60	60	60
Nephropathy	48	60	47	29	20	6
Transitional cell hyperplasia	5	34**	27**	0	6*	19**
Pigmentation	41	58**	59**	33	60**	60**
Hydronephrosis	0	2	13**	0	3	18**
Transitional cell papilloma	0	0	4	0	0	1
Transitional cell carcinoma	0	1	8**	0	0	1

* Significantly different (P≤0.05) from the control group by Fisher exact test
** P≤0.01
[a] Number of animals with kidney examined microscopically
[b] Number of animals with lesions
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
[d] All males and females receiving 18,000 ppm died before the 15-month interim evaluation.

with transitional cell neoplasms of the urinary bladder and was considered a secondary partial obstruction of urine outflow. There was an increase in the incidence or severity of pigmentation in exposed rats at the various interim evaluations and at the end of the stop-exposure study. The pigment, located in scattered epithelial cells of the proximal tubules, was believed to be primarily hemosiderin derived from the breakdown of erythrocytes.

Nephropathy occurred in most of the males in the exposed and control groups. However, the average severity of nephropathy in exposed males was greater than that in controls at 3 and 6 months (Table 18).

At the 9- and 15-month interim evaluations, the effect was still evident in the 6,000 ppm group, even though the dietary administration of *o*-nitroanisole had ceased at week 27. The apparent lack of an effect in males receiving 18,000 ppm at 9 months may have been the result of reduced feed consumption, lower body weight, or both. *o*-Nitroanisole had no effect on the incidence or severity of nephropathy in female rats at any of the interim evaluations. At the end of the stop-exposure study, the incidences or severity of nephropathy in males and females that received 18,000 ppm were decreased and may have been related to the decreased survival, lower body weights, and reduced feed consumption of these groups.

Hyperplasia of the transitional epithelium (urothelium) lining the renal pelvis was observed in some males and females that received 18,000 ppm at 6 months, some males and females that received 6,000 and 18,000 ppm at 9 months, and some males that received 6,000 ppm at 15 months. At the end of the stop-exposure study, the incidence of hyperplasia was significantly increased in all exposed groups of males and females. In addition, papillomas of the transitional epithelium were seen in three males and one female receiving 18,000 ppm, while carcinomas were seen in one male receiving 6,000 ppm and six males and one female receiving 18,000 ppm (Plate 17); none were observed in the controls (Tables 18, E1, and F1). Neoplasms arising from the transitional epithelium of the renal pelvis are extremely rare in NTP historical controls; none have been seen in the current historical control database (male, 0/798; female, 0/797).

Liver: At the 3- and 6-month interim evaluations, the absolute liver weights of males and females that received 6,000 ppm and females that received 18,000 ppm were significantly greater than those of the controls (Tables H4 and H5). In addition, the relative liver weights of males and females in all exposed groups were significantly greater than those of the controls. The absolute liver weight of males in the 18,000 ppm group was similar to that of controls, despite the substantially lower mean body weight. At 9 and 15 months, any potential chemical-related effect on liver weights was partially obscured by the effects on body weight. However, the relative liver weights of males and females receiving 6,000 ppm and females receiving 18,000 ppm were significantly increased at 9 months, and that of females receiving 6,000 ppm was significantly increased at 15 months (Tables H6 and H7).

The lesions observed in the livers of exposed rats are consistent with the differences in absolute and relative liver weights noted above (Tables 19, E4, and F4). Generalized centrilobular hypertrophy was observed at 3 and 6 months in all males and females that received 18,000 ppm. Focal hepatocellular necrosis, consisting of scattered individual or small clusters of cells in the centrilobular regions, was also seen in all males and females receiving 18,000 ppm at 3 months and at 6 months (Plate 18). Multifocal hepatocellular cytoplasmic vacuolation was seen in several males and females in the 18,000 ppm groups at 3 months, and a dose-related increased incidence of this lesion was seen in male rats at 6 months. There were no chemical-related increased incidences of hypertrophy, necrosis, or cytoplasmic vacuolation at 9 or 15 months.

Accumulation of golden or greenish brown pigment in scattered Kupffer cells was seen in all males and females receiving 18,000 ppm at 3 and 6 months, and in all but one male and all females receiving 18,000 ppm at 9 months (Table 19). Similar pigment-filled Kupffer cells were not seen in the controls. In the core groups of the stop-exposure study, pigment-filled Kupffer cells were also seen in most males and all females that received 18,000 ppm. In addition, a number of control females had similar pigment while none was observed in the control males. The pigment had staining properties consistent with hemosiderin.

TABLE 19
Incidences of Selected Liver Lesions in Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole

	Male			Female		
	0 ppm	6,000 ppm	18,000 ppm	0 ppm	6,000 ppm	18,000 ppm
3-Month Interim Evaluation						
n[a]	10	10	10	10	10	10
Hypertrophy[b]	0	0	10**(2.2)[c]	0	0	10**(2.0)
Cytoplasmic vacuolation	0	0	3 (1.3)	1 (2.0)	0	3 (1.7)
Necrosis	2 (2.0)	0	10 (1.0)	1 (2.0)	3 (1.0)	10**(1.3)
Pigmentation	0	0	10**(1.9)	0	1 (1.0)	10**(2.2)
6-Month Interim Evaluation						
n	10	10	10	10	10	10
Hypertrophy	0	0	10**(2.6)	0	0	10**(2.4)
Cytoplasmic vacuolation	0	3 (1.0)	6**(1.3)	0	0	1 (2.0)
Necrosis	0	1 (1.0)	10**(1.8)	0	0	10**(1.9)
Pigmentation	0	3 (1.0)	10**(2.0)	0	9**(1.0)	10**(2.0)
9-Month Interim Evaluation						
n	10	10	6	10	10	6
Pigmentation	0	0	5**(1.4)	1 (1.0)	7**(1.0)	6**(2.0)
15-Month Interim Evaluation						
n	9	3	–[d]	8	10	–
Pigmentation	0	1 (1.0)	–	0	2 (1.0)	–
2-Year Study						
n	21	27	34	22	20	34
Pigmentation	0	1 (1.0)	30**(1.7)	9 (1.6)	2 (1.0)	34**(1.8)

** Significantly different ($P \leq 0.01$) from the control group by Fisher exact test
[a] Number of animals with liver examined microscopically
[b] Number of animals with lesions
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
[d] All males and female receiving 18,000 ppm died before the 15-month interim evaluation.

Spleen: Relative spleen weights of exposed male and female rats were significantly greater than those of controls at 3 and 6 months (Tables H4 and H5). At 3 months, the absolute spleen weights of all exposed males and females were significantly increased; there were significant increases in the absolute spleen weights of all exposed female groups and of males receiving 18,000 ppm at 6 months. At the 9-month interim evaluation, the absolute spleen weights of male and female rats receiving 18,000 ppm and the relative spleen weights of all exposed male groups and of females receiving 18,000 ppm remained significantly increased (Table H6). The chemical-related increases in relative spleen weights were associated with the splenic congestion observed histologically. The red pulp of nearly all exposed rats at the 3-, 6-, and 9-month interim evaluations contained increased numbers of erythrocytes (Tables 20, E4, and F4). The congestion was generally more severe in the 18,000 ppm groups than in the 6,000 ppm groups. In the core groups of the stop-exposure study, the incidence of congestion in males that received 18,000 ppm was significantly increased, reflecting the large number of males in the 18,000 ppm group which died early.

Testis: At 3 and 6 months the absolute and relative testis weights of males receiving 18,000 ppm were significantly lower than those of the controls, while the relative testis weight of males receiving 6,000 ppm was significantly greater than that of controls (Tables H4 and H5). At 9 months the findings were similar, except that the relative testis weight of the 18,000 ppm group was significantly greater than that of controls (Table H6). These differences may be due to the chemical-related lower mean body weights of the exposed males which would largely obscure any direct effect of *o*-nitroanisole on testis weight.

Degeneration and atrophy of the seminiferous epithelium of the testes were observed at the 3- and 6-month interim evaluations in most males that received 18,000 ppm, while at 9 months only three of the six males that received 18,000 ppm exhibited atrophy (Table E4). The lesions were generally mild to moderate at 3 and 6 months and minimal at 9 months. The lesions were characterized by the degeneration and loss of spermatogenic cells, decreased numbers of mature spermatozoa, and the presence of cellular debris and multinucleated cells in the tubule lumens (Plates 19 and 20). At the end of the stop-exposure study, atrophy associated with aging or with interstitial cell neoplasms was seen in most control males, and the incidences of atrophy in the exposed groups were lower than in the controls. This decreased incidence was largely due to the early deaths of exposed rats, which precluded the development of interstitial cell neoplasms and aging changes.

Uterus: The absolute uterine weights of exposed females were significantly lower than those of the controls at 3 and 6 months, while at 9 months only that of the 18,000 ppm group was significantly lower (Tables H4, H5 and H6). Although relative uterine weights were not affected at 3 and 9 months, those of the exposed groups at 6 months were significantly lower than that of the controls. Again, it is difficult to determine if the differences in uterine weight were caused, in part, by *o*-nitroanisole because of the marked chemical-related reduction in mean body weights in the exposed groups.

Uterine atrophy was observed microscopically in all exposed females at 3 and 6 months, and in 3 of 6 females receiving 18,000 ppm at 9 months (Table F4). In general, the uteri of females in the 6,000 ppm group were less severely affected than those in the 18,000 ppm group. Histologically, the atrophy was characterized by reduced thickness of the endometrium and myometrium, and reduced amounts of cytoplasm in the affected cells, as compared with controls.

TABLE 20
Incidences of Selected Splenic Lesions in Rats in the Stop-Exposure Feed Study of o-Nitroanisole

	Male			Female		
	0 ppm	6,000 ppm	18,000 ppm	0 ppm	6,000 ppm	18,000 ppm
3-Month Interim Evaluation						
n[a]	10	10	10	10	10	10
Congestion[b]	0	9**(2.8)[c]	10**(4.0)	0	10**(2.5)	10**(3.9)
Pigmentation	10 (1.4)	10 (2.9)	10 (3.0)	10 (1.9)	10 (2.9)	10 (2.6)
Capsule, hypertrophy	0	10**(1.0)	10**(2.5)	0	10**(1.5)	10**(2.2)
Capsule, inflammation	0	1 (2.0)	10**(2.8)	0	6**(1.8)	9**(2.6)
Lymphoid depletion	0	0	10**(2.9)	0	0	10**(2.8)
6-Month Interim Evaluation						
n	10	10	10	10	10	10
Congestion	0	10**(2.5)	10**(3.9)	0	10**(2.2)	10**(2.8)
Pigmentation	0	10**(2.6)	8**(1.9)	5 (2.8)	10*(2.7)	9 (2.0)
Capsule, hypertrophy	0	7**(2.0)	10**(3.2)	0	10**(2.0)	10**(2.8)
Capsule, inflammation	0	0	10**(2.6)	0	2 (2.0)	10**(2.6)
Lymphoid depletion	0	0	10**(3.2)	0	0	10**(2.7)
9-Month Interim Evaluation						
n	10	10	6	10	10	6
Congestion	0	10**(2.2)	5**(2.8)	3 (2.0)	10**(2.0)	5 (2.4)
Pigmentation	10 (2.5)	10 (2.3)	1** (1.0)	5 (2.6)	10*(2.4)	4 (2.0)
Capsule, hypertrophy	0	8**(1.4)	6**(2.2)	0	8**(1.5)	6**(2.2)
Capsule, inflammation	0	2 (1.5)	6**(1.7)	0	0	6**(2.0)
15-Month Interim Evaluation						
n	9	3	–[d]	8	10	–
Congestion	7 (2.0)	1 (2.0)	–	4 (2.0)	3 (2.0)	–
Pigmentation	6 (2.2)	2 (2.5)	–	5 (2.4)	7 (2.4)	–
Capsule, hypertrophy	0	2*(1.0)	–	0	9**(1.6)	–
Capsule, inflammation	0	1 (1.0)	–	0	1 (2.0)	–
2-Year Study						
n	21	27	34	22	20	34
Congestion	5 (2.2)	15*(2.1)	23**(2.0)	12 (2.2)	7 (2.0)	24 (2.1)
Pigmentation	6 (2.2)	14 (2.1)	19*(2.3)	16 (2.6)	12 (2.3)	15 (2.1)
Capsule, hypertrophy	0	15**(1.5)	34**(2.6)	0	9**(1.4)	33**(2.3)
Capsule, inflammation	0	5*(1.2)	33**(2.2)	0	0	30**(2.1)
Lymphoid depletion	1 (1.0)	0	20**(2.4)	4 (1.8)	5 (2.2)	16*(2.3)

* Significantly different ($P \leq 0.05$) from the control group by Fisher exact test
** $P \leq 0.01$
[a] Number of animals with spleen examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked.
[d] All males and females receiving 18,000 ppm died before the 15-month interim evaluation.

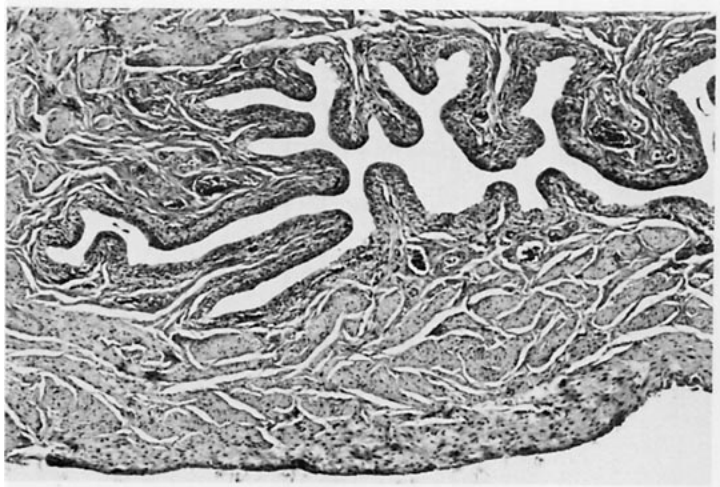


PLATE 4
Urinary Bladder: For comparison with Plate 6. A control female rat in the stop-exposure feed study of *o*-nitroanisole. H&E ×20

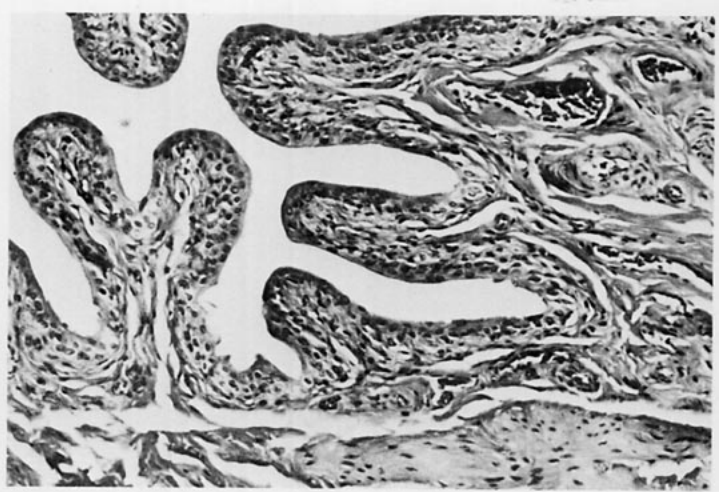


PLATE 5
Urinary Bladder: Higher magnification. Note the thickness of the transitional epithelium lining the bladder lumen and compare with Plate 7. Female control rat from the stop-exposure feed study of *o*-nitroanisole. H&E ×50

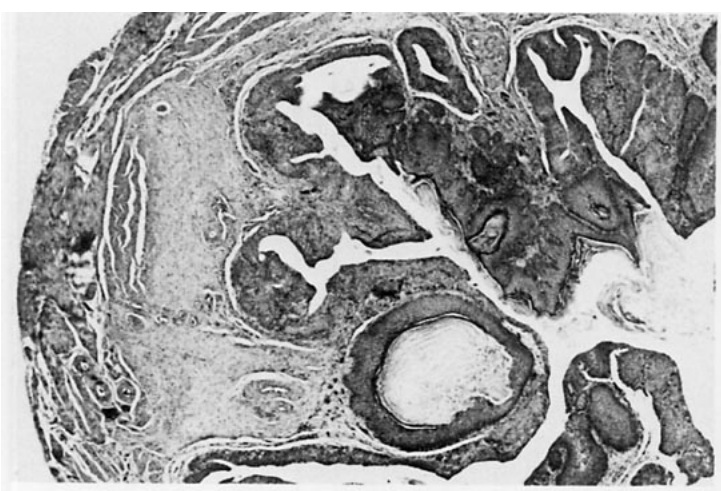


PLATE 6
Urinary Bladder: Note the diffuse hyperplasia of the transitional epithelium and compare with Plate 4. Female rat given 18,000 ppm *o*-nitroanisole at the 3-month interim evaluation of the stop-exposure feed study. H&E ×10

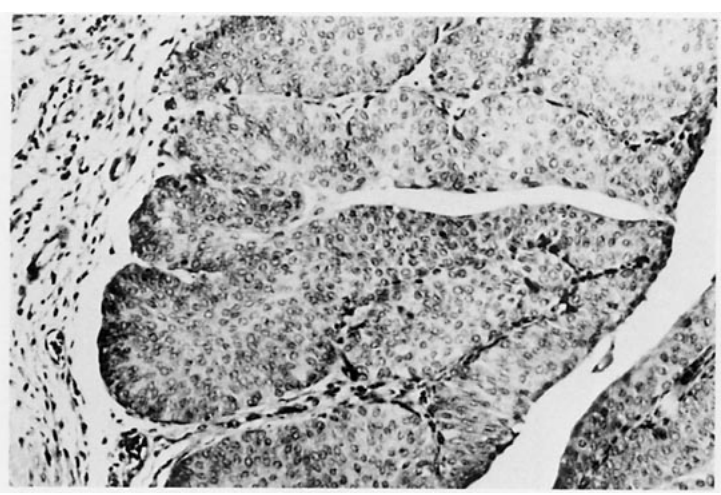


PLATE 7
Urinary Bladder: Higher magnification. The increased cellularity of the transitional epithelium (hyperplasia) causes the epithelium to form thick irregular folds. Compare with control in Plate 5. Female rat given 18,000 ppm *o*-nitroanisole at the 3-month interim of the stop-exposure feed study. H&E ×50

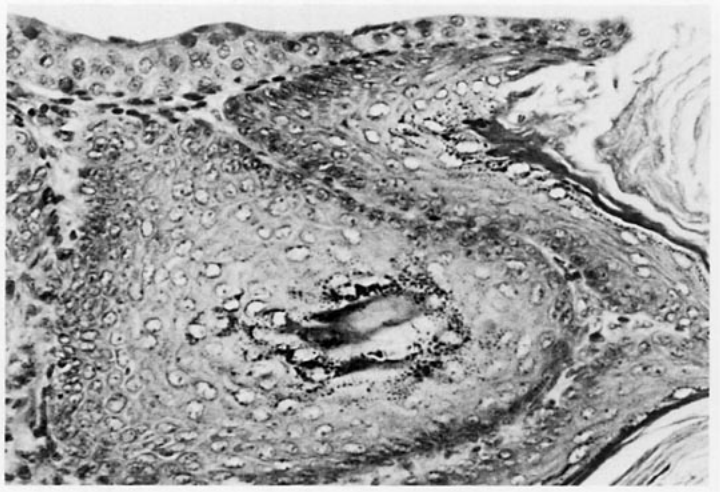


PLATE 8
Urinary Bladder: The focus of squamous metaplasia consists of well-differentiated, keratinizing, stratified squamous epithelium. Compare with normal and hyperplastic transitional epithelium in Plates 5 and 7. Female rat given 18,000 ppm *o*-nitroanisole at the 3-month interim evaluation of the stop-exposure feed study. H&E ×80

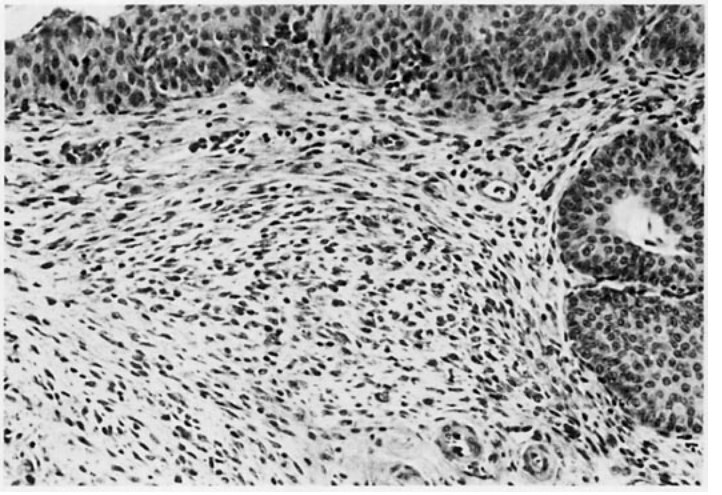


PLATE 9
Urinary Bladder: Note the proliferation of delicate fibrous connective tissue beneath the hyperplastic transitional epithelium. Male rat given 18,000 ppm *o*-nitroanisole at the 3-month interim evaluation of the stop-exposure feed study. H&E ×50

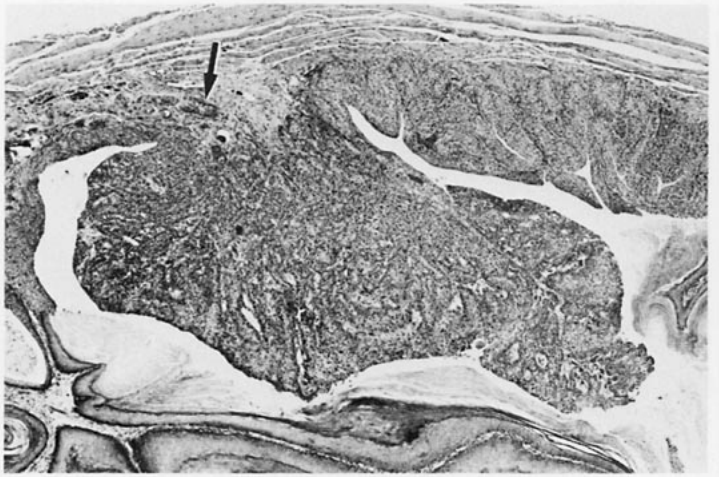


PLATE 10
Urinary Bladder: This carcinoma of the transitional epithelium is primarily exophytic but there is early invasion of the submucosa (arrow; see Plate 11). Female rat given 18,000 ppm *o*-nitroanisole at the 6-month interim evaluation of the stop-exposure feed study. H&E ×10

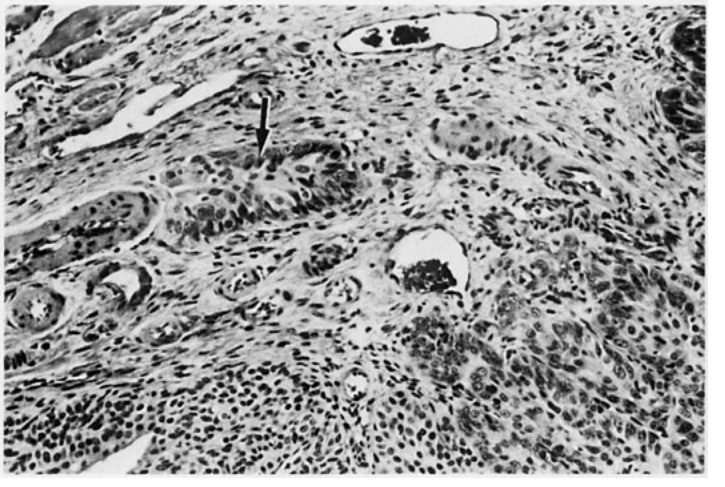


PLATE 11
Urinary Bladder: Higher magnification of Plate 10. This is the base of the carcinoma and shows anaplastic epithelial cells with clusters of cells extending into the submucosa (arrow). Female rat given 18,000 ppm *o*-nitroanisole at the 6-month interim evaluation of the stop-exposure feed study. H&E ×50

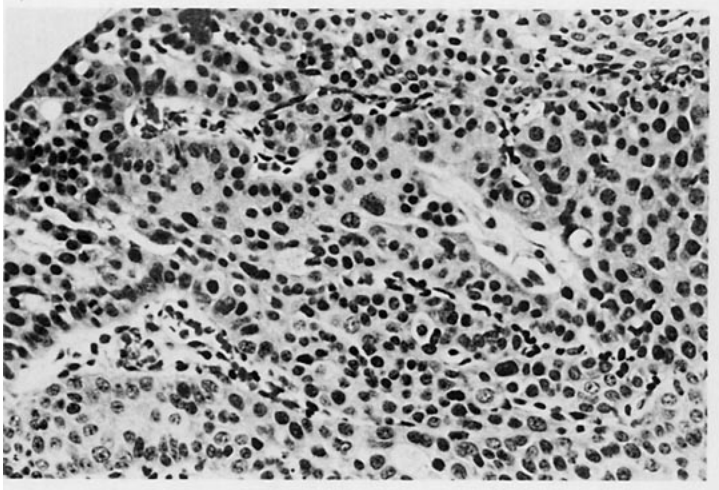


PLATE 12
Urinary Bladder: Higher magnification of Plate 10. The main body of the carcinoma consists of cords and clusters of transitional epithelial cells separated by a delicate fibrovascular stroma. There is mild pleomorphism of the neoplastic cells. Female rat given 18,000 ppm *o*-nitroanisole at the 6-month interim evaluation of the stop-exposure feed study. H&E ×80

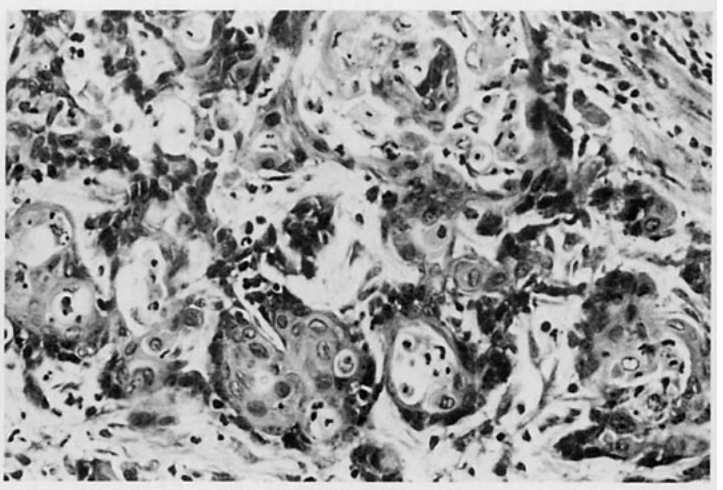


PLATE 13
Urinary Bladder: Squamous cell carcinoma with irregular cords and clusters of anaplastic squamous cells invading the bladder wall. Male rat given 18,000 ppm *o*-nitroanisole at the 9-month interim evaluation of the stop-exposure feed study. H&E ×80

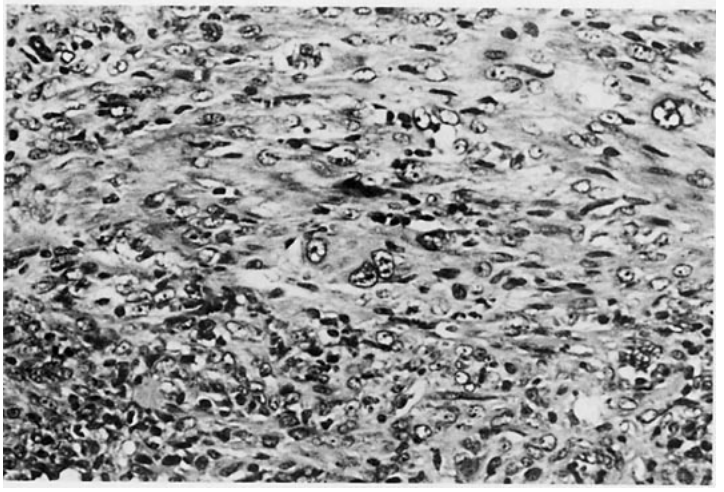


PLATE 14
Urinary Bladder: Sarcoma consisting of pleomorphic spindle cells with variable amounts of fibrillar cytoplasm and intercellular collagen. Male rat given 18,000 ppm *o*-nitroanisole at the 9-month interim evaluation of the stop-exposure feed study. H&E ×80

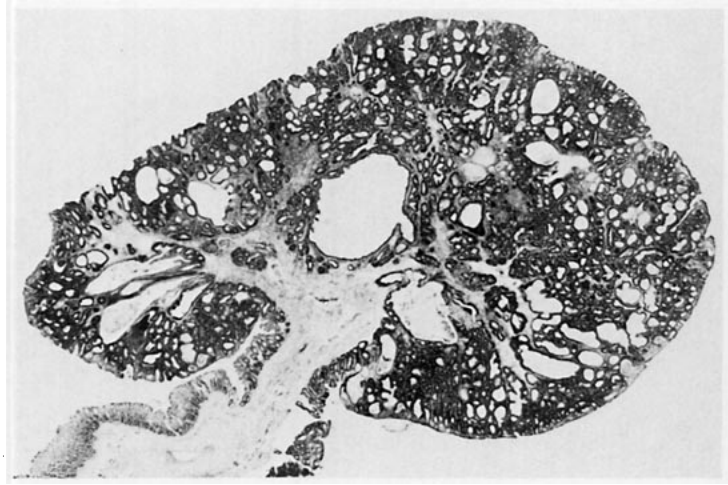


PLATE 15
Colon: Adenomatous polyp in a female rat given 18,000 ppm *o*-nitroanisole at the 9-month interim evaluation of the stop-exposure feed study. H&E ×10

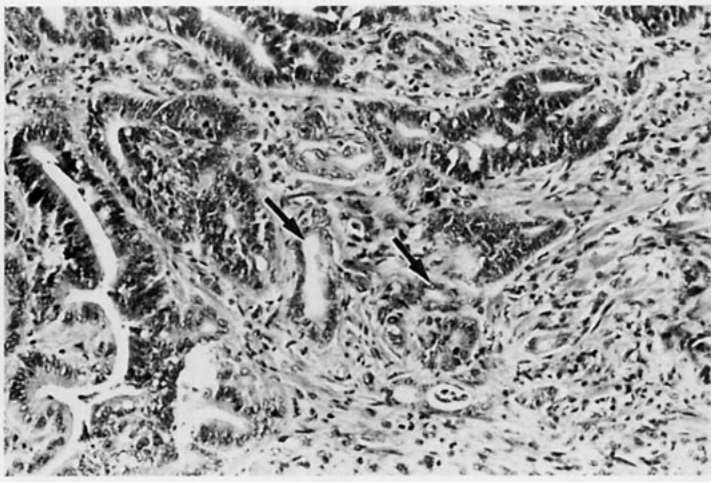


PLATE 16
Large Intestine: Carcinoma with gland-like tubules consisting of anaplastic epithelium (arrows). Male rat given 18,000 ppm *o*-nitroanisole at the 9-month interim evaluation of the stop-exposure feed study. H&E ×50

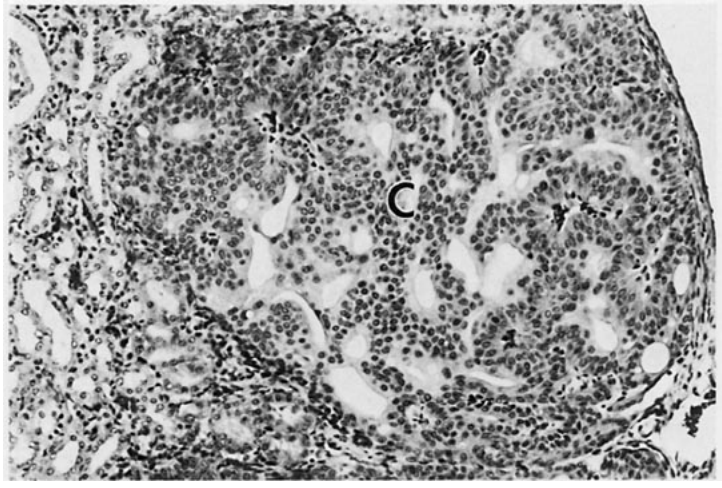


PLATE 17
Kidney: Carcinoma (C) of the pelvic urothelium (transitional epithelium) consisting of interconnecting cords of epithelial cells invading the kidney. Male rat given 18,000 ppm *o*-nitroanisole at the 9-month interim evaluation of the stop-exposure feed study. H&E ×40

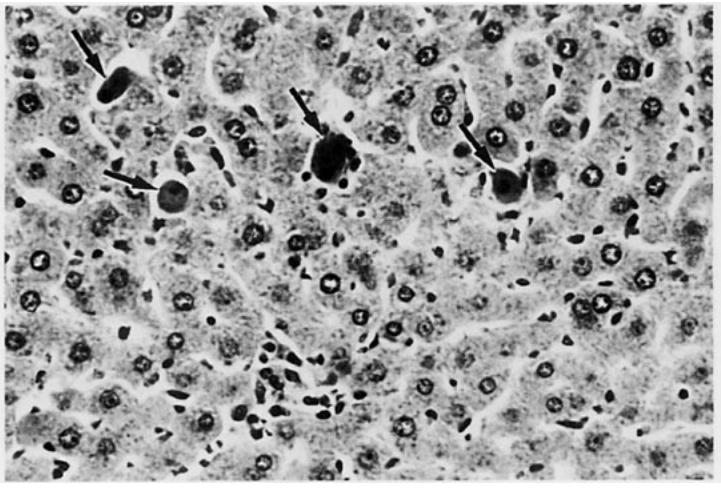


PLATE 18
Liver: Scattered necrotic hepatocytes with shrunken pyknotic nuclei and darkly stained cytoplasm (arrows). Male rat given 18,000 ppm *o*-nitroanisole at the 6-month interim evaluation of the stop-exposure feed study. H&E ×100

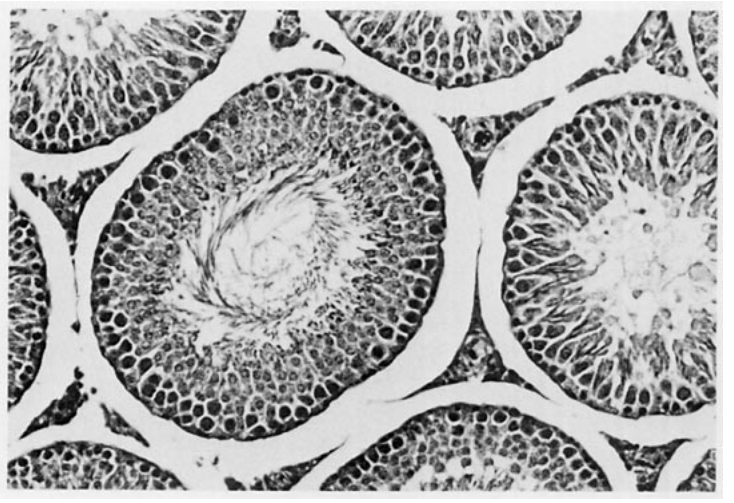


PLATE 19
Testis: For comparison with Plate 20. Control male rat in the stop-exposure feed study of *o*-nitroanisole. H&E ×50

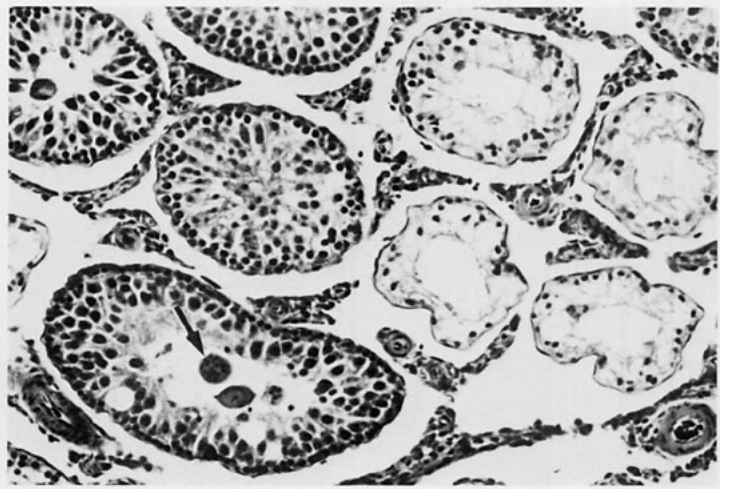


PLATE 20
Testis: Degeneration and atrophy of the seminiferous epithelium. Note the tubules containing only a few scattered sertoli cells and the degenerate multinucleate spermatids (arrows) in other tubules. Male rat given 18,000 ppm *o*-nitroanisole at the 3-month interim evaluation of the stop-exposure feed study. H&E ×50

Mice

14-Day Study

All mice survived until the end of the study (Table 21). Mean body weight gains and final mean body weights of all groups of exposed male mice were significantly lower than those of the controls. The mean body weight gain and final mean body weight of females receiving 4,000 ppm were significantly lower than those of the controls; mean body weight gains and final mean body weights of females receiving 2,000 ppm or less were similar to those of the controls. Feed consumption by males and females in the 4,000 ppm groups and females in the 2,000 ppm group was lower than that by the controls. Dietary levels of 250, 500, 1,000, 2,000, and 4,000 ppm resulted in average daily consumption levels of 25, 51, 96, 198, and 194 mg/kg for males and 36, 48, 142, 142, and 215 mg/kg for females.

At necropsy there were significant decreases in absolute brain, kidney, and liver weights of males and in absolute kidney and thymus weights of females in the 2,000 and 4,000 ppm groups (Table H8). There were significant decreases in relative kidney weights of males and the relative thymus weights of females receiving 2,000 and 4,000 ppm. In addition, there were significant increases in the relative liver weight of females and the relative heart weights of males and females receiving 4,000 ppm. These differences were primarily attributed to chemicalrelated reductions in final mean body weights; any potential direct effect of *o*-nitroanisole on these organs was masked by the more general effects associated with the lower final mean body weights. The apparent inconsistencies in absolute and relative organ weights were likely due to the disproportionate effect on adipose deposits and skeletal muscle versus the effects on glandular organs.

TABLE 21
Survival, Mean Body Weights, and Feed Consumption of Mice in the 14-Day Feed Study of *o*-Nitroanisole

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 2
Male							
0	5/5	22.4 ± 0.5	27.4 ± 0.9	5.0 ± 0.6		2.5	2.9
250	5/5	22.2 ± 0.6	24.8 ± 0.6*	2.6 ± 0.2**	91	2.2	2.7
500	5/5	23.0 ± 0.3	25.8 ± 0.4*	2.8 ± 0.2**	94	2.4	2.7
1,000	5/5	22.8 ± 0.2	25.6 ± 0.2*	2.8 ± 0.2**	93	2.1	2.6
2,000	5/5	22.4 ± 0.4	23.6 ± 0.5**	1.2 ± 0.4**	86	2.4	2.3
4,000	5/5	23.4 ± 0.7	19.0 ± 0.6**	-4.4 ± 0.2**	69	1.7	0.5
Female							
0	5/5	18.6 ± 0.2	19.2 ± 0.2	0.6 ± 0.2		1.9	2.1
250	5/5	17.6 ± 0.2	20.4 ± 0.5	2.8 ± 0.7	106	2.5	3.0
500	5/5	17.8 ± 0.4	19.0 ± 0.3	1.2 ± 0.4	99	2.1	1.5
1,000	5/5	17.6 ± 0.2	20.0 ± 0.3	2.4 ± 0.2	104	2.7	2.7
2,000	5/5	17.2 ± 0.4	18.0 ± 0.8	0.8 ± 0.7	94	2.0	0.6
4,000	5/5	18.0 ± 0.6	15.6 ± 0.9**	-2.4 ± 0.4**	81	1.2	0.7

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Number of animals surviving at 14 days/number initially in group
[b] Weights given as mean ± standard error.
[c] Feed consumption is expressed as grams/animal per day.

13-WEEK STUDY

Two males in the 200 ppm group and one male in the 600 ppm group died from wounds caused by fighting (Table 22). All other mice survived until the end of the study. The mean body weight gains and final mean body weights of male mice receiving 6,000 ppm and all exposed groups of female mice were significantly lower than those of the controls. Feed consumption by male and female mice that received 6,000 ppm was lower than that by controls, which may have been related to decreased palatability of the diet containing *o*-nitroanisole (Table 23). Dietary levels of 60, 200, 600, 2,000, and 6,000 ppm resulted in average daily consumption levels of 6, 20, 66, 180, and 540 mg/kg for males and 8, 22, 66, 200, and 540 mg/kg for females. Although male and female mice in the 6,000 ppm groups developed yellow stained fur in the perineum, there were no other clinical findings associated with chemical administration.

TABLE 22
Survival and Mean Body Weights of Mice in the 13-Week Feed Study of *o*-Nitroanisole

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	20.3 ± 0.2	31.8 ± 0.5	11.5 ± 0.6	
60	10/10	20.1 ± 0.3	30.4 ± 0.5	10.3 ± 0.4	96
200	8/10[c]	20.5 ± 0.2	29.9 ± 1.3	9.5 ± 1.2	94
600	9/10[d]	20.0 ± 0.2	29.2 ± 1.3	9.3 ± 1.3	92
2,000	10/10	20.2 ± 0.2	29.6 ± 1.3	9.4 ± 1.2	93
6,000	10/10	20.4 ± 0.3	25.5 ± 0.5**	5.1 ± 0.5**	80
Female					
0	10/10	16.9 ± 0.3	25.0 ± 0.6	8.1 ± 0.4	
60	10/10	16.5 ± 0.2	22.5 ± 0.2**	6.1 ± 0.2**	90
200	10/10	16.4 ± 0.3	23.5 ± 0.5**	7.1 ± 0.4**	94
600	10/10	16.4 ± 0.2	23.1 ± 0.4**	6.6 ± 0.4**	92
2,000	10/10	16.6 ± 0.2	23.4 ± 0.2**	6.8 ± 0.2**	94
6,000	10/10	16.3 ± 0.3	20.1 ± 0.6**	3.7 ± 0.5**	80

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Week of death: 4, 13
[d] Week of death: 2

TABLE 23
Feed Consumption by Mice in the 13-Week Feed Study of *o*-Nitroanisole[a]

Week of Study	0 ppm	60 ppm	200 ppm	600 ppm	2,000 ppm	6,000 ppm
Male						
1	2.0	2.2	2.5	1.9	2.2	1.2
2	2.3	2.4	3.2	2.5	2.5	1.1
3	3.0	2.5	3.6	3.5	3.0	1.6
4	2.7	3.5	2.5	3.3	2.3	2.2
5	2.5	2.7	3.4	3.0	3.0	2.2
6	2.7	2.6	3.0	2.9	2.6	2.1
7	3.0	2.7	3.1	3.8	3.3	2.5
8	3.2	3.2	2.4	3.4	2.9	2.6
9	3.2	3.0	3.1	3.2	3.1	2.6
10	3.0	3.7	2.7	3.6	3.6	2.5
11	3.6	3.2	3.8	3.4	3.4	2.6
12	3.3	3.6	2.6	3.4	3.1	2.3
13	3.6	3.3	3.8	3.4	3.2	2.5
Female						
1	1.4	2.2	2.1	2.1	1.8	0.8
2	2.1	2.4	2.4	1.8	2.0	1.3
3	2.7	2.6	3.1	3.1	2.1	1.0
4	2.3	2.7	2.2	2.5	2.4	1.7
5	2.0	2.4	2.4	2.6	2.2	1.9
6	2.9	2.3	2.8	2.4	2.2	1.4
7	2.5	3.3	2.0	2.6	2.5	2.4
8	2.8	2.5	2.4	2.9	1.9	2.0
9	3.3	3.2	2.8	2.5	2.5	2.0
10	3.2	3.1	2.8	2.6	2.7	1.5
11	3.3	3.6	2.9	3.1	2.3	2.1
12	3.2	3.5	2.8	2.7	2.5	2.2
13	3.6	3.0	2.8	2.9	2.5	2.0

[a] Feed consumption is expressed as grams/animal per day.

Small but significant decreases in hemoglobin concentrations and hematocrit values were seen primarily in male and female mice receiving 2,000 and 6,000 ppm; a significant decrease in erythrocyte count was observed only in females that received 6,000 ppm (Table I6). Lower values were observed for hematocrit and hemoglobin in males from the 600 ppm group as well. The methemoglobin concentration was significantly increased only in males receiving 6,000 ppm.

The relative liver weights of females receiving 600 ppm and males and females receiving 2,000 and 6,000 ppm were significantly greater than those of the controls (Table H9). In addition, the absolute liver weights of females that received 600 ppm or more were also significantly increased, although those of males were not. These increases were attributed to the ingestion of *o*-nitroanisole. Differences in the absolute or relative weights of brain, heart, kidney, lung, spleen, testis, or thymus occurred in various exposed groups of males and females and were attributed primarily to the lower final mean body weights of the 6,000 ppm groups and were not considered biologically significant.

Liver: Hepatocyte hypertrophy associated with the ingestion of *o*-nitroanisole was seen only in male mice. The lesion was observed in mice receiving 200 ppm or more and increased in severity with increasing exposure levels (0 ppm, 0/10; 60 ppm, 0/10; 200 ppm, 3/9 (2.0); 600 ppm, 9/10 (2.8); 2,000 ppm, 10/10 (3.7); 6,000 ppm, 10/10 (3.8)). The lesion occurred primarily in the centrilobular and midzonal regions of the liver lobules. There were occasional scattered cells exhibiting cytoplasmic vacuolation or necrosis, particularly at higher exposure levels.

Dose selection rationale: Lower final mean body weights, slightly reduced feed consumption, increased liver weights, and slight differences in several hematologic parameters attributable to *o*-nitroanisole were observed in male and female mice that received 6,000 ppm. In addition, a microscopic liver lesion was observed in all male mice receiving 2,000 and 6,000 ppm and was attributed to *o*-nitroanisole administration. However, these toxic responses were rather mild and at lower exposure levels the effects became marginal to nonexistent. It was considered unlikely that the toxicity which occurred at 6,000 ppm would become life threatening, and by the end of the 13-week study, feed consumption by males receiving 6,000 ppm was increasing and approaching that by the controls. This suggested that the animals might eventually recover from their initial reaction to the 6,000 ppm concentration. Therefore, 6,000 ppm was selected as the high exposure level for the 2-year study in mice. To provide a broad range for dose response, 666 and 2,000 ppm were selected for the remaining exposure levels.

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female mice are shown in Table 24 and in the Kaplan-Meier curves in Figure 6. Survival of groups of male mice receiving 666, 2,000, and 6,000 ppm was similar to that of the controls. Although survival of females receiving 666 ppm was significantly lower than that of the controls, that of the 6,000 ppm group was slightly greater than that of controls. Thus, the ingestion of *o*-nitroanisole at dietary concentrations up to 6,000 ppm had no effect on the survival of male or female mice in the 2-year study.

Body Weights, Feed Consumption, and Clinical Findings

The ingestion of *o*-nitroanisole was associated with a dose-related reduction in mean body weight. The mean body weights of male and female mice receiving 2,000 and 6,000 ppm were lower than those of the controls throughout the study (Tables 25 and 26, and Figure 7). The mean body weights of the 6,000 ppm groups were within 20% of controls until week 17 for males and week 12 for females. Thereafter, the difference in mean body weight between the 6,000 ppm groups and the controls continued to increase. At the end of the study the final mean body weight of males receiving 6,000 ppm was 33% lower than that of the controls and the final mean body weight of females receiving 6,000 ppm was 43% lower than that of the controls. In the 2,000 ppm groups, the final mean body weight of males was 11% lower than that of controls and the final mean body weight of females was 18% lower than that of controls. The final mean body weights of male and female mice receiving 666 ppm were within 10% of the controls. Feed consumption by high-dose male and female mice was lower than that by the controls throughout the study (Tables K5 and K6). Dietary levels of 666, 2,000 and 6,000 ppm resulted in average daily consumption levels of 80, 240, and 830 mg/kg for males and 100, 320, and 1,200 mg/kg for females. Discolored urine in male and female mice was the only clinical finding attributable to *o*-nitroanisole administration.

Pathology and Statistical Analyses of Results

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

Liver: The absolute liver weight of males that received 2,000 ppm and the relative liver weights of all groups of exposed male mice were significantly greater than those of the controls at the 15-month interim evaluation (Table H10). The absence of a significant increase in absolute liver weight in males receiving 6,000 ppm may have been related to the significantly lower mean body weight of this group. Relative liver weights of females in the 2,000 and 6,000 ppm groups were also significantly greater than those of the controls, although the absolute liver weight of females that received 6,000 ppm was significantly lower than that of the controls. This inconsistency is also primarily due to the lower mean body weight of females receiving 6,000 ppm.

The increased liver weights at the 15-month interim evaluation were associated with generalized centrilobular cytologic alteration, which was also seen in exposed rats in the 2-year study (Tables 27, C5, and D5). The lesion was more frequent and severe in exposed males than in exposed females. The cytologic alteration consisted of enlargement of the centrilobular hepatocytes (hypertrophy), enlargement of the nuclei, and increased eosinophilic staining of the cytoplasm. Focal necrosis was seen in a number of males receiving 2,000 and 6,000 ppm at the 15-month interim evaluation, but not in females, controls, or 666 ppm males. In the 2-year study, the incidence of focal necrosis was significantly increased in all exposed male groups. The necrosis occurred primarily in the centrilobular or midzonal regions of the liver lobules and was characterized by infrequent, scattered individual cells or small foci of cells exhibiting nuclear pyknosis or karyorrhexis. These changes were often accompanied by small erythrocyte-filled spaces, diagnosed as hemorrhage, and individual Kupffer cells filled with golden brown or greenish brown pigment.

TABLE 24
Survival of Mice in the 2-Year Feed Study of o-Nitroanisole

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	9	10
Natural deaths	1	2	3	3
Moribund kills	14	5	8	7
Missexed[a]	0	0	1	0
Animals surviving to study termination	35	43	39	40
Percent probability of survival at end of study[b]	70	86	78	80
Mean survival (days)[c]	673	676	680	661
Survival analysis[d]	P=0.836N	P=0.095N	P=0.543N	P=0.435N
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Natural deaths	5	8	7	0
Moribund kills	7	16	10	5
Animals surviving to study termination	38	26	33	45
Percent probability of survival at end of study	77	53	66	91
Mean survival (days)	654	647	655	670
Survival analysis	P=0.005N	P=0.028	P=0.368	P=0.110N

[a] Censored from survival analyses
[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 dosed columns. A negative trend or lower mortality in a dose group is indicated by N.

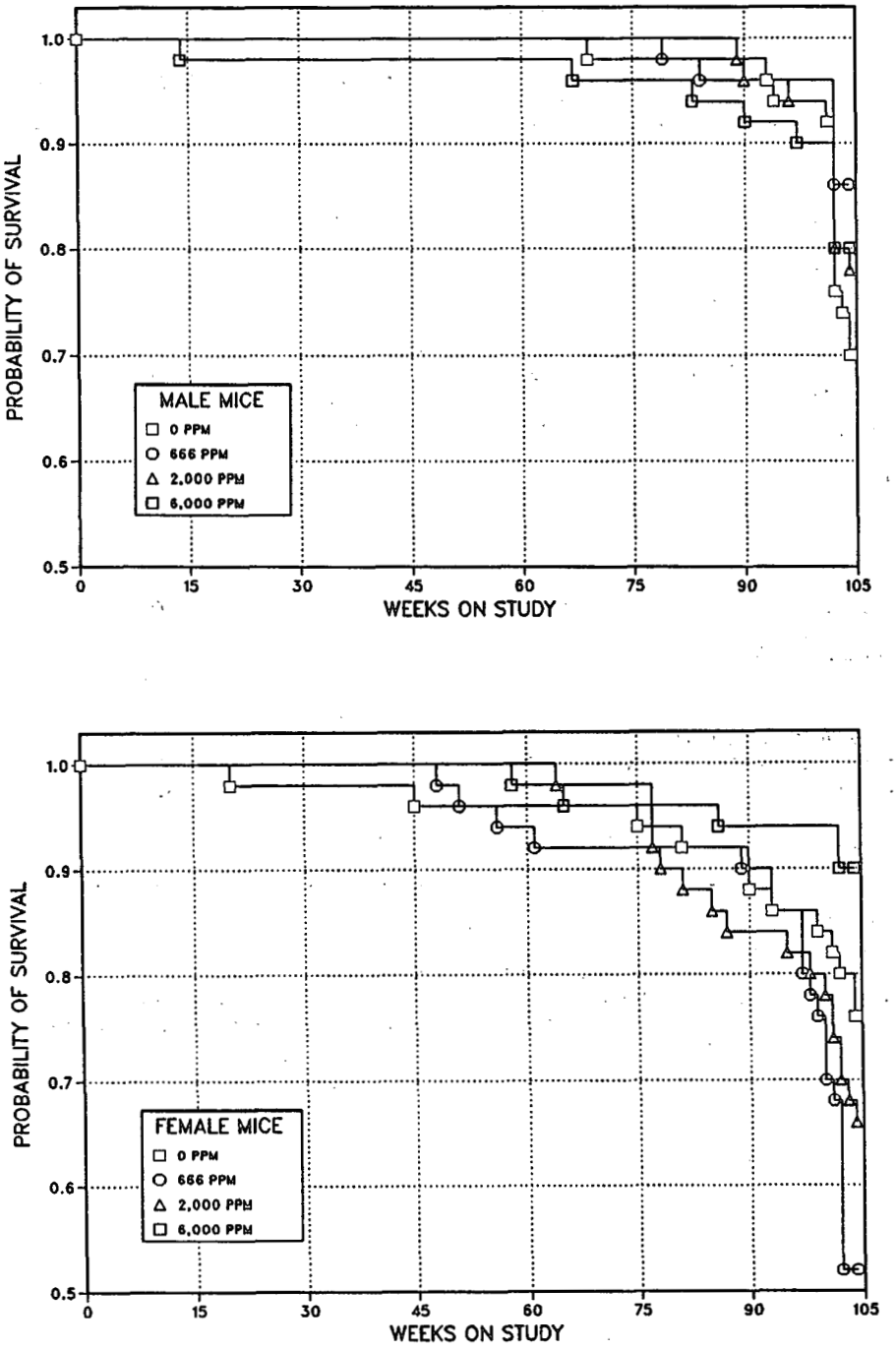


FIGURE 6
Kaplan-Meier Survival Curves for Male and Female Mice Administered *o*-Nitroanisole in Feed for 2 Years

TABLE 25
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	666 ppm Av. Wt. (g)	666 ppm Wt. (% of controls)	666 ppm No. of Survivors	2,000 ppm Av. Wt. (g)	2,000 ppm Wt. (% of controls)	2,000 ppm No. of Survivors	6,000 ppm Av. Wt. (g)	6,000 ppm Wt. (% of controls)	6,000 ppm No. of Survivors
1	23.2	60	23.0	99	60	22.9	99	60	22.0	95	60
2	25.1	60	24.7	98	60	24.7	98	60	21.2	85	60
3	25.9	60	25.7	99	60	25.6	99	60	21.7	84	60
4	27.0	60	26.8	99	60	26.7	99	60	23.0	85	60
5	27.6	60	27.4	99	60	27.3	99	60	23.4	85	60
6	29.1	60	28.7	99	60	28.3	97	60	24.8	85	60
7	29.8	60	29.4	99	60	29.1	98	60	25.4	85	60
8	30.6	60	30.0	98	60	29.7	97	60	25.8	84	60
9	30.9	60	30.7	99	60	30.2	98	60	26.1	85	60
10	31.1	60	30.7	99	60	30.6	98	60	25.9	83	60
11	31.5	60	31.3	99	60	31.0	98	60	26.5	84	60
12	32.6	60	32.3	99	60	31.8	98	60	27.1	83	60
13	32.7	60	32.5	99	60	31.9	98	60	27.3	84	60
17	35.1	60	34.5	98	60	34.0	97	60	27.6	79	59
21	37.8	60	37.3	99	60	36.5	97	60	28.0	74	59
25	39.6	60	38.4	97	60	37.7	95	60	28.9	73	59
29	41.6	60	40.3	97	60	39.5	95	60	29.1	70	59
33	43.7	60	42.3	97	60	41.7	95	60	30.1	69	59
37	44.5	60	43.2	97	60	42.4	95	60	30.1	68	59
41	45.0	60	44.2	98	60	42.7	95	60	30.4	68	59
45	45.0	60	43.8	97	60	43.1	96	60	30.0	67	59
49	45.7	60	44.1	97	60	43.7	96	60	29.9	65	59
53	46.7	60	45.2	97	60	44.7	96	60	30.5	65	59
57	46.9	60	45.9	98	60	45.3	97	60	31.0	66	59
61	47.8	60	46.5	97	60	45.6	95	60	30.9	65	59
65	48.0	60	47.6	99	60	46.6	97	60	31.5	66	59
69[a]	49.2	50	48.0	98	50	47.2	96	50	31.7	64	48
73	49.0	49	48.2	98	50	47.2	96	50	31.8	65	48
77	48.7	49	48.3	99	50	47.4	97	50	31.9	66	48
81	48.9	49	47.9	98	49	46.9	96	50	31.8	65	48
85	48.4	49	47.4	98	48	46.3	96	50	31.8	66	47
89	47.9	49	47.6	99	48	45.8	96	49	31.8	66	47
93	47.7	49	46.5	98	48	44.8	94	48	31.7	67	46
97	48.0	47	46.6	97	48	43.8	91	47	31.6	66	45
101	47.6	46	46.1	97	48	42.2	89	47	32.0	67	45
Terminal sacrifice		35			43			39			40
Mean for weeks											
1-13	29.0		28.7	99		28.4	98		24.6	85	
14-52	42.0		40.9	97		40.1	95		29.3	70	
53-101	48.1		47.1	98		45.7	95		31.5	65	

[a] Interim evaluation occurred during week 65.

TABLE 26
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole

Weeks on Study	0 ppm		666 ppm			2,000 ppm			6,000 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	18.0	60	18.6	103	60	17.9	99	60	17.2	96	60
2	20.3	60	20.8	103	60	19.9	98	60	18.1	89	60
3	21.7	60	21.9	101	60	21.1	97	60	18.3	84	60
4	23.0	60	23.2	101	60	22.3	97	60	19.2	84	60
5	23.6	60	23.9	101	60	23.0	98	60	19.7	84	60
6	24.4	60	25.1	103	60	24.1	99	60	21.0	86	60
7	25.2	60	25.2	100	60	24.6	98	60	21.2	84	60
8	25.6	60	25.8	101	60	24.6	96	60	21.2	83	60
9	25.7	60	26.3	102	60	25.1	98	60	21.6	84	60
10	26.3	60	27.0	103	60	25.8	98	60	22.2	84	60
11	26.7	60	27.1	102	60	26.0	97	60	21.8	82	60
12	27.1	60	27.5	102	60	26.2	97	60	21.4	79	60
13	27.7	60	28.3	102	60	26.3	95	60	22.7	82	60
17	29.7	60	30.2	102	60	27.9	94	60	22.2	75	60
21	32.7	59	33.3	102	60	30.2	92	60	23.4	72	60
25	34.1	59	34.7	102	60	30.9	91	60	23.4	69	60
29	36.7	59	37.3	102	60	32.9	90	60	24.4	67	60
33	38.8	59	39.0	101	60	34.8	90	60	24.7	64	60
37	39.0	59	39.9	102	60	35.6	91	60	24.5	63	60
41	40.4	59[a]	41.2	102	60	35.9	89	60	25.0	62	60
45	40.9	59	41.1	101	60	36.3	89	60	25.0	61	60
49	42.5	58	42.2	99	59	37.4	88	60	24.7	58	60
53	43.7	58	43.5	100	58	37.9	87	60	25.1	57	60
57	44.9	58	44.6	99	57	39.0	87	60	25.4	57	60
61	47.4	58	46.3	98	57	40.3	85	60	25.4	54	59
65	48.1	58	47.7	99	56	41.2	86	59	25.6	53	59
69[b]	49.6	48	47.4	96	46	42.1	85	49	26.1	53	48
73	49.6	48	47.1	95	46	42.1	85	49	26.1	53	48
77	51.0	47	48.0	94	46	42.2	83	49	26.7	52	48
81	51.1	47	47.9	94	46	42.3	83	45	26.6	52	48
85	51.7	46	48.2	93	46	42.1	81	44	26.7	52	48
89	51.1	46	48.0	94	46	42.7	84	42	27.1	53	47
93	49.8	44	46.3	93	44	41.7	84	42	26.7	54	47
97	49.6	43	45.6	92	42	41.7	84	41	27.0	54	47
101	48.0	42	44.6	93	35	39.2	82	37	27.2	57	47
Terminal sacrifice		38			26			33			45
Mean for weeks											
1-13	24.3		24.7	102		23.6	97		20.4	84	
14-52	37.2		37.7	101		33.5	90		24.1	65	
53-101	48.9		46.6	95		41.1	84		26.3	54	

[a] The number of animals weighed for this week is fewer than the number of animals surviving.
[b] Interim evaluation occurred during week 65.

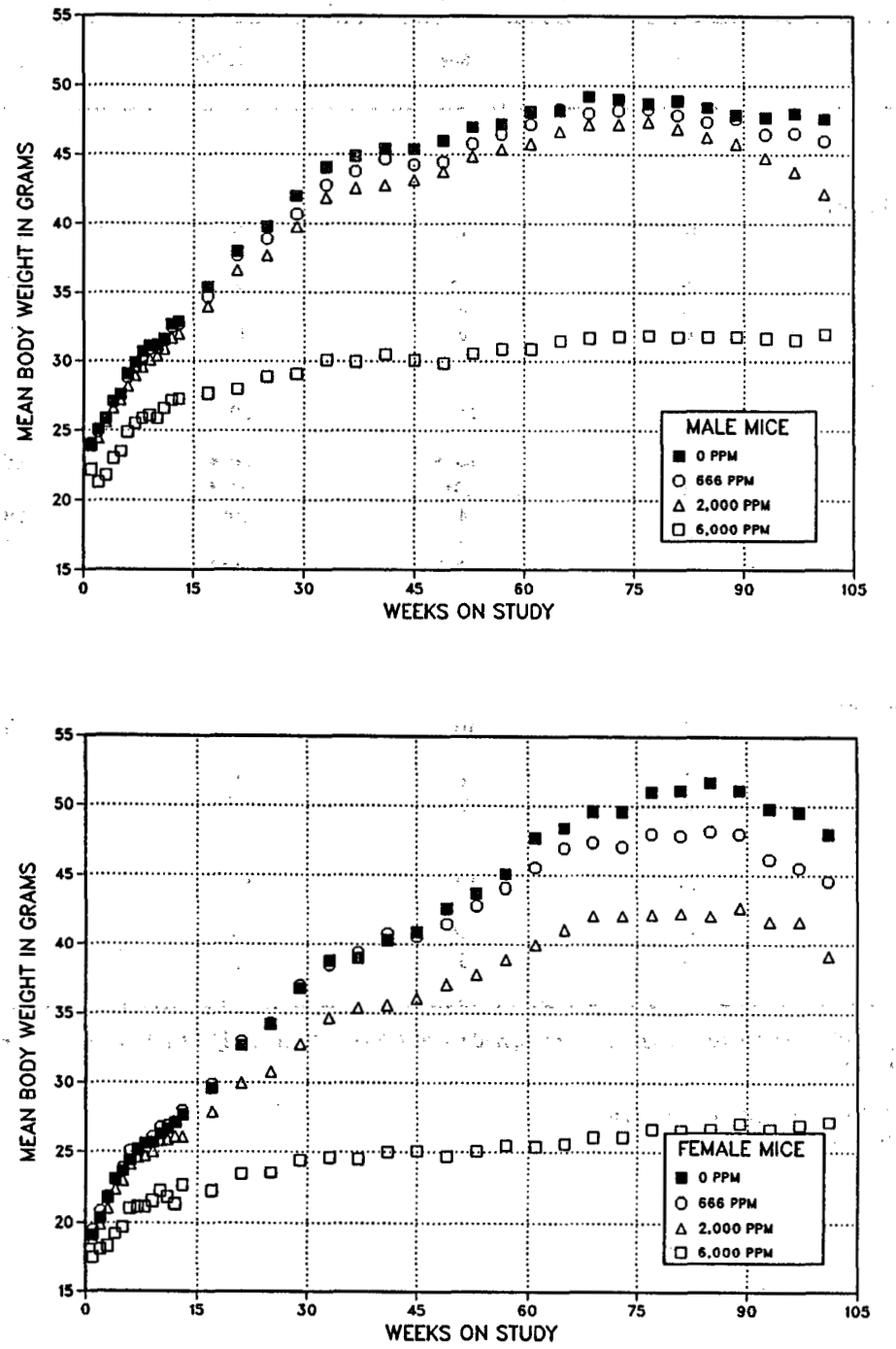


FIGURE 7
Growth Curves for Male and Female Mice Administered *o*-Nitroanisole in Feed for 2 Years

TABLE 27
Incidences of Selected Liver Lesions in Mice in the 2-Year Feed Study of *o*-Nitroanisole

Dose (ppm)	0	666	2,000	6,000
Male				
15-Month Interim Evaluation				
n[a]	10	10	9	10
Cytologic alteration[b]	0	7°°	9°°	10°°
Necrosis	0	0	2	4
Eosinophilic focus	0	0	0	1
2-Year Study				
n	50	50	50	50
Cytologic alteration	0	44°°	49°°	49°°
Necrosis	3	13°	27°°	34°°
Hemorrhage	1	4	20°°	28°°
Kupffer cell pigmentation	0	0	3	16°°
Eosinophilic focus	1	15°°	16°°	13°°
Female				
15-Month Interim Evaluation				
n	10	10	10	10
Cytologic alteration	0	1	9°°	9°°
Eosinophilic focus	0	1	0	1
2-Year Study				
n	50	50	50	50
Cytologic alteration	0	9°°	14°°	41°°
Eosinophilic focus	11	6	21°	16

° Significantly different (P≤0.05) from the control group by the logistic regression test (2-year study) or the Fisher exact test (15-month interim evaluations)
°° P≤0.01
[a] Number of animals with liver examined microscopically
[b] Number of animals with lesion

At the 15-month interim evaluation, eosinophilic foci occurred in one male and one female that received 6,000 ppm and one female that received 666 ppm (Table 27). In the 2-year study, however, the incidences of eosinophilic foci were significantly increased in all exposed male groups. In females, eosinophilic foci occurred more frequently in the 2,000 and 6,000 ppm groups, but only the incidence in the 2,000 ppm group was significantly increased.

Hepatocellular adenomas or carcinomas also occurred in a few mice at the 15-month interim evaluation (Tables 28, C1, and D1). In the 2-year study, hepatocellular adenomas were significantly increased in all exposed male groups, although the incidence of adenoma in males receiving 6,000 ppm was lower than that in males receiving 2,000 ppm (Tables 28 and C3). Hepatoblastomas, rare morphological variants of hepatocellular carcinoma, occurred in all groups of exposed male mice, but not in the controls. Thus, the incidences of hepatocellular neoplasms (hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma) were significantly increased in the 2,000 and 6,000 ppm groups (Table C3). The incidences of hepatocellular adenoma or hepatocellular adenoma or carcinoma (combined) were significantly increased in females that received 2,000 ppm (Table D3).

Basophilic, eosinophilic, mixed cell, and clear cell foci are considered preneoplastic lesions. Foci, hepatocellular adenoma, and hepatocellular carcinoma constitute a morphological continuum. The foci were circumscribed lesions generally consisting of enlarged hepatocytes with either basophilic, eosinophilic, clear cytoplasm, or a mixture of cells with different staining properties. There was generally little or no compression of surrounding parenchyma and the hepatic cords of the lesion blended with those at the periphery. Hepatocellular adenomas were larger and usually exhibited greater distortion or alteration of hepatic architecture with loss of normal lobular structure. Hepatocellular carcinomas exhibited heterogeneous growth patterns with hepatic trabeculae four or more cell layers thick.

Hepatoblastomas were a morphological variant of hepatocellular carcinomas with typical small undifferentiated cells containing hyperchromatic nuclei and scant basophilic cytoplasm. These primitive appearing cells were usually within a larger neoplasm consisting primarily of neoplastic hepatocytes similar to those found in adenomas or carcinomas.

Nose: Several inflammatory and degenerative lesions of the nasal mucosa occurred more frequently in exposed male and female mice than in controls at the 15-month interim evaluation and in the 2-year study (Tables C5 and D5). In the 2-year study, the incidences of exudate, dilatation, and hyperplasia of the septal and Bowman's glands, hyaline degeneration of the mucosal epithelium, and respiratory metaplasia of the olfactory epithelium were significantly increased in females that received 2,000 and 6,000 ppm and, with the exception of hyaline degeneration, in males that received 6,000 ppm (Table 29). The inflammatory exudate consisted of mucus, degenerating neutrophils, and cellular debris on the mucosal surface or within the lumens of the septal glands and Bowman's glands. The lumens of the glands were often dilated and the glandular epithelial cells were enlarged and prominent. The hyaline degeneration was characterized by the accumulation of large hyaline droplets in secretory cells of the respiratory epithelium and olfactory epithelium, particularly near the junction of these two epithelial types. The respiratory metaplasia of the olfactory epithelium was multifocal in distribution and often located on the dorsal wall of the dorsal meatus and posterior medial aspects of the nasoturbinates. In the affected areas the specialized olfactory epithelium was replaced by ciliated columnar epithelium.

Lung: Focal proliferation of the bronchiolar epithelium was observed in exposed mice, particularly males, but not in controls (males: 0 ppm, 0/50; 666 ppm, 2/50; 2,000 ppm, 13/50; 6,000 ppm, 14/50; females: 0/50; 3/50; 5/50; 4/50; Tables C5 and D5). The lesion was characterized by subtle extension of the cuboidal bronchiolar epithelium into the adjacent alveoli. Usually only one or a few bronchioles in the lung sections were affected.

Kidney: The relative kidney weights of all exposed males and of females receiving 6,000 ppm were significantly greater than those of the controls at the 15-month interim evaluation (Table H10). Although absolute kidney weights of males receiving 666 and 2,000 ppm were slightly greater than the controls, that of males receiving 6,000 ppm was significantly lower than that of controls. The increases in relative kidney weights of the 666 and 2,000 ppm males suggest a direct chemical-related effect, but the

TABLE 28
Incidences of Liver Neoplasms in Mice in the 2-Year Feed Study of *o*-Nitroanisole

Dose (ppm)	0	666	2,000	6,000
Male				
15-Month Interim Evaluation				
Hepatocellular Adenoma				
Overall rate[a]	2/10	0/10	0/9	1/10
Hepatocellular Carcinoma				
Overall rate	0/10	1/10	0/9	0/10
Hepatoblastoma				
Overall rate	0/10	0/10	0/9	0/10
2-Year Study				
Hepatocellular Adenoma				
Overall rate	14/50 (28%)	26/50 (52%)	41/50 (82%)	29/50 (58%)
Adjusted rate[b]	36.3%	56.3%	89.0%	64.4%
Terminal rate[c]	11/35 (31%)	23/43 (53%)	34/39 (87%)	24/40 (60%)
First incidence (days)	709	549	617	673
Logistic regression test[d]	P=0.012	P=0.014	P<0.001	P=0.001
Hepatocellular Carcinoma				
Overall rate	7/50 (14%)	12/50 (24%)	11/50 (22%)	7/50 (14%)
Hepatoblastoma				
Overall rate	0/50 (0%)	3/50 (6%)	17/50 (34%)	9/50 (18%)
Adjusted rate	0.0%	6.4%	37.1%	21.3%
Terminal rate	0/35 (0%)	1/43 (2%)	11/39 (28%)	7/40 (18%)
First incidence (days)	–[e]	582	617	709
Logistic regression test	P=0.016	P=0.093	P<0.001	P=0.002
Hepatocellular Adenoma, Carcinoma, or Hepatoblastoma[f]				
Overall rate	21/50 (42%)	33/50 (66%)	46/50 (92%)	34/50 (68%)
Adjusted rate	49.0%	66.0%	93.8%	75.5%
Terminal rate	14/35 (40%)	26/43 (60%)	36/39 (92%)	29/40 (73%)
First incidence (days)	647	549	617	673
Logistic regression test	P=0.030	P=0.013	P<0.001	P=0.005

(continued)

TABLE 28
Incidences of Liver Neoplasms in Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

Dose (ppm)	0	666	2,000	6,000
Female				
15-Month Interim Evaluation				
Hepatocellular Adenoma				
Overall rate	0/10	1/10	2/10	0/10
Hepatocellular Carcinoma				
Overall rate	0/10	0/10	0/10	0/10
Hepatoblastoma				
Overall rate	0/10	0/10	0/10	0/10
2-Year Study				
Hepatocellular Adenoma				
Overall rate	14/50 (28%)	20/50 (40%)	36/50 (72%)	18/50 (36%)
Adjusted rate	36.8%	60.9%	83.6%	39.1%
Terminal rate	14/38 (37%)	14/26 (54%)	26/33 (79%)	17/45 (38%)
First incidence (days)	728 (T)	619	546	710
Logistic regression test	P=0.450N	P=0.080	P<0.001	P=0.412
Hepatocellular Carcinoma				
Overall rate	5/50 (10%)	2/50 (4%)	8/50 (16%)	3/50 (6%)
Hepatoblastoma				
Overall rates	1/50 (2%)	1/50 (2%)	2/50 (4%)	0/50 (0%)
Hepatocellular Adenoma, Carcinoma, or Hepatoblastoma[g]				
Overall rate	17/50 (34%)	22/50 (44%)	37/50 (74%)	20/50 (40%)
Adjusted rate	43.5%	63.4%	85.9%	43.5%
Terminal rate	16/38 (42%)	14/26 (54%)	27/33 (82%)	19/45 (42%)
First incidence (days)	693	619	546	710
Logistic regression test	P=0.388N	P=0.124	P<0.001	P=0.487

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined microscopically
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard lesions in animals dying prior to terminal kill as nonfatal. A negative trend or a lower incidence in a dose group is indicated by N.
[e] Not applicable; no neoplasms in animal group
[f] 2-Year historical incidence for control groups in NTP feed study (mean ± standard deviation): 249/865 (28.8% ± 16.3%); range 0%-58%
[g] Historical incidence: 98/863 (11.4% ± 7.7%); range 0%-34%

TABLE 29
Selected Nasal Lesions of Mice in the 2-Year Feed Study of *o*-Nitroanisole

Dose (ppm)	0	666	2,000	6,000
Male				
15-Month Interim Evaluation				
n[a]	10	0[b]	2	10
Exudate[c]	0		0	1
Glandular dilatation	2		2	10°
Glandular hyperplasia	0		0	10°°
Hyaline degeneration	0		0	0
Olfactory epithelium metaplasia	0		0	10°°
2-Year Study				
n	50	50	50	50
Exudate	4	4	6	49°°
Glandular dilatation	3	6	12°	49°°
Glandular hyperplasia	1	2	12°°	49°°
Hyaline degeneration	0	0	0	0
Olfactory epithelium metaplasia	0	0	7°°	46°°
Female				
15-Month Interim Evaluation				
n	10	5	10	10
Exudate	0	0	0	3
Glandular dilatation	1	0	9°°	10°°
Glandular hyperplasia	0	0	6°	10°°
Hyaline degeneration	7	5	6	10
Olfactory epithelium metaplasia	0	0	7°°	10°°
2-Year Study				
n	50	50	50	50
Exudate	6	5	27°°	49°°
Glandular dilatation	9	12	36°°	49°°
Glandular hyperplasia	2	4	34°°	50°°
Hyaline degeneration	8	7	12	45°°
Olfactory epithelium metaplasia	1	1	20°°	49°°

° Significantly different ($P \leq 0.05$) from the control group by logistic regression (2-year study) or Fisher exact text (15-month interim evaluations)
°° $P \leq 0.01$
[a] Number of animals with nose examined microscopically
[b] Nose not examined in this dose group
[c] Number of animals with lesion

kidney weight differences in the 6,000 ppm groups are largely attributable to the significantly lower mean body weights.

There were no differences in the incidences of kidney lesions between control and female mice receiving 6,000 ppm at the 15-month interim evaluation (Tables C5 and D5). In male mice, however, renal tubule regeneration occurred less frequently in the 6,000 ppm group than in the controls. In the 2-year study, the incidences of renal tubule regeneration in females that received 2,000 ppm and males and females that received 6,000 ppm were significantly decreased (Table 30). Moreover, the average severity of the lesion was also lower in males receiving 6,000 ppm than in controls, but not substantially lower in exposed females. Focal renal tubule regeneration is the most overt histologic manifestation of chronic renal disease in aging mice and consists of focal collections of tubules with epithelium having basophilic cytoplasm and enlarged vesicular nuclei. The incidence of lymphoid hyperplasia in males and females that received 6,000 ppm was also significantly decreased. There was also a significantly decreased incidence of focal mineralization in females receiving 6,000 ppm.

Pituitary gland: An adenoma of the pars distalis was seen in one control female and a carcinoma was seen in one female that received 2,000 ppm at the 15-month interim evaluation (Table D1). In the 2-year study, however, there was a significantly decreased incidence of pars distalis adenomas in females receiving 6,000 ppm and a corresponding decreased incidence of focal hyperplasia (adenoma: 7/49, 6/47, 8/48, 0/48; hyperplasia: 9/49, 10/47, 5/48, 0/48; Tables D1 and D5). These lesions may be related to nutritional or physiological changes associated with the lower mean body weights of female mice in the 6,000 ppm group, rather than to a direct chemical-related effect on the pituitary gland.

TABLE 30
Incidences of Selected Kidney Lesions in Mice in the 2-Year Feed Study of *o*-Nitroanisole

Dose (ppm)	0	666	2,000	6,000
Males				
n[a]	50	50	50	50
Regeneration, renal tubule[b]	48 (2.3)[c]	46 (2.1)	48 (2.2)	32*(1.0)
Hyperplasia, lymphoid	20 (1.7)	16 (1.5)	25 (1.4)	8*(1.3)
Mineralization	41 (1.9)	48 (2.4)	50 (2.4)	36 (1.0)
Females				
n	50	50	50	50
Regeneration, renal tubule	33 (1.4)	28 (1.2)	17*(1.1)	12*(1.0)
Hyperplasia, lymphoid	22 (1.5)	21 (1.5)	23 (1.5)	14*(1.6)
Mineralization	22 (1.1)	18 (1.2)	12 (1.1)	9*(1.0)

* Significantly different (P≤0.05) from the control group by logistic regression
[a] Number of animals with kidney examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal, 2 = mild, 3 = moderate, 4 = marked

Harderian gland: The harderian glands, specialized lacrimal glands located posterior to the eyes, were examined microscopically only when they were observed to be enlarged at necropsy. The incidences of harderian gland adenoma or carcinoma (combined) in males that received 2,000 and 6,000 ppm were significantly decreased (10/50, 4/50, 2/50, 3/50; Table C3). However, the incidence in the concurrent controls is substantially higher than that in the NTP historical controls and is the highest observed in an individual control group (48/872 (6%), range 0%-20%; Table C4b). Thus, the decreased incidences in the exposed groups may not be chemical related.

Adrenal gland: Adrenal cortical adenomas in males occurred in the control, 666, and 2,000 ppm groups, but not in the 6,000 ppm group. Although the incidence of adenomas in the 6,000 ppm group was significantly decreased (Table C3), the incidence in control males is substantially higher than that in NTP historical controls and is the highest observed in an individual control group (14/851 (2%), range 0%-14%; Table C4c). As with the harderian gland neoplasms, the decreased incidence in males receiving 6,000 ppm is not considered chemical related.

Genetic Toxicology

o-Nitroanisole was tested in two laboratories using a preincubation protocol for induction of gene mutations in five strains of *Salmonella typhimurium* in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table G1). In the first study (Haworth *et al.*, 1983), concentrations of 33 to 2,150 μg/plate were tested in strains TA98, TA100, TA1535, and TA1537; positive responses were observed only in strain TA100, with and without S9. In the second study, strains TA97, TA98, TA100, and TA1535 were tested with concentrations up to 3,333 μg/plate; positive responses were again noted for TA100, with and without S9, and also for TA1535, without S9. Both of these strains have the same DNA target site, and are reverted via base substitution. In cytogenetic tests with Chinese hamster ovary cells, *o*-nitroanisole induced sister chromatid exchanges with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table G2; Galloway *et al.*, 1987); at higher doses (above 123 μg/mL without S9, and above 811 μg/mL with S9), delayed harvest times were used to offset *o*-nitroanisole-induced cell cycle delay and allow for accumulation of sufficient metaphase cells for analysis. In the Chinese hamster ovary cell chromosomal aberrations test (Table G3; Galloway *et al.*, 1987), *o*-nitroanisole induced a significant increase in aberrations at the highest dose (1,060 μg/mL) tested in the presence of S9 activation; this response was due mainly to an increase in breaks which occurred in the long arm of the X chromosome. No increase in aberrations was observed in either of the two trials conducted without S9. *o*-Nitroanisole was positive in the mouse lymphoma L5178Y cell assay for induction of trifluorothymidine resistance in the absence of S9 activation; it was not tested with S9 (Table G4). The first of three trials was considered inconclusive because although a negative response was obtained at the highest nonlethal dose tested, the relative total growth of the treated cultures was not markedly decreased. In the remaining two trials, a dose-related increase in trifluorothymidine-resistant colonies was observed and significantly increased responses occurred at doses where the relative total growth was depressed below 50%.

DISCUSSION AND CONCLUSIONS

o-Nitroanisole is used primarily as a precursor in the synthesis of *o*-anisidine, an intermediate in the manufacture of many azo dyes. *o*-Nitroanisole is one of a series of single ring aromatic amines which have been evaluated for carcinogenic potential by the NTP. This class of chemicals was selected for evaluation because of occupational and consumer exposure and because several aromatic amines have been identified as human bladder carcinogens. Most of these single ring compounds have been used or are still used in the manufacture of dyes.

During 14-day and 13-week studies administration of *o*-nitroanisole caused an anemia in both rats and mice which was characterized by increased levels of methemoglobin and accelerated destruction of erythrocytes. In the 13-week rat study, reduced mean body weights and decreased feed consumption were observed in groups receiving the two highest dietary concentrations. In addition, absolute and relative liver, kidney, and spleen weights were increased in exposed male and female rats, and absolute and relative thymus weights were decreased in exposed females and increased in exposed males. In rats, lesions associated with *o*-nitroanisole exposure were present in the spleen, liver, and kidney, but the most severely affected organ was the urinary bladder. Diffuse hyperplasia of the transitional epithelium of the urinary bladder occurred in all rats that received 6,000 and 18,000 ppm in the 13-week study. Focal squamous metaplasia of the urinary bladder occurred in all females and two males receiving 18,000 ppm. Transitional cell neoplasms were present in three males and four females that received 18,000 ppm. The Pathology Working Group that reviewed the 13-week study questioned whether or not the lesions would persist or regress if chemical exposure was discontinued. Therefore, to investigate the biological potential of these lesions, a stop-exposure study with interim evaluations at 3, 6, 9, and 15 months was added to the design of the 2-year rat study. The only chemical-related lesion present in mice during the 13-week study was hepatocellular hypertrophy which occurred only in male mice and increased in severity with exposure levels above 200 ppm.

During the 2-year studies survival of male rats that received 2,000 ppm was lower than that of the controls, primarily as a result of an increased severity of nephropathy. However, the survival of female rats receiving 2,000 ppm or less, male rats receiving 222 and 666 ppm, all exposed male mice, and female mice receiving 2,000 and 6,000 ppm was similar to that of the controls. Survival of male and female rats that received 6,000 and 18,000 ppm in the stop-exposure study was markedly reduced as a result of moribund deaths associated with the presence of urinary bladder neoplasms. The mean body weights of the stop-exposure groups were also much lower than those of the controls.

The dose-response trend for increased incidences of urinary bladder neoplasms in rats is illustrated in Table 31. Continuous administration of 222 or 666 ppm *o*-nitroanisole had no effect on the bladder over the 2-year duration of the study. Exposure to 2,000 ppm for 2 years caused marginal increased incidences of transitional cell neoplasms in female rats and slightly increased incidences of nonneoplastic proliferative lesions of the bladder in both males and females. Exposure to 6,000 ppm for 3 months increased the incidence of transitional cell hyperplasia in female rats, and after 3 months of exposure to 18,000 ppm, the incidence of hyperplasia of the transitional epithelium was increased in both sexes and a transitional cell carcinoma was observed in a male rat. These results were similar to the observations in the 13-week study. After 6 months of exposure to 6,000 ppm, transitional cell hyperplasia was observed in all male and female rats examined; transitional cell papillomas were present in two male rats, while 6 months of exposure to 18,000 ppm resulted in transitional cell carcinomas in all male and female rats examined. Therefore, increasing the dietary exposure level from 2,000 to 6,000 ppm was associated with an increase in the incidence of neoplasms and markedly reduced latency for development of both carcinomas and preneoplastic lesions.

A similar type of dose response for the induction of urinary bladder neoplasms has been observed in

TABLE 31
Response of the Male Rat Urinary Bladder to *o*-Nitroanisole

Dose (ppm)	Exposure Time (weeks)	Study Length (weeks)	Transitional Hyperplasia	Transitional Papilloma	Transitional Carcinoma
222	103	103	0	0	0
666	103	103	0	0	0
2,000	103	103	0	2/50	0
6,000	13	13	0	0	0
6,000	26	28	10/10	2/10	0
6,000	26	40	10/10	2/10	3/10
18,000	13	13	9/10	0	1/10
18,000	26	28	0	0	10/10

F344/N rats exposed to *N*-butyl-*N*-(4-hydroxybutyl)-nitrosamine (BBN) (Ito *et al.*, 1984), or to the well-studied bladder carcinogen *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) (Arai *et al.*, 1983; Hasegawa *et al.*, 1986). For both compounds, the incidence of bladder neoplasms increases and the latency decreases as exposure concentration increases, so at higher dose levels neoplasms may be induced after a shorter period of chemical exposure.

From an analysis of the FANFT data in the context of a biologically based two-event model of carcinogenesis, Greenfield *et al.* (1984) have proposed that this type of response can be expected for a chemical which affects neoplasm formation both by its ability to produce lesions in the DNA of a target cell population and its ability to stimulate increased proliferation of the target cell population. For the present discussion the target cell population is the transitional epithelium of the urinary bladder and its precursor or stem cells. For the FANFT data the model assumes that at low doses the neoplasm incidence will increase primarily as a result of the genotoxic effects of the chemical; at these dose levels cell proliferative effects are minimal. As the dose increases, potentially preneoplastic genetic damage also increases; however, because of cytotoxicity, regenerative proliferation of the transitional epithelium of the urinary bladder also occurs. The superposition of increased genetic damage and increased cell proliferation results in an increase in neoplasm incidence substantially greater than would occur from either one alone. Over the range of dose concentrations at which cell proliferation increases, the slope of the dose response curve increases sharply and the latency for neoplasm development decreases.

Qualitatively there appears to be reasonable agreement between the predictions of the model and the current results for *o*-nitroanisole. After 3 months of exposure to 18,000 ppm, hyperplasia had increased the thickness of the transitional epithelium to at least 30 cell layers, compared to a 3- to 10-cell layer thickness for the transitional epithelium of controls. In addition, absolute and relative urinary bladder weights of the 18,000 ppm groups were significantly increased at the 3-, 6-, and 9-month interim evaluations. Exposure to 2,000 ppm for 13 weeks had no effect on the bladder; exposure to 2,000 ppm for 2 years caused focal hyperplasia in six females and two males, a transitional cell papilloma in one female, and a carcinoma in another. Therefore, between 2,000 and 6,000 ppm there was a marked increase in both cell proliferation and neoplasm incidence and a marked reduction in neoplasm latency.

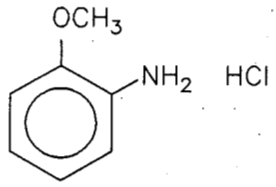
Numerous factors may be involved with increasing the rate of cell proliferation in the urinary bladder, and these have been discussed in recent publications (Cohen *et al.*, 1991; Okamura *et al.*, 1991). For most chemicals the underlying cause of increased proliferation has not been specifically identified, although it is often attributed to regenerative hyperplasia associated with some type of chemical-related cytotoxicity or irritant response. The character of the toxicity responsible for inducing hyperplasia in the bladder of rats that received 6,000 or 18,000 ppm is uncertain.

The major route of metabolism of *o*-nitroanisole is oxidative demethylation to *o*-nitrophenol, which appears in the urine predominantly as the sulfate conjugate. A second pathway involves nitroreduction to *o*-anisidine; at blood concentrations at which the metabolism and elimination of *o*-nitroanisole is linear, *o*-anisidine is a minor metabolite formed in the liver. However, at higher doses the *o*-nitrophenyl sulfate pathway may saturate, leading to the formation of proportionately more *o*-anisidine. The metabolism of *o*-anisidine has not been determined. However, it is also likely to be oxidatively demethylated to *o*-aminophenol, which in turn would normally be sulfated or glucuronidated. However, in the presence of saturating levels of *o*-nitroanisole, the additional *o*-aminophenol formed would probably appear unconjugated in the urine. In theory *o*-aminophenol could be reabsorbed by the urinary bladder epithelium and oxidized to the reactive and cytotoxic *o*-quinoneimine. However, the necrosis and cell death that often accompany intracellular formation or reaction of reactive intermediates was not observed in the bladders of rats exposed to *o*-nitroanisole.

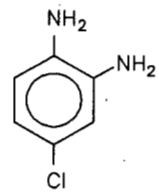
Figure 8 lists the compounds which have caused urinary bladder neoplasms in rats in previous NTP 2-year feed studies, and it is apparent that several of these compounds bear a close structural resemblance to *o*-nitroanisole. Moreover, most are genotoxic and induce bladder neoplasms over the same range of exposures as *o*-nitroanisole, suggesting that a common mechanism may be involved. The most potent rat bladder carcinogen to be evaluated by the NTP is *o*-anisidine, and therefore it is tempting to try to relate some common structural feature or metabolite of the other compounds to *o*-anisidine (NCI, 1978b). The major route of metabolism of *o*-toluidine is 4-hydroxylation to 3-methyl-4-aminophenol (4-hydroxy-*o*-toluidine) followed by conjugation (NCI, 1979a). It is also likely that *p*-cresidine is oxidatively demethylated to *o*-amino-4-methylphenol and conjugated (NCI, 1979b). The major route of metabolism of 4-amino-2-nitrophenol is probably direct conjugation, with nitro-reduction to 2,4-diaminophenol in the liver being a minor route (NCI, 1978a).

Exposure to *o*-nitroanisole caused a marginal increased incidence of renal tubule neoplasms in rats in the 2-year feed study. Renal tubule adenomas were present in one male in each of the 222, 666, and 2,000 ppm groups, and renal tubule carcinomas were present in two additional males that received 2,000 ppm. The increased incidence in the 2,000 ppm group was statistically significant and the incidence and the severity of nephropathy were increased in exposed animals. However, very few preneoplastic proliferative lesions were present; focal hyperplasia of the renal tubule epithelium was present in three 222 ppm males and two 2,000 ppm males. Among rats in the stop-exposure study, hyperplasia of the transitional epithelium lining the renal pelvis was first observed at the 6-month interim evaluation but was present in rats from both the 6,000 and 18,000 ppm groups throughout the duration of the study. At the end of the stop-exposure study, transitional cell papillomas were present in three males and one female and transitional cell carcinomas were present in six males and one female that received 18,000 ppm. Because of early mortality in the 6,000 and 18,000 ppm groups due to the presence of urinary bladder neoplasms, it is likely that these incidences are an underestimate of the carcinogenic potential of *o*-nitroanisole in the kidney.

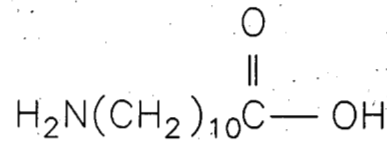
Consumption of diets containing *o*-nitroanisole for 2 years caused a dose-related increased incidence of focal hyperplasia of the forestomach mucosa as well as a slight dose-related increased incidence of forestomach ulcers in male and female rats. In addition, squamous cell papillomas or carcinomas were present in one female receiving 222 ppm, two males receiving 666 ppm, and two males and two females receiving 2,000 ppm. Among groups of rats from the



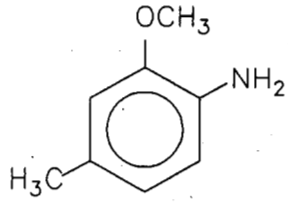
o-Anisidine Hydrochloride



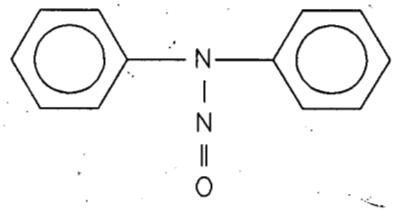
4-Chloro-*o*-phenylenediamine



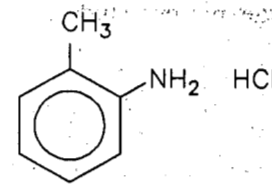
11-Aminoundecanoic Acid



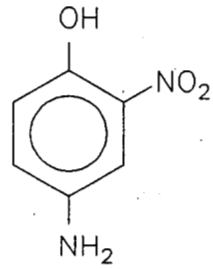
m-Cresidine



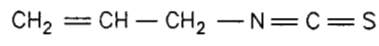
n-Nitrosodiphenylamine



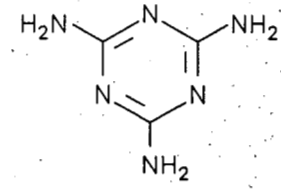
o-Toluidine Hydrochloride



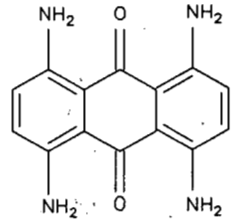
4-Amino-2-nitrophenol



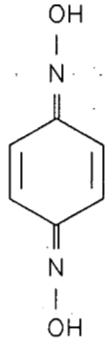
Allyl Isothiocyanate



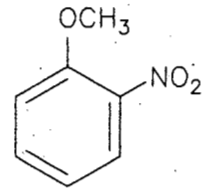
Melamine



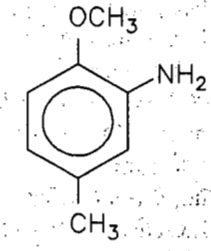
C.I. Disperse Blue 1



p-Benzoquinone Dioxime



o-Nitroanisole



p-Cresidine

FIGURE 8
Compounds Causing Bladder Neoplasms in Rats

stop-exposure study, adenomatous polyps of the large intestine were observed at all interim evaluations. At the end of the stop-exposure study, the incidence of adenomatous polyps was increased in the exposed groups, and the incidence of carcinomas of the large intestine was significantly increased in both the 6,000 and 18,000 ppm groups. Spontaneous neoplasms of the forestomach and large intestine are uncommon in F344/N rats and the increased incidences observed in the present study are considered to be related to chemical exposure.

The incidence of mononuclear cell leukemia was increased and exceeded the historical control rate in male rats that received 666 and 2,000 ppm and female rats that received 2,000 ppm of *o*-nitroanisole for 2 years. The incidence of mononuclear cell leukemia in control rats from the stop-exposure study was approximately the same as that for controls in the 2-year study; however, the incidence of mononuclear cell leukemia in exposed rats of the stop-exposure study was very low, most likely as a result of the markedly reduced survival in these groups.

Exposure to *o*-nitroanisole was associated with increased absolute and relative liver weights and increased incidences of liver lesions in both rats and mice. The increased absolute and relative liver weights were consistent with the liver being the primary organ involved with metabolism of *o*-nitroanisole. In rats the lesions were primarily nonneoplastic and although a few hepatocellular neoplasms were present in exposed rats, the incidences were low and not dose related. The incidences of focal necrosis and preneoplastic foci of cellular alteration were increased in exposed male mice. In addition, the incidences of hepatocellular adenoma and hepatocellular carcinoma or hepatoblastoma (combined) were significantly increased in male mice receiving 2,000 and 6,000 ppm; the incidence of hepatocellular adenoma or carcinoma (combined) was significantly increased in all exposed groups of male mice. The strong dose-related increased incidence of neoplasms in male mice was considered clear evidence of carcinogenic activity. In female mice the incidence of hepatocellular adenoma was significantly increased in the 2,000 ppm group but was not significantly increased in the 666 or 6,000 ppm groups. However, the significant depression in mean body weight (54% of control from week 53 to week 101) in 6,000 ppm female mice undoubtedly influenced the incidence of hepatocellular neoplasms in this group.

As a group, the other structurally similar chemicals which caused urinary bladder neoplasms in rats did not produce uniform results in mice. *o*-Anisidine and *p*-cresidine produced bladder neoplasms in male and female mice, and *p*-cresidine produced liver neoplasms in female mice (NCI, 1978b; 1979b). *o*-Toluidine caused hemangiosarcomas in male mice and liver neoplasms in female mice (NCI, 1979a), while C.I. Disperse Blue 1 produced an equivocal response in the liver of male mice and no evidence in female mice (NTP, 1986), and 4-amino-2-nitrophenol was negative in male and female mice (NCI, 1978a). Therefore, the response in mice was different for each chemical and each sex, and in general, mice were less responsive than rats.

The effectiveness of four of the most commonly used *in vitro* short-term genetic toxicity tests for prediction of chemical carcinogenicity was evaluated using 114 chemicals tested by the NTP. The tests used were induction of gene mutations in *Salmonella typhimurium* (SAL) and mouse lymphoma L5178Y cells (MLA), and induction of sister chromatid exchanges (SCE) and chromosome aberrations (Abs) in Chinese hamster ovary (CHO) cells (Tennant *et al.*, 1987; Zeiger *et al.*, 1990). The (SAL) assay was shown to have the lowest sensitivity, the highest specificity, and the highest positive predictivity for carcinogenicity of the four *in vitro* tests. The other tests had lower predictivities for carcinogenicity, and no combination of the four tests was more predictive for carcinogenicity than *S. typhimurium* alone.

The aromatic nitro group of *o*-nitroanisole is a molecular feature which provides an alert to potential DNA reactivity (Ashby and Tennant, 1991). *o*-Nitroanisole gave positive results in all four (SAL, MLA, SCE, Abs) of the NTP *in vitro* genetic toxicity tests, and one of the metabolites of *o*-nitroanisole (*o*-anisidine) was also mutagenic in these same four assays. Chemicals that are mutagenic in *S. typhimurium* and contain a structural alert are more likely to induce neoplasms in both rats and mice than chemicals that do not have these characteristics. These positive results in genotoxicity assays, and the structurally alerting nitro group, were predictive of the results of the bioassay, where

evidence of carcinogenicity was observed in both rats and mice (Tennant *et al.*, 1990).

CONCLUSIONS

Under the conditions of these feed studies there was *clear evidence of carcinogenic activity** of *o*-nitroanisole in male and female F344 rats that received diets containing 6,000 or 18,000 ppm for 6 months based on overall increased incidences of benign and malignant neoplasms of the urinary bladder, transitional cell neoplasms of the kidney, and benign and malignant neoplasms of the large intestine. There was a chemical-related increased incidence of mononuclear cell leukemia in male and female rats receiving diets containing 222, 666, or 2,000 ppm *o*-nitroanisole for 2 years. Marginally increased incidences of uncommon renal tubule neoplasms in male rats and forestomach neoplasms in male and female rats were considered uncertain findings. There was *clear evidence of carcinogenic activity* of *o*-nitroanisole in male $B6C3F_1$ mice based on increased incidences of benign and malignant hepatocellular neoplasms. There was *some evidence of carcinogenic activity* of *o*-nitroanisole in female $B6C3F_1$ mice based on increased incidences of hepatocellular adenomas.

Increased severity of nephropathy in male rats, and increased incidences of focal hyperplasia of the renal tubule epithelium and forestomach ulcers in male rats, and of transitional cell hyperplasia of the urinary bladder, focal hyperplasia of the forestomach, and hyperplasia of transitional epithelium of the kidney pelvis in male and female rats were associated with exposure to *o*-nitroanisole.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 12. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appear on page 14.

REFERENCES

Arai, M., St. John, M., Fukushima, S., Friedell, G.H., and Cohen, S.M. (1983). Long term dose response study of *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide-induced urinary bladder carcinogenesis. *Cancer Lett.* 18, 261-269.

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

Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity, and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* 257, 299-306.

Boorman, G., Montgomery, C., Jr., Eustis, S., Wolfe, M., McConnell, E., and Hardisty, J. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), ed. 1, pp. 345-357. Noyes Publications, Park Ridge, NJ.

Chiu, C.W., Less, L.H., Wang, C.Y., and Bryan, G.T. (1978). Mutagenicity of some commercially available nitro compounds for *Salmonella typhimurium*. *Mutat. Res.* 58, 11-22.

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

Cohen, S.M., Ellwein, L.B., Okamura, T., Masui, T., Johansson, S.L., Smith, R.A., Wehner, J.M., Khachab, M., Chappel, C.I., Schoenig, G.P., Emerson, J.L., and Garland, E.M. (1991). Comparative bladder tumor promoting activity of sodium saccharin, sodium ascorbate, related acids, and calcium salts in rats. *Cancer Res.* 51, 1766-1777.

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

Dinse, G.E., and Lagakos, S.W. (1983). Regression analysis of tumour prevalence data. *Appl. Statist.* 32, 236-248.

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

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* 6, 241-252.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* 50, 1095-1121.

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

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

Garberg, P., Akerblom, E.L., and Bolcsfoldi, G. (1988). Evaluation of a genotoxicity test measuring DNA-strand breaks in mouse lymphoma cells by alkaline unwinding and hydroxyapatite elution. *Mutat. Res.* 203, 155-176.

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

Greenfield, R.E., Ellwein, L.B., and Cohen, S.M. (1984). A general probabilistic model of carcinogenesis: Analysis of experimental urinary bladder cancer. *Carcinogenesis* 5, 437-445.

Hasegawa, R., Cohen, S.M., St. John, M., Cano, M., and Ellwein, L.B. (1986). Effect of dose on the induction of urothelial proliferation by *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide and its relationship to bladder carcinogenesis in the rat. *Carcinogenesis* **7**, 633-636.

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

Haseman, J.K., Huff, J., and Boorman, G.A. (1984). Use of historical control data in carcinogenicity studies in rodents. *Toxicol. Pathol.* **12**, 126-135.

Haseman, J.K., Huff, J.E., Rao, G.N., Arnold, J.E., Boorman, G.A., and McConnell, E.E. (1985). Neoplasms observed in untreated and corn oil gavage control groups of F344/N rats and (C57BL/6N × C3H/HeN)F_1 (B6C3F_1) mice. *JNCI* **75**, 975-984.

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

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods*. John Wiley and Sons, New York.

Ito, N., Shirai, T., Fukushima, S., and Hirose, M. (1984). Dose-response study of urinary bladder carcinogenesis in rats by *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine. *J. Cancer Res. Clin. Oncol.* **108**, 169-173.

Jonckheere, A. (1954). A distribution-free k-sample test against ordered alternatives. *Biometrika* **41**, 133-145.

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

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

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

McKnight, B., and Crowley, J. (1984). Tests for differences in tumor incidence based on animal carcinogenesis experiments. *J. Am. Stat. Assoc.* **79**, 639-648.

The Merck Index (1983). 10th ed. (M. Windholz, Ed.), p. 945. Merck and Company, Rahway, NJ.

Miller, M.J., Sipes, I.G., Perry, D.E., and Carter, D.E. (1985). Pharmacokinetics of *o*-nitroanisole in Fischer 344 rats. *Drug Metab. Disp.* **13**, 527-531.

Myhr, B., Bowers, L., and Caspary, W.J. (1985). Assays for the induction of gene mutations at the thymidine kinase locus in L5178Y mouse lymphoma cells in culture. *Prog. Mutat. Res.* **5**, 555-568.

Natake, M., Danno, G., Maeda, T., Kawamura, K., and Kanazawa, K. (1979). Formation of DNA-damaging and mutagenic activity in the reaction systems containing nitrite and butylated hydroxyanisole, tryptophan, or cysteine. *J. Nutr. Sci. Vitaminol.* **25**, 317-332.

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

National Cancer Institute (NCI) (1978a). Bioassay of 4-Amino-2-nitrophenol for Possible Carcinogenicity (CAS No. 119-34-6). Technical Report Series No. 94. NIH Publication No. 78-1344. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Cancer Institute (NCI) (1978b). Bioassay of *o*-Anisidine Hydrochloride for Possible Carcinogenicity (CAS No. 134-29-0). Technical Report Series No. 89. NIH Publication No. 78-1339. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Cancer Institute (NCI) (1979a). Bioassy of *o*-Toluidine Hydrochloride for Possible Carcinogenicity (CAS No. 636-21-5). Technical Report Series No. 153. NIH Publication No. 79-1709. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Cancer Institute (NCI) (1979b). Bioassy of *p*-Cresidine for Possible Carcinogenicity (CAS No. 120-71-8). Technical Report Series No. 142. NIH Publication No. 79-1397. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

National Institutes of Health (NIH) (1978). Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. National Institutes of Health, Bethesda, MD.

National Toxicology Program (NTP) (1986). Toxicology and Carcinogenesis Studies of C.I. Disperse Blue 1 (CAS No. 2475-45-8) in F344/N Rats and B6C3F$_1$ Mice (Feed Studies). Technical Report Series No. 299. NIH Publication No. 86-2555. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Okamura, T., Garland, E.M., Masui, T., Sakata, T., St. John, M., and Cohen, S. (1991). Lack of bladder tumor promoting activity in rats fed sodium saccharin in AIN-7GA diet. *Cancer Res.* 51, 1778-1782.

Sadtler Standard Spectra. IR No. 5864. Sadtler Research Laboratories, Philadelphia.

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

Shirley, E. (1977). A non-parametric equivalent of William's test for contrasting increasing dose levels of a treatment. *Biometrics* 33, 386-389.

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

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

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

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

Tokiwa, H., Nakagawa, R., and Ohnishi, Y. (1981). Mutagenic assay of aromatic nitro compounds with *Salmonella typhimurium*. *Mutat. Res.* 91, 321-325.

Wangenheim, J., and Bolcsfoldi, G. (1988). Mouse lymphoma L5178Y thymidine kinase locus assay of 50 compounds. *Mutagenesis* 3, 193-205.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* 27, 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* 28, 519-531.

Yoon, J.S., Mason, J.M., Valencia, R., Woodruff, R.C., and Zimmering, S. (1985). Chemical mutagenesis testing in *Drosophila*. IV. Results of 45 coded compounds tested for the National Toxicology Program. *Environ. Mutagen.* 7, 349-367.

Yoshimi, N., Sugie, S., Iwata, H., Niwa, K., Mori, H., Hashida, C., and Shimizu, H. (1988). The genotoxicity of a variety of aniline derivatives in a DNA repair test with primary cultured rat hepatocytes. *Mutat. Res.* 206, 183-191.

Yuan, J., Jameson, C.W., Goehl, T.J., Collins, B., Corniffe, G., Kuhn, G., and Castro, C. (1991). Effects of physical binding of *o*-nitroanisole with feed upon its systemic availability in male F344 rats. *Bull. Environ. Contam. Toxicol.* 46, 152-159.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four *in vitro* genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* **16** (Suppl. 18), 1-14.

Zeiger, E. Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1992). *Salmonella* mutagenicity tests. V. Results from the testing of 311 chemicals. *Environ. Mol. Mutagen.* **19** (Suppl. 21), 2-141.

APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR FEED STUDY OF *o*-NITROANISOLE

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

	0 ppm	222 ppm	666 ppm	2,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10[b]
Early deaths				
Moribund	16	13	24	35
Natural deaths	2	3	2	6
Survivors				
Died last week of study				1
Terminal sacrifice	32	34	24	8
Animals examined microscopically	60	60	60	59
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(9)
Mesentery	(2)	(2)	(2)	
Cardiovascular System				
None				
Endocrine System				
Adrenal gland, medulla	(10)			(9)
Ganglioneuroma	1 (10%)			
Pituitary gland	(10)	(1)		
Pars distalis, adenoma	3 (30%)	1 (100%)		
General Body System				
None				
Genital System				
Epididymis	(10)	(10)	(10)	(9)
Preputial gland	(10)	(10)	(9)	(9)
Carcinoma		1 (10%)	1 (11%)	1 (11%)
Testes	(10)	(10)	(10)	(9)
Bilateral, interstitial cell, adenoma	4 (40%)	1 (10%)	4 (40%)	4 (44%)
Interstitial cell, adenoma	1 (10%)	5 (50%)	5 (50%)	3 (33%)
Hematopoietic System				
Bone marrow	(10)			(9)
Spleen	(10)	(10)	(10)	(9)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
15-Month Interim Evaluation (continued)				
Integumentary System				
Skin	(10)	(1)		(9)
Subcutaneous tissue, scrotum, fibrosarcoma		1 (100%)		
Musculoskeletal System				
Skeletal muscle	(1)			
Nervous System				
Brain	(10)			(9)
Glioma malignant	1 (10%)			
Respiratory System				
Lung	(10)	(1)		(9)
Alveolar/bronchiolar adenoma, multiple	1 (10%)	1 (100%)		
Special Senses System				
None				
Urinary System				
None				
Systemic Lesions				
Multiple organs[c]	(10)	(10)	(10)	(9)
Leukemia mononuclear		1 (10%)		2 (22%)
Mesothelioma malignant	1 (10%)			
Neoplasm Summary				
Total animals with primary neoplasms[d]	8	7	9	8
Total primary neoplasms	12	11	10	10
Total animals with benign neoplasms	8	6	9	7
Total benign neoplasms	10	8	9	7
Total animals with malignant neoplasms	2	2	1	3
Total malignant neoplasms	2	3	1	3

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study				
Alimentary System				
Intestine large, cecum	(48)	(48)	(49)	(47)
Intestine large, colon	(48)	(48)	(50)	(48)
Intestine large, rectum	(46)	(49)	(50)	(49)
Intestine small, duodenum	(49)	(47)	(50)	(47)
Intestine small, ileum	(48)	(47)	(48)	(46)
Intestine small, jejunum	(48)	(47)	(48)	(48)
Adenocarcinoma				1 (2%)
Liver	(50)	(50)	(50)	(50)
Hepatocellular carcinoma		1 (2%)		
Hepatocellular adenoma		3 (6%)	1 (2%)	1 (2%)
Hepatocellular adenoma, multiple				1 (2%)
Mesentery	(10)	(11)	(5)	(9)
Histiocytic sarcoma	1 (10%)			
Pancreas	(49)	(49)	(50)	(48)
Carcinoma, metastatic				1 (2%)
Histiocytic sarcoma	1 (2%)			
Acinar cell, adenoma	5 (10%)	3 (6%)		5 (10%)
Pharynx		(1)		
Palate, squamous cell papilloma		1 (100%)		
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)	1 (2%)
Squamous cell papilloma			1 (2%)	1 (2%)
Stomach, glandular	(50)	(49)	(50)	(50)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Schwannoma benign			1 (2%)	
Endocrine System				
Adrenal gland, cortex	(48)	(50)	(50)	(49)
Adenoma	2 (4%)		1 (2%)	
Adrenal gland, medulla	(49)	(50)	(50)	(49)
Pheochromocytoma malignant	4 (8%)	3 (6%)	2 (4%)	
Pheochromocytoma benign	7 (14%)	5 (10%)	8 (16%)	9 (18%)
Bilateral, pheochromocytoma malignant	2 (4%)			
Bilateral, pheochromocytoma benign		2 (4%)		1 (2%)
Islets, pancreatic	(49)	(49)	(50)	(48)
Adenoma	1 (2%)	3 (6%)	4 (8%)	2 (4%)
Adenoma, multiple		1 (2%)		
Mixed tumor benign			2 (4%)	1 (2%)
Parathyroid gland	(47)	(46)	(47)	(48)
Adenoma			1 (2%)	1 (2%)
Pituitary gland	(50)	(50)	(49)	(49)
Pars distalis, adenoma	14 (28%)	11 (22%)	9 (18%)	4 (8%)
Pars distalis, carcinoma	1 (2%)		1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(49)	(50)	(50)	(50)
C-cell, adenoma	1 (2%)	2 (4%)	2 (4%)	
C-cell, carcinoma	1 (2%)	2 (4%)		1 (2%)
Follicular cell, adenoma	1 (2%)			1 (2%)
Follicular cell, carcinoma	1 (2%)	1 (2%)	2 (4%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(49)
Adenoma	3 (6%)		1 (2%)	1 (2%)
Carcinoma	6 (12%)	4 (8%)	3 (6%)	8 (16%)
Squamous cell carcinoma	2 (4%)			
Bilateral, adenoma	1 (2%)			
Bilateral, carcinoma	1 (2%)			
Prostate	(50)	(50)	(50)	(50)
Sarcoma		1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	40 (80%)	38 (76%)	36 (72%)	35 (70%)
Interstitial cell, adenoma	8 (16%)	7 (14%)	9 (18%)	10 (20%)
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(49)
Lymph node	(50)	(50)	(50)	(50)
Mediastinal, histiocytic sarcoma	1 (2%)			
Pancreatic, histiocytic sarcoma	1 (2%)			
Lymph node, mandibular	(50)	(48)	(50)	(50)
Lymph node, mesenteric	(49)	(48)	(49)	(48)
Histiocytic sarcoma	1 (2%)			
Spleen	(50)	(49)	(50)	(50)
Carcinoma, metastatic, harderian gland				1 (2%)
Hemangiosarcoma	1 (2%)			2 (4%)
Sarcoma				1 (2%)
Thymus	(45)	(48)	(42)	(47)
Thymoma benign		1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(48)	(49)	(47)	(50)
Adenoma		1 (2%)		
Fibroadenoma	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma	1 (2%)			
Basal cell carcinoma				1 (2%)
Basosquamous tumor benign		1 (2%)		
Hemangioma	1 (2%)			
Keratoacanthoma	3 (6%)	1 (2%)		2 (4%)
Sebaceous gland, carcinoma		1 (2%)		
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)	
Subcutaneous tissue, basal cell carcinoma	1 (2%)			
Subcutaneous tissue, fibroma	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, lipoma	1 (2%)			
Subcutaneous tissue, myxosarcoma				1 (2%)
Subcutaneous tissue, schwannoma malignant		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, osteoma			1 (2%)	
Femur, chondroma		1 (2%)		
Tibia, chondroma		1 (2%)		
Skeletal muscle				(2)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)			
Glioma malignant				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	2 (4%)	2 (4%)	
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	1 (2%)	
Carcinoma, metastatic, thyroid gland			1 (2%)	
Pheochromocytoma malignant, metastatic, multiple, adrenal gland	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Lumen, endothelium, squamous cell carcinoma	1 (2%)			
Respiratory epithelium, squamous cell carcinoma		1 (2%)	1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Special Senses System				
Ear			(1)	
Pinna, schwannoma malignant			1 (100%)	
Eye	(1)	(1)	(2)	(2)
Harderian gland				(2)
Carcinoma				1 (50%)
Zymbal's gland		(1)		(1)
Carcinoma		1 (100%)		1 (100%)
Urinary System				
Kidney	(49)	(50)	(50)	(49)
Renal tubule, adenoma		1 (2%)	1 (2%)	1 (2%)
Renal tubule, carcinoma				2 (4%)
Urinary bladder	(50)	(50)	(50)	(50)
Transitional epithelium, carcinoma				1 (2%)
Systemic Lesions[a]				
Multiple organs	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Leukemia mononuclear	26 (52%)	25 (50%)	42 (84%)	34 (68%)
Mesothelioma malignant	1 (2%)		1 (2%)	3 (6%)
Neoplasm Summary				
Total animals with primary neoplasms	50	49	50	50
Total primary neoplasms	147	133	140	137
Total animals with benign neoplasms	50	48	47	48
Total benign neoplasms	96	90	85	78
Total animals with malignant neoplasms	35	33	45	44
Total malignant neoplasms	51	43	55	59
Total animals with metastatic neoplasms	1		1	2
Total metastatic neoplasms	1		1	2

[a] Number of animals examined microscopically at site and number of animals with lesion.
[b] Includes one animal killed moribund before the interim evaluation.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

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

Number of Days on Study	4 8 4	4 9 6	5 7 5	5 9 9	6 0 3	6 1 3	6 1 7	6 3 3	6 3 8	6 6 9	6 6 9	6 6 9	6 7 3	6 7 6	6 8 3	6 9 5	6 9 6	7 1 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	0 0 5 1	0 0 7 1	0 0 3 1	0 0 4 1	0 0 7 2	0 0 3 2	0 0 9 1	0 0 8 1	0 0 8 2	0 0 4 2	0 0 6 1	0 0 8 3	0 0 3 3	0 0 9 2	0 0 2 1	0 1 0 1	0 0 3 4	0 0 1 1	0 0 1 2	0 0 1 3	0 0 1 4	0 0 1 5	0 0 2 2	0 0 2 3	0 0 2 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+	+			+	+																	+		
Histiocytic sarcoma		X																							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Acinar cell, adenoma																				X				X	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pheochromocytoma malignant											X										X				
Pheochromocytoma benign										X			X	X		X					X				
Bilateral, pheochromocytoma malignant																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adenoma																					X				
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M

+: 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 *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	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 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	
Carcass ID Number	0 0 2 5	0 0 3 5	0 0 4 3	0 0 4 4	0 0 4 5	0 0 5 2	0 0 5 3	0 0 5 4	0 0 5 5	0 0 6 2	0 0 6 3	0 0 6 4	0 0 6 5	0 0 7 3	0 0 7 4	0 0 7 5	0 0 8 4	0 0 8 5	0 0 9 3	0 0 9 4	0 0 9 5	0 1 0 2	0 1 0 3	0 1 0 4	0 1 0 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery						+								+			+				+		+		10
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Acinar cell, adenoma							X	X							X											5
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Adenoma																X						X				2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant									X						X											4
Pheochromocytoma benign																		X	X							7
Bilateral, pheochromocytoma malignant			X														X									2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	4 8 4	4 9 6	5 7 5	5 9 9	6 0 3	6 1 3	6 1 7	6 3 3	6 3 8	6 6 9	6 6 9	6 6 9	6 7 3	6 7 6	6 8 3	6 9 5	6 9 6	7 1 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	0 0 5 1	0 0 7 1	0 0 3 1	0 0 4 1	0 0 7 2	0 0 3 2	0 0 9 1	0 0 8 1	0 0 8 2	0 0 4 2	0 0 6 1	0 0 8 3	0 0 3 3	0 0 9 2	0 0 2 1	0 0 0 1	0 1 0 1	0 0 3 4	0 0 1 1	0 0 1 2	0 0 1 3	0 0 1 4	0 0 1 5	0 0 2 2	0 0 2 3	0 0 2 4
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X						X					X	X			X				
Pars distalis, carcinoma																									
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma																							X		
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma				X						X															
Squamous cell carcinoma														X		X									
Bilateral, adenoma					X																				
Bilateral, carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear, multiple									X																
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
Interstitial cell, adenoma						X					X							X		X					
Hematopoietic System																									
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, histiocytic sarcoma		X																							
Pancreatic, histiocytic sarcoma		X																							
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Histiocytic sarcoma		X																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	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 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	
Carcass ID Number	0 0 2 5	0 0 3 5	0 0 4 3	0 0 4 4	0 0 4 5	0 0 5 2	0 0 5 3	0 0 5 4	0 0 5 5	0 0 6 2	0 0 6 3	0 0 6 4	0 0 6 5	0 0 7 3	0 0 7 4	0 0 7 5	0 0 7 8	0 0 8 4	0 0 8 5	0 0 9 3	0 0 9 4	0 0 9 5	0 1 0 2	0 1 0 3	0 1 0 4	0 1 0 5	Total Tissues/ Tumors
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X		X			X			X	X	X				X								14
Pars distalis, carcinoma										X																1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma												X														1
C-cell, carcinoma			X																							1
Follicular cell, adenoma																										1
Follicular cell, carcinoma	X																									1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X									X		X								3
Carcinoma	X													X									X		X	6
Squamous cell carcinoma																										2
Bilateral, adenoma																										1
Bilateral, carcinoma																		X								1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear, multiple																										1
Bilateral, interstitial cell, adenoma	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														8
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, histiocytic sarcoma																										1
Pancreatic, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																			X							1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	45

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	4 8 4	4 9 6	5 7 5	5 9 9	6 0 3	6 1 3	6 1 7	6 3 3	6 6 8	6 6 9	6 6 9	6 6 9	6 7 3	6 7 6	6 8 3	6 9 5	6 9 6	7 1 6	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	0 0 5 1	0 0 7 1	0 0 3 1	0 0 4 1	0 0 7 2	0 0 3 2	0 0 9 1	0 0 8 1	0 0 8 2	0 0 4 2	0 0 6 1	0 0 8 3	0 0 3 3	0 0 9 2	0 0 2 1	0 1 0 1	0 0 3 4	0 0 1 1	0 0 1 2	0 0 1 3	0 0 1 4	0 0 1 5	0 0 2 2	0 0 2 3	0 0 2 4
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Fibroadenoma																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma					X																				
Hemangioma																									
Keratoacanthoma																X									
Squamous cell papilloma																									
Subcutaneous tissue, basal cell carcinoma																							X		
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																	X								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X																							
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma malignant, metastatic, multiple, adrenal gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumen, endothelium, squamous cell carcinoma																		X							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+																					
Urinary System																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Leukemia mononuclear		X	X				X	X	X	X	X		X		X	X					X		X		
Mesothelioma malignant	X																								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	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 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	
Carcass ID Number	0 0 2 5	0 0 3 5	0 0 4 3	0 0 4 4	0 0 4 5	0 0 5 2	0 0 5 3	0 0 5 4	0 0 5 5	0 0 6 2	0 0 6 3	0 0 6 4	0 0 6 5	0 0 7 3	0 0 7 4	0 0 7 5	0 0 8 4	0 0 8 5	0 0 9 3	0 0 9 4	0 0 9 5	0 1 0 2	0 1 0 3	0 1 0 4	0 1 0 5	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroadenoma																						X			X	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Hemangioma																								X		1
Keratoacanthoma		X							X																	3
Squamous cell papilloma																									X	1
Subcutaneous tissue, basal cell carcinoma																										1
Subcutaneous tissue, fibroma								X																		1
Subcutaneous tissue, lipoma								X																		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												2
Alveolar/bronchiolar carcinoma			X																							1
Pheochromocytoma malignant, metastatic, multiple, adrenal gland																	X									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lumen, endothelium, squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear	X	X		X	X				X		X			X					X	X	X	X	X	X	X	26
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm

Number of Days on Study	0 6 3	4 2 3	5 1 1	5 5 1	5 5 9	5 8 9	6 3 8	6 4 1	6 4 2	6 4 7	6 4 7	6 5 5	6 8 1	6 8 2	6 8 7	7 1 9	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 6 1	0 3 7 1	0 4 5 1	0 3 7 2	0 3 7 3	0 3 8 1	0 4 1 1	0 4 6 2	0 4 3 1	0 3 8 2	0 4 1 2	0 3 9 1	0 4 5 2	0 4 6 3	0 4 3 2	0 4 0 1	0 4 7 4	0 3 7 5	0 3 8 3	0 3 8 4	0 3 8 5	0 3 9 2	0 3 9 3	0 3 9 4	0 3 9 5
Alimentary System																									
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma																									
Mesentery		+				+				+	+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																									
Pharynx							+																		
Palate, squamous cell papilloma							X																		
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant														X											
Pheochromocytoma benign																		X			X		X		
Bilateral, pheochromocytoma benign																				X					X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Adenoma																									
Adenoma, multiple																					X				
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma							X	X											X			X			X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma												X					X								
Follicular cell, carcinoma					X																				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	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 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	
Carcass ID Number	0 4 0 2	0 4 2 2	0 4 2 1	0 4 3 3	0 4 3 4	0 4 3 5	0 4 4 1	0 4 0 3	0 4 0 4	0 4 0 5	0 4 1 3	0 4 1 4	0 4 1 5	0 4 2 2	0 4 2 3	0 4 2 4	0 4 2 5	0 4 4 3	0 4 4 4	0 4 4 5	0 4 5 3	0 4 5 4	0 4 5 5	0 4 6 4	0 4 6 5	Total Tissues/ Tumors	
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Intestine small, duodenum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Intestine small, ileum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Intestine small, jejunum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocellular carcinoma											X															1	
Hepatocellular adenoma				X								X		X												3	
Mesentery				+		+			+			+	+			+					+					11	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Acinar cell, adenoma							X													X	X					3	
Pharynx																										1	
Palate, squamous cell papilloma																										1	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Stomach, glandular	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Tooth																					+					1	
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Pheochromocytoma malignant		X													X											3	
Pheochromocytoma benign														X						X						5	
Bilateral, pheochromocytoma benign																										2	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Adenoma				X								X									X					3	
Adenoma, multiple																										1	
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Pars distalis, adenoma		X	X				X									X				X			X			11	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
C-cell, adenoma														X								X				2	
C-cell, carcinoma																										2	
Follicular cell, carcinoma																										1	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm (continued)

Number of Days on Study	0	4	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7
	6	2	1	5	5	8	3	4	4	4	4	5	8	8	8	1	2	2	2	2	2	2	2	2	2
	3	3	1	1	9	9	8	1	2	7	7	5	1	2	7	9	8	8	8	8	8	9	9	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	4	3	4	3	3	3	4	4	4	3	4	3	4	4	4	4	3	3	3	3	3	3	3	3	3
	6	7	5	7	7	8	1	6	3	8	1	9	5	6	3	0	7	7	8	8	8	9	9	9	9
	1	1	1	2	3	1	1	2	1	2	2	1	2	3	2	1	4	5	3	4	5	2	3	4	5
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																		X							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
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																									
Blood									+																
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma																							X		
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																									
Keratoacanthoma																									
Squamous cell papilloma																									
Sebaceous gland, carcinoma																		X							
Subcutaneous tissue, fibroma							X																X		
Subcutaneous tissue, fibrosarcoma												X													
Subcutaneous tissue, schwannoma malignant												X													

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm (continued)

Number of Days on Study	7 2 9	7 2 9	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 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	
Carcass ID Number	0 4 0 2	0 4 2 2	0 4 2 1	0 4 3 3	0 4 3 4	0 4 3 5	0 4 4 1	0 4 0 3	0 4 0 4	0 4 0 5	0 4 1 3	0 4 1 4	0 4 1 5	0 4 2 2	0 4 2 3	0 4 2 4	0 4 2 5	0 4 4 3	0 4 4 4	0 4 4 5	0 4 5 3	0 4 5 4	0 4 5 5	0 4 6 4	0 4 6 5	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma			X															X				X				4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																							X			1
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	38
Interstitial cell, adenoma												X						X		X						7
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48
Thymoma benign						X																				1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Fibroadenoma							X																			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor benign																						X				1
Keratoacanthoma															X											1
Squamous cell papilloma				X																						1
Sebaceous gland, carcinoma																										1
Subcutaneous tissue, fibroma								X																		3
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, schwannoma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm (continued)

Number of Days on Study	0 6 3	4 2 3	5 1 1	5 5 1	5 5 9	5 8 9	6 3 8	6 4 1	6 4 2	6 4 7	6 4 7	6 5 5	6 8 1	6 8 2	6 8 7	7 1 9	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 4 6 1	0 3 7 1	0 4 5 1	0 3 7 2	0 3 7 3	0 3 8 1	0 4 1 1	0 4 6 2	0 4 3 1	0 3 8 2	0 4 1 2	0 3 9 1	0 4 5 2	0 4 6 3	0 4 3 2	0 4 0 1	0 3 7 4	0 3 7 5	0 3 8 3	0 3 8 4	0 3 8 5	0 3 9 2	0 3 9 3	0 3 9 4	0 3 9 5
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, chondroma																								X	
Tibia, chondroma							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X												
Alveolar/bronchiolar carcinoma																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, squamous cell carcinoma																X									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																					+				
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X		X			X		X	X			X			X			X	X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm (continued)

Number of Days on Study	729	729	731	731	731	731	731	732	732	732	732	732	732	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	04402	04422	04423	04433	04443	04453	04461	04403	04404	04405	04413	04414	04415	04422	04423	04424	04425	04443	04444	04445	04453	04454	04455	04463	04465	04465	Total Tissues/ Tumors
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femur, chondroma																											1
Tibia, chondroma																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X					2
Alveolar/bronchiolar carcinoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory epithelium, squamous cell carcinoma																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																											1
Zymbal's gland							+																				1
Carcinoma							X																				1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																				X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X	X		X			X		X	X		X	X		X	X		X			X			25

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	7 2 2	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 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 5	7 3 5	7 3 5	
Carcass ID Number	0 3 3 3	0 2 5 3	0 2 5 4	0 2 5 5	0 2 6 5	0 2 7 5	0 2 8 4	0 2 8 5	0 2 9 3	0 2 9 4	0 2 9 5	0 3 0 3	0 3 0 4	0 3 0 5	0 3 1 4	0 3 1 5	0 3 2 2	0 3 2 3	0 3 2 4	0 3 2 5	0 3 3 4	0 3 3 5	0 3 4 3	0 3 4 4	0 3 4 5	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																				X					1
Mesentery																				+		+			5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																								X	1
Squamous cell papilloma																						X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma benign																						X			1
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X			1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant		X																							2
Pheochromocytoma benign	X			X								X								X					8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X											—		4
Mixed tumor benign																									2
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Adenoma					X																				1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X											X	X							X	X		9
Pars distalis, carcinoma																									1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																									2
Follicular cell, carcinoma							X																		2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	4 3 7	5 3 3	5 5 7	5 5 8	5 9 6	6 0 4	6 3 2	6 3 7	6 4 1	6 4 6	6 4 6	6 4 7	6 5 7	6 6 7	6 6 7	6 6 7	6 6 9	6 7 9	6 8 3	6 8 6	6 8 7	6 9 5	7 1 6	7 1 8	7 2 2
Carcass ID Number	0 2 8 1	0 3 1 1	0 2 8 2	0 2 7 1	0 3 0 1	0 3 1 2	0 2 7 2	0 3 3 1	0 2 5 1	0 3 0 2	0 3 4 1	0 2 9 1	0 2 6 1	0 2 6 2	0 2 6 3	0 2 6 4	0 2 5 2	0 2 8 3	0 2 1 3	0 3 4 2	0 3 7 3	0 2 7 4	0 3 3 2	0 2 9 2	0 3 2 1
General Body System																									
None																									
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma					X								X												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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			
Interstitial cell, adenoma													X											X	
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	M	+	M	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Fibroadenoma							X																		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Subcutaneous tissue, fibroma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, osteoma																		X							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	7 2 2	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 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 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 3 3 3	0 2 5 3	0 2 5 4	0 2 5 5	0 2 6 5	0 2 7 5	0 2 8 4	0 2 8 5	0 2 9 3	0 2 9 4	0 2 9 5	0 3 0 3	0 3 0 4	0 3 0 5	0 3 1 4	0 3 1 5	0 3 1 5	0 3 2 2	0 3 2 3	0 3 2 4	0 3 2 5	0 3 3 4	0 3 3 5	0 3 4 3	0 3 4 4	0 3 4 5	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Coagulating gland															+											1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															1
Carcinoma							X																			3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	36
Interstitial cell, adenoma	X			X			X			X				X			X				X					9
Hematopoietic System																+										1
Blood																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Fibroadenoma																					X					2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Subcutaneous tissue, fibroma												X														2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, osteoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	7	7	7
	3	3	5	5	9	0	3	3	4	4	4	4	5	6	6	6	6	7	8	8	9	1	2
	7	3	7	8	6	4	2	7	1	6	6	7	7	7	7	7	9	9	3	6	7	5	6	8	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	2	3	2	2	3	3	2	3	2	3	3	2	2	2	2	2	2	2	3	3	2	2	3	2	3
	8	1	8	7	0	1	7	3	5	0	4	9	6	6	6	6	5	8	1	4	7	7	3	9	2
	1	1	2	1	1	2	2	1	1	2	1	1	1	2	3	4	2	3	3	2	3	4	2	2	1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, thyroid gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, squamous cell carcinoma				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear				+																					
Pinna, schwannoma malignant				X																					
Eye				+																					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X		X	X		X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	7 2 2	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 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 5	7 3 5	7 3 5	
Carcass ID Number	0 3 3 3	0 2 5 3	0 2 5 4	0 2 5 5	0 2 6 5	0 2 7 5	0 2 8 4	0 2 8 5	0 2 9 3	0 2 9 4	0 2 9 5	0 3 0 3	0 3 0 4	0 3 0 5	0 3 1 4	0 3 1 5	0 3 2 2	0 3 2 3	0 3 2 4	0 3 2 5	0 3 3 4	0 3 3 5	0 3 4 3	0 3 4 4	0 3 4 5	Total Tissues/ Tumors
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X								X										2
Alveolar/bronchiolar carcinoma						X																			1
Carcinoma, metastatic, thyroid gland							X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory epithelium, squamous cell carcinoma																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																									
Ear																									1
Pinna, schwannoma malignant																									1
Eye								+																	2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma				X																					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X	X	42
Mesothelioma malignant																				X					1

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

Number of Days on Study	4 8 1	4 9 1	5 0 2	5 1 1	5 1 8	5 1 8	5 2 9	5 5 4	5 6 1	5 6 3	5 8 9	5 8 9	5 8 9	6 0 4	6 0 4	6 1 3	6 2 1	6 3 2	6 3 2	6 3 2	6 3 2	6 3 3	6 4 1	6 4 2	6 4 6
Carcass ID Number	0 1 5 1	0 1 9 1	0 2 2 1	0 1 6 1	0 1 3 1	0 1 3 5	0 1 5 2	0 2 0 1	0 1 8 1	0 2 1 1	0 1 4 1	0 1 7 1	0 1 8 2	0 1 2 2	0 2 2 2	0 2 2 3	0 1 6 2	0 1 4 2	0 1 9 2	0 1 9 3	0 2 1 3	0 2 1 4	0 1 4 3	0 1 7 2	0 1 6 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenocarcinoma								X																	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma															X										
Hepatocellular adenoma, multiple																									
Mesentery			+						+						+		+								
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Carcinoma, metastatic																									
Acinar cell, adenoma																X									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																X		X							
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenoma					X																				
Mixed tumor benign																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Adenoma																									
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X															X			X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	6 4 6	6 5 5	6 5 5	6 5 8	6 6 3	6 6 7	6 6 9	6 8 6	6 8 6	6 8 7	6 8 7	6 9 5	6 9 7	6 9 7	6 9 9	7 1 5	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0		
Carcass ID Number	0 1 7 3	0 1 3 2	0 1 8 3	0 2 0 2	0 1 3 3	0 1 6 4	0 1 7 4	0 1 6 5	0 2 0 3	0 1 8 4	0 2 2 4	0 1 9 4	0 1 4 4	0 1 4 5	0 1 5 3	0 1 3 4	0 2 2 5	0 1 5 4	0 1 5 5	0 1 7 5	0 2 0 4	0 1 8 5	0 1 9 5	0 2 0 5	0 2 1 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Hepatocellular adenoma, multiple																X										1
Mesentery								+			+			+		+								+		9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, metastatic													X													1
Acinar cell, adenoma												X	X			X										4
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma					X																					1
Squamous cell papilloma																			X							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel																+										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign									X						X		X	X				X	X	X		9
Bilateral, pheochromocytoma benign																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma	X																									2
Mixed tumor benign																	X									1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Adenoma																			X							1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma															X											4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	4 8 1	4 9 1	5 0 2	5 1 1	5 1 8	5 1 8	5 2 9	5 5 4	5 6 1	5 6 3	5 8 9	5 8 9	5 8 9	6 0 4	6 0 4	6 1 3	6 2 1	6 3 2	6 3 2	6 3 2	6 3 2	6 3 3	6 4 1	6 4 2	6 4 6
Carcass ID Number	0 1 5 1	0 1 9 1	0 2 2 1	0 1 6 1	0 1 3 1	0 1 3 5	0 1 5 2	0 2 0 1	0 1 8 1	0 2 1 1	0 1 4 1	0 1 7 1	0 1 8 2	0 1 2 2	0 2 2 2	0 2 2 3	0 1 6 2	0 1 4 2	0 1 9 2	0 1 9 3	0 2 1 3	0 2 1 4	0 1 4 3	0 1 7 2	0 1 6 3
Endocrine System (continued)																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, carcinoma													X												
Follicular cell, adenoma		X																							
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma					X				X												X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X	X		X			X		X			X		X	X			X	X	X	X		X
Interstitial cell, adenoma	X						X					X	X						X	X				X	
Hematopoietic System																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland																									
Hemangiosarcoma					X																				
Sarcoma																									
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																		X							
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, myxosarcoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	6 4 6	6 5 5	6 5 5	6 5 8	6 6 3	6 6 7	6 6 9	6 8 6	6 8 6	6 8 7	6 8 7	6 9 5	6 9 7	6 9 7	6 9 9	7 1 5	7 2 8	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 1 7 3	0 1 3 2	0 1 8 3	0 2 0 2	0 1 3 3	0 1 6 4	0 1 7 4	0 1 6 5	0 2 0 3	0 1 8 4	0 2 2 4	0 1 9 4	0 1 4 4	0 1 4 5	0 1 5 3	0 1 3 4	0 2 2 5	0 1 5 4	0 1 5 5	0 1 7 5	0 2 0 4	0 1 8 5	0 1 9 5	0 2 0 5	0 2 1 5	Total Tissues/ Tumors
Endocrine System (continued)																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, carcinoma																										1
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X																	1
Carcinoma		X										X					X	X							X	8
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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		35
Interstitial cell, adenoma							X					X													X	10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland									X																	1
Hemangiosarcoma													X													2
Sarcoma										X																1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma													X													1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																									X	1
Keratoacanthoma												X														2
Subcutaneous tissue, fibroma												X														1
Subcutaneous tissue, myxosarcoma	X																									1

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

	0 ppm	222 ppm	666 ppm	2,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rates[a]	7/49 (14%)	7/50 (14%)	8/50 (16%)	10/49 (20%)
Adjusted rates[b]	18.9%	20.6%	25.8%	73.0%
Terminal rates[c]	3/31 (10%)	7/34 (21%)	3/24 (13%)	6/9 (67%)
First incidence (days)	669	728 (T)	604	613
Life table tests[d]	P<0.001	P=0.563N	P=0.352	P=0.003
Logistic regression tests[d]	P=0.024	P=0.602N	P=0.496	P=0.050
Cochran-Armitage test[d]	P=0.212			
Fisher exact test[d]		P=0.597N	P=0.517	P=0.297
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rates	6/49 (12%)	3/50 (6%)	2/50 (4%)	0/49 (0%)
Adjusted rates	18.2%	8.4%	7.7%	0.0%
Terminal rates	5/31 (16%)	2/34 (6%)	1/24 (4%)	0/9 (0%)
First incidence (days)	669	682	718	–[e]
Life table tests	P=0.119N	P=0.213N	P=0.224N	P=0.173N
Logistic regression tests	P=0.057N	P=0.229N	P=0.164N	P=0.094N
Cochran-Armitage test	P=0.018N			
Fisher exact test		P=0.233N	P=0.128N	P=0.013N
Adrenal Medulla: Pheochromocytoma (Benign or Malignant)				
Overall rates	12/49 (24%)	10/50 (20%)	10/50 (20%)	10/49 (20%)
Adjusted rates	32.2%	28.5%	31.9%	73.0%
Terminal rates	7/31 (23%)	9/34 (26%)	4/24 (17%)	6/9 (67%)
First incidence (days)	669	682	604	613
Life table tests	P=0.007	P=0.346N	P=0.568	P=0.030
Logistic regression tests	P=0.187	P=0.385N	P=0.429N	P=0.276
Cochran-Armitage test	P=0.441N			
Fisher exact test		P=0.384N	P=0.384N	P=0.405N
Kidney (Renal Tubule): Adenoma or Carcinoma				
Overall rates	0/49 (0%)	1/50 (2%)	1/50 (2%)	3/49 (6%)
Adjusted rates	0.0%	2.9%	4.2%	21.9%
Terminal rates	0/32 (0%)	1/34 (3%)	1/24 (4%)	1/9 (11%)
First incidence (days)	–	728 (T)	728 (T)	663
Life table tests	P=0.001	P=0.512	P=0.443	P=0.016
Logistic regression tests	P=0.011	P=0.512	P=0.443	P=0.048
Cochran-Armitage test	P=0.062			
Fisher exact test		P=0.505	P=0.505	P=0.121
Liver: Hepatocellular Adenoma				
Overall rates	0/50 (0%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rates	0.0%	8.8%	4.2%	12.4%
Terminal rates	0/32 (0%)	3/34 (9%)	1/24 (4%)	0/9 (0%)
First incidence (days)	–	728 (T)	728 (T)	604
Life table tests	P=0.096	P=0.131	P=0.443	P=0.106
Logistic regression tests	P=0.258	P=0.131	P=0.443	P=0.237
Cochran-Armitage test	P=0.429			
Fisher exact test		P=0.121	P=0.500	P=0.247

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	0/50 (0%)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted rates	0.0%	11.8%	4.2%	12.4%
Terminal rates	0/32 (0%)	4/34 (12%)	1/24 (4%)	0/9 (0%)
First incidence (days)	–	728 (T)	728 (T)	604
Life table tests	P=0.137	P=0.070	P=0.443	P=0.106
Logistic regression tests	P=0.321	P=0.070	P=0.443	P=0.237
Cochran-Armitage test	P=0.533			
Fisher exact test		P=0.059	P=0.500	P=0.247
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	3/50 (6%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rates	8.2%	8.4%	12.5%	0.0%
Terminal rates	2/32 (6%)	2/34 (6%)	3/24 (13%)	0/9 (0%)
First incidence (days)	496	681	728 (T)	–
Life table tests	P=0.313N	P=0.640N	P=0.548	P=0.285N
Logistic regression tests	P=0.112N	P=0.658N	P=0.663N	P=0.076N
Cochran-Armitage test	P=0.082N			
Fisher exact test		P=0.661N	P=0.661N	P=0.121N
Mammary Gland: Fibroadenoma				
Overall rates	3/50 (6%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted rates	9.1%	2.9%	6.3%	7.7%
Terminal rates	2/32 (6%)	1/34 (3%)	1/24 (4%)	0/9 (0%)
First incidence (days)	716	728 (T)	632	697
Life table tests	P=0.586	P=0.285N	P=0.590N	P=0.698
Logistic regression tests	P=0.527N	P=0.292N	P=0.525N	P=0.626N
Cochran-Armitage test	P=0.340N			
Fisher exact test		P=0.309N	P=0.500N	P=0.309N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rates	3/50 (6%)	2/50 (4%)	2/50 (4%)	1/50 (2%)
Adjusted rates	9.1%	5.9%	6.3%	7.7%
Terminal rates	2/32 (6%)	2/34 (6%)	1/24 (4%)	0/9 (0%)
First incidence (days)	716	728 (T)	632	697
Life table tests	P=0.627	P=0.473N	P=0.590N	P=0.698
Logistic regression tests	P=0.471N	P=0.484N	P=0.525N	P=0.626N
Cochran-Armitage test	P=0.268N			
Fisher exact test		P=0.500N	P=0.500N	P=0.309N
Pancreas: Adenoma				
Overall rates	5/49 (10%)	3/49 (6%)	0/50 (0%)	5/48 (10%)
Adjusted rates	15.6%	8.8%	0.0%	33.4%
Terminal rates	5/32 (16%)	3/34 (9%)	0/24 (0%)	1/9 (11%)
First incidence (days)	728 (T)	728 (T)	–	613
Life table tests	P=0.021	P=0.321N	P=0.062N	P=0.070
Logistic regression tests	P=0.111	P=0.321N	P=0.062N	P=0.239
Cochran-Armitage test	P=0.397			
Fisher exact test		P=0.357N	P=0.027N	P=0.617

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
Pancreatic Islets: Adenoma				
Overall rates	1/49 (2%)	4/49 (8%)	4/50 (8%)	2/48 (4%)
Adjusted rates	3.1%	11.8%	11.9%	5.9%
Terminal rates	1/32 (3%)	4/34 (12%)	1/24 (4%)	0/9 (0%)
First incidence (days)	728 (T)	728 (T)	596	518
Life table tests	P=0.257	P=0.197	P=0.140	P=0.307
Logistic regression tests	P=0.582N	P=0.197	P=0.190	P=0.620
Cochran-Armitage test	P=0.556N			
Fisher exact test		P=0.181	P=0.187	P=0.492
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	14/50 (28%)	11/50 (22%)	9/49 (18%)	4/49 (8%)
Adjusted rates	38.3%	29.8%	30.0%	17.0%
Terminal rates	10/32 (31%)	9/34 (26%)	5/23 (22%)	0/9 (0%)
First incidence (days)	613	638	557	518
Life table tests	P=0.404N	P=0.279N	P=0.405N	P=0.387N
Logistic regression tests	P=0.029N	P=0.331N	P=0.218N	P=0.037N
Cochran-Armitage test	P=0.009N			
Fisher exact test		P=0.322N	P=0.185N	P=0.010N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	15/50 (30%)	11/50 (22%)	10/49 (20%)	4/49 (8%)
Adjusted rates	41.1%	29.8%	32.5%	17.0%
Terminal rates	11/32 (34%)	9/34 (26%)	5/23 (22%)	0/9 (0%)
First incidence (days)	613	638	557	518
Life table tests	P=0.387N	P=0.209N	P=0.430N	P=0.342N
Logistic regression tests	P=0.025N	P=0.253N	P=0.234N	P=0.027N
Cochran-Armitage test	P=0.007N			
Fisher exact test		P=0.247N	P=0.193N	P=0.005N
Preputial Gland: Adenoma				
Overall rates	4/50 (8%)	0/50 (0%)	1/50 (2%)	1/49 (2%)
Adjusted rates	11.3%	0.0%	4.2%	5.6%
Terminal rates	3/32 (9%)	0/34 (0%)	1/24 (4%)	0/9 (0%)
First incidence (days)	603	–	728 (T)	686
Life table tests	P=0.620N	P=0.060N	P=0.257N	P=0.523N
Logistic regression tests	P=0.404N	P=0.064N	P=0.191N	P=0.297N
Cochran-Armitage test	P=0.303N			
Fisher exact test		P=0.059N	P=0.181N	P=0.187N
Preputial Gland: Carcinoma				
Overall rates	7/50 (14%)	4/50 (8%)	3/50 (6%)	8/49 (16%)
Adjusted rates	19.4%	11.8%	8.8%	45.1%
Terminal rates	5/32 (16%)	4/34 (12%)	1/24 (4%)	3/9 (33%)
First incidence (days)	599	728 (T)	596	518
Life table tests	P=0.005	P=0.242N	P=0.261N	P=0.038
Logistic regression tests	P=0.168	P=0.267N	P=0.158N	P=0.372
Cochran-Armitage test	P=0.234			
Fisher exact test		P=0.262N	P=0.159N	P=0.483

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
Preputial Gland: Adenoma or Carcinoma				
Overall rates	11/50 (22%)	4/50 (8%)	4/50 (8%)	9/49 (18%)
Adjusted rates	29.9%	11.8%	12.7%	48.1%
Terminal rates	8/32 (25%)	4/34 (12%)	2/24 (8%)	3/9 (33%)
First incidence (days)	599	728 (T)	596	518
Life table tests	P=0.012	P=0.041N	P=0.114N	P=0.091
Logistic regression tests	P=0.289	P=0.049N	P=0.048N	P=0.605N
Cochran-Armitage test	P=0.411			
Fisher exact test		P=0.045N	P=0.045N	P=0.421N
Skin: Keratoacanthoma				
Overall rates	3/50 (6%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Adjusted rates	8.9%	2.9%	0.0%	10.0%
Terminal rates	2/32 (6%)	1/34 (3%)	0/24 (0%)	0/9 (0%)
First incidence (days)	695	728 (T)	–	632
Life table tests	P=0.324	P=0.290N	P=0.171N	P=0.478
Logistic regression tests	P=0.547	P=0.302N	P=0.139N	P=0.681N
Cochran-Armitage test	P=0.617N			
Fisher exact test		P=0.309N	P=0.121N	P=0.500N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Basal Cell Adenoma or Carcinoma				
Overall rates	6/50 (12%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rates	16.8%	5.9%	3.8%	20.0%
Terminal rates	4/32 (13%)	2/34 (6%)	0/24 (0%)	1/9 (11%)
First incidence (days)	603	728 (T)	722	632
Life table tests	P=0.347	P=0.125N	P=0.106N	P=0.515
Logistic regression tests	P=0.576N	P=0.138N	P=0.065N	P=0.452N
Cochran-Armitage test	P=0.367N			
Fisher exact test		P=0.134N	P=0.056N	P=0.243N
Skin (Subcutaneous Tissue): Fibroma				
Overall rates	1/50 (2%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rates	3.1%	8.0%	6.3%	7.1%
Terminal rates	1/32 (3%)	2/34 (6%)	1/24 (4%)	0/9 (0%)
First incidence (days)	728 (T)	638	632	695
Life table tests	P=0.519	P=0.327	P=0.436	P=0.503
Logistic regression tests	P=0.532N	P=0.299	P=0.494	P=0.613
Cochran-Armitage test	P=0.424N			
Fisher exact test		P=0.309	P=0.500	P=0.753N
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rates	1/50 (2%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rates	3.1%	10.4%	6.3%	7.1%
Terminal rates	1/32 (3%)	2/34 (6%)	1/24 (4%)	0/9 (0%)
First incidence (days)	728 (T)	638	632	695
Life table tests	P=0.587	P=0.201	P=0.436	P=0.503
Logistic regression tests	P=0.429N	P=0.175	P=0.494	P=0.613
Cochran-Armitage test	P=0.340N			
Fisher exact test		P=0.181	P=0.500	P=0.753N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of o-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
Testes: Adenoma				
Overall rates	48/50 (96%)	45/50 (90%)	45/50 (90%)	45/50 (90%)
Adjusted rates	96.0%	97.8%	100.0%	100.0%
Terminal rates	30/32 (94%)	33/34 (97%)	24/24 (100%)	9/9 (100%)
First incidence (days)	484	511	557	481
Life table tests	P<0.001	P=0.261N	P=0.193	P<0.001
Logistic regression tests	P=0.493	P=0.336N	P=0.247N	P=0.519N
Cochran-Armitage test	P=0.312N			
Fisher exact test		P=0.218N	P=0.218N	P=0.218N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	2/49 (4%)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted rates	6.3%	11.2%	6.1%	2.5%
Terminal rates	2/32 (6%)	3/34 (9%)	0/24 (0%)	0/9 (0%)
First incidence (days)	728 (T)	655	637	589
Life table tests	P=0.611N	P=0.355	P=0.624	P=0.699
Logistic regression tests	P=0.300N	P=0.335	P=0.684	P=0.559N
Cochran-Armitage test	P=0.235N			
Fisher exact test		P=0.349	P=0.684N	P=0.492N
All Organs: Mononuclear Cell Leukemia				
Overall rates	26/50 (52%)	25/50 (50%)	42/50 (84%)	34/50 (68%)
Adjusted rates	60.9%	60.2%	91.2%	89.0%
Terminal rates	16/32 (50%)	18/34 (53%)	20/24 (83%)	6/9 (67%)
First incidence (days)	496	423	437	491
Life table tests	P<0.001	P=0.445N	P<0.001	P<0.001
Logistic regression tests	P=0.033	P=0.515N	P<0.001	P=0.114
Cochran-Armitage test	P=0.041			
Fisher exact test		P=0.500N	P<0.001	P=0.076
All Organs: Malignant Mesothelioma				
Overall rates	1/50 (2%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rates	2.0%	0.0%	4.2%	8.0%
Terminal rates	0/32 (0%)	0/34 (0%)	1/24 (4%)	0/9 (0%)
First incidence (days)	484	–	728 (T)	502
Life table tests	P=0.038	P=0.508N	P=0.726	P=0.257
Logistic regression tests	P=0.115	P=0.363N	P=0.733N	P=0.672
Cochran-Armitage test	P=0.082			
Fisher exact test		P=0.500N	P=0.753N	P=0.309
All Organs: Benign Neoplasms				
Overall rates	50/50 (100%)	48/50 (96%)	47/50 (94%)	48/50 (96%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	32/32 (100%)	34/34 (100%)	24/24 (100%)	9/9 (100%)
First incidence (days)	484	511	557	481
Life table tests	P<0.001	P=0.310N	P=0.175	P<0.001
Logistic regression tests	P=0.604N	P=0.500N	P=0.131N	P=0.434N
Cochran-Armitage test	P=0.360N			
Fisher exact test		P=0.247N	P=0.121N	P=0.247N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
All Organs: Malignant Neoplasms				
Overall rates	35/50 (70%)	33/50 (66%)	45/50 (90%)	44/50 (88%)
Adjusted rates	74.2%	73.1%	91.8%	97.3%
Terminal rates	20/32 (63%)	22/34 (65%)	20/24 (83%)	8/9 (89%)
First incidence (days)	484	423	437	481
Life table tests	P<0.001	P=0.372N	P=0.010	P<0.001
Logistic regression tests	P=0.009	P=0.427N	P=0.016	P=0.167
Cochran-Armitage test	P=0.006			
Fisher exact test		P=0.415N	P=0.011	P=0.024
All Organs: Benign or Malignant Neoplasms				
Overall rates	50/50 (100%)	49/50 (98%)	50/50 (100%)	50/50 (100%)
Adjusted rates	100.0%	100.0%	100.0%	100.0%
Terminal rates	32/32 (100%)	34/34 (100%)	24/24 (100%)	9/9 (100%)
First incidence (days)	484	423	437	481
Life table tests	P<0.001	P=0.378N	P=0.086	P<0.001
Logistic regression tests	[f]	–	–	–
Cochran-Armitage test	P=0.585			
Fisher exact test		P=0.500N	P=1.000N	P=1.000N

(T)Terminal sacrifice

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

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

[c] Observed incidence at terminal kill

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

[e] Not applicable; no neoplasms in animal group

[f] Value of statistic cannot be computed

TABLE A4a
Historical Incidence of Leukemia in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
C.I. Pigment Red 3	22/50
Nitrofuratoin	23/50
o-Nitroanisole	26/50
Polysorbate 80	23/50
Rhodamine 6G	27/50
Roxarsone	27/50
Overall Historical Incidence	
Total	385/800 (48.1%)
Standard deviation	7.7%
Range	32%-62%

[a] Data as of 3 April 1991

TABLE A4b
Historical Incidence of Liver Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	1/50	0/50	1/50
o-Nitroanisole	0/50	0/50	0/50
Polysorbate 80	2/50	0/50	2/50
Rhodamine 6G	4/50	1/50	5/50
Roxarsone	0/50	2/50	2/50
Overall Historical Incidence			
Total	19/799 (2.4%)	7/799 (0.9%)	24/799 (3.0%)
Standard deviation	2.9%	1.8%	3.4%
Range	0%-8%	0%-6%	0%-10%

[a] Data as of 3 April 1991

TABLE A4c
Historical Incidence of Squamous Cell Papillomas and Carcinomas of the Forestomach in Untreated Male F344/N Rats[a]

Study	Incidence in Controls	
	Squamous Cell Papilloma	Squamous Cell Carcinoma
Historical Incidence at Southern Research Institute		
C.I. Pigment Red 3	0/50	0/50
Nitrofurantoin	0/50	0/50
o-Nitroanisole	0/50	0/50
Polysorbate 80	0/50	0/50
Rhodamine 6G	0/50	0/50
Roxarsone	0/50	0/50
Overall Historical Incidence		
Total	2/800 (0.3%)	1/800 (0.1%)
Standard deviation	0.7%	0.5%
Range	0%-2%	0%-2%

[a] Data as of 3 April 1991

TABLE A4d
Historical Incidence of Renal Tubule Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
C.I. Pigment Red 3	0/50	1/50	1/50
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	0/49	0/49	0/49
Polysorbate 80	0/50	1/50	1/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	1/50	1/50	2/50
Overall Historical Incidence			
Total	5/798 (0.6%)	6/798 (0.8%)	11/798 (1.4%)
Standard deviation	1.6%	1.2%	1.9%
Range	0%-6%	0%-4%	0%-6%

[a] Data as of 3 April 1991

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of o-Nitroanisole[a]

	0 ppm	222 ppm	666 ppm	2,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-month interim evaluation	10	10	10	10[b]
Early deaths				
Moribund	16	13	24	35
Natural deaths	2	3	2	6
Survivors				
Died last week of study				1
Terminal sacrifice	32	34	24	8
Animals examined microscopically	60	60	60	59
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)			(9)
Parasite metazoan	4 (40%)			4 (44%)
Intestine small, jejunum	(10)			(9)
Parasite metazoan				1 (11%)
Liver	(10)	(10)	(10)	(9)
Basophilic focus	5 (50%)	1 (10%)		1 (11%)
Clear cell focus	3 (30%)		1 (10%)	1 (11%)
Clear cell focus, multiple	2 (20%)	1 (10%)		
Degeneration, cystic	1 (10%)			
Eosinophilic focus		1 (10%)	3 (30%)	
Eosinophilic focus, multiple		1 (10%)		
Hepatodiaphragmatic nodule			1 (10%)	2 (22%)
Hepatodiaphragmatic nodule, multiple	1 (10%)			
Inflammation, granulomatous, multiple	5 (50%)	4 (40%)	6 (60%)	7 (78%)
Mixed cell focus	2 (20%)			
Vacuolization cytoplasmic	8 (80%)	10 (100%)	8 (80%)	8 (89%)
Bile duct, hyperplasia	10 (100%)	10 (100%)	7 (70%)	9 (100%)
Mesentery	(2)	(2)	(2)	
Accessory spleen			1 (50%)	
Fat, hemorrhage, focal			1 (50%)	
Fat, inflammation, granulomatous, focal	1 (50%)	1 (50%)		
Fat, necrosis, focal		1 (50%)		
Pancreas	(10)		(1)	(9)
Acinus, atrophy				1 (11%)
Stomach, forestomach	(10)		(1)	(9)
Epithelium, hyperplasia			1 (100%)	1 (11%)
Stomach, glandular	(10)		(1)	(9)
Serosa, fibrosis, focal				1 (11%)
Cardiovascular System				
Heart	(10)	(1)		(9)
Inflammation, chronic	6 (60%)			5 (56%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
15-Month Interim Evaluation (continued)				
Endocrine System				
Adrenal gland, cortex	(10)			(9)
Accessory adrenal cortical nodule	1 (10%)			1 (11%)
Hyperplasia, focal	1 (10%)			
Vacuolization cytoplasmic, focal	1 (10%)			
Pituitary gland	(10)	(1)		(9)
Pars distalis, hyperplasia, focal	3 (30%)			2 (22%)
Thyroid gland	(10)			(9)
C-cell, hyperplasia				1 (11%)
Follicle, cyst				1 (11%)
General Body System				
None				
Genital System				
Epididymis	(10)	(10)	(10)	(9)
Depletion cellular				1 (11%)
Preputial gland	(10)	(10)	(9)	(9)
Atrophy			2 (22%)	
Cyst	3 (30%)	2 (20%)	2 (22%)	
Hyperplasia	1 (10%)			
Prostate	(10)			(9)
Granuloma				1 (11%)
Inflammation, suppurative	3 (30%)			1 (11%)
Seminal vesicle	(10)		(1)	(9)
Atrophy			1 (100%)	
Testes	(10)	(10)	(10)	(9)
Atrophy			1 (10%)	3 (33%)
Degeneration				1 (11%)
Bilateral, interstitial cell, hyperplasia	6 (60%)	3 (30%)	5 (50%)	1 (11%)
Interstitial cell, hyperplasia	1 (10%)	4 (40%)	4 (40%)	5 (56%)
Hematopoietic System				
Lymph node	(10)		(1)	(9)
Mediastinal, hyperplasia, lymphoid	1 (10%)			
Pancreatic, hyperplasia, lymphoid			1 (100%)	
Spleen	(10)	(10)	(10)	(9)
Congestion	1 (10%)		1 (10%)	3 (33%)
Capsule, fibrosis, focal		1 (10%)		
Capsule, hypertrophy		5 (50%)	6 (60%)	8 (89%)
Integumentary System				
Skin	(10)	(1)		(9)
Subcutaneous tissue, cyst epithelial inclusion				1 (11%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
15-Month Interim Evaluation (continued)				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(1)		(9)
Alveolar epithelium, hyperplasia	1 (10%)			
Inflammation, granulomatous, focal				2 (22%)
Nose	(10)			(9)
Lumen, fungus				1 (11%)
Lumen, inflammation, suppurative				1 (11%)
Submucosa, pigmentation				7 (78%)
Special Senses System				
Eye			(1)	
Cataract			1 (100%)	
Retina, degeneration			1 (100%)	
Urinary System				
Kidney	(10)	(10)	(10)	(9)
Fibrosis, focal	1 (10%)			
Nephropathy, chronic	10 (100%)	10 (100%)	10 (100%)	9 (100%)
Pelvis, dilatation	1 (10%)			
2-Year Study				
Alimentary System				
Intestine large, cecum	(48)	(48)	(49)	(47)
Dilatation			1 (2%)	
Parasite metazoan	1 (2%)		3 (6%)	1 (2%)
Intestine large, colon	(48)	(48)	(50)	(48)
Dilatation			1 (2%)	
Mineralization				1 (2%)
Parasite metazoan	5 (10%)	4 (8%)	2 (4%)	9 (19%)
Intestine large, rectum	(46)	(49)	(50)	(49)
Dilatation			1 (2%)	1 (2%)
Edema				1 (2%)
Parasite metazoan	9 (20%)	4 (8%)	13 (26%)	8 (16%)
Intestine small, duodenum	(49)	(47)	(50)	(47)
Ectopic tissue		1 (2%)		
Intestine small, ileum	(48)	(47)	(48)	(46)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	4 (8%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Alimentery System (continued)				
Intestine small, jejunum	(48)	(47)	(48)	(48)
Artery, thrombus				1 (2%)
Wall, inflammation, chronic				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	1 (2%)
Basophilic focus	3 (6%)	2 (4%)	2 (4%)	4 (8%)
Basophilic focus, multiple	29 (58%)	27 (54%)	11 (22%)	3 (6%)
Clear cell focus	6 (12%)	4 (8%)	1 (2%)	2 (4%)
Clear cell focus, multiple	7 (14%)	6 (12%)	4 (8%)	3 (6%)
Degeneration, cystic	10 (20%)	10 (20%)	14 (28%)	24 (48%)
Eosinophilic focus	6 (12%)	10 (20%)	15 (30%)	13 (26%)
Eosinophilic focus, multiple	2 (4%)	8 (16%)	6 (12%)	14 (28%)
Hematopoietic cell proliferation	1 (2%)			1 (2%)
Hemorrhage		1 (2%)		
Hepatodiaphragmatic nodule	4 (8%)	3 (6%)	2 (4%)	4 (8%)
Hyperplasia, nodular	7 (14%)	2 (4%)	18 (36%)	14 (28%)
Inflammation, granulomatous, multiple	2 (4%)	2 (4%)	2 (4%)	
Mixed cell focus	4 (8%)		2 (4%)	2 (4%)
Mixed cell focus, multiple	2 (4%)	2 (4%)	1 (2%)	
Necrosis		1 (2%)		2 (4%)
Thrombus, multiple		1 (2%)		
Vacuolization cytoplasmic	5 (10%)	4 (8%)	4 (8%)	1 (2%)
Bile duct, hyperplasia	46 (92%)	44 (88%)	46 (92%)	40 (80%)
Centrilobular, degeneration	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Centrilobular, necrosis				1 (2%)
Vein, thrombus				1 (2%)
Mesentery	(10)	(11)	(5)	(9)
Polyarteritis				2 (22%)
Thrombus, multiple				1 (11%)
Fat, hemorrhage, focal	2 (20%)			2 (22%)
Fat, inflammation, granulomatous, focal	1 (10%)	4 (36%)		
Fat, necrosis, focal	7 (70%)	9 (82%)	3 (60%)	3 (33%)
Pancreas	(49)	(49)	(50)	(48)
Basophilic focus	2 (4%)			
Ectopic tissue	1 (2%)			2 (4%)
Edema		1 (2%)	1 (2%)	
Fibrosis, focal				1 (2%)
Inflammation, chronic				1 (2%)
Polyarteritis	1 (2%)	1 (2%)		2 (4%)
Acinar cell, atrophy	18 (37%)	21 (43%)	18 (36%)	13 (27%)
Acinar cell, basophilic focus		2 (4%)		
Acinar cell, hyperplasia	6 (12%)	10 (20%)	4 (8%)	6 (13%)
Acinar cell, hyperplasia, focal		1 (2%)		
Acinar cell, vacuolization cytoplasmic			1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Cytomegaly	1 (2%)	8 (16%)	4 (8%)	
Fibrosis, focal		1 (2%)		
Infiltration cellular, lipocyte		39 (78%)	6 (12%)	
Inflammation, suppurative	1 (2%)			
Acinar cell, atrophy		1 (2%)	1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Alimentery System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema	3 (6%)	3 (6%)	5 (10%)	11 (22%)
Inflammation, chronic	2 (4%)	2 (4%)	1 (2%)	12 (24%)
Mineralization			1 (2%)	1 (2%)
Perforation		1 (2%)		
Ulcer	3 (6%)	3 (6%)	6 (12%)	15 (30%)
Ulcer, multiple			2 (4%)	1 (2%)
Epithelium, hyperplasia	3 (6%)	16 (32%)	25 (50%)	32 (64%)
Stomach, glandular	(50)	(49)	(50)	(50)
Edema			4 (8%)	1 (2%)
Erosion				1 (2%)
Erosion, multiple			1 (2%)	
Inflammation, chronic				1 (2%)
Mineralization		1 (2%)	1 (2%)	6 (12%)
Polyarteritis				1 (2%)
Ulcer			1 (2%)	1 (2%)
Ulcer, multiple			1 (2%)	
Artery, thrombus				1 (2%)
Mucosa, pigmentation, focal				1 (2%)
Cardiovascular System				
Blood vessel				(1)
Aorta, mineralization				1 (100%)
Mesenteric artery, mineralization				1 (100%)
Heart	(50)	(50)	(50)	(50)
Inflammation, chronic	43 (86%)	46 (92%)	42 (84%)	40 (80%)
Mineralization				1 (2%)
Atrium, congestion	2 (4%)	1 (2%)		
Atrium, thrombus		2 (4%)	1 (2%)	1 (2%)
Endocrine System				
Adrenal gland, cortex	(48)	(50)	(50)	(49)
Accessory adrenal cortical nodule	8 (17%)	5 (10%)	5 (10%)	2 (4%)
Degeneration, cystic			1 (2%)	1 (2%)
Hyperplasia, focal	3 (6%)	7 (14%)	4 (8%)	2 (4%)
Hypertrophy, focal	5 (10%)	2 (4%)	1 (2%)	1 (2%)
Hypertrophy, multiple				1 (2%)
Vacuolization cytoplasmic			2 (4%)	11 (22%)
Vacuolization cytoplasmic, focal	9 (19%)	10 (20%)	11 (22%)	8 (16%)
Vacuolization cytoplasmic, focal, multiple		1 (2%)		
Vacuolization cytoplasmic, multiple, focal		1 (2%)		1 (2%)
Spindle cell, hyperplasia, focal				1 (2%)
Adrenal gland, medulla	(49)	(50)	(50)	(49)
Hemorrhage				1 (2%)
Hyperplasia	1 (2%)			
Hyperplasia, focal	4 (8%)	9 (18%)	11 (22%)	10 (20%)
Bilateral, hyperplasia, focal		1 (2%)		
Islets, pancreatic	(49)	(49)	(50)	(48)
Hyperplasia	1 (2%)	2 (4%)	2 (4%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Parathyroid gland	(47)	(46)	(47)	(48)
Hyperplasia	2 (4%)	1 (2%)	3 (6%)	14 (29%)
Pituitary gland	(50)	(50)	(49)	(49)
Pars distalis, cyst	2 (4%)	1 (2%)	6 (12%)	2 (4%)
Pars distalis, cyst, multiple		1 (2%)		
Pars distalis, hemorrhage	4 (8%)			
Pars distalis, hyperplasia, focal	3 (6%)	9 (18%)	11 (22%)	5 (10%)
Pars intermedia, cyst			2 (4%)	1 (2%)
Thyroid gland	(49)	(50)	(50)	(50)
Ultimobranchial cyst		1 (2%)		1 (2%)
Artery, polyarteritis				1 (2%)
Bilateral, C-cell, hyperplasia		1 (2%)		
C-cell, hyperplasia			3 (6%)	1 (2%)
C-cell, hyperplasia, focal	7 (14%)	3 (6%)	3 (6%)	3 (6%)
Follicle, cyst	4 (8%)	5 (10%)	6 (12%)	5 (10%)
Follicular cell, degeneration				1 (2%)
Follicular cell, hyperplasia		1 (2%)	1 (2%)	
General Body System				
None				
Genital System				
Coagulating gland			(1)	
Inflammation, suppurative			1 (100%)	
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	1 (2%)			
Preputial gland	(50)	(50)	(50)	(49)
Abscess			1 (2%)	1 (2%)
Atrophy	6 (12%)	13 (26%)	16 (32%)	13 (27%)
Atrophy, multiple		3 (6%)	1 (2%)	
Autolysis			1 (2%)	
Cyst	7 (14%)	18 (36%)	24 (48%)	16 (33%)
Cyst, multiple	2 (4%)	4 (8%)	7 (14%)	1 (2%)
Hyperplasia	2 (4%)		5 (10%)	2 (4%)
Hyperplasia, focal	1 (2%)	3 (6%)		
Inflammation, chronic	2 (4%)	1 (2%)	1 (2%)	
Inflammation, suppurative	3 (6%)	5 (10%)	3 (6%)	2 (4%)
Bilateral, atrophy				4 (8%)
Prostate	(50)	(50)	(50)	(50)
Cyst	1 (2%)			3 (6%)
Inflammation, chronic	4 (8%)	6 (12%)	2 (4%)	3 (6%)
Inflammation, suppurative	24 (48%)	15 (30%)	17 (34%)	17 (34%)
Epithelium, hyperplasia		1 (2%)		
Seminal vesicle	(50)	(50)	(50)	(50)
Atrophy	12 (24%)	12 (24%)	7 (14%)	2 (4%)
Hyperplasia, glandular			1 (2%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Genital System (continued)				
Testes	(50)	(50)	(50)	(50)
Atrophy	16 (32%)	13 (26%)	15 (30%)	17 (34%)
Necrosis				1 (2%)
Arteriole, inflammation, chronic				1 (2%)
Bilateral, atrophy		1 (2%)	2 (4%)	1 (2%)
Bilateral, interstitial cell, hyperplasia	3 (6%)	5 (10%)	3 (6%)	5 (10%)
Interstitial cell, atrophy			2 (4%)	
Interstitial cell, hyperplasia	16 (32%)	6 (12%)	15 (30%)	10 (20%)
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(49)
Myelofibrosis		1 (2%)	2 (4%)	2 (4%)
Myeloid cell, hyperplasia	1 (2%)			
Lymph node	(50)	(50)	(50)	(50)
Iliac, cyst				1 (2%)
Inguinal, hyperplasia, lymphoid	3 (6%)		1 (2%)	3 (6%)
Mediastinal, angiectasis	9 (18%)	5 (10%)	2 (4%)	2 (4%)
Mediastinal, cyst, multiple			1 (2%)	
Mediastinal, hyperplasia, lymphoid	2 (4%)	2 (4%)	1 (2%)	
Mediastinal, pigmentation	2 (4%)		1 (2%)	4 (8%)
Pancreatic, angiectasis	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Pancreatic, cyst, multiple			1 (2%)	
Pancreatic, hyperplasia, lymphoid	1 (2%)	1 (2%)		3 (6%)
Pancreatic, pigmentation	2 (4%)			
Renal, angiectasis				4 (8%)
Renal, hyperplasia, lymphoid			1 (2%)	1 (2%)
Renal, pigmentation			1 (2%)	
Lymph node, mandibular	(50)	(48)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Cyst				1 (2%)
Cyst, multiple	3 (6%)	6 (13%)	3 (6%)	
Fibrosis			1 (2%)	
Hyperplasia, lymphoid	4 (8%)	3 (6%)	3 (6%)	2 (4%)
Lymph node, mesenteric	(49)	(48)	(49)	(48)
Angiectasis	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Edema	1 (2%)			1 (2%)
Hemorrhage		1 (2%)		
Hyperplasia, lymphoid	1 (2%)	6 (13%)	1 (2%)	1 (2%)
Spleen	(50)	(49)	(50)	(50)
Congestion		7 (14%)		
Fibrosis, focal	7 (14%)	5 (10%)	8 (16%)	9 (18%)
Hematopoietic cell proliferation	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, histiocytic, lymphoid			1 (2%)	
Inflammation, granulomatous, multiple			1 (2%)	
Necrosis			2 (4%)	1 (2%)
Capsule, hypertrophy		1 (2%)		
Pigmentation				1 (2%)
Thymus	(45)	(48)	(42)	(47)
Fibrosis			1 (2%)	
Hyperplasia, lymphoid	1 (2%)	1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(48)	(49)	(47)	(50)
Hyperplasia, lobular	10 (21%)	21 (43%)	13 (28%)	23 (46%)
Duct, cyst	7 (15%)	17 (35%)	16 (34%)	7 (14%)
Duct, hemorrhage	1 (2%)	3 (6%)		
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Hyperkeratosis		1 (2%)		
Inflammation, suppurative				1 (2%)
Ulcer				1 (2%)
Dermis, fibrosis		1 (2%)		
Epidermis, hyperplasia	1 (2%)			1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Calvarium, hyperostosis				1 (2%)
Fibrous osteodystrophy		1 (2%)	1 (2%)	
Osteoporosis	1 (2%)			
Femur, fibrous osteodystrophy				4 (8%)
Maxilla, fibrous osteodystrophy				3 (6%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	6 (12%)	3 (6%)	4 (8%)	2 (4%)
Hemorrhage	2 (4%)		3 (6%)	1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Atelectasis, focal	1 (2%)			
Erythrophagocytosis		1 (2%)		
Hemorrhage, focal		1 (2%)		
Hemorrhage, multiple				1 (2%)
Infiltration cellular, lymphocyte		1 (2%)		
Infiltration cellular, histiocyte, focal			4 (8%)	
Infiltration cellular, histiocyte, multiple		2 (4%)		
Inflammation, granulomatous, focal		2 (4%)	1 (2%)	
Inflammation, granulomatous, multiple	3 (6%)			1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)		
Mineralization				1 (2%)
Alveolar epithelium, hyperplasia	2 (4%)		1 (2%)	
Alveolar epithelium, hyperplasia, focal		1 (2%)	1 (2%)	
Alveolus, pigmentation				1 (2%)
Mediastinum, polyarteritis, multiple				1 (2%)
Mediastinum, thrombus, multiple				1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(50)
Metaplasia, squamous				2 (4%)
Lumen, foreign body	1 (2%)	3 (6%)	5 (10%)	2 (4%)
Lumen, fungus	10 (20%)	9 (18%)	9 (18%)	14 (28%)
Lumen, inflammation, suppurative	9 (18%)	12 (24%)	13 (26%)	14 (28%)
Respiratory epithelium, hyperkeratosis			1 (2%)	
Respiratory epithelium, hyperplasia			1 (2%)	
Septum, inflammation, chronic			1 (2%)	
Submucosa, inflammation, suppurative			1 (2%)	
Submucosa, pigmentation		45 (90%)	37 (74%)	45 (90%)
Special Senses System				
Eye	(1)	(1)	(2)	(2)
Cataract	1 (100%)	1 (100%)		1 (50%)
Retina, degeneration	1 (100%)	1 (100%)	1 (50%)	1 (50%)
Harderian gland				(2)
Hemorrhage				1 (50%)
Urinary System				
Kidney	(49)	(50)	(50)	(49)
Cyst	1 (2%)	2 (4%)	2 (4%)	6 (12%)
Cyst, multiple		1 (2%)		7 (14%)
Hydronephrosis				1 (2%)
Nephropathy, chronic	49 (100%)	50 (100%)	50 (100%)	49 (100%)
Renal tubule, hyperplasia		3 (6%)		2 (4%)
Renal tubule, mineralization		2 (4%)		
Renal tubule, pigmentation	45 (92%)	41 (82%)	48 (96%)	46 (94%)
Transitional epithelium, hyperplasia	7 (14%)	9 (18%)	9 (18%)	30 (61%)
Ureter				(1)
Transitional epithelium, hyperplasia				1 (100%)
Urinary bladder	(50)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)
Transitional epithelium, hyperplasia				2 (4%)

[a] Number of animals examined microscopically at site and number of animals with lesion.
[b] Includes one animal killed moribund before the interim evaluation.

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR FEED STUDY OF *o*-NITROANISOLE

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

	0 ppm	222 ppm	666 ppm	2,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10[b]
Early deaths				
Moribund	17	7	18	14
Natural deaths		2	6	3
Survivors				
Terminal sacrifice	33	41	26	33
Animals examined microscopically	60	60	60	59
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(9)
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(10)	(3)	(1)	(9)
Pars distalis, adenoma		2 (67%)	1 (100%)	
Pars distalis, adenoma, multiple				1 (11%)
Thyroid gland	(10)		(1)	(9)
C-cell, adenoma				1 (11%)
C-cell, carcinoma			1 (100%)	1 (11%)
General Body System				
None				
Genital System				
Clitoral gland	(10)	(10)	(10)	(9)
Adenoma			1 (10%)	
Uterus	(10)	(10)	(10)	(9)
Polyp stromal	3 (30%)			2 (22%)
Hematopoietic System				
Spleen	(10)	(10)	(10)	(9)
Integumentary System				
None				
Musculoskeletal System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
15-Month Interim Evaluation (continued)				
Nervous System				
None				
Respiratory System				
Lung	(10)		(1)	(9)
Alveolar/bronchiolar adenoma			1 (100%)	
Special Senses System				
Ear			(1)	
Pinna, schwannoma malignant			1 (100%)	
Urinary System				
None				
Systemic Lesions				
Multiple organs[c]	(10)	(10)	(10)	(9)
Leukemia mononuclear			1 (10%)	
Neoplasm Summary				
Total animals with primary neoplasms[d]	3	2	5	3
Total primary neoplasms	3	2	6	5
Total animals with benign neoplasms	3	2	3	2
Total benign neoplasms	3	2	3	4
Total animals with malignant neoplasms			3	1
Total malignant neoplasms			3	1
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Intestine large, cecum	(50)	(49)	(46)	(49)
Intestine large, colon	(50)	(49)	(46)	(49)
Intestine large, rectum	(50)	(49)	(46)	(49)
Intestine small, ileum	(50)	(49)	(46)	(48)
Intestine small, jejunum	(50)	(49)	(47)	(48)
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma				3 (6%)
Sarcoma stromal, metastatic, uterus			1 (2%)	
Mesentery	(9)	(6)	(11)	(12)
Hemangiosarcoma		1 (17%)		
Fat, fibrosarcoma	1 (11%)			
Fat, lipoma		1 (17%)		
Fat, sarcoma stromal, metastatic, uterus			1 (9%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(50)	(50)	(49)	(50)
Acinar cell, adenoma				1 (2%)
Acinar cell, adenoma, multiple				1 (2%)
Pharynx			(2)	
Palate, squamous cell carcinoma			1 (50%)	
Salivary glands	(50)	(49)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma		1 (2%)		1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Tongue	(1)			
Squamous cell papilloma	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Adenoma	1 (2%)	5 (10%)		2 (4%)
Adrenal gland, medulla	(50)	(50)	(50)	(49)
Pheochromocytoma malignant			1 (2%)	1 (2%)
Pheochromocytoma benign	1 (2%)			1 (2%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Adenoma	2 (4%)	1 (2%)	2 (4%)	
Carcinoma			1 (2%)	
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	28 (56%)	28 (56%)	27 (54%)	19 (38%)
Pars distalis, carcinoma	1 (2%)			
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, c-cell, adenoma	1 (2%)			
C-cell, adenoma	4 (8%)	3 (6%)	2 (4%)	3 (6%)
C-cell, adenoma, multiple		1 (2%)		
C-cell, carcinoma	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Follicular cell, adenoma			1 (2%)	
Follicular cell, carcinoma		2 (4%)	1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(45)	(47)	(50)	(48)
Adenoma	3 (7%)	5 (11%)	3 (6%)	3 (6%)
Carcinoma	4 (9%)	1 (2%)	2 (4%)	2 (4%)
Bilateral, carcinoma			1 (2%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Genital System (continued)				
Ovary	(50)	(50)	(50)	(50)
Thecoma benign		1 (2%)		
Uterus	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma				1 (2%)
Leiomyoma				1 (2%)
Leiomyosarcoma		1 (2%)		
Polyp stromal	9 (18%)	13 (26%)	8 (16%)	8 (16%)
Polyp stromal, multiple				1 (2%)
Sarcoma stromal			3 (6%)	1 (2%)
Cervix, adenocarcinoma				1 (2%)
Cervix, leiomyoma	1 (2%)			
Cervix, leiomyosarcoma			1 (2%)	
Vagina		(3)	(1)	(3)
Polyp			1 (100%)	
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(49)
Lymph node	(50)	(50)	(50)	(50)
Lymph node, mandibular	(48)	(49)	(50)	(50)
Lymph node, mesenteric	(48)	(50)	(50)	(47)
Spleen	(50)	(50)	(50)	(50)
Sarcoma		1 (2%)		
Thymus	(47)	(49)	(47)	(48)
Thymoma benign	1 (2%)			
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenocarcinoma	2 (4%)		2 (4%)	
Adenoma	1 (2%)			
Carcinoma				1 (2%)
Fibroadenoma	17 (34%)	17 (34%)	12 (24%)	8 (16%)
Fibroadenoma, multiple		1 (2%)	3 (6%)	1 (2%)
Skin	(50)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)			
Subcutaneous tissue, fibroma		2 (4%)		
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, lipoma		1 (2%)		
Subcutaneous tissue, sarcoma			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Maxilla, squamous cell carcinoma, metastatic, nose	1 (2%)			
Skeletal muscle	(1)		(1)	(1)
Abdominal, lipoma			1 (100%)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland	1 (2%)			
Sarcoma			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			2 (4%)	3 (6%)
Squamous cell carcinoma				1 (2%)
Nose	(50)	(50)	(50)	(50)
Respiratory epithelium, squamous cell carcinoma	1 (2%)			
Special Senses System				
Eye		(4)	(1)	(5)
Harderian gland	(1)	(2)		(2)
Zymbal's gland	(1)	(1)		(1)
Carcinoma	1 (100%)	1 (100%)		1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Myxosarcoma			1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Transitional epithelium, carcinoma				1 (2%)
Transitional epithelium, papilloma				1 (2%)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Leukemia mononuclear	14 (28%)	11 (22%)	14 (28%)	26 (52%)
Neoplasm Summary				
Total animals with primary neoplasms	46	46	46	46
Total primary neoplasms	99	101	93	95
Total animals with benign neoplasms	40	44	38	35
Total benign neoplasms	73	80	62	57
Total animals with malignant neoplasms	21	18	27	32
Total malignant neoplasms	26	21	31	38
Total animals with metastatic neoplasms	2		1	
Total metastatic neoplasms	2		2	

[a] Number of animals examined microscopically at site and number of animals with lesion.
[b] Includes one animal killed moribund before the interim evaluation.
[c] Number of animals with any tissue examined microscopically
[d] Primary neoplasms: all neoplasms except metastatic neoplasms

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

Number of Days on Study	4 3 8	4 8 0	4 9 4	5 1 8	6 1 3	6 1 3	6 3 4	6 6 3	6 6 9	6 7 3	6 8 7	6 8 7	6 9 4	7 0 0	7 0 0	7 0 0	7 2 3	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 5 6 1	0 5 3 1	0 5 7 1	0 5 5 1	0 5 3 2	0 5 4 1	0 5 0 1	0 5 6 2	0 5 0 2	0 5 0 3	0 5 0 4	0 5 7 2	0 5 2 1	0 5 2 2	0 5 2 3	0 5 7 3	0 5 5 2	0 4 9 1	0 4 9 2	0 4 9 3	0 4 9 4	0 4 9 5	0 5 0 5	0 5 1 1	0 5 1 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+			+			+				+							+				+	
Fat, fibrosarcoma						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																				+					
Squamous cell papilloma																				X					
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X	X			X	X	X		X		X	X	X					X	X	X	X
Pars distalis, carcinoma																									
Pars intermedia, adenoma									X																
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma																								X	
C-cell, carcinoma									X																

+: 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 *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	05113	05114	05142	05163	05215	05224	05225	05233	05243	05253	05263	05274	05284	05295	05303	05315	05325	05336	05346	05357	05371	05382	05393	05404	05415	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery														+	+		+									9
Fat, fibrosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Squamous cell papilloma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					2
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X	X		X	X	X		X	X			X			X	X	X	X		X	X	28
Pars distalis, carcinoma			X																							1
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma			X																							1
C-cell, adenoma	X							X								X										4
C-cell, carcinoma																								X		2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	4 3 8	4 8 0	4 9 4	5 1 8	6 1 3	6 1 3	6 3 4	6 6 3	6 6 9	6 7 3	6 8 7	6 8 7	6 9 4	7 0 0	7 0 0	7 0 0	7 2 3	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 5 6 1	0 5 3 1	0 5 7 1	0 5 5 1	0 5 3 2	0 5 4 1	0 5 0 1	0 5 6 2	0 5 0 2	0 5 0 3	0 5 0 4	0 5 7 2	0 5 2 1	0 5 2 2	0 5 2 3	0 5 7 3	0 5 5 2	0 4 9 1	0 4 9 2	0 4 9 3	0 4 9 4	0 4 9 5	0 5 0 5	0 5 1 1	0 5 1 2
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+
Adenoma																									
Carcinoma				X																					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								X	
Polyp stromal	X	X																		X					
Cervix, leiomyoma									X																
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Adenoma																									
Fibroadenoma	X	X			X							X										X			X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Maxilla, squamous cell carcinoma, metastatic, nose							X																		
Skeletal muscle																				+					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	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 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	
Carcass ID Number	0 5 1 3	0 5 1 4	0 5 4 2	0 5 6 3	0 5 1 5	0 5 2 4	0 5 2 5	0 5 3 3	0 5 3 4	0 5 3 5	0 5 4 3	0 5 4 4	0 5 4 5	0 5 5 3	0 5 5 4	0 5 5 5	0 5 6 4	0 5 6 5	0 5 7 4	0 5 7 5	0 5 8 1	0 5 8 2	0 5 8 3	0 5 8 4	0 5 8 5	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma											X										X			X		3
Carcinoma							X									X		X								4
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Polyp stromal		X										X	X						X		X	X				9
Cervix, leiomyoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymoma benign										X																1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma								X								X										2
Adenoma																					X					1
Fibroadenoma				X		X		X		X	X	X	X	X				X	X			X				17
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma				X																						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Maxilla, squamous cell carcinoma, metastatic, nose																										1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland			X																							1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	4	4	4	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	8	9	1	1	1	3	6	6	7	8	8	9	0	0	0	2	2	2	2	2	2	2	2	2	2	2
	8	0	4	8	3	3	4	3	9	3	7	7	4	0	0	0	3	8	8	8	8	8	9	9	9	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	4	4	4	4	4	5	5	5	5
	6	3	7	5	3	4	0	6	0	0	0	7	2	2	2	7	5	9	9	9	9	9	0	1	1	1	1
	1	1	1	1	2	1	1	2	2	3	4	2	1	2	3	3	2	1	2	3	4	5	5	1	2	1	2
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, squamous cell carcinoma						X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																											
Harderian gland							+																				
Lacrimal gland						+																					
Zymbal's gland											+																
Carcinoma											X																
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X				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 *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	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 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	
Carcass ID Number	0 5 1 3	0 5 1 4	0 5 4 2	0 5 6 3	0 5 1 5	0 5 2 4	0 5 2 5	0 5 3 3	0 5 3 4	0 5 3 5	0 5 4 3	0 5 4 4	0 5 4 5	0 5 5 3	0 5 5 4	0 5 5 5	0 5 6 4	0 5 6 5	0 5 7 4	0 5 7 5	0 5 8 1	0 5 8 2	0 5 8 3	0 5 8 4	0 5 8 5	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory epithelium, squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										1
Lacrimal gland																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X												X					X		X						14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm

Number of Days on Study	3 3 3	4 3 6	5 3 3	5 9 8	6 4 6	6 7 2	7 2 3	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	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 1	7 3 1	7 3 1	7 3 2	7 3 2
Carcass ID Number	0 9 1 1	0 9 1 2	0 8 7 1	0 8 9 1	0 9 4 1	0 8 8 2	0 8 5 1	0 8 5 2	0 9 1 3	0 8 5 3	0 8 5 4	0 8 5 5	0 8 6 1	0 8 6 2	0 8 6 3	0 8 6 4	0 8 6 5	0 8 7 2	0 8 7 3	0 8 9 2	0 8 7 4	0 8 7 5	0 8 8 1	0 8 8 3	0 8 8 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																	+								+
Hemangiosarcoma																									
Fat, lipoma																	X								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X																
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X	X		X												
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X		X		X	X	X	X		X	X		X	X		X				X		X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, adenoma, multiple																									
C-cell, carcinoma										X													X		
Follicular cell, carcinoma									X																
General Body System																									
Tissue NOS		+																							

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm (continued)

Number of Days on Study	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 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 8 8 5	0 8 9 3	0 8 9 4	0 8 9 5	0 9 0 1	0 9 0 2	0 9 0 3	0 9 0 4	0 9 0 5	0 9 1 4	0 9 1 5	0 9 2 1	0 9 2 2	0 9 2 3	0 9 2 4	0 9 2 5	0 9 3 1	0 9 3 2	0 9 3 3	0 9 3 4	0 9 3 5	0 9 4 2	0 9 4 3	0 9 4 4	0 9 4 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+		+									+				+							6
Hemangiosarcoma																			X							1
Fat, lipoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X							X			5
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X	X	X	X	X	X	X		X		X	X				X			X				28
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma					X		X	X																		3
C-cell, adenoma, multiple																X										1
C-cell, carcinoma																										2
Follicular cell, carcinoma																									X	2
General Body System																										
Tissue NOS																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm (continued)

Number of Days on Study	3 3 3	4 3 6	5 3 3	5 9 8	6 4 6	6 7 2	7 2 3	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	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 1	7 3 1	7 3 1	7 3 2	7 3 2
Carcass ID Number	0 9 1 1	0 9 1 2	0 8 7 1	0 8 9 1	0 9 4 1	0 8 8 2	0 8 5 1	0 8 5 2	0 9 1 3	0 8 5 3	0 8 5 4	0 8 5 5	0 8 6 1	0 8 6 2	0 8 6 3	0 8 6 4	0 8 6 5	0 8 7 2	0 8 7 3	0 8 9 2	0 8 7 4	0 8 7 5	0 8 8 1	0 8 8 3	0 8 8 4
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma											X														
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thecoma benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma					X																				
Polyp stromal					X															X			X		
Vagina	+								+																
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma								X																	
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma		X					X	X							X	X	X				X	X	X	X	X
Fibroadenoma, multiple																				X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																	X								
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm (continued)

Number of Days on Study	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 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 5	7 3 5	7 3 5	
Carcass ID Number	0 8 8 5	0 8 9 3	0 8 9 4	0 8 9 5	0 9 0 1	0 9 0 2	0 9 0 3	0 9 0 4	0 9 0 5	0 9 1 4	0 9 1 5	0 9 2 1	0 9 2 2	0 9 2 3	0 9 2 4	0 9 2 5	0 9 3 1	0 9 3 2	0 9 3 3	0 9 3 4	0 9 3 5	0 9 4 2	0 9 4 3	0 9 4 4	0 9 4 5	Total Tissues/ Tumors
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		47
Adenoma								X				X			X	X											5
Carcinoma																									X		1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thecoma benign																							X				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leiomyosarcoma																											1
Polyp stromal			X		X		X				X		X					X	X		X	X	X				13
Vagina			+																								3
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Sarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Fibroadenoma		X				X			X									X	X		X						17
Fibroadenoma, multiple																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Subcutaneous tissue, fibroma			X																		X						2
Subcutaneous tissue, fibrosarcoma																											1
Subcutaneous tissue, lipoma													X														1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm (continued)

Number of Days on Study	3	4	5	5	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	3	3	9	4	7	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	3	3	3	3
	3	6	3	8	6	2	3	7	7	8	8	8	9	9	9	9	9	9	9	9	1	1	1	2	2
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	9	9	8	8	9	8	8	8	9	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
	1	1	7	9	4	8	5	5	1	5	5	5	6	6	6	6	6	7	7	9	7	7	8	8	8
	1	2	1	1	1	2	1	2	3	3	4	5	1	2	3	4	5	2	3	2	4	5	1	3	4
Special Senses System																									
Eye									+															+	
Harderian gland												+													
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ureter							M																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X	X								X						X			X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 222 ppm (continued)

Number of Days on Study	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 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 5	7 3 5	7 3 5	
Carcass ID Number	0 8 8 5	0 8 9 3	0 8 9 4	0 8 9 5	0 9 0 1	0 9 0 2	0 9 0 3	0 9 0 4	0 9 0 5	0 9 1 4	0 9 1 5	0 9 2 1	0 9 2 2	0 9 2 3	0 9 2 4	0 9 2 5	0 9 3 1	0 9 3 2	0 9 3 3	0 9 3 4	0 9 3 5	0 9 4 2	0 9 4 3	0 9 4 4	0 9 4 5	Total Tissues/ Tumors
Special Senses System																											
Eye								+													+					4
Harderian gland															+											2
Zymbal's gland								+																		1
Carcinoma								X																		1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ureter																											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X											X					X	X					X			11

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm

Number of Days on Study	3 0 2	4 1 6	4 5 9	5 2 5	5 3 3	5 3 6	5 6 3	5 7 1	5 7 1	5 8 9	6 1 0	6 1 3	6 3 0	6 3 2	6 3 3	6 4 1	6 4 6	6 5 8	6 8 3	6 8 3	6 9 5	7 1 0	7 1 6	7 1 9	7 2 9
Carcass ID Number	0 7 5 1	0 7 5 2	0 7 6 1	0 8 0 1	0 8 1 1	0 7 3 5	0 7 9 1	0 8 2 1	0 8 2 2	0 7 4 1	0 7 3 1	0 8 0 2	0 7 5 3	0 8 1 2	0 8 2 3	0 7 7 1	0 7 5 4	0 7 3 2	0 7 8 1	0 8 2 4	0 7 6 2	0 8 0 3	0 7 6 3	0 7 4 2	0 7 3 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+
Intestine small	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal, metastatic, uterus			X																						
Mesentery			+	+			+	+	+									+		+	+				
Fat, sarcoma stromal, metastatic, uterus			X																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																		+							
Palate, squamous cell carcinoma																		X							
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant												X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X					X					
Carcinoma											X														
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X			X	X		X		X	X	X	X		X		X	X	X	X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma																									
Follicular cell, adenoma													X												
Follicular cell, carcinoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	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 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 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 7 3 4	0 7 4 3	0 7 4 4	0 7 4 5	0 7 5 5	0 7 6 4	0 7 6 5	0 7 7 2	0 7 7 3	0 7 7 4	0 7 7 5	0 7 8 2	0 7 8 3	0 7 8 4	0 7 8 5	0 7 9 2	0 7 9 3	0 7 9 4	0 7 9 5	0 8 0 4	0 8 0 5	0 8 1 3	0 8 1 4	0 8 1 5	0 8 2 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma stromal, metastatic, uterus																										1
Mesentery				+		+													+							11
Fat, sarcoma stromal, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pharynx								+																		2
Palate, squamous cell carcinoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										2
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X		X			X	X	X	X	X	X	X	X			X	X		X			27
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X																	X	2
C-cell, carcinoma																							X			1
Follicular cell, adenoma																										1
Follicular cell, carcinoma	X																									1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	3	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	
	0	1	5	2	3	3	6	7	7	8	1	1	3	3	3	4	4	5	8	8	9	1	1	1	2
	2	6	9	5	3	6	3	1	1	9	0	3	0	2	3	1	6	8	3	3	5	0	6	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	7	7	8	8	7	7	8	8	7	7	8	7	8	8	7	7	7	7	8	7	8	7	7	7
	5	5	6	0	1	3	9	2	2	4	3	0	5	1	2	7	5	3	8	2	6	0	6	4	3
	1	2	1	1	1	5	1	1	2	1	1	2	3	2	3	1	4	2	1	4	2	3	3	2	3
General Body System																									
Tissue NOS		+																							
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X				X			
Carcinoma																X		X							
Bilateral, carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X						X											X			
Sarcoma stromal			X														X							X	
Cervix, leiomyosarcoma																									
Vagina																								+	
Polyp																								X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma						X												X							
Fibroadenoma		X	X	X																					
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Abdominal, lipoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	729	729	729	729	730	000	000	000	000	011	111	111	111	111	122	222	222	225	555	555	555	555	735	
Carcass ID Number	07734	07743	07744	07745	07755	07764	07765	07772	07773	07774	07775	07782	07783	07784	07785	07792	07793	07794	07795	08004	08005	08013	08114	08125	**Total Tissues/ Tumors**
General Body System																									
Tissue NOS																									1
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X										3
Carcinoma																									2
Bilateral, carcinoma		X																							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal	X						X					X							X			X			8
Sarcoma stromal																									3
Cervix, leiomyosarcoma						X																			1
Vagina																									1
Polyp																									1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																									2
Fibroadenoma				X	X		X	X		X				X			X	X	X						12
Fibroadenoma, multiple	X					X																		X	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle											+														1
Abdominal, lipoma											X														1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	3	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	
	0	1	5	2	3	3	6	7	7	8	1	1	3	3	3	4	4	5	8	8	9	1	1	1	2
	2	6	9	5	3	6	3	1	1	9	0	3	0	2	3	1	6	8	3	3	5	0	6	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	7	7	7	8	8	7	7	8	8	7	7	8	7	8	8	7	7	7	7	8	7	8	7	7	7
	5	5	6	0	1	3	9	2	2	4	3	0	5	1	2	7	5	3	8	2	6	0	6	4	3
	1	2	1	1	1	5	1	1	2	1	1	2	3	2	3	1	4	2	1	4	2	3	3	2	3
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma						X																			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Myxosarcoma							X																		
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 *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	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 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 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 7 3 4	0 7 4 3	0 7 4 4	0 7 4 5	0 7 5 5	0 7 6 4	0 7 6 5	0 7 7 2	0 7 7 3	0 7 7 4	0 7 7 5	0 7 8 2	0 7 8 3	0 7 8 4	0 7 8 5	0 7 9 2	0 7 9 3	0 7 9 4	0 7 9 5	0 8 0 4	0 8 0 5	0 8 1 3	0 8 1 4	0 8 1 5	0 8 2 5	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X														X							2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye															+											1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Myxosarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X				X	X							X	X						14

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

Number of Days on Study	3 8 6	4 7 6	5 0 0	5 2 1	5 5 7	6 0 4	6 0 4	6 1 3	6 3 1	6 3 4	6 4 7	6 5 5	6 6 3	6 8 7	7 1 6	7 2 0	7 2 2	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 5	0 6 2 1	0 6 7 1	0 6 3 1	0 6 5 1	0 6 2 2	0 6 8 1	0 6 7 2	0 7 0 1	0 6 1 1	0 6 8 2	0 6 9 1	0 6 7 3	0 6 9 2	0 6 7 4	0 6 3 2	0 6 0 2	0 7 1 2	0 6 6 3	0 6 6 4	0 6 6 5	0 6 1 3	0 6 2 3	0 6 5 2	0 6 6 1	0 6 8 3
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X		
Mesentery			+						+			+		+		+			+		+				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell, adenoma																					X					
Acinar cell, adenoma, multiple																										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																										
Squamous cell papilloma																										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																										
Pheochromocytoma benign																		X								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X						X			X				X	X		X	X	X	X	X	X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X																
C-cell, carcinoma		X																								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	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 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 6 2 4	0 6 2 5	0 6 3 3	0 6 3 4	0 6 3 5	0 6 4 1	0 6 4 2	0 6 4 3	0 6 4 4	0 6 4 5	0 6 5 3	0 6 5 4	0 6 5 5	0 6 6 2	0 6 6 3	0 6 6 4	0 6 6 5	0 6 8 4	0 6 8 5	0 6 9 3	0 6 9 4	0 6 9 5	0 6 9 3	0 7 0 4	0 7 0 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma													X													2
Mesentery		+										+				+	+								+	12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell, adenoma																										1
Acinar cell, adenoma, multiple																X										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																									X	1
Squamous cell papilloma																							X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X							X												2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Pheochromocytoma malignant								X																		1
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X						X				X	X					X		X		X	19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X			X																						3
C-cell, carcinoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of o-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	3 8 6	4 7 6	5 0 0	5 2 1	5 5 7	6 0 4	6 0 4	6 1 3	6 3 1	6 3 4	6 4 7	6 5 5	6 6 3	6 8 7	7 1 6	7 2 0	7 2 2	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 5	0 6 2 1	0 6 7 1	0 6 3 1	0 6 5 1	0 6 2 2	0 6 8 1	0 6 7 2	0 7 0 1	0 6 6 1	0 6 8 2	0 6 9 1	0 6 7 3	0 6 9 2	0 6 7 4	0 7 3 2	0 6 0 2	0 7 1 2	0 6 1 3	0 6 1 4	0 6 1 5	0 6 2 3	0 6 5 2	0 6 6 1	0 6 8 3
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenoma																						X			X
Carcinoma																	X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Leiomyoma	X																								
Polyp stromal								X				X						X	X	X			X		
Polyp stromal, multiple																									
Sarcoma stromal											X														
Cervix, adenocarcinoma																									
Vagina									+		+												+		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X																							
Fibroadenoma										X	X									X			X		
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	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 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 6 2 4	0 6 2 5	0 6 3 3	0 6 3 4	0 6 3 5	0 6 4 1	0 6 4 2	0 6 4 3	0 6 4 4	0 6 4 5	0 6 5 3	0 6 5 4	0 6 5 5	0 6 6 2	0 6 6 3	0 6 6 4	0 6 6 5	0 6 8 4	0 6 8 5	0 6 9 3	0 6 9 4	0 6 9 5	0 7 0 3	0 7 0 4	0 7 0 5	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Adenoma												X														3
Carcinoma									X																	2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma														X												1
Leiomyoma																										1
Polyp stromal					X										X											8
Polyp stromal, multiple										X																1
Sarcoma stromal																										1
Cervix, adenocarcinoma											X															1
Vagina																										3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma	X																	X						X	X	8
Fibroadenoma, multiple															X											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	3	4	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7
	8	7	0	2	5	0	0	1	3	3	4	5	6	8	1	2	2	2	2	2	2	2	2	2	2
	6	6	0	1	7	4	4	3	1	4	7	5	3	7	6	0	2	9	9	9	9	9	9	9	9
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	6	6	6	6	6	6	6	6	7	6	6	6	6	6	6	6	7	6	6	6	6	6	6	6	6
	7	2	7	3	5	2	8	7	0	1	8	9	7	9	7	3	0	1	1	1	1	2	5	6	8
	5	1	1	1	1	2	1	2	1	1	2	1	3	2	4	2	2	2	3	4	5	3	2	1	3
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X								X										
Squamous cell carcinoma																								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye			+																+						
Harderian gland			+																		+				
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																									
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X		X	X		X		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 *o*-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	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 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 6 2 4	0 6 2 5	0 6 3 3	0 6 3 4	0 6 3 5	0 6 4 1	0 6 4 2	0 6 4 3	0 6 4 4	0 6 4 5	0 6 5 3	0 6 5 4	0 6 5 5	0 6 6 2	0 6 6 3	0 6 6 4	0 6 6 5	0 6 8 4	0 6 8 5	0 6 9 3	0 6 9 4	0 6 9 5	0 7 0 3	0 7 0 4	0 7 0 5	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X									3
Squamous cell carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+			+											+											5
Harderian gland																										2
Zymbal's gland																				+						1
Carcinoma																				X						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, carcinoma												X														1
Transitional epithelium, papilloma																				X						1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X			X				X		X		X	X	X			X	X		X			26

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

	0 ppm	222 ppm	666 ppm	2,000 ppm
Adrenal Cortex: Adenoma				
Overall rates[a]	1/50 (2%)	5/50 (10%)	0/50 (0%)	2/50 (4%)
Adjusted rates[b]	2.5%	12.2%	0.0%	6.1%
Terminal rates[c]	0/33 (0%)	5/41 (12%)	0/26 (0%)	2/33 (6%)
First incidence (days)	687	728 (T)	–[e]	728 (T)
Life table tests[d]	P=0.541N	P=0.156	P=0.557N	P=0.491
Logistic regression tests[d]	P=0.538N	P=0.123	P=0.506N	P=0.490
Cochran-Armitage test[d]	P=0.500N			
Fisher exact test[d]		P=0.102	P=0.500N	P=0.500
Clitoral Gland: Adenoma				
Overall rates	3/45 (7%)	5/47 (11%)	3/50 (6%)	3/48 (6%)
Adjusted rates	10.0%	13.2%	10.1%	9.7%
Terminal rates	3/30 (10%)	5/38 (13%)	1/26 (4%)	3/31 (10%)
First incidence (days)	728 (T)	728 (T)	658	728 (T)
Life table tests	P=0.495N	P=0.491	P=0.580	P=0.650N
Logistic regression tests	P=0.478N	P=0.491	P=0.642	P=0.650N
Cochran-Armitage test	P=0.426N			
Fisher exact test		P=0.382	P=0.610N	P=0.630N
Clitoral Gland: Carcinoma				
Overall rates	4/45 (9%)	1/47 (2%)	3/50 (6%)	2/48 (4%)
Adjusted rates	11.9%	2.6%	9.4%	6.1%
Terminal rates	3/30 (10%)	1/38 (3%)	1/26 (4%)	1/31 (3%)
First incidence (days)	518	728 (T)	641	722
Life table tests	P=0.483N	P=0.128N	P=0.579N	P=0.329N
Logistic regression tests	P=0.426N	P=0.171N	P=0.437N	P=0.309N
Cochran-Armitage test	P=0.422N			
Fisher exact test		P=0.167N	P=0.441N	P=0.308N
Clitoral Gland: Adenoma or Carcinoma				
Overall rates	7/45 (16%)	6/47 (13%)	5/50 (10%)	5/48 (10%)
Adjusted rates	21.7%	15.8%	16.2%	15.5%
Terminal rates	6/30 (20%)	6/38 (16%)	2/26 (8%)	4/31 (13%)
First incidence (days)	518	728 (T)	641	722
Life table tests	P=0.411N	P=0.333N	P=0.488N	P=0.360N
Logistic regression tests	P=0.361N	P=0.434N	P=0.353N	P=0.349N
Cochran-Armitage test	P=0.324N			
Fisher exact test		P=0.466N	P=0.307N	P=0.334N
Liver: Hepatocellular Adenoma				
Overall rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	0.0%	9.1%
Terminal rates	0/33 (0%)	0/41 (0%)	0/26 (0%)	3/33 (9%)
First incidence (days)	–	–	–	728 (T)
Life table tests	P=0.008	–	–	P=0.120
Logistic regression tests	P=0.008	–	–	P=0.120
Cochran-Armitage test	P=0.009			
Fisher exact test		–	–	P=0.121

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	0/50 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rates	0.0%	0.0%	7.7%	7.8%
Terminal rates	0/33 (0%)	0/41 (0%)	2/26 (8%)	1/33 (3%)
First incidence (days)	–	–	728 (T)	604
Life table tests	P=0.035	–	P=0.187	P=0.126
Logistic regression tests	P=0.036	–	P=0.187	P=0.122
Cochran-Armitage test	P=0.037			
Fisher exact test		–	P=0.247	P=0.121
Mammary Gland: Adenoma or Carcinoma				
Overall rates	3/50 (6%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted rates	9.1%	0.0%	5.2%	2.0%
Terminal rates	3/33 (9%)	0/41 (0%)	0/26 (0%)	0/33 (0%)
First incidence (days)	728 (T)	–	536	476
Life table tests	P=0.456N	P=0.086N	P=0.590N	P=0.306N
Logistic regression tests	P=0.409N	P=0.086N	P=0.492N	P=0.292N
Cochran-Armitage test	P=0.429N			
Fisher exact test		P=0.121N	P=0.500N	P=0.309N
Mammary Gland: Fibroadenoma				
Overall rates	17/50 (34%)	18/50 (36%)	15/50 (30%)	9/50 (18%)
Adjusted rates	44.5%	40.7%	49.5%	25.1%
Terminal rates	13/33 (39%)	15/41 (37%)	12/26 (46%)	7/33 (21%)
First incidence (days)	438	436	416	634
Life table tests	P=0.048N	P=0.397N	P=0.479	P=0.064N
Logistic regression tests	P=0.026N	P=0.500	P=0.426N	P=0.057N
Cochran-Armitage test	P=0.023N			
Fisher exact test		P=0.500	P=0.415N	P=0.055N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rates	17/50 (34%)	18/50 (36%)	15/50 (30%)	9/50 (18%)
Adjusted rates	44.5%	40.7%	49.5%	25.1%
Terminal rates	13/33 (39%)	15/41 (37%)	12/26 (46%)	7/33 (21%)
First incidence (days)	438	436	416	634
Life table tests	P=0.048N	P=0.397N	P=0.479	P=0.064N
Logistic regression tests	P=0.026N	P=0.500	P=0.426N	P=0.057N
Cochran-Armitage test	P=0.023N			
Fisher exact test		P=0.500	P=0.415N	P=0.055N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rates	18/50 (36%)	18/50 (36%)	17/50 (34%)	10/50 (20%)
Adjusted rates	47.3%	40.7%	52.1%	26.6%
Terminal rates	14/33 (42%)	15/41 (37%)	12/26 (46%)	7/33 (21%)
First incidence (days)	438	436	416	476
Life table tests	P=0.066N	P=0.314N	P=0.378	P=0.070N
Logistic regression tests	P=0.031N	P=0.580N	P=0.491N	P=0.058N
Cochran-Armitage test	P=0.031N			
Fisher exact test		P=0.582N	P=0.500N	P=0.059N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
Pancreatic Islets: Adenoma or Carcinoma				
Overall rates	2/50 (4%)	1/50 (2%)	3/49 (6%)	0/50 (0%)
Adjusted rates	5.4%	2.2%	8.2%	0.0%
Terminal rates	1/33 (3%)	0/41 (0%)	0/26 (0%)	0/33 (0%)
First incidence (days)	673	672	610	–
Life table tests	P=0.255N	P=0.456N	P=0.407	P=0.251N
Logistic regression tests	P=0.211N	P=0.505N	P=0.517	P=0.240N
Cochran-Armitage test	P=0.220N			
Fisher exact test		P=0.500N	P=0.490	P=0.247N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	28/50 (56%)	28/50 (56%)	27/50 (54%)	19/50 (38%)
Adjusted rates	66.3%	60.8%	66.3%	48.0%
Terminal rates	19/33 (58%)	23/41 (56%)	13/26 (50%)	13/33 (39%)
First incidence (days)	613	533	525	386
Life table tests	P=0.103N	P=0.214N	P=0.263	P=0.087N
Logistic regression tests	P=0.031N	P=0.492N	P=0.531	P=0.061N
Cochran-Armitage test	P=0.025N			
Fisher exact test		P=0.580N	P=0.500N	P=0.054N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rates	29/50 (58%)	28/50 (56%)	27/50 (54%)	19/50 (38%)
Adjusted rates	68.7%	60.8%	66.3%	48.0%
Terminal rates	20/33 (61%)	23/41 (56%)	13/26 (50%)	13/33 (39%)
First incidence (days)	613	533	525	386
Life table tests	P=0.085N	P=0.161N	P=0.312	P=0.062N
Logistic regression tests	P=0.023N	P=0.406N	P=0.560N	P=0.040N
Cochran-Armitage test	P=0.018N			
Fisher exact test		P=0.500N	P=0.420N	P=0.036N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rates	0/50 (0%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rates	0.0%	7.3%	2.2%	0.0%
Terminal rates	0/33 (0%)	3/41 (7%)	0/26 (0%)	0/33 (0%)
First incidence (days)	–	728 (T)	533	–
Life table tests	P=0.302N	P=0.162	P=0.500	–
Logistic regression tests	P=0.277N	P=0.162	P=0.623	–
Cochran-Armitage test	P=0.281N			
Fisher exact test		P=0.121	P=0.500	–
Thyroid Gland (C-cell): Adenoma				
Overall rates	5/50 (10%)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted rates	15.2%	9.8%	7.7%	8.4%
Terminal rates	5/33 (15%)	4/41 (10%)	2/26 (8%)	2/33 (6%)
First incidence (days)	728 (T)	728 (T)	728 (T)	634
Life table tests	P=0.382N	P=0.365N	P=0.319N	P=0.361N
Logistic regression tests	P=0.376N	P=0.365N	P=0.319N	P=0.372N
Cochran-Armitage test	P=0.331N			
Fisher exact test		P=0.500N	P=0.218N	P=0.357N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rates	7/50 (14%)	6/50 (12%)	3/50 (6%)	4/50 (8%)
Adjusted rates	20.1%	14.6%	11.5%	10.2%
Terminal rates	6/33 (18%)	6/41 (15%)	3/26 (12%)	2/33 (6%)
First incidence (days)	669	728 (T)	728 (T)	476
Life table tests	P=0.282N	P=0.344N	P=0.270N	P=0.275N
Logistic regression tests	P=0.251N	P=0.405N	P=0.252N	P=0.261N
Cochran-Armitage test	P=0.229N			
Fisher exact test		P=0.500N	P=0.159N	P=0.262N
Uterus: Stromal Polyp				
Overall rates	9/50 (18%)	13/50 (26%)	8/50 (16%)	9/50 (18%)
Adjusted rates	24.4%	30.8%	25.6%	25.1%
Terminal rates	7/33 (21%)	12/41 (29%)	5/26 (19%)	7/33 (21%)
First incidence (days)	438	646	533	613
Life table tests	P=0.473N	P=0.410	P=0.540	P=0.590
Logistic regression tests	P=0.405N	P=0.234	P=0.489N	P=0.600N
Cochran-Armitage test	P=0.384N			
Fisher exact test		P=0.235	P=0.500N	P=0.602N
Uterus: Stromal Sarcoma				
Overall rates	0/50 (0%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rates	0.0%	0.0%	8.5%	2.5%
Terminal rates	0/33 (0%)	0/41 (0%)	0/26 (0%)	0/33 (0%)
First incidence (days)	–	–	459	647
Life table tests	P=0.370	–	P=0.097	P=0.486
Logistic regression tests	P=0.403	–	P=0.163	P=0.512
Cochran-Armitage test	P=0.387			
Fisher exact test		–	P=0.121	P=0.500
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	9/50 (18%)	13/50 (26%)	11/50 (22%)	10/50 (20%)
Adjusted rates	24.4%	30.8%	31.9%	26.9%
Terminal rates	7/33 (21%)	12/41 (29%)	5/26 (19%)	7/33 (21%)
First incidence (days)	438	646	459	613
Life table tests	P=0.538	P=0.410	P=0.248	P=0.485
Logistic regression tests	P=0.492N	P=0.234	P=0.452	P=0.506
Cochran-Armitage test	P=0.485N			
Fisher exact test		P=0.235	P=0.402	P=0.500
All Organs: Mononuclear Cell Leukemia				
Overall rates	14/50 (28%)	11/50 (22%)	14/50 (28%)	26/50 (52%)
Adjusted rates	32.7%	24.6%	37.3%	58.5%
Terminal rates	6/33 (18%)	8/41 (20%)	5/26 (19%)	15/33 (45%)
First incidence (days)	494	533	302	500
Life table tests	P=0.001	P=0.204N	P=0.351	P=0.024
Logistic regression tests	P<0.001	P=0.339N	P=0.523N	P=0.013
Cochran-Armitage test	P<0.001			
Fisher exact test		P=0.322N	P=0.588N	P=0.012

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of o-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
All Organs: Benign Neoplasms				
Overall rates	40/50 (80%)	44/50 (88%)	38/50 (76%)	35/50 (70%)
Adjusted rates	88.7%	91.7%	88.0%	83.1%
Terminal rates	28/33 (85%)	37/41 (90%)	21/26 (81%)	26/33 (79%)
First incidence (days)	438	436	416	386
Life table tests	P=0.284N	P=0.280N	P=0.196	P=0.266N
Logistic regression tests	P=0.057N	P=0.237	P=0.544N	P=0.204N
Cochran-Armitage test	P=0.046N			
Fisher exact test		P=0.207	P=0.405N	P=0.178N
All Organs: Malignant Neoplasms				
Overall rates	21/50 (42%)	18/50 (36%)	27/50 (54%)	32/50 (64%)
Adjusted rates	47.5%	39.0%	60.0%	70.6%
Terminal rates	11/33 (33%)	13/41 (32%)	9/26 (35%)	20/33 (61%)
First incidence (days)	494	533	302	476
Life table tests	P=0.007	P=0.173N	P=0.066	P=0.045
Logistic regression tests	P=0.005	P=0.353N	P=0.265	P=0.025
Cochran-Armitage test	P=0.004			
Fisher exact test		P=0.341N	P=0.158	P=0.022
All Organs: Benign or Malignant Neoplasms				
Overall rates	46/50 (92%)	46/50 (92%)	46/50 (92%)	46/50 (92%)
Adjusted rates	92.0%	95.8%	92.0%	93.8%
Terminal rates	29/33 (88%)	39/41 (95%)	22/26 (85%)	30/33 (91%)
First incidence (days)	438	436	302	386
Life table tests	P=0.284	P=0.083N	P=0.116	P=0.523
Logistic regression tests	P=0.586N	P=0.626N	P=0.508N	P=0.627N
Cochran-Armitage test	P=0.589			
Fisher exact test		P=0.643N	P=0.643N	P=0.643N

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

TABLE B4a
Historical Incidence of Leukemia in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
C.I. Pigment Red 3	10/50
Nitrofuratoin	13/50
o-Nitroanisole	14/50
Polysorbate 80	26/50
Rhodamine 6G	11/50
Roxarsone	14/50
Overall Historical Incidence	
Total	213/800 (26.6%)
Standard deviation	8.8%
Range	14%-52%

[a] Data as of 3 April 1991

TABLE B4b
Historical Incidence of Liver Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
C.I. Pigment Red 3	0/50	0/50	0/50
Nitrofurantoin	0/50	0/50	0/50
o-Nitroanisole	0/50	0/50	0/50
Polysorbate 80	0/50	0/50	0/50
Rhodamine 6G	0/50	0/50	0/50
Roxarsone	0/50	0/50	0/50
Overall Historical Incidence			
Total	3/800 (0.4%)	1/800 (0.1%)	4/800 (0.5%)
Standard deviation	1.5%	0.5%	1.6%
Range	0%-6%	0%-2%	0%-6%

[a] Data as of 3 April 1991

TABLE B4c
Historical Incidence of Squamous Cell Papillomas and Carcinomas of the Forestomach in Untreated Female F344/N Rats[a]

Study	Incidence in Controls	
	Squamous Cell Papilloma	Squamous Cell Carcinoma
Historical Incidence at Southern Research Institute		
C.I. Pigment Red 3	0/50	0/50
Nitrofurantoin	0/50	0/50
o-Nitroanisole	0/50	0/50
Polysorbate 80	0/50	0/50
Rhodamine 6G	0/50	0/50
Roxarsone	1/50	0/50
Overall Historical Incidence		
Total	1/800 (0.1%)	0/800 (0.0%)
Standard deviation	0.5%	
Range	0%-2%	

[a] Data as of 3 April 1991

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

	0 ppm	222 ppm	666 ppm	2,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10[b]
Early deaths				
Moribund	17	7	18	14
Natural deaths		2	6	3
Survivors				
Terminal sacrifice	33	41	26	33
Animals examined microscopically	60	60	60	59
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)			(9)
Parasite metazoan	2 (20%)			1 (11%)
Liver	(10)	(10)	(10)	(9)
Basophilic focus	2 (20%)		4 (40%)	2 (22%)
Basophilic focus, multiple	7 (70%)	9 (90%)	5 (50%)	1 (11%)
Clear cell focus		1 (10%)		
Eosinophilic focus			1 (10%)	
Hepatodiaphragmatic nodule			1 (10%)	1 (11%)
Inflammation, granulomatous, multiple	5 (50%)	5 (50%)	2 (20%)	5 (56%)
Mixed cell focus	1 (10%)		2 (20%)	1 (11%)
Necrosis				1 (11%)
Bile duct, hyperplasia	3 (30%)	1 (10%)	4 (40%)	4 (44%)
Hepatocyte, Kupffer cell, pigmentation				1 (11%)
Mesentery	(1)	(2)		(4)
Fat, inflammation, granulomatous, focal		1 (50%)		3 (75%)
Fat, necrosis, focal	1 (100%)	1 (50%)		2 (50%)
Stomach, forestomach	(10)	(1)		(9)
Epithelium, hyperplasia		1 (100%)		1 (11%)
Cardiovascular System				
Heart	(10)			(9)
Inflammation, chronic	1 (10%)			2 (22%)
Endocrine System				
Adrenal gland, cortex	(10)			(9)
Spindle cell, hyperplasia, focal	1 (10%)			
Pituitary gland	(10)	(3)	(1)	(9)
Pars distalis, cyst, multiple		1 (33%)	1 (100%)	1 (11%)
Pars distalis, hyperplasia, focal	1 (10%)			
Pars intermedia, cyst				1 (11%)
General Body System				
None				

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Clitoral gland	(10)	(10)	(10)	(9)
Cyst	3 (30%)	2 (20%)	3 (30%)	1 (11%)
Cyst, multiple			1 (10%)	
Hyperplasia				2 (22%)
Ovary	(10)			
Cyst	1 (10%)			
Bilateral, cyst	1 (10%)			
Uterus	(10)	(10)	(10)	(9)
Dilatation	2 (20%)	1 (10%)	1 (10%)	1 (11%)
Cervix, abscess		1 (10%)		
Cervix, cyst		1 (10%)		
Endometrium, hyperplasia, cystic	2 (20%)	1 (10%)		
Hematopoietic System				
Bone marrow	(10)			(9)
Hyperplasia, reticulum cell	1 (10%)			
Lymph node	(10)			(9)
Mediastinal, hyperplasia, lymphoid	1 (10%)			
Pancreatic, pigmentation	1 (10%)			
Spleen	(10)	(10)	(10)	(9)
Hematopoietic cell proliferation		10 (100%)	8 (80%)	
Pigmentation		10 (100%)	10 (100%)	1 (11%)
Capsule, hypertrophy		3 (30%)	3 (30%)	
Thymus	(10)			(9)
Hyperplasia, lymphoid	1 (10%)			
Integumentary System				
Mammary gland	(10)			(9)
Duct, cyst	1 (10%)			
Musculoskeletal System				
Bone	(10)			(9)
Calvarium, hyperostosis	1 (10%)			
Nervous System				
None				
Respiratory System				
Nose	(10)	(3)	(6)	(9)
Submucosa, pigmentation	8 (80%)	3 (100%)	6 (100%)	9 (100%)
Special Senses System				
None				

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)	(10)	(10)	(9)
Cyst			1 (10%)	
Inflammation, chronic, focal	1 (10%)			
Nephropathy, chronic	3 (30%)	9 (90%)	5 (50%)	4 (44%)
Renal tubule, dilatation	1 (10%)		6 (60%)	7 (78%)
Renal tubule, mineralization	1 (10%)	6 (60%)	7 (70%)	5 (56%)
2-Year Study				
Alimentary System				
Intestine large, cecum	(50)	(49)	(46)	(49)
Parasite metazoan	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Intestine large, colon	(50)	(49)	(46)	(49)
Parasite metazoan	3 (6%)	5 (10%)	1 (2%)	2 (4%)
Intestine large, rectum	(50)	(49)	(46)	(49)
Parasite metazoan	3 (6%)	4 (8%)	2 (4%)	6 (12%)
Intestine small	(50)	(49)	(48)	(50)
Wall, foreign body				1 (2%)
Intestine small, ileum	(50)	(49)	(46)	(48)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	
Intestine small, jejunum	(50)	(49)	(47)	(48)
Inflammation, granulomatous				1 (2%)
Ulcer				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)
Basophilic focus	2 (4%)		4 (8%)	3 (6%)
Basophilic focus, multiple	37 (74%)	41 (82%)	34 (68%)	26 (52%)
Clear cell focus	5 (10%)		3 (6%)	3 (6%)
Clear cell focus, multiple	1 (2%)	1 (2%)		2 (4%)
Cytomegaly	1 (2%)			
Degeneration, multiple			1 (2%)	
Eosinophilic focus	3 (6%)	8 (16%)	5 (10%)	9 (18%)
Eosinophilic focus, multiple	5 (10%)	2 (4%)	3 (6%)	5 (10%)
Hematopoietic cell proliferation				1 (2%)
Hepatodiaphragmatic nodule	4 (8%)	3 (6%)	10 (20%)	8 (16%)
Hyperplasia, nodular	4 (8%)	1 (2%)	3 (6%)	14 (28%)
Inflammation, granulomatous, multiple	36 (72%)	30 (60%)	20 (40%)	21 (42%)
Karyomegaly	1 (2%)			
Mixed cell focus	2 (4%)	4 (8%)	2 (4%)	5 (10%)
Mixed cell focus, multiple		1 (2%)		
Necrosis			2 (4%)	
Pigmentation			1 (2%)	
Vacuolization cytoplasmic	10 (20%)	3 (6%)	5 (10%)	5 (10%)
Bile duct, hyperplasia	29 (58%)	30 (60%)	34 (68%)	43 (86%)
Centrilobular, degeneration	1 (2%)			
Centrilobular, necrosis				1 (2%)
Centrilobular, vacuolization cytoplasmic				1 (2%)
Serosa, fibrosis		1 (2%)		
Serosa, inflammation, granulomatous		1 (2%)		
Vein, thrombus				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(9)	(6)	(11)	(12)
Inflammation, chronic				1 (8%)
Fat, inflammation, granulomatous		1 (17%)		
Fat, inflammation, granulomatous, focal	2 (22%)		1 (9%)	1 (8%)
Fat, necrosis, focal	7 (78%)	5 (83%)	9 (82%)	10 (83%)
Fat, necrosis, focal, multiple			1 (9%)	
Pancreas	(50)	(50)	(49)	(50)
Basophilic focus	3 (6%)			
Basophilic focus, multiple		1 (2%)	1 (2%)	2 (4%)
Ectopic tissue				1 (2%)
Acinar cell, atrophy	14 (28%)	11 (22%)	15 (31%)	12 (24%)
Acinar cell, hyperplasia	6 (12%)	4 (8%)	4 (8%)	5 (10%)
Pharynx			(2)	
Palate, epithelium, hyperplasia			1 (50%)	
Salivary glands	(50)	(49)	(50)	(50)
Cytomegaly			1 (2%)	
Infiltration cellular, lipocyte			1 (2%)	
Inflammation, chronic	1 (2%)			
Inflammation, suppurative	1 (2%)			
Acinar cell, atrophy	1 (2%)		1 (2%)	1 (2%)
Acinar cell, hyperplasia	1 (2%)			1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema	4 (8%)	1 (2%)	5 (10%)	5 (10%)
Inflammation, chronic	4 (8%)	2 (4%)	2 (4%)	6 (12%)
Inflammation, suppurative			2 (4%)	
Ulcer	1 (2%)		2 (4%)	6 (12%)
Ulcer, multiple	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Epithelium, hyperplasia	8 (16%)	8 (16%)	13 (26%)	28 (56%)
Stomach, glandular	(50)	(50)	(50)	(50)
Edema	1 (2%)			
Erosion		1 (2%)	1 (2%)	2 (4%)
Erosion, multiple	1 (2%)			
Hyperplasia, lymphoid			1 (2%)	
Mineralization		1 (2%)	1 (2%)	
Necrosis, focal, multiple		1 (2%)	1 (2%)	
Ulcer		1 (2%)		2 (4%)
Ulcer, multiple			1 (2%)	
Epithelium, hyperplasia	1 (2%)			
Epithelium, hyperplasia, focal		1 (2%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Inflammation, chronic	34 (68%)	45 (90%)	41 (82%)	39 (78%)
Atrium, congestion		1 (2%)		
Atrium, thrombus	1 (2%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	6 (12%)	4 (8%)	2 (4%)	7 (14%)
Cyst				1 (2%)
Degeneration, cystic			1 (2%)	2 (4%)
Hyperplasia, focal	4 (8%)	10 (20%)	5 (10%)	6 (12%)
Hyperplasia, focal, multiple			1 (2%)	
Hypertrophy, focal	7 (14%)	11 (22%)	6 (12%)	5 (10%)
Hypertrophy, focal, multiple		2 (4%)		
Necrosis, focal, multiple		1 (2%)		
Vacuolization cytoplasmic	1 (2%)	3 (6%)	2 (4%)	
Vacuolization cytoplasmic, focal	14 (28%)	15 (30%)	8 (16%)	11 (22%)
Vacuolization cytoplasmic, multiple		2 (4%)		
Bilateral, hyperplasia				1 (2%)
Bilateral, hypertrophy, focal	1 (2%)			
Bilateral, vacuolization cytoplasmic	1 (2%)	1 (2%)		3 (6%)
Bilateral, vacuolization cytoplasmic, focal		1 (2%)		1 (2%)
Spindle cell, hyperplasia, focal	1 (2%)			
Adrenal gland, medulla	(50)	(50)	(50)	(49)
Degeneration, cystic, focal		1 (2%)		
Hyperplasia, focal	3 (6%)	4 (8%)	3 (6%)	
Vacuolization cytoplasmic, focal	1 (2%)			
Parathyroid gland	(49)	(46)	(49)	(47)
Cyst			1 (2%)	
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, angiectasis				1 (2%)
Pars distalis, cyst	4 (8%)	4 (8%)	3 (6%)	5 (10%)
Pars distalis, cyst, multiple	4 (8%)	4 (8%)	1 (2%)	6 (12%)
Pars distalis, hyperplasia				4 (8%)
Pars distalis, hyperplasia, focal	5 (10%)	6 (12%)	6 (12%)	7 (14%)
Pars intermedia, cyst			1 (2%)	
Pars intermedia, hyperplasia				1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)	
Ultimobranchial cyst	1 (2%)		2 (4%)	
C-cell, hyperplasia	5 (10%)	3 (6%)	1 (2%)	2 (4%)
C-cell, hyperplasia, focal	9 (18%)	7 (14%)	5 (10%)	5 (10%)
Follicle, cyst	1 (2%)			
General Body System				
None				

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Genital System				
Clitoral gland	(45)	(47)	(50)	(48)
Abscess	1 (2%)			
Atrophy	1 (2%)			
Cyst	14 (31%)	23 (49%)	18 (36%)	15 (31%)
Cyst, multiple	1 (2%)			
Hyperplasia	8 (18%)		1 (2%)	6 (13%)
Hyperplasia, focal	1 (2%)	4 (9%)	1 (2%)	
Inflammation, suppurative	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Bilateral, cyst	7 (16%)	3 (6%)	11 (22%)	11 (23%)
Ovary	(50)	(50)	(50)	(50)
Cyst	5 (10%)	3 (6%)	5 (10%)	5 (10%)
Cyst, multiple				1 (2%)
Inflammation, granulomatous, multiple		1 (2%)		
Bilateral, cyst	1 (2%)		1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Abscess		1 (2%)		
Dilatation	2 (4%)	3 (6%)	2 (4%)	4 (8%)
Fibrosis, focal				1 (2%)
Hemorrhage				1 (2%)
Hyperplasia, glandular	2 (4%)	2 (4%)	2 (4%)	5 (10%)
Infiltration cellular, lipocyte			1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)	
Cervix, cyst	2 (4%)			
Cervix, hemorrhage				1 (2%)
Cervix, inflammation, suppurative	1 (2%)	1 (2%)		
Cervix, myometrium, hyperplasia				3 (6%)
Endometrium, hyperplasia, cystic	7 (14%)	6 (12%)	9 (18%)	12 (24%)
Vein, thrombus				1 (2%)
Vagina		(3)	(1)	(3)
Inflammation, suppurative		1 (33%)		
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(49)
Myelofibrosis	2 (4%)	1 (2%)		
Erythroid cell, hyperplasia			1 (2%)	
Lymph node	(50)	(50)	(50)	(50)
Inguinal, hyperplasia, lymphoid	1 (2%)			
Mediastinal, angiectasis	6 (12%)	2 (4%)	5 (10%)	6 (12%)
Mediastinal, congestion				1 (2%)
Mediastinal, hemorrhage			1 (2%)	1 (2%)
Mediastinal, hyperplasia, lymphoid		3 (6%)		2 (4%)
Mediastinal, infiltration cellular, histiocyte			1 (2%)	
Mediastinal, pigmentation		1 (2%)		2 (4%)
Pancreatic, angiectasis		2 (4%)		6 (12%)
Pancreatic, hyperplasia, lymphoid			1 (2%)	
Renal, cyst, multiple		1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(48)	(49)	(50)	(50)
Angiectasis	1 (2%)	2 (4%)		
Congestion		1 (2%)		
Cyst		1 (2%)		
Cyst, multiple	3 (6%)	2 (4%)	3 (6%)	
Hyperplasia, lymphoid	7 (15%)	2 (4%)	2 (4%)	1 (2%)
Pigmentation				2 (4%)
Lymph node, mesenteric	(48)	(50)	(50)	(47)
Angiectasis	1 (2%)	3 (6%)	2 (4%)	1 (2%)
Edema		1 (2%)		
Hemorrhage				1 (2%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic				1 (2%)
Spleen	(50)	(50)	(50)	(50)
Atrophy		1 (2%)	1 (2%)	
Congestion		2 (4%)		
Fibrosis				1 (2%)
Fibrosis, focal	2 (4%)	1 (2%)	1 (2%)	
Hematopoietic cell proliferation	2 (4%)	2 (4%)	5 (10%)	3 (6%)
Inflammation, granulomatous		2 (4%)		1 (2%)
Necrosis			1 (2%)	
Pigmentation	3 (6%)	5 (10%)	2 (4%)	1 (2%)
Capsule, fibrosis		1 (2%)		
Capsule, hypertrophy		1 (2%)		
Capsule, inflammation, granulomatous		1 (2%)		
Thymus	(47)	(49)	(47)	(48)
Congestion				1 (2%)
Cyst		3 (6%)		1 (2%)
Cyst, multiple		1 (2%)		
Hyperplasia, lymphoid		1 (2%)		1 (2%)
Mediastinum, edema				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Hyperplasia, lobular	19 (38%)	26 (52%)	22 (44%)	21 (42%)
Duct, cyst	38 (76%)	36 (72%)	33 (66%)	34 (68%)
Skin	(50)	(50)	(50)	(50)
Hyperkeratosis		2 (4%)		1 (2%)
Epidermis, hyperplasia				1 (2%)
Parakeratosis		2 (4%)		
Ulcer		2 (4%)		
Nipple, hyperkeratosis			1 (2%)	
Nipple, hyperplasia		1 (2%)		
Subcutaneous tissue, edema				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteopetrosis	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Calvarium, hyperostosis	6 (12%)	5 (10%)	4 (8%)	5 (10%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	10 (20%)	6 (12%)	13 (26%)	6 (12%)
Embolus bacterial, multiple		1 (2%)		
Hemorrhage		2 (4%)	2 (4%)	
Hemorrhage, multiple			1 (2%)	2 (4%)
Inflammation, suppurative, multiple		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Atelectasis	1 (2%)			
Congestion			1 (2%)	
Edema	1 (2%)			
Embolus bacterial, multiple		1 (2%)		
Hemorrhage, multiple		1 (2%)		
Infiltration cellular, lymphocyte	2 (4%)			
Infiltration cellular, lymphocyte, focal				1 (2%)
Infiltration cellular, histiocyte, focal	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Infiltration cellular, histiocyte, multiple	1 (2%)	1 (2%)		2 (4%)
Inflammation, granulomatous, focal	3 (6%)	2 (4%)		4 (8%)
Inflammation, granulomatous, multiple				1 (2%)
Inflammation, suppurative, multiple		1 (2%)		
Mineralization, focal		1 (2%)		
Alveolar epithelium, hyperplasia		1 (2%)	1 (2%)	2 (4%)
Alveolar epithelium, hyperplasia, focal		3 (6%)	1 (2%)	
Alveolus, pigmentation				2 (4%)
Nose	(50)	(50)	(50)	(50)
Metaplasia, squamous		1 (2%)		
Lumen, foreign body		1 (2%)		
Lumen, fungus	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Lumen, hyperkeratosis		1 (2%)		
Lumen, inflammation, suppurative	4 (8%)	3 (6%)	2 (4%)	1 (2%)
Nasolacrimal duct, hemorrhage		1 (2%)		
Nasolacrimal duct, inflammation, suppurative	1 (2%)			
Submucosa, hemorrhage		2 (4%)		
Submucosa, pigmentation	46 (92%)	48 (96%)	46 (92%)	50 (100%)
Special Senses System				
Eye		(4)	(1)	(5)
Cataract		4 (100%)	1 (100%)	4 (80%)
Inflammation, suppurative				1 (20%)
Retina, degeneration		4 (100%)	1 (100%)	4 (80%)
Harderian gland	(1)	(2)		(2)
Hemorrhage	1 (100%)	2 (100%)		1 (50%)
Zymbal's gland	(1)	(1)		(1)
Inflammation, suppurative		1 (100%)		1 (100%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	222 ppm	666 ppm	2,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst		2 (4%)		
Fibrosis, focal	1 (2%)			
Hydronephrosis		1 (2%)		
Infarct		1 (2%)		
Infarct, multiple			1 (2%)	
Inflammation, chronic	1 (2%)			
Inflammation, suppurative		1 (2%)		
Mineralization		2 (4%)		
Nephropathy, chronic	39 (78%)	46 (92%)	46 (92%)	44 (88%)
Papilla, necrosis		1 (2%)		
Pelvis, dilatation			1 (2%)	
Renal tubule, dilatation				1 (2%)
Renal tubule, mineralization	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Renal tubule, necrosis				1 (2%)
Renal tubule, pigmentation	41 (82%)	47 (94%)	45 (90%)	46 (92%)
Transitional epithelium, hyperplasia		1 (2%)	1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Calculus gross observation		1 (2%)		
Hemorrhage		1 (2%)		
Hemorrhage, focal				1 (2%)
Inflammation, chronic				2 (4%)
Inflammation, suppurative		1 (2%)		
Transitional epithelium, hyperplasia		1 (2%)		6 (12%)

[a] Number of animals examined microscopically at site and number of animals with lesion.
[b] Includes one animal killed moribund before the interim evaluation.

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR FEED STUDY OF *o*-NITROANISOLE

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

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	10
Missexed			1	
Early deaths				
Moribund	14	5	8	7
Natural deaths	1	2	3	3
Survivors				
Terminal sacrifice	35	43	39	40
Animals examined microscopically	60	60	59	60
15-Month Interim Evaluation				
Alimentary System				
Intestine small, jejunum	(10)		(1)	(10)
Liver	(10)	(10)	(9)	(10)
Hepatocellular carcinoma		1 (10%)		
Hepatocellular adenoma	2 (20%)			
Hepatocellular adenoma, multiple				1 (10%)
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
Testes	(10)			(10)
Hemangiosarcoma				1 (10%)
Hematopoietic System				
Lymph node, mesenteric	(10)	(1)	(1)	(10)
Integumentary System				
None				
Musculoskeletal System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
15-Month Interim Evaluation (continued)				
Nervous System				
None				
Respiratory System				
Lung	(10)	(4)		(10)
Alveolar/bronchiolar adenoma		3 (75%)		
Alveolar/bronchiolar carcinoma		1 (25%)		
Special Senses System				
None				
Urinary System				
None				
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(9)	(10)
Lymphoma malignant mixed			1 (11%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	2	4	1	2
Total primary neoplasms	2	5	1	2
Total animals with benign neoplasms	2	3		1
Total benign neoplasms	2	3		1
Total animals with malignant neoplasms		2	1	1
Total malignant neoplasms		2	1	1
2-Year Study				
Alimentary System				
Intestine large, cecum	(49)	(49)	(49)	(49)
Intestine small, duodenum	(50)	(48)	(49)	(50)
Carcinoma		1 (2%)		
Intestine small, ileum	(49)	(48)	(47)	(49)
Carcinoma		1 (2%)		
Intestine small, jejunum	(50)	(48)	(47)	(50)
Carcinoma		1 (2%)		1 (2%)
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	2 (4%)	1 (2%)	
Hemangiosarcoma, multiple	1 (2%)			
Hepatoblastoma		2 (4%)	14 (28%)	8 (16%)
Hepatoblastoma, multiple		1 (2%)	3 (6%)	1 (2%)
Hepatocellular carcinoma	5 (10%)	11 (22%)	10 (20%)	6 (12%)
Hepatocellular carcinoma, multiple	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hepatocellular adenoma	10 (20%)	16 (32%)	15 (30%)	16 (32%)
Hepatocellular adenoma, multiple	4 (8%)	10 (20%)	26 (52%)	13 (26%)
Histiocytic sarcoma			1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(4)	(2)	(4)	
Hemangioma	1 (25%)			
Hepatoblastoma, metastatic, liver			2 (50%)	
Pancreas	(50)	(49)	(49)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma	3 (6%)		2 (4%)	1 (2%)
Stomach, glandular	(50)	(50)	(49)	(50)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(48)
Adenoma	5 (10%)	3 (6%)	2 (4%)	
Capsule, adenoma	2 (4%)	3 (6%)		
Adrenal gland, medulla	(50)	(49)	(50)	(48)
Pheochromocytoma malignant				1 (2%)
Pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(50)	(49)	(49)	(50)
Adenoma	2 (4%)	1 (2%)		
Pituitary gland	(47)	(46)	(49)	(48)
Pars distalis, adenoma		1 (2%)		
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(49)	(49)	(50)	(50)
Follicular cell, adenoma	2 (4%)	2 (4%)		
General Body System				
Tissue NOS	(1)		(1)	
Histiocytic sarcoma			1 (100%)	
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Penis			(1)	
Fibrous histiocytoma			1 (100%)	
Prostate	(50)	(50)	(50)	(49)
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Interstitial cell, adenoma			1 (2%)	1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of o-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)			
Lymph node	(50)	(50)	(50)	(50)
Lymph node, mandibular	(48)	(49)	(49)	(49)
Lymph node, mesenteric	(47)	(49)	(46)	(50)
Histiocytic sarcoma				1 (2%)
Spleen	(50)	(50)	(49)	(48)
Hemangiosarcoma	1 (2%)			
Thymus	(47)	(47)	(45)	(48)
Histiocytic sarcoma			1 (2%)	
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)			
Subcutaneous tissue, hemangioma		1 (2%)		
Subcutaneous tissue, hemangiosarcoma	1 (2%)			1 (2%)
Musculoskeletal System				
Skeletal muscle	(1)		(1)	
Hepatoblastoma, metastatic, liver			1 (100%)	
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	9 (18%)	2 (4%)	3 (6%)
Alveolar/bronchiolar adenoma, two, multiple		1 (2%)	1 (2%)	
Alveolar/bronchiolar adenoma, three, multiple			1 (2%)	
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)		1 (2%)
Pheochromocytoma malignant, metastatic, adrenal gland				1 (2%)
Hepatoblastoma, metastatic, liver			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	3 (6%)			
Histiocytic sarcoma			1 (2%)	
Special Senses System				
Harderian gland	(10)	(4)	(2)	(3)
Adenoma	8 (80%)	4 (100%)	2 (100%)	3 (100%)
Adenoma, two, multiple	1 (10%)			
Carcinoma	1 (10%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Renal tubule, adenoma	1 (2%)		1 (2%)	
Urinary bladder	(50)	(50)	(49)	(50)
Transitional epithelium, papilloma	1 (2%)			
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Lymphoma malignant lymphocytic	1 (2%)			1 (2%)
Lymphoma malignant mixed	2 (4%)	6 (12%)	3 (6%)	2 (4%)
Lymphoma malignant undifferentiated cell	1 (2%)	1 (2%)	1 (2%)	5 (10%)
Neoplasm Summary				
Total animals with primary neoplasms	38	41	49	41
Total primary neoplasms	66	81	88	67
Total animals with benign neoplasms	29	37	45	31
Total benign neoplasms	47	52	53	37
Total animals with malignant neoplasms	16	23	27	26
Total malignant neoplasms	19	29	35	30
Total animals with metastatic neoplasms	3		2	1
Total metastatic neoplasms	3		4	1

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

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

Number of Days on Study	4 7 9	6 4 7	6 5 2	7 0 3	7 0 8	7 0 9	7 0 9	7 0 9	7 0 9	7 1 0	7 1 1	7 1 1	7 1 1	7 2 5	7 2 2	7 2 2	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 1 4 1	0 2 4 1	0 3 4 1	0 4 4 1	0 0 1 1	0 1 6 1	0 2 2 1	0 4 1 1	0 4 7 1	0 1 5 1	0 0 3 1	0 0 9 1	0 2 5 1	0 2 8 1	0 4 0 1	0 0 2 1	0 0 4 1	0 0 5 1	0 0 6 1	0 0 7 1	0 0 8 1	0 1 0 1	0 1 1 1	0 1 2 1	0 1 3 1
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X												
Hemangiosarcoma, multiple																			X							
Hepatocellular carcinoma		X				X			X																	
Hepatocellular carcinoma, multiple					X																					
Hepatocellular adenoma								X					X						X					X	X	
Hepatocellular adenoma, multiple										X																
Mesentery				+		+		+					+													
Hemangioma						X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma										X																
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth										+												+	+		+	
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X													X
Capsule, adenoma																										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X																	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X					

+: 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 *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	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 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 1 7 1	0 1 8 1	0 1 9 1	0 2 0 1	0 2 1 1	0 2 3 1	0 2 6 1	0 2 7 1	0 2 9 1	0 3 0 1	0 3 1 1	0 3 2 1	0 3 3 1	0 3 5 1	0 3 6 1	0 3 7 1	0 3 8 1	0 3 9 1	0 4 2 1	0 4 3 1	0 4 5 1	0 4 6 1	0 4 8 1	0 4 9 1	0 5 0 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hemangiosarcoma, multiple																										1
Hepatocellular carcinoma									X												X					5
Hepatocellular carcinoma, multiple																			X							2
Hepatocellular adenoma				X		X	X															X			X	10
Hepatocellular adenoma, multiple	X							X												X						4
Mesentery																										4
Hemangioma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma	X												X													3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth				+	+	+	+	+			+			+												11
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X	X			X								5
Capsule, adenoma							X																X			2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	4 7 9	6 4 7	6 5 2	7 0 3	7 0 8	7 0 9	7 0 9	7 0 9	7 0 9	7 1 0	7 1 1	7 1 1	7 1 5	7 2 2	7 2 2	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 1 4 1	0 2 4 1	0 3 4 1	0 4 4 1	0 0 1 1	0 1 6 1	0 2 1 1	0 4 1 1	0 4 7 1	0 1 5 1	0 0 3 1	0 0 9 1	0 2 5 1	0 2 8 1	0 4 0 1	0 0 2 1	0 0 4 1	0 0 5 1	0 0 6 1	0 0 7 1	0 0 8 1	0 1 0 1	0 1 1 1	0 1 2 1	0 1 3 1
Endocrine System (continued)																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
Tissue NOS				+																					
Genital System																									
Coagulating gland																						+			+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland			+		+	+	+	+		+	+	+	+		+			+		+		+	+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, hemangiosarcoma														X											
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	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 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 1 7 1	0 1 8 1	0 1 9 1	0 2 0 1	0 2 1 1	0 2 3 1	0 2 6 1	0 2 7 1	0 2 9 1	0 3 0 1	0 3 1 1	0 3 2 1	0 3 3 1	0 3 5 1	0 3 6 1	0 3 7 1	0 3 8 1	0 3 9 1	0 4 2 1	0 4 3 1	0 4 5 1	0 4 6 1	0 4 8 1	0 4 9 1	0 5 0 1	Total Tissues/ Tumors
Endocrine System (continued)																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma															X					X						2
General Body System																										
Tissue NOS																										1
Genital System																										
Coagulating gland								+																	+	4
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+		+			+			+			+		+		+		+			+			+		24
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																					2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	M	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																					1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	M	47
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
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	467	467	562	700	708	709	709	709	709	710	711	711	711	722	722	722	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	01441	02411	03411	04411	40111	01611	02211	04111	04711	05111	01011	03911	00111	02511	02211	04811	04011	00211	04411	05111	06111	07111	08111	00111	01111	02111	03111
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																											
Alveolar/bronchiolar carcinoma			X																								
Hepatocellular carcinoma, metastatic, liver		X				X															X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																											
Eye							+			+																	
Harderian gland							+		+	+							+		+								
Adenoma							X		X	X							X		X								
Adenoma, two, multiple																											
Carcinoma																											
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma											X																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																											
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																											
Lymphoma malignant mixed																X											
Lymphoma malignant undifferentiated cell type				X																							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	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 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 1 7 1	0 1 8 1	0 1 9 1	0 2 0 1	0 2 1 1	0 2 3 1	0 2 6 1	0 2 7 1	0 2 9 1	0 3 0 1	0 3 1 1	0 3 2 1	0 3 3 1	0 3 5 1	0 3 6 1	0 3 7 1	0 3 8 1	0 3 9 1	0 4 2 1	0 4 3 1	0 4 5 1	0 4 6 1	0 4 8 1	0 4 9 1	0 5 0 1	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X			X								X	X		X			5
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver																										3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																								+		3
Harderian gland	+											+		+								+		+		10
Adenoma	X											X		X												8
Adenoma, two, multiple																						X				1
Carcinoma																								X		1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma																									X	1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																							X			1
Lymphoma malignant mixed								X																		2
Lymphoma malignant undifferentiated cell type																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	2 0 1 1	2 0 2 1	2 0 4 1	2 0 6 1	2 0 7 1	2 0 9 1	2 1 0 1	2 1 1 1	2 1 2 1	2 1 3 1	2 1 4 1	2 1 5 1	2 1 6 1	2 1 7 1	2 1 8 1	2 1 9 1	2 2 1 1	2 2 2 1	2 2 3 1	2 2 4 1	2 2 6 1	2 2 7 1	2 2 8 1	2 2 9 1	2 3 0 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	M	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+		48
Carcinoma																							X			1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Hepatoblastoma		X																								2
Hepatoblastoma, multiple																										1
Hepatocellular carcinoma		X													X	X	X			X					X	11
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma											X		X		X						X	X				16
Hepatocellular adenoma, multiple		X			X				X							X	X							X		10
Mesentery																				+						2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth	+	+	+	+		+		+	+					+	+	+		+			+				+	20
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X		X									3
Capsule, adenoma					X		X											X								3
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																			X							1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	5	5	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	4	8	0	0	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	9	2	9	9	0	0	0	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8	8
Carcass ID Number	2	2	2	2	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2
	0	0	0	2	8	9	2	8	8	8	8	8	8	8	8	9	9	9	9	9	9	9	9	9	0
	8	5	3	0	8	5	5	1	2	3	4	5	6	7	9	0	1	2	3	4	6	7	8	9	0
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Endocrine System (continued)																									
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Pars distalis, adenoma							X																		
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Coagulating gland							+																		
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland							+			+				+	+		+		+		+			+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	2 0 1 1	2 0 2 1	2 0 4 1	2 0 6 1	2 0 7 1	2 0 9 1	2 1 0 1	2 1 1 1	2 1 2 1	2 1 3 1	2 1 4 1	2 1 5 1	2 1 6 1	2 1 7 1	2 1 8 1	2 1 9 1	2 2 1 1	2 2 2 1	2 2 3 1	2 2 4 1	2 2 6 1	2 2 7 1	2 2 8 1	2 2 9 1	2 3 0 1	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma																										1
Pars intermedia, adenoma																			X							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																						X	X			2
General Body System																										
None																										
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+				+		+			+		+				+		+	24
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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
Subcutaneous tissue, hemangioma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	
Carcass ID Number	2 0 1 1	2 0 2 1	2 0 4 1	2 0 6 1	2 0 7 1	2 0 9 1	2 1 0 1	2 1 1 1	2 1 2 1	2 1 3 1	2 1 4 1	2 1 5 1	2 1 6 1	2 1 7 1	2 1 8 1	2 1 9 1	2 2 1 1	2 2 2 1	2 2 3 1	2 2 4 1	2 2 6 1	2 2 7 1	2 2 8 1	2 2 9 1	2 3 0 1	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X								X																9
Alveolar/bronchiolar adenoma, two, multiple																									X	1
Alveolar/bronchiolar carcinoma															X											2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										4
Adenoma																										4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																									X	6
Lymphoma malignant undifferentiated cell type									X																	1

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

Number of Days on Study	6 1 7	6 2 6	6 7 2	7 0 7	7 0 8	7 0 8	7 0 8	7 0 9	7 0 9	7 1 1	7 1 2	7 2 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 2 7 1	1 5 2 1	1 6 4 1	1 4 1 1	1 2 5 1	1 3 5 1	1 6 3 1	1 2 8 1	1 3 0 1	1 6 9 1	1 6 7 1	1 2 9 1	1 3 1 1	1 3 2 1	1 3 3 1	1 3 4 1	1 3 6 1	1 3 7 1	1 3 8 1	1 3 9 1	1 4 0 1	1 4 2 1	1 4 3 1	1 4 4 1	1 4 5 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	+	+	+	+	I	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	
Intestine small, jejunum	+	+	A	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Hepatoblastoma	X	X			X			X					X	X							X			X	X
Hepatoblastoma, multiple						X	X																		
Hepatocellular carcinoma		X	X						X				X									X			
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma	X									X		X	X		X	X		X		X					
Hepatocellular adenoma, multiple				X	X	X	X	X						X			X		X		X	X		X	X
Histiocytic sarcoma											X														
Mesentery	+	+																							+
Hepatoblastoma, metastatic, liver	X	X																							
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																		
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+							+				+	+							
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

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 0	7 3 0	7 3 0	7 3 0	7 3 0	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 4 6 1	1 4 7 1	1 4 8 1	1 5 6 1	1 5 7 1	1 5 8 1	1 5 9 1	1 6 0 1	1 6 1 1	1 6 2 1	1 6 5 1	1 6 6 1	1 6 8 1	1 7 0 1	1 2 1 1	1 2 2 1	1 2 3 1	1 2 4 1	1 2 6 1	1 4 9 1	1 5 0 1	1 5 1 1	1 5 3 1	1 5 4 1	1 5 5 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatoblastoma					X							X		X	X								X			14
Hepatoblastoma, multiple						X																				3
Hepatocellular carcinoma				X							X	X			X								X			10
Hepatocellular carcinoma, multiple																				X						1
Hepatocellular adenoma	X		X				X				X		X					X					X			15
Hepatocellular adenoma, multiple		X		X	X	X		X	X			X				X	X			X	X	X		X	X	26
Histiocytic sarcoma																										1
Mesentery																			+							4
Hepatoblastoma, metastatic, liver																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma														X												2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth	+			+		+								+			+			+	+		+			12
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of o-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	6 1 7	6 2 6	6 7 2	7 0 7	7 0 8	7 0 8	7 0 8	7 0 9	7 0 9	7 1 1	7 2 2	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 2 7 1	1 5 2 1	1 6 4 1	1 4 1 1	1 2 5 1	1 3 5 1	1 6 3 1	1 2 8 1	1 3 0 1	1 6 9 1	1 6 7 1	1 2 9 1	1 3 1 1	1 3 2 1	1 3 3 1	1 3 4 1	1 3 6 1	1 3 7 1	1 3 8 1	1 3 9 1	1 4 0 1	1 4 2 1	1 4 3 1	1 4 4 1	1 4 5 1
General Body System																									
Tissue NOS											+														
Histiocytic sarcoma											X														
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Fibrous histiocytoma																									
Preputial gland	+		+	+		+					+	+		+			+		+	+	+	+			+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Hepatoblastoma, metastatic, liver	X																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

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 0	7 3 0	7 3 0	7 3 0	7 3 0	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 4 6 1	1 4 7 1	1 4 8 1	1 5 6 1	1 5 7 1	1 5 8 1	1 5 9 1	1 6 0 1	1 6 1 1	1 6 2 1	1 6 5 1	1 6 6 1	1 6 8 1	1 7 0 1	1 7 2 1	1 2 1 1	1 2 2 1	1 2 3 1	1 2 4 1	1 2 6 1	1 4 9 1	1 5 0 1	1 5 1 1	1 5 3 1	1 5 4 1	1 5 5 1	Total Tissues/ Tumors
General Body System																											
Tissue NOS																											1
Histiocytic sarcoma																											1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																				+							1
Fibrous histiocytoma																				X							1
Preputial gland			+					+			+	+	+		+				+	+	+	+	+			+	25
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																					X						1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											1
Hepatoblastoma, metastatic, liver																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of o-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	6 1 7	6 2 6	6 7 2	7 0 7	7 0 8	7 0 8	7 0 8	7 0 9	7 0 9	7 1 1	7 2 2	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 2 7 1	1 5 2 1	1 6 4 1	1 4 1 1	1 2 5 1	1 3 5 1	1 6 3 1	1 2 8 1	1 3 0 1	1 6 9 1	1 6 7 1	1 2 9 1	1 3 1 1	1 3 2 1	1 3 3 1	1 3 4 1	1 3 6 1	1 3 7 1	1 3 8 1	1 3 9 1	1 4 0 1	1 4 2 1	1 4 3 1	1 4 4 1	1 4 5 1
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X																								
Alveolar/bronchiolar adenoma, two, multiple					X																				
Alveolar/bronchiolar adenoma, three, multiple																									
Hepatoblastoma, metastatic, liver	X																								
Histiocytic sarcoma											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																			+						
Adenoma																			X						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma											X														
Ureter																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Lymphoma malignant mixed									X																
Lymphoma malignant undifferentiated cell type											X														

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

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 0	7 3 0	7 3 0	7 3 0	7 3 0	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 4 6 1	1 4 7 1	1 4 8 1	1 5 6 1	1 5 7 1	1 5 8 1	1 5 9 1	1 6 0 1	1 6 1 1	1 6 2 1	1 6 5 1	1 6 6 1	1 6 8 1	1 7 0 1	1 2 1 1	1 2 2 1	1 2 3 1	1 2 4 1	1 2 6 1	1 4 9 1	1 5 0 1	1 5 1 1	1 5 3 1	1 5 4 1	1 5 5 1	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			2
Alveolar/bronchiolar adenoma, two, multiple																										1
Alveolar/bronchiolar adenoma, three, multiple															X											1
Hepatoblastoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland														+												2
Adenoma														X												2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Ureter																			+							1
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant mixed	X																						X			3
Lymphoma malignant undifferentiated cell type																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

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	7 3 2	
Carcass ID Number	0 8 0 1	0 8 2 1	0 8 3 1	0 8 4 1	0 8 5 1	1 0 3 1	1 0 4 1	1 0 5 1	1 0 6 1	1 0 7 1	1 0 9 1	1 1 0 1	0 1 8 1	0 6 1	0 8 8 1	0 8 9 1	0 9 0 1	0 9 2 1	0 9 3 1	0 9 4 1	0 9 6 1	0 9 7 1	0 9 9 1	1 0 0 1	1 0 1 1	1 0 2 1	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	I	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	M	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma	X							X																			8
Hepatoblastoma, multiple											X																1
Hepatocellular carcinoma		X				X																	X		X		6
Hepatocellular carcinoma, multiple																								X			1
Hepatocellular adenoma	X		X				X	X						X							X		X			X	16
Hepatocellular adenoma, multiple				X												X		X	X			X		X			13
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma						X																					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																								+			3
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant																											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																											
None																											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	0 9 8	4 6 6	5 7 6	6 2 7	6 7 3	7 0 8	7 0 8	7 0 9	7 1 0	7 1 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
Carcass ID Number	0 8 7 1	1 0 8 1	0 9 5 1	0 8 1 1	0 9 1 1	0 6 2 1	0 6 3 1	0 6 5 1	0 7 1 1	0 9 8 1	0 6 1 1	0 6 4 1	0 6 6 1	0 6 7 1	0 6 8 1	0 6 9 1	0 7 0 1	0 7 2 1	0 7 3 1	0 7 4 1	0 7 5 1	0 7 6 1	0 7 7 1	0 7 8 1	0 7 9 1
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland								+		+	+												+		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mediastinal, pancreatic, lymphoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X											
Alveolar/bronchiolar carcinoma																									
Pheochromocytoma malignant, metastatic, adrenal gland		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

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	7 3 2	
Carcass ID Number	0 8 0 1	0 8 2 1	0 8 3 1	0 8 4 1	0 8 5 1	1 0 3 1	1 0 4 1	1 0 5 1	1 0 6 1	1 0 7 1	1 0 9 1	1 1 0 1	1 1 0 1	0 1 8 1	0 8 8 1	0 8 9 1	0 9 0 1	0 9 2 1	0 9 3 1	0 9 4 1	0 9 6 1	0 9 7 1	0 9 9 1	0 1 0 1	1 0 1 1	1 0 2 1	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland					+				+			+				+									+	+	10
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma										X																	1
Interstitial cell, adenoma																				X							1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma															X												1
Mediastinal, pancreatic, lymphoma																											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X								X															3
Alveolar/bronchiolar carcinoma											X																1
Pheochromocytoma malignant, metastatic, adrenal gland																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

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	7 3 2	7 3 2	
Carcass ID Number	0 8 0 1	0 8 2 1	0 8 3 1	0 8 4 1	0 8 5 1	1 0 3 1	1 0 4 1	1 0 5 1	1 0 6 1	1 0 7 1	1 0 9 1	1 1 0 1	1 1 0 1	0 1 8 1	0 8 6 1	0 8 8 1	0 8 9 1	0 9 0 1	0 9 2 1	0 9 3 1	0 9 4 1	0 9 6 1	0 9 7 1	0 9 9 1	0 9 9 1	1 0 0 1	1 0 1 1	1 0 2 1	Total Tissues/ Tumors
Special Senses System																												
Harderian gland																									+			3
Adenoma																									X			3
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma														X														1
Lymphoma malignant lymphocytic															X													1
Lymphoma malignant mixed																					X							2
Lymphoma malignant undifferentiated cell type												X																5

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

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Adrenal Cortex: Adenoma				
Overall rates[a]	7/50 (14%)	6/50 (12%)	2/50 (4%)	0/48 (0%)
Adjusted rates[b]	19.3%	13.5%	5.1%	0.0%
Terminal rates[c]	6/35 (17%)	5/43 (12%)	2/39 (5%)	0/39 (0%)
First incidence (days)	715	709	728 (T)	–[e]
Life table tests[d]	P=0.004N	P=0.359N	P=0.060N	P=0.007N
Logistic regression tests[d]	P=0.005N	P=0.453N	P=0.067N	P=0.009N
Cochran-Armitage test[d]	P=0.005N			
Fisher exact test[d]		P=0.500N	P=0.080N	P=0.007N
Harderian Gland: Adenoma				
Overall rates	9/50 (18%)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted rates	22.8%	9.3%	5.1%	7.0%
Terminal rates	6/35 (17%)	4/43 (9%)	2/39 (5%)	1/40 (3%)
First incidence (days)	709	728 (T)	728 (T)	709
Life table tests	P=0.093N	P=0.066N	P=0.023N	P=0.053N
Logistic regression tests	P=0.103N	P=0.106N	P=0.026N	P=0.067N
Cochran-Armitage test	P=0.095N			
Fisher exact test		P=0.117N	P=0.026N	P=0.061N
Harderian Gland: Adenoma or Carcinoma				
Overall rates	10/50 (20%)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted rates	25.4%	9.3%	5.1%	7.0%
Terminal rates	7/35 (20%)	4/43 (9%)	2/39 (5%)	1/40 (3%)
First incidence (days)	709	728 (T)	728 (T)	709
Life table tests	P=0.065N	P=0.038N	P=0.012N	P=0.031N
Logistic regression tests	P=0.072N	P=0.065N	P=0.014N	P=0.040N
Cochran-Armitage test	P=0.067N			
Fisher exact test		P=0.074N	P=0.014N	P=0.036N
Liver: Hepatoblastoma				
Overall rates	0/50 (0%)	3/50 (6%)	17/50 (34%)	9/50 (18%)
Adjusted rates	0.0%	6.4%	37.1%	21.3%
Terminal rates	0/35 (0%)	1/43 (2%)	11/39 (28%)	7/40 (18%)
First incidence (days)	–	582	617	709
Life table tests	P=0.019	P=0.143	P<0.001	P=0.005
Logistic regression tests	P=0.016	P=0.093	P<0.001	P=0.002
Cochran-Armitage test	P=0.015			
Fisher exact test		P=0.121	P<0.001	P=0.001
Liver: Hepatocellular Adenoma				
Overall rates	14/50 (28%)	26/50 (52%)	41/50 (82%)	29/50 (58%)
Adjusted rates	36.3%	56.3%	89.0%	64.4%
Terminal rates	11/35 (31%)	23/43 (53%)	34/39 (87%)	24/40 (60%)
First incidence (days)	709	549	617	673
Life table tests	P=0.043	P=0.074	P<0.001	P=0.012
Logistic regression tests	P=0.012	P=0.014	P<0.001	P=0.001
Cochran-Armitage test	P=0.022			
Fisher exact test		P=0.012	P<0.001	P=0.002

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Liver: Hepatocellular Carcinoma				
Overall rates	7/50 (14%)	12/50 (24%)	11/50 (22%)	7/50 (14%)
Adjusted rates	16.3%	25.9%	25.5%	16.7%
Terminal rates	3/35 (9%)	9/43 (21%)	8/39 (21%)	5/40 (13%)
First incidence (days)	647	709	626	710
Life table tests	P=0.307N	P=0.269	P=0.271	P=0.558N
Logistic regression tests	P=0.326N	P=0.154	P=0.194	P=0.602
Cochran-Armitage test	P=0.315N			
Fisher exact test		P=0.154	P=0.218	P=0.613N
Liver: Hepatoblastoma or Hepatocellular Carcinoma				
Overall rates	7/50 (14%)	14/50 (28%)	23/50 (46%)	15/50 (30%)
Adjusted rates	16.3%	29.1%	48.4%	34.9%
Terminal rates	3/35 (9%)	9/43 (21%)	15/39 (38%)	12/40 (30%)
First incidence (days)	647	582	617	709
Life table tests	P=0.183	P=0.152	P=0.003	P=0.082
Logistic regression tests	P=0.148	P=0.063	P<0.001	P=0.040
Cochran-Armitage test	P=0.151			
Fisher exact test		P=0.070	P<0.001	P=0.045
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	21/50 (42%)	32/50 (64%)	45/50 (90%)	32/50 (64%)
Adjusted rates	49.0%	65.3%	91.8%	71.1%
Terminal rates	14/35 (40%)	26/43 (60%)	35/39 (90%)	27/40 (68%)
First incidence (days)	647	549	617	673
Life table tests	P=0.186	P=0.169	P<0.001	P=0.092
Logistic regression tests	P=0.068	P=0.024	P<0.001	P=0.014
Cochran-Armitage test	P=0.105			
Fisher exact test		P=0.022	P<0.001	P=0.022
Liver: Hepatocellular Adenoma, Carcinoma, or Hepatoblastoma				
Overall rates	21/50 (42%)	33/50 (66%)	46/50 (92%)	34/50 (68%)
Adjusted rates	49.0%	66.0%	93.8%	75.5%
Terminal rates	14/35 (40%)	26/43 (60%)	36/39 (92%)	29/40 (73%)
First incidence (days)	647	549	617	673
Life table tests	P=0.112	P=0.132	P<0.001	P=0.047
Logistic regression tests	P=0.030	P=0.013	P<0.001	P=0.005
Cochran-Armitage test	P=0.049			
Fisher exact test		P=0.013	P<0.001	P=0.008
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	5/50 (10%)	10/50 (20%)	4/50 (8%)	3/50 (6%)
Adjusted rates	14.3%	21.0%	9.0%	7.5%
Terminal rates	5/35 (14%)	6/43 (14%)	2/39 (5%)	3/40 (8%)
First incidence (days)	728 (T)	582	617	728 (T)
Life table tests	P=0.101N	P=0.227	P=0.447N	P=0.284N
Logistic regression tests	P=0.099N	P=0.127	P=0.512N	P=0.284N
Cochran-Armitage test	P=0.103N			
Fisher exact test		P=0.131	P=0.500N	P=0.357N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of o-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	6/50 (12%)	12/50 (24%)	4/50 (8%)	4/50 (8%)
Adjusted rates	16.1%	24.8%	9.0%	10.0%
Terminal rates	5/35 (14%)	7/43 (16%)	2/39 (5%)	4/40 (10%)
First incidence (days)	652	582	617	728 (T)
Life table tests	P=0.097N	P=0.186	P=0.325N	P=0.299N
Logistic regression tests	P=0.091N	P=0.089	P=0.400N	P=0.383N
Cochran-Armitage test	P=0.098N			
Fisher exact test		P=0.096	P=0.370N	P=0.370N
Small Intestine: Adenoma or Carcinoma				
Overall rates	0/50 (0%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rates	0.0%	6.6%	0.0%	2.5%
Terminal rates	0/35 (0%)	2/43 (5%)	0/39 (0%)	1/40 (3%)
First incidence (days)	–	549	–	728 (T)
Life table tests	P=0.605N	P=0.150	–	P=0.527
Logistic regression tests	P=0.557N	P=0.090	–	P=0.527
Cochran-Armitage test	P=0.614N			
Fisher exact test		P=0.121	–	P=0.500
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rates	3/50 (6%)	0/50 (0%)	2/50 (4%)	1/50 (2%)
Adjusted rates	8.0%	0.0%	4.7%	2.5%
Terminal rates	2/35 (6%)	0/43 (0%)	1/39 (3%)	1/40 (3%)
First incidence (days)	710	–	708	728 (T)
Life table tests	P=0.422N	P=0.094N	P=0.471N	P=0.270N
Logistic regression tests	P=0.440N	P=0.117N	P=0.496N	P=0.310N
Cochran-Armitage test	P=0.429N			
Fisher exact test		P=0.121N	P=0.500N	P=0.309N
All Organs: Hemangiosarcoma				
Overall rates	3/50 (6%)	2/50 (4%)	1/50 (2%)	2/50 (4%)
Adjusted rates	8.3%	4.3%	2.6%	4.6%
Terminal rates	2/35 (6%)	1/43 (2%)	1/39 (3%)	1/40 (3%)
First incidence (days)	722	582	728 (T)	627
Life table tests	P=0.491N	P=0.431N	P=0.272N	P=0.461N
Logistic regression tests	P=0.452N	P=0.525N	P=0.285N	P=0.497N
Cochran-Armitage test	P=0.500N			
Fisher exact test		P=0.500N	P=0.309N	P=0.500N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	4/50 (8%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rates	10.3%	6.6%	2.6%	4.6%
Terminal rates	2/35 (6%)	2/43 (5%)	1/39 (3%)	1/40 (3%)
First incidence (days)	709	582	728 (T)	627
Life table tests	P=0.301N	P=0.421N	P=0.163N	P=0.311N
Logistic regression tests	P=0.269N	P=0.521N	P=0.174N	P=0.334N
Cochran-Armitage test	P=0.305N			
Fisher exact test		P=0.500N	P=0.181N	P=0.339N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
All Organs: Malignant Lymphoma and Histiocytic Sarcoma				
Overall rates	4/50 (8%)	7/50 (14%)	4/50 (8%)	9/50 (18%)
Adjusted rates	10.2%	15.4%	9.7%	19.6%
Terminal rates	2/35 (6%)	5/43 (12%)	2/39 (5%)	4/40 (10%)
First incidence (days)	703	709	709	576
Life table tests	P=0.131	P=0.366	P=0.603N	P=0.154
Logistic regression tests	P=0.119	P=0.269	P=0.638N	P=0.119
Cochran-Armitage test	P=0.118			
Fisher exact test		P=0.262	P=0.643N	P=0.117
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	4/50 (8%)	7/50 (14%)	4/50 (8%)	8/50 (16%)
Adjusted rates	10.2%	15.4%	9.7%	17.3%
Terminal rates	2/35 (6%)	5/43 (12%)	2/39 (5%)	3/40 (8%)
First incidence (days)	703	709	709	576
Life table tests	P=0.214	P=0.366	P=0.603N	P=0.216
Logistic regression tests	P=0.204	P=0.269	P=0.638N	P=0.184
Cochran-Armitage test	P=0.200			
Fisher exact test		P=0.262	P=0.643N	P=0.178
All Organs: Benign Neoplasms				
Overall rates	29/50 (58%)	37/50 (74%)	45/50 (90%)	31/50 (62%)
Adjusted rates	68.7%	74.0%	95.7%	68.9%
Terminal rates	22/35 (63%)	30/43 (70%)	37/39 (95%)	26/40 (65%)
First incidence (days)	709	549	617	673
Life table tests	P=0.308N	P=0.419	P=0.011	P=0.490N
Logistic regression tests	P=0.476N	P=0.074	P<0.001	P=0.360
Cochran-Armitage test	P=0.369N			
Fisher exact test		P=0.069	P<0.001	P=0.419
All Organs: Malignant Neoplasms				
Overall rates	16/50 (32%)	23/50 (46%)	27/50 (54%)	26/50 (52%)
Adjusted rates	36.0%	46.0%	56.0%	53.1%
Terminal rates	8/35 (23%)	16/43 (37%)	18/39 (46%)	17/40 (43%)
First incidence (days)	647	549	617	466
Life table tests	P=0.120	P=0.293	P=0.070	P=0.099
Logistic regression tests	P=0.088	P=0.092	P=0.018	P=0.036
Cochran-Armitage test	P=0.072			
Fisher exact test		P=0.109	P=0.021	P=0.034
All Organs: Benign or Malignant Neoplasms				
Overall rates	38/50 (76%)	41/50 (82%)	49/50 (98%)	41/50 (82%)
Adjusted rates	79.1%	82.0%	98.0%	83.7%
Terminal rates	25/35 (71%)	34/43 (79%)	38/39 (97%)	32/40 (80%)
First incidence (days)	647	549	617	466
Life table tests	P=0.518	P=0.318N	P=0.127	P=0.521N
Logistic regression tests	P=0.319	P=0.318	P=0.002	P=0.253
Cochran-Armitage test	P=0.395			
Fisher exact test		P=0.312	P<0.001	P=0.312

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

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

TABLE C4a
Historical Incidence of Liver Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Carcinoma, or Hepatoblastoma
Historical Incidence at Southern Research Institute				
C.I. Pigment Red 3	8/50	5/50	0/50	12/50
Ethylene Glycol	9/54	10/54	0/54	19/54
Nitrofurantoin	2/50	9/50	0/50	10/50
o-Nitroanisole	14/50	7/50	0/50	21/50
Polysorbate 80	5/49	11/49	0/49	15/49
Rhodamine 6G	5/49	10/49	0/49	13/49
Roxarsone	9/50	4/50	0/50	12/50
Overall Historical Incidence				
Total	145/865 (16.8%)	122/865 (14.1%)	0/865 (0.0%)	249/865 (28.8%)
Standard deviation	8.2%	7.2%		10.9%
Range	4%-38%	3%-27%		10%-58%

[a] Data as of 3 April 1991

TABLE C4b
Historical Incidence of Harderian Gland Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
C.I. Pigment Red 3	2/50	0/50	2/50
Ethylene Glycol	0/54	0/54	0/54
Nitrofurantoin	2/50	0/50	2/50
o-Nitroanisole	9/50	1/50	10/50
Polysorbate 80	0/49	0/49	0/49
Rhodamine 6G	7/50	0/50	7/50
Roxarsone	1/50	0/50	1/50
Overall Historical Incidence			
Total	45/872 (5.2%)	3/872 (0.3%)	48/872 (5.5%)
Standard deviation	4.8%	0.8%	5.3%
Range	0%-18%	0%-2%	0%-20%

[a] Data as of 3 April 1991

TABLE C4c
Historical Incidence of Adrenal Cortex Adenomas in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls
Historical Incidence at Southern Research Institute	
C.I. Pigment Red 3	0/50
Ethylene Glycol	4/54
Nitrofuratoin	0/50
o-Nitroanisole	7/50
Polysorbate 80	0/49
Rhodamine 6G	0/49
Roxarsone	0/50
Overall Historical Incidence	
Total	14/851 (1.6%)
Standard deviation	3.7%
Range	0%-14%

[a] Data as of 3 April 1991

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

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	10
Missexed			1	
Early deaths				
Moribund	14	5	8	7
Natural deaths	1	2	3	3
Survivors				
Terminal sacrifice	35	43	39	40
Animals examined microscopically	60	60	59	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(9)	(10)
Basophilic focus	1 (10%)			
Clear cell focus		1 (10%)		
Eosinophilic focus				1 (10%)
Inflammation, chronic active		2 (20%)	5 (56%)	3 (30%)
Hepatocyte, cytologic alterations		7 (70%)	9 (100%)	10 (100%)
Hepatocyte, vacuolization cytoplasmic	4 (40%)	2 (20%)	3 (33%)	
Lobules, necrosis			2 (22%)	4 (40%)
Mesentery	(2)			
Fat, inflammation, chronic	1 (50%)			
Fat, necrosis	1 (50%)			
Pancreas	(10)			(10)
Atrophy				1 (10%)
Inflammation, chronic	1 (10%)			
Salivary glands	(10)			(10)
Inflammation, chronic	1 (10%)			
Stomach, glandular	(10)			(10)
Cyst	1 (10%)			
Cardiovascular System				
Heart	(10)			(10)
Myocardium, inflammation, chronic	1 (10%)			
Endocrine System				
Adrenal gland, cortex	(10)			(10)
Accessory adrenal cortical nodule				1 (10%)
Hypertrophy, focal	1 (10%)			1 (10%)
Subcapsular, hyperplasia	4 (40%)			1 (10%)
Islets, pancreatic	(10)			(10)
Hyperplasia	3 (30%)			
Parathyroid gland	(10)			(10)
Cyst	2 (20%)			1 (10%)
Thyroid gland	(10)			(10)
Degeneration, cystic	1 (10%)			1 (10%)
Follicle, dilatation	1 (10%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
15-Month Interim Evaluation (continued)				
General Body System				
None				
Genital System				
Preputial gland	(3)	(1)	(2)	
Atrophy	2 (67%)	1 (100%)	1 (50%)	
Ectasia	3 (100%)	1 (100%)	2 (100%)	
Inflammation, chronic	2 (67%)		1 (50%)	
Hematopoietic System				
Lymph node, mandibular	(10)			(10)
Hemorrhage	1 (10%)			
Lymph node, mesenteric	(10)	(1)	(1)	(10)
Hemorrhage	1 (10%)		1 (100%)	
Thymus	(10)			(10)
Cyst	3 (30%)			1 (10%)
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
Brain	(10)			(10)
Thalamus, mineralization	8 (80%)			6 (60%)
Respiratory System				
Lung	(10)	(4)		(10)
Hemorrhage	1 (10%)			
Infiltration cellular, histiocyte		1 (25%)		
Nose	(10)		(2)	(10)
Exudate				1 (10%)
Glands, dilatation	2 (20%)		2 (100%)	10 (100%)
Glands, hyperplasia				10 (100%)
Olfactory epithelium, metaplasia				10 (100%)
Special Senses System				
None				

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
15-Month Interim Evaluation (continued)				
Urinary System				
Kidney	(10)			(10)
Cyst	1 (10%)			1 (10%)
Inflammation, chronic	2 (20%)			1 (10%)
Mineralization	4 (40%)			2 (20%)
Renal tubule, regeneration	10 (100%)			5 (50%)
Urinary bladder	(10)			(10)
Inflammation, chronic	1 (10%)			1 (10%)
2-Year Study				
Alimentary System				
Gallbladder	(49)	(45)	(47)	(46)
Dilatation	1 (2%)	1 (2%)		
Intestine large, cecum	(49)	(49)	(49)	(49)
Edema				1 (2%)
Hyperplasia, lymphoid		1 (2%)		
Intestine small, duodenum	(50)	(48)	(49)	(50)
Inflammation, chronic			1 (2%)	
Metaplasia, squamous		1 (2%)		
Mucosa, hyperplasia				3 (6%)
Intestine small, ileum	(49)	(48)	(47)	(49)
Hyperplasia, lymphoid			1 (2%)	2 (4%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			1 (2%)
Basophilic focus	3 (6%)	1 (2%)	1 (2%)	
Clear cell focus	9 (18%)	7 (14%)	9 (18%)	2 (4%)
Eosinophilic focus	1 (2%)	15 (30%)	16 (32%)	13 (26%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Hemorrhage	1 (2%)	4 (8%)	20 (40%)	28 (56%)
Infiltration cellular, mixed cell			1 (2%)	
Inflammation, chronic	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Mixed cell focus	1 (2%)	3 (6%)		
Regeneration, focal		1 (2%)		
Centrilobular, necrosis	1 (2%)	1 (2%)		
Hepatocyte, cytologic alterations		44 (88%)	49 (98%)	49 (98%)
Hepatocyte, cytomegaly	1 (2%)			
Hepatocyte, vacuolization cytoplasmic	6 (12%)	7 (14%)		
Kupffer cell, hyperplasia	2 (4%)			
Kupffer cell, pigmentation			3 (6%)	16 (32%)
Lobules, necrosis	3 (6%)	13 (26%)	27 (54%)	34 (68%)
Oval cell, hyperplasia		1 (2%)		1 (2%)
Mesentery	(4)	(2)	(4)	
Hemorrhage			1 (25%)	
Inflammation, pyogranulomatous		1 (50%)		
Fat, necrosis	2 (50%)	1 (50%)	1 (25%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Pancreas	(50)	(49)	(49)	(50)
Atrophy	1 (2%)			
Focal cellular change	1 (2%)			
Hyperplasia, focal	1 (2%)			
Hyperplasia, lymphoid	2 (4%)		3 (6%)	5 (10%)
Infiltration cellular, histiocyte				1 (2%)
Duct, hyperplasia		1 (2%)		
Acinar cell, vacuolization cytoplasmic				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid	16 (32%)	21 (42%)	20 (40%)	10 (20%)
Acinar cell, vacuolization cytoplasmic				1 (2%)
Inflammation, chronic	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Cyst	2 (4%)			1 (2%)
Diverticulum	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Erosion	1 (2%)			1 (2%)
Inflammation, chronic	2 (4%)			
Inflammation, suppurative		2 (4%)		
Mucosa, hyperplasia	6 (12%)	2 (4%)		4 (8%)
Stomach, glandular	(50)	(50)	(49)	(50)
Cyst	7 (14%)	15 (30%)	11 (22%)	8 (16%)
Dysplasia		1 (2%)	1 (2%)	
Erosion	1 (2%)			1 (2%)
Hemorrhage			1 (2%)	
Inflammation, chronic			1 (2%)	1 (2%)
Inflammation, subacute			1 (2%)	
Mucosa, hyperplasia			1 (2%)	
Tooth	(11)	(20)	(12)	(3)
Dysplasia	10 (91%)	18 (90%)	12 (100%)	3 (100%)
Inflammation, suppurative	1 (9%)	2 (10%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Thrombus	1 (2%)	2 (4%)		
Artery, inflammation, chronic active		1 (2%)		
Myocardium, degeneration	2 (4%)			
Myocardium, inflammation, chronic	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Myocardium, mineralization	2 (4%)		1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(48)
Accessory adrenal cortical nodule	8 (16%)	1 (2%)	5 (10%)	9 (19%)
Angiectasis			1 (2%)	
Basophilic focus		1 (2%)		
Clear cell focus	1 (2%)	3 (6%)	6 (12%)	
Developmental malformation			2 (4%)	
Hyperplasia, diffuse				1 (2%)
Hyperplasia, focal	24 (48%)	21 (42%)	23 (46%)	21 (44%)
Infiltration cellular, mononuclear cell				1 (2%)
Capsule, hyperplasia	6 (12%)	6 (12%)	5 (10%)	4 (8%)
Adrenal gland, medulla	(50)	(49)	(50)	(48)
Hyperplasia		1 (2%)		2 (4%)
Islets, pancreatic	(50)	(49)	(49)	(50)
Hyperplasia	21 (42%)	20 (41%)	9 (18%)	2 (4%)
Parathyroid gland	(50)	(49)	(50)	(48)
Cyst	2 (4%)	3 (6%)	2 (4%)	3 (6%)
Hyperplasia			1 (2%)	
Infiltration cellular, histiocyte				1 (2%)
Pigmentation			1 (2%)	
Pituitary gland	(47)	(46)	(49)	(48)
Pars distalis, cyst	1 (2%)	4 (9%)	7 (14%)	1 (2%)
Pars distalis, hyperplasia		1 (2%)	1 (2%)	
Pars intermidia, cytoplasmic alteration				1 (2%)
Thyroid gland	(49)	(49)	(50)	(50)
Degeneration, cystic	12 (24%)	11 (22%)	9 (18%)	6 (12%)
Hemorrhage	1 (2%)			
Inflammation, chronic			1 (2%)	
Inflammation, suppurative	1 (2%)			
Follicular cell, hyperplasia	3 (6%)	6 (12%)	6 (12%)	1 (2%)
General Body System				
None				
Genital System				
Coagulating gland	(4)	(1)		
Dilatation	2 (50%)			
Epididymis	(50)	(50)	(50)	(50)
Atypical cells	1 (2%)			1 (2%)
Fibrosis			3 (6%)	
Granuloma sperm		1 (2%)	1 (2%)	
Hyperplasia, lymphoid		1 (2%)		
Inflammation, chronic	1 (2%)		5 (10%)	
Thrombus				1 (2%)
Preputial gland	(24)	(24)	(25)	(10)
Ectasia	18 (75%)	20 (83%)	24 (96%)	10 (100%)
Fibrosis			1 (4%)	
Inflammation, chronic	13 (54%)	7 (29%)	13 (52%)	4 (40%)
Inflammation, suppurative	6 (25%)	4 (17%)	4 (16%)	1 (10%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Genital System (continued)				
Prostate	(50)	(50)	(50)	(49)
Inflammation, suppurative	1 (2%)			
Seminal vesicle	(50)	(50)	(50)	(50)
Dilatation	6 (12%)	3 (6%)	1 (2%)	
Testes	(50)	(50)	(50)	(50)
Granuloma sperm			1 (2%)	
Hypospermia	2 (4%)	1 (2%)		1 (2%)
Mineralization		1 (2%)	2 (4%)	2 (4%)
Interstitial cell, hyperplasia		2 (4%)		1 (2%)
Seminiferous tubule, atrophy	3 (6%)	1 (2%)	4 (8%)	2 (4%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Angiectasis		2 (4%)		1 (2%)
Hypercellularity	1 (2%)	10 (20%)	6 (12%)	7 (14%)
Lymph node	(50)	(50)	(50)	(50)
Inguinal, hyperplasia, lymphoid	2 (4%)	1 (2%)		1 (2%)
Inguinal, pigmentation	1 (2%)		1 (2%)	
Mediastinal, hemorrhage			1 (2%)	
Mediastinal, inflammation, suppurative		1 (2%)		
Mediastinal, inflammation, pyogranulomatous		1 (2%)		
Pancreatic, hemorrhage	1 (2%)	1 (2%)		
Lymph node, mandibular	(48)	(49)	(49)	(49)
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia, lymphoid		1 (2%)		
Infiltration cellular, mast cell			1 (2%)	
Lymph node, mesenteric	(47)	(49)	(46)	(50)
Hematopoietic cell proliferation	4 (9%)	16 (33%)	6 (13%)	3 (6%)
Hemorrhage	19 (40%)	23 (47%)	21 (46%)	14 (28%)
Hyperplasia, histiocytic	1 (2%)	2 (4%)		
Hyperplasia, lymphoid	4 (9%)	4 (8%)	4 (9%)	7 (14%)
Hyperplasia, reticulum cell		1 (2%)		
Infiltration cellular, mast cell		2 (4%)	1 (2%)	
Spleen	(50)	(50)	(49)	(48)
Angiectasis				3 (6%)
Congestion	1 (2%)	3 (6%)		1 (2%)
Hematopoietic cell proliferation	10 (20%)	12 (24%)	10 (20%)	7 (15%)
Pigmentation, hemosiderin		1 (2%)		
Lymphoid follicle, atrophy			1 (2%)	1 (2%)
Lymphoid follicle, hyperplasia	3 (6%)	7 (14%)	4 (8%)	2 (4%)
Red pulp, atrophy	1 (2%)	1 (2%)		1 (2%)
Red pulp, hyperplasia	2 (4%)			
Thymus	(47)	(47)	(45)	(48)
Cyst	8 (17%)	7 (15%)	6 (13%)	6 (13%)
Depletion		1 (2%)	1 (2%)	2 (4%)
Epithelial cell, hyperplasia			1 (2%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Acanthosis	4 (8%)	1 (2%)	4 (8%)	1 (2%)
Hair follicle, atrophy				1 (2%)
Inflammation, acute			1 (2%)	
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)	
Inflammation, suppurative	2 (4%)			
Subcutaneous tissue, edema	1 (2%)		1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis		1 (2%)	1 (2%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Cyst		1 (2%)		
Inflammation, chronic	1 (2%)			
Pigmentation				2 (4%)
Thalamus, mineralization	41 (82%)	43 (86%)	44 (88%)	40 (80%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)			1 (2%)
Hemorrhage	2 (4%)	1 (2%)	2 (4%)	6 (12%)
Hyperplasia, lymphoid		5 (10%)	6 (12%)	1 (2%)
Infiltration cellular, megakaryocyte				1 (2%)
Infiltration cellular, histiocyte	5 (10%)	5 (10%)	1 (2%)	1 (2%)
Inflammation, chronic	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Inflammation, suppurative		3 (6%)		
Thrombus			1 (2%)	
Alveolar epithelium, hyperplasia	5 (10%)	4 (8%)	2 (4%)	2 (4%)
Bronchiole, epithelium, proliferation		2 (4%)	13 (26%)	14 (28%)
Nose	(50)	(50)	(50)	(50)
Exudate	4 (8%)	4 (8%)	6 (12%)	49 (98%)
Glands, dilatation	3 (6%)	6 (12%)	12 (24%)	49 (98%)
Glands, hyperplasia	1 (2%)	2 (4%)	12 (24%)	49 (98%)
Olfactory epithelium, cyst				18 (36%)
Olfactory epithelium, metaplasia			7 (14%)	46 (92%)
Olfactory epithelium, necrosis				1 (2%)
Special Senses System				
Eye	(3)			
Cataract	1 (33%)			
Cornea, hyperplasia	2 (67%)			
Cornea, inflammation, chronic active	2 (67%)			
Cornea, mineralization	1 (33%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Casts protein	12 (24%)	14 (28%)	18 (36%)	5 (10%)
Cyst	27 (54%)	30 (60%)	16 (32%)	4 (8%)
Fibrosis			1 (2%)	1 (2%)
Glomerulosclerosis	2 (4%)	1 (2%)	1 (2%)	
Hydronephrosis	6 (12%)			
Hyperplasia, lymphoid	20 (40%)	16 (32%)	25 (50%)	8 (16%)
Inflammation, chronic	1 (2%)		1 (2%)	
Inflammation, suppurative	1 (2%)			
Metaplasia, osseous	2 (4%)		3 (6%)	
Mineralization	41 (82%)	48 (96%)	50 (100%)	36 (72%)
Pelvis, transitional epithelium, hyperplasia	1 (2%)			
Renal tubule, atrophy		1 (2%)		
Renal tubule, cytoplasmic alteration			1 (2%)	
Renal tubule, dilatation	3 (6%)			
Renal tubule, hyperplasia		1 (2%)	2 (4%)	
Renal tubule, pigmentation			5 (10%)	1 (2%)
Renal tubule, regeneration	48 (96%)	46 (92%)	48 (96%)	32 (64%)
Renal tubule, vacuolization cytoplasmic			1 (2%)	
Urinary bladder	(50)	(50)	(49)	(50)
Dilatation	3 (6%)	1 (2%)		
Edema			1 (2%)	
Hyperplasia, lymphoid	1 (2%)	4 (8%)	5 (10%)	5 (10%)
Mucosa, hyperplasia			1 (2%)	

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

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR FEED STUDY OF *o*-NITROANISOLE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of o-Nitroanisole[a]

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	7	16	10	5
Natural deaths	5	8	7	
Survivors				
Terminal sacrifice	38	26	33	45
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine small, duodenum	(10)			(10)
Fibrous histiocytoma	1 (10%)			
Liver	(10)	(10)	(10)	(10)
Hepatocellular adenoma		1 (10%)	1 (10%)	
Hepatocellular adenoma, multiple			1 (10%)	
Mesentery	(1)			
Fibrous histiocytoma	1 (100%)			
Pancreas	(10)			(10)
Fibrous histiocytoma	1 (10%)			
Stomach, glandular	(10)			(10)
Fibrous histiocytoma	1 (10%)			
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(10)		(1)	(10)
Pars distalis, adenoma	1 (10%)			
Pars distalis, carcinoma			1 (100%)	
General Body System				
None				
Genital System				
Ovary	(10)			(10)
Adenoma	1 (10%)			
Fibrous histiocytoma	1 (10%)			
Uterus	(10)	(6)	(8)	(10)
Fibrous histiocytoma	1 (10%)			
Sarcoma stromal		1 (17%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node	(10)	(1)		(10)
Iliac, fibrous histiocytoma	1 (10%)			
Renal, fibrous histiocytoma	1 (10%)			
Lymph node, mesenteric	(10)			(10)
Fibrous histiocytoma	1 (10%)			
Spleen	(10)	(2)	(1)	(10)
Fibrous histiocytoma	1 (10%)			
Thymus	(10)			(10)
Fibrous histiocytoma	1 (10%)			
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)		(1)	(10)
Alveolar/bronchiolar adenoma	1 (10%)		1 (100%)	
Fibrous histiocytoma	1 (10%)			
Special Senses System				
None				
Urinary System				
Kidney	(10)			(10)
Fibrous histiocytoma	1 (10%)			
Urinary bladder	(10)			(10)
Fibrous histiocytoma	1 (10%)			
Neoplasm Summary				
Total animals with primary neoplasms[b]	4	2	4	
Total primary neoplasms	17	2	4	
Total animals with benign neoplasms	3	1	3	
Total benign neoplasms	3	1	3	
Total animals with malignant neoplasms	1	1	1	
Total malignant neoplasms	14	1	1	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Gallbladder	(48)	(48)	(48)	(48)
Intestine large, cecum	(50)	(48)	(50)	(49)
Histiocytic sarcoma	1 (2%)			
Leiomyosarcoma		1 (2%)		
Intestine large, colon	(49)	(48)	(50)	(50)
Intestine large, rectum	(50)	(50)	(50)	(49)
Fibrosarcoma, metastatic, skin		1 (2%)		
Intestine small, duodenum	(50)	(49)	(50)	(49)
Carcinoma	1 (2%)			
Intestine small, ileum	(49)	(48)	(50)	(49)
Histiocytic sarcoma	1 (2%)			
Intestine small, jejunum	(50)	(49)	(49)	(50)
Carcinoma	2 (4%)			
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)		
Hepatoblastoma	1 (2%)	1 (2%)	1 (2%)	
Hepatoblastoma, multiple			1 (2%)	
Hepatocellular carcinoma	4 (8%)	1 (2%)	7 (14%)	3 (6%)
Hepatocellular carcinoma, multiple	1 (2%)	1 (2%)	1 (2%)	
Hepatocellular adenoma	12 (24%)	11 (22%)	11 (22%)	11 (22%)
Hepatocellular adenoma, multiple	2 (4%)	9 (18%)	25 (50%)	7 (14%)
Histiocytic sarcoma	2 (4%)		1 (2%)	
Osteosarcoma, metastatic, bone		1 (2%)	1 (2%)	
Mesentery	(9)	(7)	(5)	(2)
Hemangioma		1 (14%)		
Histiocytic sarcoma	1 (11%)			
Pancreas	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Salivary glands	(49)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Squamous cell papilloma	3 (6%)	1 (2%)	6 (12%)	2 (4%)
Stomach, glandular	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)			
Tongue		(1)		
Tooth		(2)		
Fibrosarcoma		1 (50%)		
Squamous cell carcinoma		1 (50%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Capsule, carcinoma	1 (2%)			
Adrenal gland, medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant			1 (2%)	
Pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	2 (4%)		1 (2%)	
Pituitary gland	(49)	(47)	(48)	(48)
Pars distalis, adenoma	7 (14%)	6 (13%)	8 (17%)	
Pars intermedia, adenoma	1 (2%)	1 (2%)	3 (6%)	
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, adenoma	1 (2%)	1 (2%)		
General Body System				
Tissue NOS			(2)	(1)
Genital System				
Ovary	(49)	(50)	(48)	(50)
Adenoma	1 (2%)	1 (2%)		1 (2%)
Cystadenoma	1 (2%)			
Cystadenocarcinoma				1 (2%)
Granulosa cell tumor malignant		1 (2%)		
Granulosa-theca tumor benign			1 (2%)	
Histiocytic sarcoma	1 (2%)			
Luteoma		1 (2%)		
Osteosarcoma, metastatic, bone	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Histiocytic sarcoma	1 (2%)			
Hemangioma				1 (2%)
Leiomyoma	1 (2%)	1 (2%)	1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)			
Polyp stromal	3 (6%)	5 (10%)	4 (8%)	2 (4%)
Sarcoma stromal		1 (2%)		1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Lymph node	(50)	(50)	(50)	(50)
Axillary, histiocytic sarcoma	1 (2%)			
Bronchial, histiocytic sarcoma	1 (2%)			
Bronchial, osteosarcoma, metastatic, bone		1 (2%)		
Iliac, histiocytic sarcoma	1 (2%)			
Inguinal, fibrosarcoma, metastatic, skin		1 (2%)		
Inguinal, histiocytic sarcoma	1 (2%)			
Lumbar, histiocytic sarcoma	1 (2%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of o-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node (continued)				
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Mediastinal, hepatoblastoma, metastatic, liver		1 (2%)		
Mediastinal, histiocytic sarcoma	2 (4%)		1 (2%)	
Mediastinal, osteosarcoma, metastatic, bone		1 (2%)		
Renal, histiocytic sarcoma	1 (2%)		1 (2%)	
Lymph node, mandibular	(49)	(49)	(49)	(49)
Histiocytic sarcoma	2 (4%)		1 (2%)	
Squamous cell carcinoma, metastatic, tooth		1 (2%)		
Lymph node, mesenteric	(47)	(47)	(48)	(48)
Histiocytic sarcoma	2 (4%)		1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma		2 (4%)		
Histiocytic sarcoma	1 (2%)		1 (2%)	
Thymus	(47)	(44)	(47)	(49)
Hepatoblastoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrosarcoma		1 (2%)		
Subcutaneous tissue, sarcoma				1 (2%)
Subcutaneous tissue, hemangioma	1 (2%)			
Subcutaneous tissue, hemangiosarcoma		1 (2%)		
Subcutaneous tissue, schwannoma malignant		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma	2 (4%)	1 (2%)	1 (2%)	
Skeletal muscle		(1)		
Nervous System				
Brain	(49)	(50)	(50)	(50)
Cranial nerve, schwannoma malignant		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	4 (8%)	2 (4%)	2 (4%)	
Alveolar/bronchiolar adenoma, two, multiple			1 (2%)	
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Respiratory System (continued)				
Lung (continued)				
Fibrosarcoma, metastatic, skin		1 (2%)		
Hepatoblastoma, metastatic, liver		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	1 (2%)	2 (4%)		
Histiocytic sarcoma	2 (4%)		1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)	1 (2%)	1 (2%)	
Squamous cell carcinoma, metastatic, tooth		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Mucosa, adenoma	1 (2%)			
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Harderian gland	(1)	(3)	(3)	(1)
Adenoma		3 (100%)	3 (100%)	1 (100%)
Carcinoma	1 (100%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Fibrosarcoma, metastatic, skin		1 (2%)		
Osteosarcoma, metastatic, bone	1 (2%)	1 (2%)		
Renal tubule, carcinoma		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[c]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)		1 (2%)	
Lymphoma malignant histiocytic		1 (2%)		
Lymphoma malignant lymphocytic	2 (4%)	6 (12%)	3 (6%)	1 (2%)
Lymphoma malignant mixed	3 (6%)	6 (12%)	10 (20%)	4 (8%)
Lymphoma malignant undifferentiated cell		1 (2%)	1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms	39	44	47	28
Total primary neoplasms	67	78	94	37
Total animals with benign neoplasms	31	31	43	22
Total benign neoplasms	42	43	66	25
Total animals with malignant neoplasms	20	27	24	10
Total malignant neoplasms	25	35	28	12
Total animals with metastatic neoplasms	3	7	1	
Total metastatic neoplasms	6	16	2	

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

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

Number of Days on Study	1 3 5 5 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 3 1 2 6 2 3 4 9 0 0 2 2 2 2 2 2 2 3 3 3 3 3 3 3 3 7 2 5 4 7 0 8 3 5 8 2 2 9 9 9 9 9 1 1 1 1 1 1 1 1
Carcass ID Number	2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 7 5 6 6 6 8 6 7 5 4 6 8 7 7 8 8 4 4 4 4 4 4 4 4 7 4 3 8 6 1 4 1 2 7 0 8 6 8 9 0 2 1 2 3 4 5 6 8 9 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Alimentary System	
Esophagus	+ +
Gallbladder	+ + + + + + + + M A + + + + + + + + + + + + + + +
Intestine large	+ +
Intestine large, cecum	+ +
Histiocytic sarcoma	X
Intestine large, colon	+ + + + + + + M + + + + + + + + + + + + + + + + +
Intestine large, rectum	+ +
Intestine small	+ +
Intestine small, duodenum	+ +
Carcinoma	X
Intestine small, ileum	M +
Histiocytic sarcoma	X
Intestine small, jejunum	+ +
Carcinoma	X X
Liver	+ +
Hemangiosarcoma	X
Hepatoblastoma	
Hepatocellular carcinoma	X X
Hepatocellular carcinoma, multiple	X
Hepatocellular adenoma	X X X
Hepatocellular adenoma, multiple	
Histiocytic sarcoma	X X
Mesentery	+ + + +
Histiocytic sarcoma	X
Pancreas	+ +
Histiocytic sarcoma	X
Salivary glands	+ +
Histiocytic sarcoma	X
Stomach	+ +
Stomach, forestomach	+ +
Squamous cell papilloma	X X
Stomach, glandular	+ +
Carcinoma	
Cardiovascular System	
Heart	+ +
Histiocytic sarcoma	X

+: 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 *o*-Nitroanisole: 0 ppm (continued)

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 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 5 0 1	2 5 1 1	2 5 3 1	2 5 5 1	2 5 6 1	2 5 7 1	2 5 8 1	2 5 9 1	2 6 1 1	2 6 2 1	2 6 5 1	2 6 7 1	2 6 9 1	2 7 0 1	2 7 2 1	2 7 3 1	2 7 4 1	2 7 5 1	2 8 3 1	2 8 4 1	2 8 5 1	2 8 6 1	2 8 7 1	2 8 9 1	2 9 0 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatoblastoma						X																				1
Hepatocellular carcinoma									X					X												4
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma				X		X	X	X			X	X		X					X					X		12
Hepatocellular adenoma, multiple																		X			X					2
Histiocytic sarcoma																										2
Mesentery		+												+		+	+		+		+					9
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Histiocytic sarcoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																							X			3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma											X															1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	1 3 7	3 1 2	5 2 5	5 6 4	6 2 7	6 3 0	6 4 8	6 9 3	7 0 5	7 0 8	7 2 2	7 2 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	2 7 7 1	2 5 4 1	2 6 3 1	2 6 8 1	2 6 6 1	2 8 1 1	2 6 4 1	2 7 1 1	2 5 2 1	2 4 7 1	2 6 0 1	2 8 8 1	2 7 6 1	2 7 8 1	2 7 9 1	2 8 0 1	2 8 2 1	2 4 1 1	2 4 2 1	2 4 3 1	2 4 4 1	2 4 5 1	2 4 6 1	2 4 8 1	2 4 9 1
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, carcinoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																	X		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																X	X	X			X				X
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+
Adenoma																									
Cystadenoma																									
Histiocytic sarcoma											X														
Osteosarcoma, metastatic, bone		X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X								
Histiocytic sarcoma												X													
Leiomyoma																									
Osteosarcoma, metastatic, bone		X																							
Polyp stromal																			X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, histiocytic sarcoma											X														
Bronchial, histiocytic sarcoma											X														
Iliac, histiocytic sarcoma												X													
Inguinal, histiocytic sarcoma											X														
Lumbar, histiocytic sarcoma											X														
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																					X				
Mediastinal, histiocytic sarcoma											X	X													
Renal, histiocytic sarcoma											X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

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 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 5 0 1 1	2 5 1 1 1	2 5 3 1 1	2 5 5 1 1	2 5 6 1 1	2 5 7 1 1	2 5 8 1 1	2 5 9 1 1	2 6 1 1 1	2 6 2 1 1	2 6 5 1 1	2 6 7 1 1	2 6 9 1 1	2 7 0 1 1	2 7 2 1 1	2 7 3 1 1	2 7 4 1 1	2 7 5 1 1	2 8 3 1 1	2 8 4 1 1	2 8 5 1 1	2 8 6 1 1	2 8 7 1 1	2 8 9 1 1	2 9 0 1 1	Total Tissues/ Tumors
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, carcinoma							X																			1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign							X																			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma							X			X																7
Pars intermedia, adenoma																									X	1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																									X	1
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma													X													1
Cystadenoma						X																				1
Histiocytic sarcoma																										1
Osteosarcoma, metastatic, bone																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Histiocytic sarcoma																										1
Leiomyoma												X														1
Osteosarcoma, metastatic, bone																										1
Polyp stromal					X											X										3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, histiocytic sarcoma																										1
Bronchial, histiocytic sarcoma																										1
Iliac, histiocytic sarcoma																										1
Inguinal, histiocytic sarcoma																										1
Lumbar, histiocytic sarcoma																										1
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Mediastinal, histiocytic sarcoma																										2
Renal, histiocytic sarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	1 3 5 5 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	3 1 2 6 2 3 4 9 0 0 2 2 2 2 2 2 2 3 3 3 3 3 3 3
	7 2 5 4 7 0 8 3 5 8 2 2 9 9 9 9 1 1 1 1 1 1 1 1
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
	7 5 6 6 6 8 6 7 5 4 6 8 7 7 7 8 8 4 4 4 4 4 4 4
	7 4 3 8 6 1 4 1 2 7 0 8 6 8 9 0 2 1 2 3 4 5 6 8 9
	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Hematopoietic System (continued)	
Lymph node, mandibular	+ +
Histiocytic sarcoma	X X
Lymph node, mesenteric	+ + + + + + + M + + + + + + + + + + + + + + + +
Histiocytic sarcoma	X X
Spleen	+ +
Hemangioma	
Histiocytic sarcoma	X
Thymus	+ M + + + + + + + M + + + + + + + + + + + + + +
Integumentary System	
Mammary gland	+ +
Skin	+ +
Subcutaneous tissue, hemangioma	X
Musculoskeletal System	
Bone	+ +
Osteosarcoma	X X
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X X
Alveolar/bronchiolar carcinoma	X
Hepatocellular carcinoma, metastatic, liver	
Histiocytic sarcoma	X X
Osteosarcoma, metastatic, bone	X
Nose	+ +
Mucosa, adenoma	X
Trachea	+ +
Special Senses System	
Eye	
Harderian gland	
Carcinoma	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

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 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 5 0 1	2 5 1 1	2 5 1 1	2 5 3 1	2 5 5 1	2 5 6 1	2 5 7 1	2 5 8 1	2 5 9 1	2 6 1 1	2 6 2 1	2 6 5 1	2 6 6 1	2 6 7 1	2 6 9 1	2 7 0 1	2 7 2 1	2 7 3 1	2 7 4 1	2 7 5 1	2 8 3 1	2 8 4 1	2 8 5 1	2 8 6 1	2 8 7 1	2 8 9 1	2 9 0 1	Total Tissues/ Tumors
Hematopoietic System (continued)																												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		49
Histiocytic sarcoma																												2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+		47
Histiocytic sarcoma																												2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangioma										X																		1
Histiocytic sarcoma																												1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		47
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Subcutaneous tissue, hemangioma																												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Osteosarcoma																												2
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+		49
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma																									X			4
Alveolar/bronchiolar carcinoma	X																											2
Hepatocellular carcinoma, metastatic, liver																X												1
Histiocytic sarcoma																												2
Osteosarcoma, metastatic, bone																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Mucosa, adenoma																												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																												
Eye																						+						1
Harderian gland																						+						1
Carcinoma																						X						1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	1	3	5	5	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	3	1	2	6	2	3	4	9	0	0	2	2	2	2	2	2	2	3	3	3	3	3	3	3	3
	7	2	5	4	7	0	8	3	5	8	2	2	9	9	9	9	9	1	1	1	1	1	1	1	1
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	7	5	6	6	6	8	6	7	5	4	6	8	7	7	7	8	8	4	4	4	4	4	4	4	4
	7	4	3	8	6	1	4	1	2	7	0	8	6	8	9	0	2	1	2	3	4	5	6	8	9
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X	X													
Lymphoma malignant lymphocytic																				X					
Lymphoma malignant mixed										X															

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 0 ppm (continued)

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 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 5 0 1	2 5 1 1	2 5 3 1	2 5 5 1	2 5 6 1	2 5 7 1	2 5 8 1	2 5 9 1	2 6 1 1	2 6 2 1	2 6 5 1	2 6 7 1	2 6 9 1	2 7 0 1	2 7 2 1	2 7 3 1	2 7 4 1	2 7 5 1	2 8 3 1	2 8 4 1	2 8 5 1	2 8 6 1	2 8 7 1	2 8 9 1	2 9 0 1	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant lymphocytic																				X						2
Lymphoma malignant mixed									X				X													3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm

Number of Days on Study	3 3 3 4 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 3 5 9 2 1 4 4 7 7 7 8 9 9 0 0 0 0 1 1 1 1 1 1 1 2 1 3 2 5 9 6 8 4 6 9 2 1 5 0 0 4 8 0 0 0 1 1 1 4 8
Carcass ID Number	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 5 2 6 5 4 5 6 5 6 5 2 2 4 3 4 2 3 3 3 7 4 4 5 3 2 8 9 1 5 4 2 4 3 5 4 8 4 7 8 0 6 4 3 9 0 3 5 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Alimentary System	
Esophagus	+ +
Gallbladder	+ + + + + + + + M + + + + + + + + + + + + + + +
Intestine large	+ +
Intestine large, cecum	+ + + + + + + + + A + + + + + + + + + + + + + +
Leiomyosarcoma	X
Intestine large, colon	+ +
Intestine large, rectum	+ +
Fibrosarcoma, metastatic, skin	X
Intestine small	+ + + + + + + + + A + + + + + + + + + + + + + +
Intestine small, duodenum	+ + + + + + + + + A + + + + + + + + + + + + + +
Intestine small, ileum	+ + + + + + + + + A + M + + + + + + + + + + + +
Intestine small, jejunum	+ + + + + + + + + A + + + + + + + + + + + + + +
Liver	+ +
Hemangiosarcoma	X
Hepatoblastoma	X
Hepatocellular carcinoma	X
Hepatocellular carcinoma, multiple	X
Hepatocellular adenoma	X X X
Hepatocellular adenoma, multiple	X X X X
Osteosarcoma, metastatic, bone	X
Mesentery	+ + +
Hemangioma	X
Pancreas	+ +
Salivary glands	+ +
Stomach	+ +
Stomach, forestomach	+ +
Squamous cell papilloma	
Stomach, glandular	+ +
Tongue	+
Tooth	+ +
Fibrosarcoma	X
Squamous cell carcinoma	X
Cardiovascular System	
Heart	+ +
Endocrine System	
Adrenal gland	+ +
Adrenal gland, cortex	+ +
Adrenal gland, medulla	+ +
Islets, pancreatic	+ +
Parathyroid gland	+ + + + + + + + + M + + + + + + + + + + + + + +

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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 0	7 3 0	7 3 0	
Carcass ID Number	4 2 2 1	4 2 3 1	4 2 5 1	4 2 7 1	4 6 3 1	4 6 6 1	4 6 7 1	4 6 8 1	4 3 1 1	4 3 2 1	4 3 5 1	4 3 6 1	4 3 7 1	4 4 1 1	4 4 2 1	4 4 6 1	4 4 8 1	4 4 9 1	4 5 0 1	4 5 6 1	4 5 7 1	4 5 9 1	4 6 0 1	4 6 2 1	4 6 9 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	48
Leiomyosarcoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+		+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatoblastoma																										1
Hepatocellular carcinoma																										1
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X			X	X			X			X						X		X				X			11
Hepatocellular adenoma, multiple															X	X				X					X	X	9
Osteosarcoma, metastatic, bone																										1
Mesentery										+							+		+							7
Hemangioma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma												X														1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Tooth																										2
Fibrosarcoma																										1
Squamous cell carcinoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	48

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	3	3	3	4	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7
	3	5	9	2	1	4	4	7	7	7	8	9	9	0	0	0	0	1	1	1	1	1	1	1	2
	1	3	2	5	9	6	8	4	6	9	2	1	5	0	0	4	8	0	0	0	1	1	1	4	8
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	5	2	6	5	4	5	6	5	6	5	2	2	4	3	4	2	3	3	3	7	4	4	5	3	2
	8	9	1	5	4	2	4	3	5	4	8	4	7	8	0	6	4	3	9	0	3	5	1	0	1
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pars distalis, adenoma																X						X			
Pars intermedia, adenoma																									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland																					+				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Granulosa cell tumor malignant		X																							
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leiomyoma																									
Polyp stromal													X								X			X	
Sarcoma stromal																								X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bronchial, osteosarcoma, metastatic, bone											X														
Inguinal, fibrosarcoma, metastatic, skin			X																						
Mediastinal, hepatoblastoma, metastatic, liver																							X		
Mediastinal, osteosarcoma, metastatic, bone											X														
Lymph node, mandibular	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, tooth															X										
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X											X					
Thymus	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Hepatoblastoma, metastatic, liver																							X		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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 0	7 3 0	7 3 0	
Carcass ID Number	4 2 2 1	4 2 3 1	4 2 5 1	4 2 7 1	4 6 3 1	4 6 6 1	4 6 7 1	4 6 8 1	4 3 1 1	4 3 2 1	4 3 5 1	4 3 6 1	4 3 7 1	4 4 1 1	4 4 2 1	4 4 6 1	4 4 8 1	4 4 9 1	4 5 0 1	4 5 6 1	4 5 7 1	4 5 9 1	4 6 0 1	4 6 2 1	4 6 9 1	Total Tissues/ Tumors
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	I	+	47
Pars distalis, adenoma	X												X						X			X				6
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																	X									1
General Body System																										
None																										
Genital System																										
Clitoral gland																							+			2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																					1
Granulosa cell tumor malignant				+																						1
Luteoma																X										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma														X												1
Leiomyoma															X											1
Polyp stromal										X			X													5
Sarcoma stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bronchial, osteosarcoma, metastatic, bone																										1
Inguinal, fibrosarcoma, metastatic, skin																										1
Mediastinal, hepatoblastoma, metastatic, liver																										1
Mediastinal, osteosarcoma, metastatic, bone																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic, tooth																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	+	44
Hepatoblastoma, metastatic, liver																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	3 3 3 4 6 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 3 5 9 2 1 4 4 7 7 7 8 9 9 0 0 0 0 1 1 1 1 1 1 2 1 3 2 5 9 6 8 4 6 9 2 1 5 0 0 4 8 0 0 0 1 1 1 4 8
Carcass ID Number	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 5 2 6 5 4 5 6 5 6 5 2 2 4 3 4 2 3 3 3 7 4 4 5 3 2 8 9 1 5 4 2 4 3 5 4 8 4 7 8 0 6 4 3 9 0 3 5 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Integumentary System	
Mammary gland	+ +
Carcinoma	X
Skin	+ +
Subcutaneous tissue, fibrosarcoma	X
Subcutaneous tissue, hemangiosarcoma	X
Subcutaneous tissue, schwannoma malignant	X
Musculoskeletal System	
Bone	+ +
Osteosarcoma	X
Skeletal muscle	+
Nervous System	
Brain	+ +
Cranial nerve, schwannoma malignant	X
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X
Alveolar/bronchiolar carcinoma	X
Fibrosarcoma, metastatic, skin	X
Hepatoblastoma, metastatic, liver	X
Hepatocellular carcinoma, metastatic, liver	X X
Osteosarcoma, metastatic, bone	X
Squamous cell carcinoma, metastatic, tooth	X
Nose	+ +
Trachea	+ +
Special Senses System	
Eye	+
Harderian gland	+ +
Adenoma	X X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	7228	7228	7228	7228	7228	7228	7228	7228	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	7330	
Carcass ID Number	42211	42311	42511	42711	43611	43611	43711	43811	44111	44211	44511	44611	44711	45111	45211	45611	45811	45911	46011	46611	46711	46911	47011	47111	47211	47311	Total Tissues/ Tumors
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																											1
Subcutaneous tissue, hemangiosarcoma																											1
Subcutaneous tissue, schwannoma malignant																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																											1
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranial nerve, schwannoma malignant																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																					2
Alveolar/bronchiolar carcinoma																											1
Fibrosarcoma, metastatic, skin																											1
Hepatoblastoma, metastatic, liver																											1
Hepatocellular carcinoma, metastatic, liver																											2
Osteosarcoma, metastatic, bone																											1
Squamous cell carcinoma, metastatic, tooth																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																											1
Harderian gland																										+	3
Adenoma																										X	3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of o-Nitroanisole: 666 ppm (continued)

Number of Days on Study	3	3	3	4	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	
	3	5	9	2	1	4	4	7	7	7	8	9	9	0	0	0	0	1	1	1	1	1	1	1	2
	1	3	2	5	9	6	8	4	6	9	2	1	5	0	0	4	8	0	0	0	1	1	1	4	8
Carcass ID Number	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	5	2	6	5	4	5	6	5	6	5	2	2	4	3	4	2	3	3	3	7	4	4	5	3	2
	8	9	1	5	4	2	4	3	5	4	8	4	7	8	0	6	4	3	9	0	3	5	1	0	1
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin								X																	
Osteosarcoma, metastatic, bone											X														
Renal tubule, carcinoma													X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic						X																			
Lymphoma malignant lymphocytic										X						X			X						
Lymphoma malignant mixed													X					X							
Lymphoma malignant undifferentiated cell type																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 666 ppm (continued)

Number of Days on Study	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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 0	7 3 0	7 3 0	
Carcass ID Number	4 2 2 1	4 2 3 1	4 2 5 1	4 2 7 1	4 6 3 1	4 6 6 1	4 6 7 1	4 6 8 1	4 3 1 1	4 3 2 1	4 3 5 1	4 3 6 1	4 3 7 1	4 4 1 1	4 4 2 1	4 4 6 1	4 4 8 1	4 4 9 1	4 5 0 1	4 5 6 1	4 5 7 1	4 5 9 1	4 6 0 1	4 6 2 1	4 6 9 1	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Osteosarcoma, metastatic, bone																										1
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant lymphocytic				X	X												X									6
Lymphoma malignant mixed								X		X				X							X					6
Lymphoma malignant undifferentiated cell type																		X								1

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

Number of Days on Study	4 4 5	5 3 9	5 3 9	5 3 9	5 4 6	5 6 4	5 9 2	6 0 3	6 6 4	6 8 6	7 0 0	7 0 2	7 0 4	7 0 8	7 1 1	7 2 1	7 2 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5
Carcass ID Number	3 7 4 1	3 6 8 1	3 7 0 1	3 7 5 1	4 0 4 1	3 8 9 1	4 0 1 1	3 9 2 1	3 6 7 1	3 9 0 1	3 9 6 1	3 8 3 1	3 7 7 1	4 0 0 1	3 9 8 1	3 9 5 1	3 6 9 1	3 7 1 1	3 7 2 1	3 7 3 1	4 0 9 1	4 1 0 1	3 6 1 1	3 6 2 1	3 6 3 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma															X										
Hepatoblastoma, multiple									X																
Hepatocellular carcinoma										X					X	X									
Hepatocellular carcinoma, multiple																		X							
Hepatocellular adenoma						X						X				X			X	X					
Hepatocellular adenoma, multiple					X				X	X	X		X	X	X			X				X		X	X
Histiocytic sarcoma																									
Osteosarcoma, metastatic, bone						X																			
Mesentery										+	+		+	+								+			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma					X						X								X						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant												X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pars distalis, adenoma					X												X				X	X			
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

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 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 6 4 1	3 6 5 1	3 6 6 1	3 7 6 1	3 7 8 1	3 7 9 1	3 8 0 1	3 8 1 1	3 8 2 1	3 8 4 1	3 8 5 1	3 8 6 1	3 8 7 1	3 8 8 1	3 9 1 1	3 9 3 1	3 9 4 1	3 9 7 1	3 9 9 1	4 0 2 1	4 0 3 1	4 0 5 1	4 0 6 1	4 0 7 1	4 0 8 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma																										1
Hepatoblastoma, multiple																										1
Hepatocellular carcinoma				X												X	X								X	7
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma		X							X			X	X						X				X			11
Hepatocellular adenoma, multiple	X		X	X	X		X	X			X			X		X		X			X	X		X	X	25
Histiocytic sarcoma						X																				1
Osteosarcoma, metastatic, bone																										1
Mesentery																										5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma										X			X				X									6
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma									X			X							X		X					8
Pars intermedia, adenoma			X										X		X											3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	4	5	5	5	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	4	3	3	3	4	6	9	0	6	8	0	0	0	0	1	2	2	3	3	3	3	3	3	3
	5	9	9	9	6	4	2	3	4	6	0	2	4	8	1	1	2	2	2	2	2	5	5	5
Carcass ID Number	3	3	3	3	4	3	4	3	3	3	3	3	3	4	3	3	3	3	3	4	4	3	3	3
	7	6	7	7	0	8	0	9	6	9	9	8	7	0	9	9	6	7	7	7	0	1	6	6
	4	8	0	5	4	9	1	2	7	0	6	3	7	0	8	5	9	1	2	3	9	0	1	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
General Body System																								
Tissue NOS		+									+													
Genital System																								
Clitoral gland							+														+			
Ovary	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor benign																								X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Leiomyoma																							X	
Polyp stromal																								
Vagina																	+							
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, histiocytic sarcoma																								
Renal, histiocytic sarcoma																								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Histiocytic sarcoma																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Thymus	+	+	+	M	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	M	+	+
Histiocytic sarcoma																								
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma						X																		
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

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 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 6 4 1	3 6 5 1	3 6 6 1	3 7 6 1	3 7 8 1	3 7 9 1	3 8 0 1	3 8 1 1	3 8 2 1	3 8 4 1	3 8 5 1	3 8 6 1	3 8 7 1	3 8 8 1	3 8 9 1	3 9 1 1	3 9 3 1	3 9 4 1	3 9 7 1	3 9 9 1	4 0 2 1	4 0 3 1	4 0 5 1	4 0 6 1	4 0 7 1	4 0 8 1	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										2
Genital System																										
Clitoral gland																										2
Ovary	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa-theca tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																								X		1
Leiomyoma																										1
Polyp stromal					X								X	X					X							4
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, histiocytic sarcoma						X																				1
Renal, histiocytic sarcoma						X																				1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	49
Histiocytic sarcoma						X																				1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Histiocytic sarcoma						X																				1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																				1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma						X																				1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

Number of Days on Study	4	5	5	5	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	4	3	3	3	4	6	9	0	6	8	0	0	0	0	1	2	2	3	3	3	3	3	3	3
	5	9	9	9	6	4	2	3	4	6	0	2	4	8	1	1	2	2	2	2	2	2	5	5
Carcass ID Number	3	3	3	3	4	3	4	3	3	3	3	3	3	4	3	3	3	3	3	3	4	4	3	3
	7	6	7	7	0	8	0	9	6	9	9	8	7	0	9	9	6	7	7	7	0	1	6	6
	4	8	0	5	4	9	1	2	7	0	6	3	7	0	8	5	9	1	2	3	9	0	1	2
	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X																							X
Alveolar/bronchiolar adenoma, two, multiple																								
Histiocytic sarcoma																								
Osteosarcoma, metastatic, bone						X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Harderian gland															+									
Adenoma															X									
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Lymphoma malignant lymphocytic										X	X		X											
Lymphoma malignant mixed			X															X				X	X	X
Lymphoma malignant undifferentiated cell type							X																	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 2,000 ppm (continued)

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 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	
Carcass ID Number	3 6 4 1	3 6 5 1	3 6 6 1	3 7 6 1	3 7 8 1	3 7 9 1	3 8 0 1	3 8 1 1	3 8 2 1	3 8 4 1	3 8 5 1	3 8 6 1	3 8 7 1	3 8 8 1	3 8 9 1	3 9 1 1	3 9 3 1	3 9 4 1	3 9 7 1	3 9 9 1	4 0 2 1	4 0 3 1	4 0 5 1	4 0 6 1	4 0 7 1	4 0 8 1	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																											2
Alveolar/bronchiolar adenoma, two, multiple					X																						1
Histiocytic sarcoma						X																					1
Osteosarcoma, metastatic, bone																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Harderian gland					+																+						3
Adenoma					X																X						3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma						X																					1
Lymphoma malignant lymphocytic																											3
Lymphoma malignant mixed		X											X		X						X				X		10
Lymphoma malignant undifferentiated cell type																											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	735	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	33771	33881	33991	34011	34411	34421	34431	34451	34461	34471	34481	32211	32231	32241	32251	32261	32271	32281	32291	33301	33311	33321	33351	34191	35101	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										3
Hepatocellular adenoma	X	X		X					X														X		X	11
Hepatocellular adenoma, multiple								X		X									X	X						7
Mesentery													+													2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma						X																				2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Tissue NOS																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	4 0 1	4 5 2	5 9 7	7 1 0	7 1 0	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 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2
Carcass ID Number	3 1 2 1	3 0 7 1	3 4 4 1	3 3 3 1	3 3 4 1	3 0 1 1	3 0 2 1	3 0 3 1	3 0 4 1	3 0 5 1	3 0 6 1	3 0 8 1	3 0 9 1	3 1 0 1	3 1 1 1	3 1 3 1	3 1 4 1	3 1 5 1	3 1 6 1	3 1 7 1	3 1 8 1	3 1 9 1	3 2 0 1	3 2 1 1	3 3 6 1
Genital System																									
Clitoral gland										M															
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Cystadenocarcinoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma															X										
Hemangioma																									
Polyp stromal														X											
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma																								X	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	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 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	
Carcass ID Number	3 3 7 1	3 3 8 1	3 3 9 1	3 4 0 1	3 4 1 1	3 4 2 1	3 4 3 1	3 4 5 1	3 4 6 1	3 4 7 1	3 4 8 1	3 2 2 1	3 2 3 1	3 2 4 1	3 2 5 1	3 2 6 1	3 2 7 1	3 2 8 1	3 2 9 1	3 3 0 1	3 3 1 1	3 3 2 1	3 3 5 1	3 4 9 1	3 5 0 1	Total Tissues/ Tumors
Genital System																										
Clitoral gland																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Cystadenocarcinoma							X																			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Hemangioma																							X			1
Polyp stromal								X																		2
Sarcoma stromal																						X				1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

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

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of o-Nitroanisole

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Harderian Gland: Adenoma				
Overall rates[a]	0/50 (0%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rates[b]	0.0%	9.3%	8.7%	2.2%
Terminal rates[c]	0/38 (0%)	1/26 (4%)	2/33 (6%)	1/45 (2%)
First incidence (days)	–[e]	679	711	728 (T)
Life table tests[d]	P=0.437N	P=0.085	P=0.101	P=0.534
Logistic regression tests[d]	P=0.521N	P=0.116	P=0.109	P=0.534
Cochran-Armitage test[d]	P=0.555N			
Fisher exact test[d]		P=0.121	P=0.121	P=0.500
Harderian Gland: Adenoma or Carcinoma				
Overall rates	1/50 (2%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rates	2.6%	9.3%	8.7%	2.2%
Terminal rates	1/38 (3%)	1/26 (4%)	2/33 (6%)	1/45 (2%)
First incidence (days)	728 (T)	679	711	728 (T)
Life table tests	P=0.306N	P=0.217	P=0.261	P=0.724N
Logistic regression tests	P=0.381N	P=0.290	P=0.279	P=0.724N
Cochran-Armitage test	P=0.418N			
Fisher exact test		P=0.309	P=0.309	P=0.753N
Liver: Hepatocellular Adenoma				
Overall rates	14/50 (28%)	20/50 (40%)	36/50 (72%)	18/50 (36%)
Adjusted rates	36.8%	60.9%	83.6%	39.1%
Terminal rates	14/38 (37%)	14/26 (54%)	26/33 (79%)	17/45 (38%)
First incidence (days)	728 (T)	619	546	710
Life table tests	P=0.122N	P=0.011	P<0.001	P=0.473
Logistic regression tests	P=0.450N	P=0.080	P<0.001	P=0.412
Cochran-Armitage test	P=0.484			
Fisher exact test		P=0.146	P<0.001	P=0.260
Liver: Hepatocellular Carcinoma				
Overall rates	5/50 (10%)	2/50 (4%)	8/50 (16%)	3/50 (6%)
Adjusted rates	12.6%	5.1%	21.8%	6.7%
Terminal rates	4/38 (11%)	0/26 (0%)	5/33 (15%)	3/45 (7%)
First incidence (days)	693	619	686	728 (T)
Life table tests	P=0.260N	P=0.336N	P=0.208	P=0.274N
Logistic regression tests	P=0.381N	P=0.225N	P=0.241	P=0.319N
Cochran-Armitage test	P=0.430N			
Fisher exact test		P=0.218N	P=0.277	P=0.357N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rates	17/50 (34%)	21/50 (42%)	37/50 (74%)	20/50 (40%)
Adjusted rates	43.5%	62.1%	85.9%	43.5%
Terminal rates	16/38 (42%)	14/26 (54%)	27/33 (82%)	19/45 (42%)
First incidence (days)	693	619	546	710
Life table tests	P=0.100N	P=0.029	P<0.001	P=0.577N
Logistic regression tests	P=0.425N	P=0.172	P<0.001	P=0.487
Cochran-Armitage test	P=0.496			
Fisher exact test		P=0.268	P<0.001	P=0.339

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Liver: Hepatoblastoma or Hepatocellular Carcinoma				
Overall rates	6/50 (12%)	3/50 (6%)	9/50 (18%)	3/50 (6%)
Adjusted rates	15.2%	8.3%	23.7%	6.7%
Terminal rates	5/38 (13%)	0/26 (0%)	5/33 (15%)	3/45 (7%)
First incidence (days)	693	619	664	728 (T)
Life table tests	P=0.158N	P=0.397N	P=0.217	P=0.172N
Logistic regression tests	P=0.254N	P=0.256N	P=0.259	P=0.207N
Cochran-Armitage test	P=0.293N			
Fisher exact test		P=0.243N	P=0.288	P=0.243N
Liver: Hepatocellular Adenoma, Carcinoma, or Hepatoblastoma				
Overall rates	17/50 (34%)	22/50 (44%)	37/50 (74%)	20/50 (40%)
Adjusted rates	43.5%	63.4%	85.9%	43.5%
Terminal rates	16/38 (42%)	14/26 (54%)	27/33 (82%)	19/45 (42%)
First incidence (days)	693	619	546	710
Life table tests	P=0.086N	P=0.019	P<0.001	P=0.577N
Logistic regression tests	P=0.388N	P=0.124	P<0.001	P=0.487
Cochran-Armitage test	P=0.532			
Fisher exact test		P=0.206	P<0.001	P=0.339
Lung: Alveolar/bronchiolar Adenoma				
Overall rates	4/50 (8%)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted rates	10.0%	6.3%	7.9%	0.0%
Terminal rates	3/38 (8%)	1/26 (4%)	2/33 (6%)	0/45 (0%)
First incidence (days)	693	691	445	–
Life table tests	P=0.044N	P=0.477N	P=0.557N	P=0.048N
Logistic regression tests	P=0.070N	P=0.363N	P=0.503N	P=0.057N
Cochran-Armitage test	P=0.068N			
Fisher exact test		P=0.339N	P=0.500N	P=0.059N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rates	6/50 (12%)	3/50 (6%)	3/50 (6%)	0/50 (0%)
Adjusted rates	15.2%	8.4%	7.9%	0.0%
Terminal rates	5/38 (13%)	1/26 (4%)	2/33 (6%)	0/45 (0%)
First incidence (days)	693	648	445	–
Life table tests	P=0.012N	P=0.396N	P=0.303N	P=0.011N
Logistic regression tests	P=0.020N	P=0.260N	P=0.242N	P=0.014N
Cochran-Armitage test	P=0.020N			
Fisher exact test		P=0.243N	P=0.243N	P=0.013N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rates	7/49 (14%)	6/47 (13%)	8/48 (17%)	0/48 (0%)
Adjusted rates	18.9%	21.7%	22.9%	0.0%
Terminal rates	7/37 (19%)	4/24 (17%)	6/32 (19%)	0/43 (0%)
First incidence (days)	728 (T)	704	546	–
Life table tests	P=0.003N	P=0.430	P=0.386	P=0.005N
Logistic regression tests	P=0.007N	P=0.535	P=0.455	P=0.005N
Cochran-Armitage test	P=0.010N			
Fisher exact test		P=0.533N	P=0.482	P=0.007N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Pituitary Gland (Pars Intermedia): Adenoma				
Overall rates	1/49 (2%)	1/47 (2%)	3/48 (6%)	0/48 (0%)
Adjusted rates	2.7%	4.2%	9.4%	0.0%
Terminal rates	1/37 (3%)	1/24 (4%)	3/32 (9%)	0/43 (0%)
First incidence (days)	728 (T)	728 (T)	728 (T)	–
Life table tests	P=0.247N	P=0.662	P=0.254	P=0.470N
Logistic regression tests	P=0.247N	P=0.662	P=0.254	P=0.470N
Cochran-Armitage test	P=0.338N			
Fisher exact test		P=0.742	P=0.301	P=0.505N
Small Intestine: Adenoma or Carcinoma				
Overall rates	3/50 (6%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
Adjusted rates	7.0%	0.0%	0.0%	0.0%
Terminal rates	1/38 (3%)	0/26 (0%)	0/33 (0%)	0/45 (0%)
First incidence (days)	564	–	–	–
Life table tests	P=0.115N	P=0.160N	P=0.142N	P=0.105N
Logistic regression tests	P=0.138N	P=0.119N	P=0.124N	P=0.133N
Cochran-Armitage test	P=0.130N			
Fisher exact test		P=0.121N	P=0.121N	P=0.121N
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rates	3/50 (6%)	1/50 (2%)	6/50 (12%)	2/50 (4%)
Adjusted rates	7.5%	3.8%	16.2%	4.4%
Terminal rates	2/38 (5%)	1/26 (4%)	4/33 (12%)	2/45 (4%)
First incidence (days)	705	728 (T)	546	728 (T)
Life table tests	P=0.377N	P=0.432N	P=0.194	P=0.429N
Logistic regression tests	P=0.509N	P=0.350N	P=0.241	P=0.470N
Cochran-Armitage test	P=0.534N			
Fisher exact test		P=0.309N	P=0.243	P=0.500N
Uterus: Stromal Polyp				
Overall rates	3/50 (6%)	5/50 (10%)	4/50 (8%)	2/50 (4%)
Adjusted rates	7.9%	16.3%	12.1%	4.4%
Terminal rates	3/38 (8%)	2/26 (8%)	4/33 (12%)	2/45 (4%)
First incidence (days)	728 (T)	695	728 (T)	728 (T)
Life table tests	P=0.154N	P=0.197	P=0.423	P=0.423N
Logistic regression tests	P=0.209N	P=0.304	P=0.423	P=0.423N
Cochran-Armitage test	P=0.276N			
Fisher exact test		P=0.357	P=0.500	P=0.500N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rates	3/50 (6%)	5/50 (10%)	4/50 (8%)	3/50 (6%)
Adjusted rates	7.9%	16.3%	12.1%	6.7%
Terminal rates	3/38 (8%)	2/26 (8%)	4/33 (12%)	3/45 (7%)
First incidence (days)	728 (T)	695	728 (T)	728 (T)
Life table tests	P=0.271N	P=0.197	P=0.423	P=0.583N
Logistic regression tests	P=0.353N	P=0.304	P=0.423	P=0.583N
Cochran-Armitage test	P=0.446N			
Fisher exact test		P=0.357	P=0.500	P=0.661N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
All Organs: Hemangioma or Hemangiosarcoma				
Overall rates	3/50 (6%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rates	7.6%	7.9%	0.0%	2.2%
Terminal rates	2/38 (5%)	0/26 (0%)	0/33 (0%)	1/45 (2%)
First incidence (days)	722	676	–	728 (T)
Life table tests	P=0.143N	P=0.540	P=0.150N	P=0.253N
Logistic regression tests	P=0.181N	P=0.647	P=0.136N	P=0.268N
Cochran-Armitage test	P=0.196N			
Fisher exact test		P=0.661N	P=0.121N	P=0.309N
All Organs: Malignant Lymphoma and Histiocytic Sarcoma				
Overall rates	7/50 (14%)	14/50 (28%)	15/50 (30%)	5/50 (10%)
Adjusted rates	17.1%	41.3%	38.2%	10.8%
Terminal rates	4/38 (11%)	8/26 (31%)	10/33 (30%)	4/45 (9%)
First incidence (days)	708	646	539	710
Life table tests	P=0.028N	P=0.017	P=0.029	P=0.281N
Logistic regression tests	P=0.072N	P=0.050	P=0.043	P=0.331N
Cochran-Armitage test	P=0.094N			
Fisher exact test		P=0.070	P=0.045	P=0.380N
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rates	5/50 (10%)	14/50 (28%)	14/50 (28%)	5/50 (10%)
Adjusted rates	12.7%	41.3%	35.5%	10.8%
Terminal rates	4/38 (11%)	8/26 (31%)	9/33 (27%)	4/45 (9%)
First incidence (days)	708	646	539	710
Life table tests	P=0.054N	P=0.004	P=0.013	P=0.523N
Logistic regression tests	P=0.128N	P=0.014	P=0.020	P=0.585N
Cochran-Armitage test	P=0.157N			
Fisher exact test		P=0.020	P=0.020	P=0.630N
All Organs: Benign Neoplasms				
Overall rates	31/50 (62%)	31/50 (62%)	43/50 (86%)	22/50 (44%)
Adjusted rates	73.6%	80.9%	95.5%	47.8%
Terminal rates	27/38 (71%)	19/26 (73%)	31/33 (94%)	21/45 (47%)
First incidence (days)	312	619	445	710
Life table tests	P<0.001N	P=0.052	P=0.001	P=0.007N
Logistic regression tests	P=0.004N	P=0.507	P=0.004	P=0.034N
Cochran-Armitage test	P=0.015N			
Fisher exact test		P=0.582N	P=0.006	P=0.054N
All Organs: Malignant Neoplasms				
Overall rates	20/50 (40%)	27/50 (54%)	24/50 (48%)	10/50 (20%)
Adjusted rates	45.2%	58.2%	55.2%	21.7%
Terminal rates	14/38 (37%)	8/26 (31%)	14/33 (42%)	9/45 (20%)
First incidence (days)	312	331	539	710
Life table tests	P<0.001N	P=0.031	P=0.168	P=0.010N
Logistic regression tests	P=0.002N	P=0.124	P=0.273	P=0.023N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.115	P=0.273	P=0.024N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of o-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rates	39/50 (78%)	44/50 (88%)	47/50 (94%)	28/50 (56%)
Adjusted rates	84.7%	91.6%	100.0%	60.9%
Terminal rates	31/38 (82%)	22/26 (85%)	33/33 (100%)	27/45 (60%)
First incidence (days)	312	331	445	710
Life table tests	P<0.001N	P=0.005	P=0.010	P=0.001N
Logistic regression tests	P<0.001N	P=0.130	P=0.021	P=0.008N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.143	P=0.020	P=0.016N

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

TABLE D4
Historical Incidence of Liver Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Carcinoma, or Hepatoblastoma
Historical Incidence at Southern Research Institute				
C.I. Pigment Red 3	7/50	4/50	0/50	10/50
Ethylene Glycol	8/50	3/50	0/50	10/50
Nitrofurantoin	1/50	1/50	0/50	2/50
o-Nitroanisole	14/50	5/50	1/50	17/50
Polysorbate 80	2/50	1/50	0/50	3/50
Rhodamine 6G	5/50	3/50	0/50	8/50
Roxarsone	1/50	2/50	0/50	3/50
Overall Historical Incidence				
Total	74/863 (8.6%)	28/863 (3.2%)	1/863 (0.1%)	98/863 (11.4%)
Standard deviation	6.5%	2.9%	0.5%	7.6%
Range	0%-28%	0%-10%	0%-2%	3%-34%

[a] Data as of 3 April 1991

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of o-Nitroanisole[a]

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	7	16	10	5
Natural deaths	5	8	7	
Survivors				
Terminal sacrifice	38	26	33	45
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine small, duodenum	(10)			(10)
Cyst	1 (10%)			
Intestine small, ileum	(10)			(10)
Lymphoid tissue, hyperplasia	1 (10%)			
Intestine small, jejunum	(10)			(10)
Lymphoid tissue, hyperplasia	1 (10%)			
Liver	(10)	(10)	(10)	(10)
Clear cell focus			1 (10%)	
Eosinophilic focus		1 (10%)		1 (10%)
Inflammation, chronic active	7 (70%)	4 (40%)	4 (40%)	6 (60%)
Hepatocyte, cytologic alterations		1 (10%)	9 (90%)	9 (90%)
Hepatocyte, vacuolization cytoplasmic		2 (20%)		
Pancreas	(10)			
Atrophy	1 (10%)			
Salivary glands	(10)			(10)
Inflammation, chronic				1 (10%)
Stomach, forestomach	(10)		(1)	(10)
Mucosa, hyperplasia			1 (100%)	
Stomach, glandular	(10)			(10)
Cyst	2 (20%)			1 (10%)
Inflammation, acute	1 (10%)			
Cardiovascular System				
None				
Endocrine System				
Adrenal gland, cortex	(10)			(10)
Accessory adrenal cortical nodule				2 (20%)
Hyperplasia, focal	2 (20%)			
Subcapsular, hyperplasia	6 (60%)			2 (20%)
Islets, pancreatic	(10)			(10)
Cyst	1 (10%)			
Hyperplasia	2 (20%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
15-Month Interim Evaluation (continued)				
Endocrine System (continued)				
Parathyroid gland	(9)			(10)
Infiltration cellular, histiocytic				1 (10%)
Pigmentation				1 (10%)
Thyroid gland	(9)			(10)
Degeneration, cystic	3 (33%)			1 (10%)
Follicular cell, hyperplasia				1 (10%)
General Body System				
None				
Genital System				
Ovary	(10)			(10)
Angiectasis				1 (10%)
Uterus	(10)	(6)	(8)	(10)
Exudate	2 (20%)	2 (33%)	4 (50%)	3 (30%)
Hyperplasia	1 (10%)			
Hyperplasia, cystic	9 (90%)	6 (100%)	8 (100%)	5 (50%)
Epithelium, hyperplasia, focal		1 (17%)		
Hematopoietic System				
Lymph node	(10)	(1)		(10)
Bronchial, hyperplasia, lymphoid		1 (100%)		
Spleen	(10)	(2)	(1)	(10)
Hematopoietic cell proliferation	1 (10%)			
Pigmentation, hemosiderin		1 (50%)	1 (100%)	
Lymphoid follicle, hyperplasia		1 (50%)		
Thymus	(10)			(10)
Cyst	2 (20%)			2 (20%)
Integumentary System				
Skin	(10)	(2)		(10)
Hemorrhage		1 (50%)		
Inflammation, acute		1 (50%)		
Musculoskeletal System				
Bone	(10)			(10)
Femur, hyperostosis	1 (10%)			
Nervous System				
Brain	(10)			(10)
Thalamus, mineralization	9 (90%)			7 (70%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole
(continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)		(1)	(10)
Edema	1 (10%)			
Mediastinum, ectopic tissue				1 (10%)
Nose	(10)	(5)	(10)	(10)
Exudate				3 (30%)
Glands, dilatation	1 (10%)		9 (90%)	10 (100%)
Glands, hyperplasia			6 (60%)	10 (100%)
Mucosa, degeneration, hyaline	7 (70%)	5 (100%)	6 (60%)	10 (100%)
Olfactory epithelium, metaplasia			7 (70%)	10 (100%)
Special Senses System				
None				
Urinary System				
Kidney	(10)			(10)
Casts protein	2 (20%)			4 (40%)
Inflammation, chronic	6 (60%)			4 (40%)
Mineralization	1 (10%)			3 (30%)
Renal tubule, regeneration	2 (20%)			1 (10%)
Urinary bladder	(10)			(10)
Inflammation, chronic	4 (40%)			1 (10%)
2-Year Study				
Alimentary System				
Gallbladder	(48)	(48)	(48)	(48)
Cyst			1 (2%)	
Dilatation	2 (4%)		1 (2%)	
Hyperplasia, lymphoid	1 (2%)			3 (6%)
Intestine large, cecum	(50)	(48)	(50)	(49)
Edema		1 (2%)		
Intestine large, colon	(49)	(48)	(50)	(50)
Edema		1 (2%)		
Intestine large, rectum	(50)	(50)	(50)	(49)
Inflammation, chronic		1 (2%)		
Intestine small, duodenum	(50)	(49)	(50)	(49)
Mucosa, hyperplasia	1 (2%)			3 (6%)
Intestine small, ileum	(49)	(48)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)			1 (2%)
Inflammation, pyogranulomatous			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Basophilic focus	3 (6%)			
Clear cell focus		1 (2%)	4 (8%)	
Cytologic alterations		1 (2%)	1 (2%)	1 (2%)
Eosinophilic focus	11 (22%)	6 (12%)	21 (42%)	16 (32%)
Fibrosis, focal	1 (2%)			
Hematopoietic cell proliferation	5 (10%)	2 (4%)	4 (8%)	
Hemorrhage	2 (4%)	1 (2%)		2 (4%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver (continued)				
Hyperplasia, lymphoid	4 (8%)	3 (6%)	13 (26%)	6 (12%)
Infarct	1 (2%)			
Inflammation, chronic	4 (8%)	10 (20%)	5 (10%)	13 (26%)
Mineralization			1 (2%)	
Mixed cell focus		1 (2%)		
Centrilobular, necrosis	1 (2%)	1 (2%)	1 (2%)	
Hepatocyte, cytologic alterations		8 (16%)	13 (26%)	40 (80%)
Hepatocyte, vacuolization cytoplasmic	2 (4%)	1 (2%)		
Kupffer cell, hyperplasia	3 (6%)	5 (10%)	1 (2%)	
Kupffer cell, pigmentation		3 (6%)		3 (6%)
Lobules, necrosis	3 (6%)	8 (16%)	3 (6%)	2 (4%)
Periportal, inflammation	1 (2%)			
Mesentery	(9)	(7)	(5)	(2)
Accessory spleen	1 (11%)			
Inflammation, suppurative		1 (14%)	1 (20%)	
Hyperplasia, lymphoid				2 (100%)
Fat, hemorrhage			1 (20%)	
Fat, necrosis	6 (67%)	2 (29%)	1 (20%)	1 (50%)
Pancreas	(50)	(50)	(50)	(50)
Atrophy	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Cyst	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Cytoplasmic alteration	2 (4%)	3 (6%)	3 (6%)	
Focal cellular change	1 (2%)			
Hyperplasia, lymphoid	14 (28%)	8 (16%)	13 (26%)	7 (14%)
Salivary glands	(49)	(50)	(50)	(50)
Atrophy				1 (2%)
Hyperplasia, lymphoid	18 (37%)	24 (48%)	19 (38%)	20 (40%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Cyst		1 (2%)	1 (2%)	
Diverticulum	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Inflammation, suppurative	3 (6%)	4 (8%)	3 (6%)	1 (2%)
Mineralization	1 (2%)			
Ulcer	1 (2%)			
Mucosa, hyperplasia	7 (14%)	6 (12%)	7 (14%)	2 (4%)
Stomach, glandular	(50)	(50)	(50)	(50)
Cyst	17 (34%)	20 (40%)	13 (26%)	11 (22%)
Dysplasia		1 (2%)	1 (2%)	
Edema	1 (2%)		1 (2%)	1 (2%)
Epithelium, dilatation				1 (2%)
Erosion	2 (4%)	4 (8%)	2 (4%)	
Infiltration cellular, plasma cell		1 (2%)		
Inflammation, chronic	1 (2%)	2 (4%)		
Inflammation, subacute	1 (2%)			
Mineralization		1 (2%)		
Mucosa, hyperplasia	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole
(continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Epicardium, inflammation, chronic	1 (2%)			
Epicardium, inflammation, suppurative		1 (2%)	1 (2%)	
Myocardium, fibrosis		1 (2%)		
Myocardium, inflammation, chronic		2 (4%)	3 (6%)	1 (2%)
Myocardium, mineralization		1 (2%)		
Endocrine System				
Adrenal gland, cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	9 (18%)	7 (14%)	8 (16%)	14 (28%)
Basophilic focus	1 (2%)	2 (4%)	2 (4%)	
Clear cell focus	1 (2%)			
Cyst	3 (6%)	1 (2%)	2 (4%)	1 (2%)
Developmental malformation		1 (2%)		3 (6%)
Hematopoietic cell proliferation	2 (4%)		3 (6%)	
Hyperplasia, diffuse		1 (2%)		
Hyperplasia, focal	5 (10%)	6 (12%)	6 (12%)	4 (8%)
Capsule, hyperplasia	5 (10%)	2 (4%)		2 (4%)
X-zone, degeneration, fatty	1 (2%)			
Adrenal gland, medulla	(50)	(50)	(50)	(50)
Hyperplasia	3 (6%)	4 (8%)		1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	10 (20%)	12 (24%)	7 (14%)	2 (4%)
Hyperplasia, lymphoid		1 (2%)		
Parathyroid gland	(50)	(48)	(49)	(49)
Cyst		2 (4%)		2 (4%)
Ectopic thymus				2 (4%)
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Pituitary gland	(49)	(47)	(48)	(48)
Pars distalis, angiectasis	3 (6%)	2 (4%)		
Pars distalis, cyst		1 (2%)		1 (2%)
Pars distalis, hyperplasia	9 (18%)	10 (21%)	5 (10%)	
Pars intermedia, cyst				1 (2%)
Thyroid gland	(50)	(50)	(50)	(50)
Degeneration, cystic	23 (46%)	19 (38%)	25 (50%)	28 (56%)
Inflammation, chronic	2 (4%)	4 (8%)	2 (4%)	5 (10%)
Inflammation, suppurative	3 (6%)	2 (4%)		
Follicle, cyst		3 (6%)	2 (4%)	
Follicular cell, hyperplasia	9 (18%)	7 (14%)	4 (8%)	1 (2%)
General Body System				
Tissue NOS			(2)	(1)
Bacterium			1 (50%)	
Inflammation, suppurative			1 (50%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole (continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Genital System				
Clitoral gland		(2)	(2)	
Ectasia		2 (100%)	2 (100%)	
Inflammation, chronic		1 (50%)	1 (50%)	
Pigmentation		2 (100%)	1 (50%)	
Ovary	(49)	(50)	(48)	(50)
Angiectasis	12 (24%)	11 (22%)	6 (13%)	12 (24%)
Cyst	20 (41%)	17 (34%)	11 (23%)	10 (20%)
Fibrosis		1 (2%)		
Hemorrhage	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, granulomatous	1 (2%)			
Inflammation, suppurative	3 (6%)	2 (4%)	4 (8%)	
Metaplasia, osseous				1 (2%)
Mineralization		1 (2%)		
Pigmentation		1 (2%)		
Thrombus				1 (2%)
Corpus luteum, hyperplasia				1 (2%)
Granulosa cell, hyperplasia				1 (2%)
Thecal cell, hyperplasia				1 (2%)
Interstitial cell, hyperplasia			1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Angiectasis	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Exudate	8 (16%)	4 (8%)	6 (12%)	2 (4%)
Hydrometra	9 (18%)	11 (22%)	6 (12%)	15 (30%)
Hyperplasia, cystic	48 (96%)	46 (92%)	48 (96%)	47 (94%)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, chronic			1 (2%)	
Mineralization			1 (2%)	
Necrosis			1 (2%)	
Mucosa, dysplasia				2 (4%)
Mucosa, metaplasia, squamous		1 (2%)	2 (4%)	4 (8%)
Myometrium, hyperplasia				2 (4%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	1 (2%)	
Hypercellularity	3 (6%)	10 (20%)	9 (18%)	2 (4%)
Myelofibrosis	1 (2%)		1 (2%)	1 (2%)
Lymph node	(50)	(50)	(50)	(50)
Bronchial, hemorrhage		1 (2%)		
Iliac, hematopoietic cell proliferation		2 (4%)		
Iliac, hyperplasia, lymphoid		1 (2%)		
Iliac, hyperplasia, plasma cell	1 (2%)		4 (8%)	
Inguinal, hyperplasia, lymphoid			1 (2%)	
Mediastinal, hyperplasia, lymphoid	2 (4%)			
Mediastinal, hyperplasia, plasma cell	3 (6%)	1 (2%)	4 (8%)	
Mediastinal, inflammation, suppurative			2 (4%)	
Mediastinal, necrosis		1 (2%)		
Pancreatic, hematopoietic cell proliferation		1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole
(continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node (continued)				
Pancreatic, hemorrhage		1 (2%)		
Pancreatic, hyperplasia, plasma cell		1 (2%)		
Renal, hyperplasia, lymphoid	1 (2%)			
Renal, hyperplasia, plasma cell	1 (2%)		4 (8%)	
Renal, inflammation, suppurative	1 (2%)			
Lymph node, mandibular	(49)	(49)	(49)	(49)
Hematopoietic cell proliferation	1 (2%)		1 (2%)	
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid	2 (4%)	2 (4%)	1 (2%)	
Hyperplasia, mast cell	1 (2%)			
Hyperplasia, plasma cell	1 (2%)	1 (2%)		
Lymph node, mesenteric	(47)	(47)	(48)	(48)
Depletion	1 (2%)	1 (2%)		
Hematopoietic cell proliferation	3 (6%)	4 (9%)	5 (10%)	
Hemorrhage	4 (9%)	6 (13%)	9 (19%)	5 (10%)
Hyperplasia, lymphoid	2 (4%)		2 (4%)	1 (2%)
Hyperplasia, plasma cell	1 (2%)		2 (4%)	
Inflammation, suppurative			1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Congestion	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	14 (28%)	25 (50%)	17 (34%)	4 (8%)
Pigmentation, hemosiderin	9 (18%)	4 (8%)	12 (24%)	1 (2%)
Lymphoid follicle, atrophy	1 (2%)	1 (2%)	1 (2%)	
Lymphoid follicle, hyperplasia	21 (42%)	8 (16%)	11 (22%)	5 (10%)
Red pulp, atrophy	1 (2%)		2 (4%)	
Red pulp, hyperplasia	4 (8%)	1 (2%)	3 (6%)	
Thymus	(47)	(44)	(47)	(49)
Angiectasis	1 (2%)	2 (5%)	1 (2%)	
Cyst		9 (20%)	2 (4%)	3 (6%)
Depletion	2 (4%)	5 (11%)	5 (11%)	
Hyperplasia, lymphoid	2 (4%)	1 (2%)	1 (2%)	
Inflammation, suppurative		1 (2%)		
Epithelial cell, hyperplasia			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Hyperplasia, cystic	7 (14%)	7 (14%)	7 (14%)	2 (4%)
Hyperplasia, lobular	2 (4%)	1 (2%)	2 (4%)	6 (12%)
Inflammation, chronic			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Acanthosis	1 (2%)		4 (8%)	1 (2%)
Inflammation, chronic			2 (4%)	1 (2%)
Ulcer			1 (2%)	
Subcutaneous tissue, edema		1 (2%)	1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	18 (36%)	12 (24%)	13 (26%)	11 (22%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole
(continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Nervous System				
Brain	(49)	(50)	(50)	(50)
Compression			1 (2%)	
Cyst		1 (2%)		2 (4%)
Hemorrhage		1 (2%)		
Hydrocephalus	1 (2%)	1 (2%)	1 (2%)	
Pigmentation	1 (2%)			
Cerebrum, necrosis		1 (2%)		
Hippocampus, necrosis	1 (2%)			
Thalamus, mineralization	39 (80%)	45 (90%)	44 (88%)	43 (86%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	3 (6%)	1 (2%)		
Hemorrhage	2 (4%)		3 (6%)	3 (6%)
Hyperplasia, lymphoid	17 (34%)	19 (38%)	19 (38%)	20 (40%)
Infiltration cellular, histiocyte	4 (8%)	6 (12%)	4 (8%)	
Inflammation, chronic				2 (4%)
Inflammation, suppurative	3 (6%)	1 (2%)	1 (2%)	
Leukocytosis			1 (2%)	
Thrombus	2 (4%)			
Alveolar epithelium, hyperplasia	2 (4%)	3 (6%)		1 (2%)
Bronchiole, epithelium, proliferation		3 (6%)	5 (10%)	4 (8%)
Nose	(50)	(50)	(50)	(50)
Exudate	6 (12%)	5 (10%)	27 (54%)	49 (98%)
Glands, dilatation	9 (18%)	12 (24%)	36 (72%)	49 (98%)
Glands, hyperplasia	2 (4%)	4 (8%)	34 (68%)	50 (100%)
Mucosa, degeneration, hyaline	8 (16%)	7 (14%)	12 (24%)	45 (90%)
Mucosa, hyperplasia	1 (2%)			
Olfactory epithelium, cyst			2 (4%)	6 (12%)
Olfactory epithelium, metaplasia	1 (2%)	1 (2%)	20 (40%)	49 (98%)
Trachea	(50)	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)		
Special Senses System				
Eye	(1)	(1)		
Cataract	1 (100%)			
Phthisis bulbi		1 (100%)		
Cornea, hyperplasia	1 (100%)			
Cornea, inflammation, chronic active	1 (100%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *o*-Nitroanisole
(continued)

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Casts protein	20 (40%)	18 (36%)	19 (38%)	30 (60%)
Cyst	4 (8%)	2 (4%)	4 (8%)	
Glomerulosclerosis	2 (4%)		1 (2%)	
Fibrosis				1 (2%)
Hyperplasia, lymphoid	22 (44%)	21 (42%)	23 (46%)	14 (28%)
Inflammation, chronic	1 (2%)			
Inflammation, suppurative	2 (4%)			
Metaplasia, osseous	1 (2%)	1 (2%)	1 (2%)	6 (12%)
Mineralization	22 (44%)	18 (36%)	12 (24%)	9 (18%)
Glomerulus, hyperplasia			1 (2%)	
Glomerulus, necrosis		1 (2%)		
Interstitial tissue, pigmentation		1 (2%)		
Renal tubule, atrophy	2 (4%)	1 (2%)	3 (6%)	
Renal tubule, cytoplasmic alteration	1 (2%)		2 (4%)	
Renal tubule, dilatation	5 (10%)	5 (10%)	3 (6%)	
Renal tubule, necrosis	1 (2%)	3 (6%)		
Renal tubule, pigmentation	2 (4%)	1 (2%)	1 (2%)	
Renal tubule, regeneration	33 (66%)	28 (56%)	17 (34%)	12 (24%)
Urinary bladder	(50)	(50)	(50)	(50)
Edema	2 (4%)	3 (6%)		1 (2%)
Hyperplasia,lymphoid	27 (54%)	24 (48%)	25 (50%)	23 (46%)
Inflammation, granulomatous				1 (2%)
Transitional epithelium, degeneration, ballooning	1 (2%)			

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

APPENDIX E
SUMMARY OF LESIONS IN MALE RATS IN THE STOP-EXPOSURE FEED STUDY OF *o*-NITROANISOLE

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole[a]

	0 ppm	6,000 ppm	18,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
3-Month interim evaluation	10	10	10
6-Month interim evaluation	10	10	10
9-Month interim evaluation	10	10	6
15-Month interim evaluation	9	3	0
Early deaths			
Moribund	7	26	23
Natural deaths	1		11
Survivors			
Terminal sacrifice	13	1	0
Animals examined microscopically	60	60	60
***3-Month Interim Evaluation*[b]**			
Urinary System			
Urinary bladder	(9)	(9)	(10)
Transitional epithelium, carcinoma			1 (10%)
Neoplasm Summary			
Total animals with primary neoplasms[b]			1
Total primary neoplasms			1
Total animals with malignant neoplasms			1
Total malignant neoplasms			1
***6-Month Interim Evaluation*[b]**			
Alimentary System			
Intestine large, colon			(3)
Polyp adenomatous			2 (67%)
Stomach, forestomach		(2)	
Papilloma squamous		1 (50%)	
Urinary System			
Urinary bladder	(10)	(10)	(10)
Sarcoma			2 (20%)
Transitional epithelium, carcinoma			10 (100%)
Transitional epithelium, papilloma		2 (20%)	
Neoplasm Summary			
Total animals with primary neoplasms		3	10
Total primary neoplasms		3	14
Total animals with benign neoplasms		3	2
Total benign neoplasms		3	2
Total animals with malignant neoplasms			10
Total malignant neoplasms			12

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
9-Month Interim Evaluation[b]			
Alimentary System			
Intestine large, colon		(2)	(4)
Carcinoma			1 (25%)
Polyp adenomatous		1 (50%)	1 (25%)
Polyp adenomatous, multiple		1 (50%)	3 (75%)
Urinary System			
Kidney	(10)	(10)	(6)
Transitional epithelium, carcinoma			2 (33%)
Transitional epithelium, papilloma			1 (17%)
Urinary bladder	(10)	(10)	(6)
Squamous cell carcinoma			1 (17%)
Transitional epithelium, carcinoma		3 (30%)	6 (100%)
Transitional epithelium, papilloma		2 (20%)	
Neoplasm Summary			
Total animals with primary neoplasms		6	6
Total primary neoplasms		7	15
Total animals with benign neoplasms		4	4
Total benign neoplasms		4	5
Total animals with malignant neoplasms		3	6
Total malignant neoplasms		3	10
15-Month Interim Evaluation			
Alimentary System			
Intestine large, colon		(3)	
Polyp adenomatous		1 (33%)	
Polyp adenomatous, multiple		2 (67%)	
Cardiovascular System			
None			
Endocrine System			
Pituitary gland	(1)		
Pars distalis, adenoma	1 (100%)		
General Body System			
None			
Genital System			
Epididymis	(9)	(3)	
Testes	(9)	(3)	
Bilateral, interstitial cell, adenoma	3 (33%)	3 (100%)	
Interstitial cell, adenoma	3 (33%)		

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
15-Month Interim Evaluation (continued)			
Hematopoietic System			
None			
Integumentary System			
Skin	(2)		
Squamous cell papilloma	1 (50%)		
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
Lung	(1)		
Alveolar/bronchiolar adenoma	1 (100%)		
Special Senses System			
None			
Urinary System			
Urinary bladder	(9)	(3)	
Sarcoma		1 (33%)	
Transitional epithelium, carcinoma		1 (33%)	
Transitional epithelium, papilloma		2 (67%)	
Systemic Lesions			
Multiple organs[d]	(9)	(3)	
Mesothelioma malignant		2 (67%)	
Neoplasm Summary			
Total animals with primary neoplasms	6	3	
Total primary neoplasms	9	12	
Total animals with benign neoplasms	6	3	
Total benign neoplasms	9	8	
Total animals with malignant neoplasms		3	
Total malignant neoplasms		4	

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study			
Alimentary System			
Intestine large, cecum	(1)	(21)	(28)
Polyp adenomatous, multiple		1 (5%)	
Intestine large, colon	(1)	(21)	(28)
Carcinoma			3 (11%)
Carcinoma, multiple			1 (4%)
Polyp adenomatous		8 (38%)	8 (29%)
Polyp adenomatous, multiple		10 (48%)	16 (57%)
Intestine large, rectum	(1)	(21)	(28)
Polyp adenomatous		4 (19%)	1 (4%)
Polyp adenomatous, multiple		2 (10%)	
Liver	(21)	(27)	(34)
Hepatocellular carcinoma	1 (5%)		
Mesentery	(3)	(3)	(1)
Squamous cell carcinoma, metastatic, urinary bladder			1 (100%)
Pancreas	(1)	(4)	
Acinar cell, adenoma		1 (25%)	
Stomach, forestomach	(3)	(10)	(6)
Squamous cell papilloma		2 (20%)	1 (17%)
Squamous cell papilloma, multiple		1 (10%)	
Tooth	(1)		
Adamantinoma malignant	1 (100%)		
Cardiovascular System			
None			
Endocrine System			
Adrenal gland, cortex	(2)	(2)	
Adrenal gland, medulla	(2)	(2)	
Pheochromocytoma benign		2 (100%)	
Bilateral, pheochromocytoma benign	1 (50%)		
Pituitary gland	(7)		
Pars distalis, adenoma	6 (86%)		
Pars intermedia, adenoma	1 (14%)		
General Body System			
None			
Genital System			
Epididymis	(21)	(27)	(34)
Preputial gland	(6)	(6)	
Adenoma		1 (17%)	
Carcinoma	2 (33%)	1 (17%)	
Bilateral, adenoma	1 (17%)		
Prostate		(4)	(5)
Sarcoma, metastatic, urinary bladder			1 (20%)
Squamous cell carcinoma, metastatic, urinary bladder			2 (40%)

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study (continued)			
Genital System (continued)			
Testes	(21)	(27)	(34)
Bilateral, interstitial cell, adenoma	17 (81%)	9 (33%)	
Interstitial cell, adenoma	3 (14%)	11 (41%)	
Hematopoietic System			
Lymph node	(14)	(16)	(6)
Inguinal, fibrosarcoma	1 (7%)		
Lymph node, mandibular	(6)	(7)	
Lymph node, mesenteric	(5)	(9)	(2)
Spleen	(21)	(27)	(34)
Hemangiosarcoma		1 (4%)	
Thymus	(1)		(2)
Thymoma benign	1 (100%)		
Integumentary System			
Mammary gland	(1)	(1)	
Fibroadenoma	1 (100%)		
Skin	(2)	(1)	
Keratoacanthoma	2 (100%)		
Squamous cell papilloma	1 (50%)		
Subcutaneous tissue, fibroma	1 (50%)		
Subcutaneous tissue, hemangiosarcoma, multiple		1 (100%)	
Musculoskeletal System			
Bone	(1)	(1)	
Turbinate, osteoma	1 (100%)		
Skeletal muscle		(1)	
Nervous System			
Brain	(5)		
Respiratory System			
Lung	(7)	(3)	(2)
Alveolar/bronchiolar adenoma			1 (50%)
Alveolar/bronchiolar adenoma, multiple	1 (14%)		
Special Senses System			
None			

TABLE E1
Summary of the Incidence of Neoplasms in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Urinary System			
Kidney	(21)	(27)	(34)
Nephroblastoma		1 (4%)	
Renal tubule, oncocytoma benign		1 (4%)	
Transitional epithelium, carcinoma		1 (4%)	6 (18%)
Transitional epithelium, papilloma			3 (9%)
Urinary bladder	(21)	(27)	(34)
Sarcoma		1 (4%)	7 (21%)
Squamous cell carcinoma			5 (15%)
Squamous cell papilloma			4 (12%)
Transitional epithelium, carcinoma		23 (85%)	33 (97%)
Transitional epithelium, papilloma		1 (4%)	
Transitional epithelium, papilloma, multiple		2 (7%)	1 (3%)
Systemic Lesions			
Multiple organs	(21)	(27)	(34)
Leukemia mononuclear	12 (57%)	2 (7%)	
Mesothelioma malignant		4 (15%)	
Neoplasm Summary			
Total animals with primary neoplasms	20	27	34
Total primary neoplasms	54	91	90
Total animals with benign neoplasms	20	25	26
Total benign neoplasms	37	56	35
Total animals with malignant neoplasms	15	26	34
Total malignant neoplasms	17	35	55
Total animals with metastatic neoplasms			4
Total metastatic neoplasm			4

[a] Number of animals examined microscopically at site and number of animals with lesion.
[b] All organ systems listed in Table 1 (Materials and Methods) were evaluated, but neoplasms were found only in systems specified.
[c] Primary neoplasms: all neoplasms except metastatic neoplasms
[d] Number of animals with any tissue examined microscopically

TABLE E2a
Individual Animal Tumor Pathology of Male Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm

Number of Days on Study	0 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8 8 7 7 8 8 8 8 8 8 8 8	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 5 6 5 5 5 5 6 6 6 6 1 1 2 3 4 5 2 3 4 5	**Total Tissues/ Tumors**
Alimentary System		
Liver	+ + + + + + + + + +	10
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Epididymis	+ + + + + + + + + +	10
Testes	+ + + + + + + + + +	10
Hematopoietic System		
Spleen	+ + + + + + + + + +	10
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		

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

TABLE E2a
Individual Animal Tumor Pathology of Male Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	0 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8 8 7 7 8 8 8 8 8 8 8 8	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 5 6 5 5 5 5 6 6 6 6 1 1 2 3 4 5 2 3 4 5	Total Tissues/ Tumors
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ M + + + + + + + +	9
Urinary bladder	+ M + + + + + + + +	9
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE E2a
Individual Animal Tumor Pathology of Male Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm

Number of Days on Study	0 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8 8 7 7 7 7 7 8 8 8 8 8	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 2 3 3 3 3 2 2 2 2 3 9 0 0 0 0 9 9 9 9 0 1 1 2 3 4 2 3 4 5 5	**Total Tissues/ Tumors**
Alimentary System		
Liver	+ + + + + + + + + +	10
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Epididymis	+ + + + + + + + + +	10
Testes	+ + + + + + + + + +	10
Hematopoietic System		
Spleen	+ + + + + + + + + +	10
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		

TABLE E2a
Individual Animal Tumor Pathology of Male Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	0 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8 8 7 7 7 7 7 8 8 8 8 8	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 2 3 3 3 3 2 2 2 2 3 9 0 0 0 0 9 9 9 9 0 1 1 2 3 4 2 3 4 5 5	Total Tissues/ Tumors
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + + + + + + + + +	10
Urinary bladder	+ + + M + + + + + +	9
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE E2a
Individual Animal Tumor Pathology of Male Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm

Number of Days on Study	0 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8 8 7 7 7 7 7 7 8 8 8 8	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 7 7 7 8 8 8 7 7 8 8 1 2 3 1 2 3 4 5 4 5	**Total Tissues/ Tumors**
Alimentary System		
Liver	+ + + + + + + + + +	10
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Epididymis	+ + + + + + + + + +	10
Testes	+ + + + + + + + + +	10
Hematopoietic System		
Spleen	+ + + + + + + + + +	10
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
Lung	+	1

TABLE E2a
Individual Animal Tumor Pathology of Male Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	0 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8 8 7 7 7 7 7 7 8 8 8 8	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 7 7 7 8 8 8 7 7 8 8 1 2 3 1 2 3 4 5 4 5	Total Tissues/ Tumors
Special Senses System		
Eye	+	1
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + + + + + + + + +	10
Urinary bladder	+ + + + + + + + + +	10
Transitional epithelium, carcinoma	X	1
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE E2b
Individual Animal Tumor Pathology of Male Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm

Number of Days on Study	1 1 1 1 1 1 1 1 1 1 9 9 9 9 9 9 9 9 9 9 0 0 0 0 0 1 1 1 1 1	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 7 7 7 8 8 7 7 8 8 8 1 2 3 1 2 4 5 3 4 5	**Total Tissues/ Tumors**
Alimentary System		
Liver	+ + + + + + + + + +	10
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Epididymis	+ + + + + + + + + +	10
Testes	+ + + + + + + + + +	10
Hematopoietic System		
Spleen	+ + + + + + + + + +	10
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		

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

TABLE E2b
Individual Animal Tumor Pathology of Male Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	1 1 1 1 1 1 1 1 1 1 9 9 9 9 9 9 9 9 9 9 0 0 0 0 0 1 1 1 1 1	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 7 7 7 8 8 7 7 8 8 8 1 2 3 1 2 4 5 3 4 5	Total Tissues/ Tumors
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + + + + + + + + +	10
Urinary bladder	+ + + + + + + + + +	10
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE E2b
Individual Animal Tumor Pathology of Male Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm

Number of Days on Study	1 9 0	1 9 0	1 9 0	1 9 0	1 9 0	1 9 0	1 9 1	1 9 1	1 9 1	1 9 1	
Carcass ID Number	0 3 1 1	0 3 1 2	0 3 1 3	0 3 2 1	0 3 2 2	0 3 2 3	0 3 1 4	0 3 1 5	0 3 2 4	0 3 2 5	**Total Tissues/ Tumors**
Alimentary System											
Liver	+	+	+	+	+	+	+	+	+	+	10
Stomach		+						+			2
Stomach, forestomach		+						+			2
Squamous cell papilloma		X									1
Stomach, glandular		+						+			2
Cardiovascular System											
None											
Endocrine System											
None											
General Body System											
None											
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	10
Testes	+	+	+	+	+	+	+	+	+	+	10
Hematopoietic System											
Spleen	+	+	+	+	+	+	+	+	+	+	10
Integumentary System											
None											
Musculoskeletal System											
None											
Nervous System											
None											

TABLE E2b
Individual Animal Tumor Pathology of Male Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	1 9 0	1 9 0	1 9 0	1 9 0	1 9 0	1 9 0	1 9 1	1 9 1	1 9 1	1 9 1	
Carcass ID Number	0 3 1 1	0 3 1 2	0 3 1 3	0 3 2 1	0 3 2 2	0 3 2 3	0 3 1 4	0 3 1 5	0 3 2 4	0 3 2 5	Total Tissues/ Tumors
Respiratory System											
Lung				+						+	2
Special Senses System											
None											
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	10
Ureter	+	+	+	+	+	+	+	+	+	+	10
Urinary bladder	+	+	+	+	+	+	+	+	+	+	10
Transitional epithelium, papilloma			X			X					2
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	10

TABLE E2b
Individual Animal Tumor Pathology of Male Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm

Number of Days on Study	1 9 0	1 9 0	1 9 0	1 9 1	1 9 1	1 9 1	1 9 1	1 9 1	1 9 1	1 9 1	
Carcass ID Number	0 1 9 1	0 1 9 2	0 2 0 1	0 1 9 3	0 1 9 4	0 1 9 5	0 2 0 2	0 2 0 3	0 2 0 4	0 2 0 5	**Total Tissues/ Tumors**
Alimentary System											
Intestine large		+		+			+				3
Intestine large, cecum		+		+			+				3
Intestine large, colon		+		+			+				3
Polyp adenomatous				X			X				2
Intestine large, rectum		+		+			+				3
Liver	+	+	+	+	+	+	+	+	+	+	10
Cardiovascular System											
None											
Endocrine System											
None											
General Body System											
None											
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	10
Testes	+	+	+	+	+	+	+	+	+	+	10
Hematopoietic System											
Spleen	+	+	+	+	+	+	+	+	+	+	10
Integumentary System											
None											
Musculoskeletal System											
None											
Nervous System											
None											

TABLE E2b
Individual Animal Tumor Pathology of Male Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	1 1 1 1 1 1 1 1 1 1 9 9 9 9 9 9 9 9 9 9 0 0 0 1 1 1 1 1 1 1	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 1 1 2 1 1 1 2 2 2 2 9 9 0 9 9 9 0 0 0 0 1 2 1 3 4 5 2 3 4 5	**Total Tissues/ Tumors**
Respiratory System		
None		
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	M + + + + + + + + +	9
Urinary bladder	+ + + + + + + + + +	10
Sarcoma	X X	2
Transitional epithelium, carcinoma	X X X X X X X X X X	10
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE E2c
Individual Animal Tumor Pathology of Male Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm

Number of Days on Study	2 7 4	2 7 4	2 7 4	2 7 4	2 7 4	2 7 4	2 7 5	2 7 5	2 7 5	2 7 5	
Carcass ID Number	0 0 9 1	0 0 9 2	0 0 9 3	0 1 0 1	0 1 0 2	0 1 0 3	0 0 9 4	0 0 9 5	0 1 0 4	0 1 0 5	**Total Tissues/ Tumors**
Alimentary System											
Liver	+	+	+	+	+	+	+	+	+	+	10
Mesentery								+			1
Cardiovascular System											
None											
Endocrine System											
None											
General Body System											
None											
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	10
Preputial gland							+				1
Testes	+	+	+	+	+	+	+	+	+	+	10
Hematopoietic System											
Spleen	+	+	+	+	+	+	+	+	+	+	10
Integumentary System											
None											
Musculoskeletal System											
None											
Nervous System											
None											
Respiratory System											
None											

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

TABLE E2c
Individual Animal Tumor Pathology of Male Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	2	2	2	2	2	2	2	2	2	2	
	7	7	7	7	7	7	7	7	7	7	
	4	4	4	4	4	4	5	5	5	5	
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	Total Tissues/ Tumors
	0	0	0	1	1	1	0	0	1	1	
	9	9	9	0	0	0	9	9	0	0	
	1	2	3	1	2	3	4	5	4	5	
Special Senses System											
Eye								+			1
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	10
Ureter	+	+	+	+	+	+	+	+	+	+	10
Urinary bladder	+	+	+	+	+	+	+	+	+	+	10
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	10

TABLE E2c
Individual Animal Tumor Pathology of Male Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm

Number of Days on Study	274	274	274	274	275	275	275	275	275	275	
Carcass ID Number	03331	03332	03333	03341	03343	03345	03342	03343	03344	03344	**Total Tissues/ Tumors**
Alimentary System											
Intestine large				+				+			2
Intestine large, cecum				+				+			2
Intestine large, colon				+				+			2
Polyp adenomatous				X							1
Polyp adenomatous, multiple								X			1
Intestine large, rectum				+				+			2
Liver	+	+	+	+	+	+	+	+	+	+	10
Cardiovascular System											
None											
Endocrine System											
None											
General Body System											
None											
Genital System											
Epididymis	+	+	+	+	+	+	+	+	+	+	10
Preputial gland									+		1
Testes	+	+	+	+	+	+	+	+	+	+	10
Hematopoietic System											
Lymph node							+				1
Spleen	+	+	+	+	+	+	+	+	+	+	10
Integumentary System											
None											
Musculoskeletal System											
None											

TABLE E2c
Individual Animal Tumor Pathology of Male Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	2 2 2 2 2 2 2 2 2 2 7 7 7 7 7 7 7 7 7 7 4 4 4 4 5 5 5 5 5 5	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 3 3 3 3 3 3 3 3 3 3 3 3 3 4 3 3 4 4 4 4 1 2 3 1 4 5 2 3 4 5	**Total Tissues/ Tumors**
Nervous System		
None		
Respiratory System		
Lung	+ +	2
Special Senses System		
Eye	+	1
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + + + + + + + + +	10
Urinary bladder	+ + + + + + + + + +	10
Transitional epithelium, carcinoma	X X X	3
Transitional epithelium, papilloma	X X	2
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE E2c
Individual Animal Tumor Pathology of Male Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm

Number of Days on Study	2 2 2 2 2 2 7 7 7 7 7 7 4 4 4 4 5 5	
Carcass ID Number	0 0 0 0 0 0 2 2 2 2 2 2 1 2 2 2 1 1 3 3 4 5 4 5	**Total Tissues/ Tumors**
Alimentary System		
Intestine large	+ + + +	4
Intestine large, cecum	+ + + +	4
Intestine large, colon	+ + + +	4
Carcinoma	X	1
Polyp adenomatous	X	1
Polyp adenomatous, multiple	X X X	3
Intestine large, rectum	+ + + +	4
Liver	+ + + + + +	6
Stomach	+	1
Stomach, forestomach	+	1
Stomach, glandular	+	1
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Epididymis	+ + + + + +	6
Testes	+ + + + + +	6
Hematopoietic System		
Spleen	+ + + + + +	6
Integumentary System		
None		
Musculoskeletal System		
None		

TABLE E2c
Individual Animal Tumor Pathology of Male Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	2 2 2 2 2 2 7 7 7 7 7 7 4 4 4 4 5 5	
Carcass ID Number	0 0 0 0 0 0 2 2 2 2 2 2 1 2 2 2 1 1 3 3 4 5 4 5	Total Tissues/ Tumors
Nervous System		
None		
Respiratory System		
None		
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + +	6
Transitional epithelium, carcinoma	X X	2
Transitional epithelium, papilloma	X	1
Ureter	+ + + + + +	6
Urinary bladder	+ + + + + +	6
Squamous cell carcinoma	X	1
Transitional epithelium, carcinoma	X X X X X X	6
Systemic Lesions		
Multiple organs	+ + + + + +	6

TABLE E2d
Individual Animal Tumor Pathology of Male Rats at the 15-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm

Number of Days on Study	4 5 5	4 5 5	4 5 5	4 5 5	4 5 5	4 5 6	4 5 6	4 5 6	4 5 6	Total Tissues/ Tumors
Carcass ID Number	0 1 1	0 1 1	0 1 1	0 1 2	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	
Alimentary System										
Liver	+	+	+	+	+	+	+	+	+	9
Mesentery									+	1
Stomach						+				1
Stomach, forestomach						+				1
Stomach, glandular						+				1
Tongue				+						1
Cardiovascular System										
Heart				+						1
Endocrine System										
Pituitary gland		+								1
Pars distalis, adenoma		X								1
General Body System										
None										
Genital System										
Epididymis	+	+	+	+	+	+	+	+	+	9
Testes	+	+	+	+	+	+	+	+	+	9
Bilateral, interstitial cell, adenoma			X	X				X		3
Interstitial cell, adenoma		X					X		X	3
Hematopoietic System										
Lymph node				+						1
Lymph node, mesenteric				+						1
Spleen	+	+	+	+	+	+	+	+	+	9
Integumentary System										
Skin	+			+						2
Squamous cell papilloma				X						1

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

TABLE E2d
Individual Animal Tumor Pathology of Male Rats at the 15-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	4 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6	
Carcass ID Number	0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 1 1 2 2 1 1 2 2 1 2 3 2 3 4 5 4 5	**Total Tissues/ Tumors**
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
Lung	+	1
Alveolar/bronchiolar adenoma	X	1
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + + + + +	9
Ureter	+ + + + + + + + +	9
Urinary bladder	+ + + + + + + + +	9
Systemic Lesions		
Multiple organs	+ + + + + + + + +	9

TABLE E2d
Individual Animal Tumor Pathology of Male Rats at the 15-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm

Number of Days on Study	4 4 4 5 5 5 5 6 6	
Carcass ID Number	0 0 0 3 3 3 6 5 6 4 5 5	**Total Tissues/ Tumors**
Alimentary System		
Intestine large	+ + +	3
Intestine large, cecum	+ + +	3
Intestine large, colon	+ + +	3
Polyp adenomatous	X	1
Polyp adenomatous, multiple	X X	2
Intestine large, rectum	+ + +	3
Liver	+ + +	3
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Epididymis	+ + +	3
Testes	+ + +	3
Bilateral, interstitial cell, adenoma	X X X	3
Hematopoietic System		
Lymph node	+	1
Lymph node, mesenteric	+	1
Spleen	+ + +	3
Integumentary System		
None		
Musculoskeletal System		
None		

TABLE E2d
Individual Animal Tumor Pathology of Male Rats at the 15-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	4 4 4 5 5 5 5 6 6	
Carcass ID Number	0 0 0 3 3 3 6 5 6 4 5 5	Total Tissues/ Tumors
Nervous System		
None		
Respiratory System		
None		
Special Senses System		
None		
Urinary System		
Kidney	+ + +	3
Ureter	+ + +	3
Urinary bladder	+ + +	3
Sarcoma	X	1
Transitional epithelium, carcinoma	X	1
Transitional epithelium, papilloma	X X	2
Systemic Lesions		
Multiple organs	+ + +	3
Mesothelioma malignant	X X	2

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm

Number of Days on Study	4 1 0	5 6 4	5 8 2	5 9 0	6 3 9	6 4 8	7 0 1	7 0 7	7 2 8	7 2 8	7 2 8	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 1 2 1	0 0 1 1	0 0 3 1	0 0 2 1	0 0 1 2	0 0 2 2	0 0 4 1	0 0 4 2	0 0 1 3	0 0 3 2	0 0 4 4	0 0 1 4	0 0 1 5	0 0 2 3	0 0 2 4	0 0 2 5	0 0 3 3	0 0 3 4	0 0 3 5	0 0 4 3	0 0 4 5		**Total Tissues/ Tumors**
Alimentary System																							
Intestine large	+																						1
Intestine large, cecum	+																						1
Intestine large, colon	+																						1
Intestine large, rectum	+																						1
Intestine small	+																						1
Intestine small, duodenum	+																						1
Intestine small, ileum	+																						1
Intestine small, jejunum	+																						1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		21
Hepatocellular carcinoma																				X			1
Mesentery	+						+										+						3
Pancreas													+										1
Stomach			+					+			+												3
Stomach, forestomach			+					+			+												3
Stomach, glandular			+					+			+												3
Tooth	M			+																			1
Adamantinoma malignant				X																			1
Cardiovascular System																							
Heart	+						+		+			+	+										5
Endocrine System																							
Adrenal gland								+					+										2
Adrenal gland, cortex								+					+										2
Adrenal gland, medulla								+					+										2
Bilateral, pheochromocytoma benign													X										1
Pituitary gland			+					+		+	+	+						+	+				7
Pars distalis, adenoma			X					X			X	X						X	X				6
Pars intermedia, adenoma										X													1
General Body System																							
None																							

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

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	4 1 0	5 6 0	5 8 2	5 9 0	6 3 9	6 4 8	7 0 1	7 0 7	7 2 8	7 2 8	7 2 8	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 1 2 1	0 0 1 1	0 0 3 1	0 0 2 1	0 0 1 2	0 0 2 2	0 0 4 1	0 0 4 2	0 0 1 3	0 0 3 2	0 0 4 4	0 0 1 4	0 0 1 5	0 0 2 3	0 0 2 4	0 0 2 5	0 0 3 3	0 0 3 4	0 0 3 5	0 0 4 3	0 0 4 5	**Total Tissues/ Tumors**
Genital System																					
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Preputial gland		+						+	+		+				+					+	6
Carcinoma															X					X	2
Bilateral, adenoma									X												1
Seminal vesicle										+			+								2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Bilateral, interstitial cell, adenoma		X		X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	17
Interstitial cell, adenoma			X							X	X										3
Hematopoietic System																					
Lymph node	+	+	+		+	+	+	+	+		+		+		+		+	+	+		14
Inguinal, fibrosarcoma						X															1
Lymph node, mandibular	+	+			+	+	+	+													6
Lymph node, mesenteric					+	+		+					+						+		5
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Thymus												+									1
Thymoma benign												X									1
Integumentary System																					
Mammary gland													+								1
Fibroadenoma													X								1
Skin							+				+										2
Keratoacanthoma							X				X										2
Squamous cell papilloma											X										1
Subcutaneous tissue, fibroma											X										1
Musculoskeletal System																					
Bone																+					1
Turbinate, osteoma																X					1
Nervous System																					
Brain									+		+	+						+	+		5

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	4 1 0	5 6 4	5 8 2	5 9 0	6 3 9	6 4 8	7 0 1	7 0 7	7 2 8	7 2 8	7 2 8	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 1 2 1	0 0 1 1	0 0 3 1	0 0 2 1	0 0 1 2	0 0 2 2	0 0 4 1	0 0 4 2	0 0 1 3	0 0 3 2	0 0 4 4	0 0 1 4	0 0 1 5	0 0 2 3	0 0 2 4	0 0 2 5	0 0 3 3	0 0 3 4	0 0 3 5	0 0 4 3	0 0 4 5	**Total Tissues/ Tumors**
Respiratory System																						
Lung		+				+		+				+		+				+	+			7
Alveolar/bronchiolar adenoma, multiple												X										1
Nose							+															1
Special Senses System																						
None																						
Urinary System																						
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Ureter	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	19
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Systemic Lesions																						
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	21
Leukemia mononuclear		X	X		X	X	X	X	X	X				X		X		X			X	12

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm

Number of Days on Study	2 0 7	2 7 5	3 0 5	3 2 9	3 2 9	3 5 1	3 6 4	4 1 3	4 2 3	4 2 4	4 2 8	4 2 9	4 3 0	4 3 4	4 5 7	4 8 0	5 1 2	5 8 2	6 1 2	6 1 7	6 1 8	6 3 6	6 3 9	6 4 6	6 4 8	6 8 0	7 2 9	
Carcass ID Number	0 2 7 1	0 2 5 1	0 3 5 1	0 3 6 1	0 3 6 2	0 2 7 2	0 3 5 2	0 2 7 3	0 2 7 4	0 3 5 3	0 3 5 4	0 2 5 2	0 3 6 3	0 2 7 5	0 2 6 1	0 2 8 1	0 2 6 2	0 2 6 3	0 2 8 2	0 2 8 3	0 2 5 3	0 2 5 4	0 2 8 4	0 2 6 4	0 2 6 5	0 2 8 5	0 2 5 5	Total Tissues/ Tumors
Alimentary System																												
Intestine large			+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+			+	+	+	+	21
Intestine large, cecum			+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+			+	+	+	+	21
Polyp adenomatous, multiple																											X	1
Intestine large, colon			+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+			+	+	+	+	21
Polyp adenomatous			X		X				X				X	X		X								X		X		8
Polyp adenomatous, multiple				X		X	X	X		X		X			X				X	X	X							10
Intestine large, rectum			+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+			+	+	+	+	21
Polyp adenomatous					X	X															X				X			4
Polyp adenomatous, multiple																X	X											2
Intestine small															+						+							2
Intestine small, duodenum															+						+							2
Intestine small, ileum															+						+							2
Intestine small, jejunum															+						+							2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	27
Mesentery					+													+						+				3
Pancreas																		+					+		+	+		4
Acinar cell, adenoma																							X					1
Stomach								+		+		+		+	+				+		+	+	+			+		10
Stomach, forestomach								+		+		+		+	+				+		+	+	+			+		10
Squamous cell papilloma										X				X														2
Squamous cell papilloma, multiple																							X					1
Stomach, glandular								+		+		+		+	+				+		+	+	+			+		10
Cardiovascular System																												
Blood vessel																										+		1
Heart																						+				+		2
Endocrine System																												
Adrenal gland																								+	+			2
Adrenal gland, cortex																								+	+			2
Adrenal gland, medulla																								+	+			2
Pheochromocytoma benign																								X	X			2
Parathyroid gland																							+			+		2
General Body System																												
None																												

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	2 0 7	2 7 5	3 0 5	3 2 9	3 2 9	3 5 1	3 6 4	4 1 3	4 2 3	4 2 4	4 2 8	4 2 9	4 3 0	4 3 4	4 5 7	4 8 0	5 1 2	5 8 2	6 1 2	6 1 7	6 1 8	6 3 6	6 3 9	6 4 6	6 4 8	6 8 0	7 2 9	
Carcass ID Number	0 2 7 1	0 2 5 1	0 3 5 1	0 3 6 1	0 3 6 2	0 2 7 2	0 3 5 2	0 2 7 3	0 2 7 4	0 3 5 3	0 3 5 4	0 2 5 2	0 3 6 3	0 2 7 5	0 2 6 1	0 2 2 1	0 2 6 2	0 2 6 3	0 2 8 2	0 2 8 3	0 2 5 3	0 2 5 4	0 2 8 4	0 2 6 4	0 2 6 5	0 2 8 5	0 2 5 5	**Total Tissues/ Tumors**
Genital System																												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	27
Preputial gland																+			+	+	+		+	+			6
Adenoma																X											1
Carcinoma																					X						1
Prostate			+							+	+						+										4
Seminal vesicle											+																1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	27
Bilateral, interstitial cell, adenoma											X		X			X	X				X		X	X		X	X	9
Interstitial cell, adenoma					X			X	X	X		X		X				X	X	X		X			X			11
Hematopoietic System																												
Lymph node					+	+		+	+		+				+	+	+	+	+	+	+	+		+		+		16
Lymph node, mandibular						+										+	+	+	+	+			+					7
Lymph node, mesenteric					+			+							+	+			+	+	+				+		+	9
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	27
Hemangiosarcoma																					X							1
Integumentary System																												
Mammary gland																											+	1
Skin		+																										1
Subcutaneous tissue, hemangiosarcoma, multiple		X																										1
Musculoskeletal System																												
Bone																						+						1
Skeletal muscle									+																			1
Nervous System																												
None																												
Respiratory System																												
Lung			+							+															+			3
Special Senses System																												
None																												

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	2 0 7	2 7 5	3 0 5	3 2 9	3 2 9	3 5 1	3 6 4	4 1 3	4 2 3	4 2 4	4 2 8	4 2 9	4 3 0	4 3 4	4 5 7	4 8 0	5 1 2	5 8 2	6 1 2	6 1 7	6 1 8	6 3 6	6 3 9	6 4 6	6 4 8	6 8 0	7 2 9	
Carcass ID Number	0 2 7 1	0 2 5 1	0 3 5 1	0 3 6 1	0 3 6 2	0 2 7 2	0 3 5 2	0 2 7 3	0 2 7 4	0 3 5 3	0 3 5 4	0 2 5 2	0 3 6 3	0 2 7 5	0 2 6 1	0 2 2 1	0 2 6 2	0 2 6 3	0 2 8 2	0 2 8 3	0 2 5 3	0 2 5 4	0 2 8 4	0 2 6 4	0 2 6 5	0 2 8 5	0 2 5 5	**Total Tissues/ Tumors**
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	27
Nephroblastoma	X																											1
Renal tubule, oncocytoma benign																						X						1
Transitional epithelium, carcinoma																								X				1
Ureter	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	25
Urethra								+									+											2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	27
Sarcoma			X																									1
Transitional epithelium, carcinoma		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X		X	X	23
Transitional epithelium, papilloma															X													1
Transitional epithelium, papilloma, multiple																X										X		2
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	27
Leukemia mononuclear																				X						X		2
Mesothelioma malignant									X					X				X							X			4

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm

Number of Days on Study	1 5 8	2 1 0	2 1 1	2 1 6	2 1 7	2 1 8	2 1 8	2 1 9	2 2 8	2 3 3	2 3 6	2 3 8	2 4 2	2 4 7	2 4 8	2 4 9	2 4 9	2 5 4	2 5 6	2 6 2	2 6 3	2 6 6	2 6 8	2 7 2	2 7 7
Carcass ID Number	0 1 6 1	0 2 3 1	0 1 6 2	0 2 3 2	0 1 6 3	0 2 1 1	0 2 3 1	0 1 3 1	0 1 4 1	0 2 3 4	0 2 4 1	0 1 5 1	0 1 5 2	0 2 2 1	0 1 5 3	0 1 4 2	0 2 4 2	0 1 6 4	0 1 4 3	0 2 4 3	0 2 1 2	0 1 4 4	0 1 5 4	0 2 2 2	0 1 3 2
Alimentary System																									
Intestine large			+	+	+		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+		+
Intestine large, cecum			+	+	+		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+		+
Intestine large, colon			+	+	+		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+		+
Carcinoma																	X								X
Carcinoma, multiple																	X								
Polyp adenomatous			X		X						X	X	X												
Polyp adenomatous, multiple							X		X	X					X	X	X		X	X	X	X	X		X
Intestine large, rectum			+	+	+		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+		+
Polyp adenomatous																									
Intestine small			+																						
Intestine small, duodenum			+																						
Intestine small, ileum			+																						
Intestine small, jejunum			+																						
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery													+												
Squamous cell carcinoma, metastatic, urinary bladder													X												
Stomach			+			+																			+
Stomach, forestomach			+			+																			+
Squamous cell papilloma																									
Stomach, glandular			+			+																			+
Cardiovascular System																									
None																									
Endocrine System																									
None																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis	M																								
Prostate		+		+												+	+								
Sarcoma, metastatic, urinary bladder		X																							
Squamous cell carcinoma, metastatic, urinary bladder																	X								

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	2 7 7	2 8 7	2 9 2	2 9 8	2 9 8	2 9 8	3 0 0	3 1 9	3 3 5	
Carcass ID Number	0 1 6 5	0 2 4 4	0 1 3 3	0 1 3 4	0 1 4 5	0 2 4 5	0 1 3 5	0 2 3 5	0 1 5 5	**Total Tissues/ Tumors**
Alimentary System										
Intestine large	+	+	+	+	+	+	+	+		28
Intestine large, cecum	+	+	+	+	+	+	+	+		28
Intestine large, colon	+	+	+	+	+	+	+	+		28
Carcinoma		X	X							3
Carcinoma, multiple										1
Polyp adenomatous	X						X	X		8
Polyp adenomatous, multiple		X		X	X	X				16
Intestine large, rectum	+	+	+	+	+	+	+	+		28
Polyp adenomatous					X					1
Intestine small										1
Intestine small, duodenum										1
Intestine small, ileum										1
Intestine small, jejunum										1
Liver	+	+	+	+	+	+	+	+	+	34
Mesentery										1
Squamous cell carcinoma, metastatic, urinary bladder										1
Stomach			+		+		+			6
Stomach, forestomach			+		+		+			6
Squamous cell papilloma					X					1
Stomach, glandular			+		+		+			6
Cardiovascular System										
None										
Endocrine System										
None										
General Body System										
None										
Genital System										
Epididymis	+	+	+	+	+	+	+	+	+	34
Penis										
Prostate								+		5
Sarcoma, metastatic, urinary bladder										1
Squamous cell carcinoma, metastatic, urinary bladder								X		2

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	1 5 8	2 1 0	2 1 1	2 1 6	2 1 7	2 1 8	2 1 8	2 1 9	2 2 8	2 3 3	2 3 6	2 3 8	2 4 2	2 4 7	2 4 8	2 4 9	2 4 9	2 5 4	2 5 6	2 6 2	2 6 3	2 6 6	2 6 8	2 7 2	2 7 7
Carcass ID Number	0 1 6 1	0 2 3 1	0 1 6 2	0 2 3 2	0 1 6 3	0 2 1 1	0 2 3 3	0 1 3 1	0 1 4 1	0 2 3 4	0 2 4 1	0 1 5 1	0 1 5 2	0 2 2 1	0 1 5 3	0 1 4 2	0 2 4 2	0 1 6 4	0 1 4 3	0 2 4 3	0 2 1 2	0 1 4 4	0 1 5 4	0 2 2 2	0 1 3 2
Genital System (continued)																									
Seminal vesicle					+																				
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Lymph node							+						+		+		+			+					+
Lymph node, mesenteric																				+					+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus											+														
Integumentary System																									
None																									
Musculoskeletal System																									
None																									
Nervous System																									
None																									
Respiratory System																									
Lung															+					+					
Alveolar/bronchiolar adenoma																				X					
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma					X								X		X	X				X	X				
Transitional epithelium, papilloma									X	X															

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	2 7 7	2 8 7	2 9 2	2 9 8	2 9 8	2 9 8	3 0 0	3 1 9	3 3 5	
Carcass ID Number	0 1 6 5	0 2 4 4	0 1 3 3	0 1 3 4	0 1 4 5	0 2 4 5	0 1 3 5	0 2 3 5	0 1 5 5	**Total Tissues/ Tumors**
Genital System (continued)										
Seminal vesicle								+		2
Testes	+	+	+	+	+	+	+	+	+	34
Hematopoietic System										
Lymph node										6
Lymph node, mesenteric										2
Spleen	+	+	+	+	+	+	+	+	+	34
Thymus								+		2
Integumentary System										
None										
Musculoskeletal System										
None										
Nervous System										
None										
Respiratory System										
Lung										2
Alveolar/bronchiolar adenoma										1
Special Senses System										
None										
Urinary System										
Kidney	+	+	+	+	+	+	+	+	+	34
Transitional epithelium, carcinoma										6
Transitional epithelium, papilloma		X								3

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	1 5 8	2 1 0	2 1 1	2 1 6	2 1 7	2 1 8	2 1 8	2 1 9	2 2 8	2 3 3	2 3 6	2 3 8	2 4 2	2 4 7	2 4 8	2 4 9	2 4 9	2 5 4	2 5 6	2 6 2	2 6 3	2 6 6	2 6 8	2 7 2	2 7 7
Carcass ID Number	0 1 6 1	0 2 3 1	0 1 6 2	0 2 3 2	0 1 6 3	0 2 1 1	0 2 3 1	0 1 3 1	0 1 4 1	0 2 3 4	0 2 4 1	0 1 5 1	0 1 5 2	0 2 2 1	0 1 5 3	0 1 4 2	0 2 4 2	0 1 6 4	0 1 4 3	0 2 4 3	0 2 1 2	0 1 4 4	0 1 5 4	0 2 2 2	0 1 3 2
Urinary System (continued)																									
Ureter	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra																+									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma	X	X						X							X										
Squamous cell carcinoma													X				X								X
Squamous cell papilloma																		X							
Transitional epithelium, carcinoma		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transitional epithelium, papilloma, multiple											X														
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE E2e
Individual Animal Tumor Pathology of Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	2 7 7	2 8 7	2 9 2	2 9 8	2 9 8	2 9 8	3 0 0	3 1 9	3 3 5	
Carcass ID Number	0 1 6 5	0 2 4 4	0 1 3 3	0 1 3 4	0 1 4 5	0 2 4 5	0 1 3 5	0 2 3 5	0 1 5 5	Total Tissues/ Tumors
Urinary System (continued)										
Ureter	+	+	+	+	+	+	+	+	+	34
Urethra										1
Urinary bladder	+	+	+	+	+	+	+	+	+	34
Sarcoma	X					X		X		7
Squamous cell carcinoma				X				X		5
Squamous cell papilloma	X		X					X		4
Transitional epithelium, carcinoma	X	X	X	X	X	X	X	X	X	33
Transitional epithelium, papilloma, multiple										1
Systemic Lesions										
Multiple organs	+	+	+	+	+	+	+	+	+	34

TABLE E3
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole

	0 ppm	6,000 ppm	18,000 ppm
Intestine Large (Colon): Carcinoma			
Overall rate	0/21 (0%)	0/27 (0%)	4/34 (12%)
Adjusted rate	0.0%	0.0%	36.1%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	–	249
Life table test	P<0.001	–	P=0.009
Cochran-Armitage test	P=0.028		
Fisher exact test		–	P=0.136
Intestine Large (Colon): Adenomatous Polyp			
Overall rate	0/21 (0%)	18/27 (67%)	24/34 (71%)
Adjusted rate	0.0%	88.3%	95.0%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	305	211
Life table test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Intestine Large (Rectum): Adenomatous Polyp			
Overall rate	0/21 (0%)	6/27 (22%)	1/34 (3%)
Adjusted rate	0.0%	56.4%	16.7%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	329	298
Life table test	P<0.001	P=0.002	P=0.252
Cochran-Armitage test	P=0.375N		
Fisher exact test		P=0.024	P=0.618
Kidney (Pelvis and Transitional Epithelium): Carcinoma			
Overall rate	0/21 (0%)	1/27 (4%)	6/34 (18%)
Adjusted rate	0.0%	33.3%	26.8%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	648	217
Life table test	P<0.001	P=0.174	P=0.018
Cochran-Armitage test	P=0.014		
Fisher exact test		P=0.563	P=0.046
Kidney (Pelvis and Transitional Epithelium): Papilloma			
Overall rate	0/21 (0%)	0/27 (0%)	3/34 (9%)
Adjusted rate	0.0%	0.0%	19.2%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	–	228
Life table test	P=0.017	–	P=0.088
Cochran-Armitage test	P=0.063		
Fisher exact test		–	P=0.228
Mammary Gland: Fibroadenoma			
Overall rate	1/21 (5%)	0/27 (0%)	0/34 (0%)
Adjusted rate	7.7%	0.0%	0.0%
Terminal rate	1/13 (8%)	0/1 (0%)	0/0 (0%)
First incidence (days)	728 (T)	–	–
Life table test	P=1.000N	P=0.952N	–
Cochran-Armitage test	P=0.324N		
Fisher exact test		P=0.438N	P=0.382N

TABLE E3
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Skin: Keratoacanthoma or Squamous Cell Papilloma			
Overall rate	2/21 (10%)	0/27 (0%)	0/34 (0%)
Adjusted rate	13.8%	0.0%	0.0%
Terminal rate	1/13 (8%)	0/1 (0%)	0/0 (0%)
First incidence (days)	701	–	–
Life table test	P=0.993N	P=0.850N	–
Cochran-Armitage test	P=0.111N		
Fisher exact test		P=0.186N	P=0.141N
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	0/21 (0%)	3/27 (11%)	1/34 (3%)
Adjusted rate	0.0%	29.8%	16.7%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	424	298
Life table test	P=0.006	P=0.045	P=0.252
Cochran-Armitage test	P=0.613N		
Fisher exact test		P=0.169	P=0.618
Testes: Adenoma			
Overall rate	20/21 (95%)	20/27 (74%)	0/34 (0%)
Adjusted rate	100.0%	100.0%	0.0%
Terminal rate	13/13 (100%)	1/1 (100%)	0/0 (0%)
First incidence (days)	564	329	–
Life table test	P<0.001	P<0.001	–
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.055N	P<0.001N
Urinary Bladder (Transitional Epithelium): Carcinoma			
Overall rate	0/21 (0%)	23/27 (85%)	33/34 (97%)
Adjusted rate	0.0%	100.0%	100.0%
Terminal rate	0/13 (0%)	1/1 (100%)	0/0 (0%)
First incidence (days)	–	275	210
Life table test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Urinary Bladder (Transitional Epithelium): Papilloma			
Overall rate	0/21 (0%)	3/27 (11%)	1/34 (3%)
Adjusted rate	0.0%	42.9%	4.2%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	434	236
Life table test	P=0.034	P=0.025	P=0.527
Cochran-Armitage test	P=0.613N		
Fisher exact test		P=0.169	P=0.618
Urinary Bladder: Sarcoma			
Overall rate	0/21 (0%)	1/27 (4%)	7/34 (21%)
Adjusted rate	0.0%	4.0%	67.7%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	305	158
Life table test	P<0.001	P=0.535	P=0.001
Cochran-Armitage test	P=0.006		
Fisher exact test		P=0.563	P=0.027

TABLE E3
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Urinary Bladder: Squamous Cell Carcinoma			
Overall rate	0/21 (0%)	0/27 (0%)	5/34 (15%)
Adjusted rate	0.0%	0.0%	66.1%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	–	242
Life table test	P<0.001	–	P=0.002
Cochran-Armitage test	P=0.012		
Fisher exact test		–	P=0.080
Urinary Bladder: Squamous Cell Papilloma			
Overall rate	0/21 (0%)	0/27 (0%)	4/34 (12%)
Adjusted rate	0.0%	0.0%	63.7%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	–	254
Life table test	P<0.001	–	P=0.003
Cochran-Armitage test	P=0.028		
Fisher exact test		–	P=0.136
All Organs: Hemangiosarcoma			
Overall rate	0/21 (0%)	2/27 (7%)	0/34 (0%)
Adjusted rate	0.0%	17.6%	0.0%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	275	–
Life table test	P=0.596	P=0.165	–
Cochran-Armitage test	P=0.467N		
Fisher exact test		P=0.311	–
All Organs: Mononuclear Cell Leukemia			
Overall rate	12/21 (57%)	2/27 (7%)	0/34 (0%)
Adjusted rate	62.9%	41.7%	0.0%
Terminal rate	6/13 (46%)	0/1 (0%)	0/0 (0%)
First incidence (days)	564	617	–
Life table test	P=0.772N	P=0.630N	–
Cochran-Armitage test	P<0.001N		
Fisher exact test		P<0.001N	P<0.001N
All Organs: Malignant Mesothelioma			
Overall rate	0/21 (0%)	4/27 (15%)	0/34 (0%)
Adjusted rate	0.0%	40.6%	0.0%
Terminal rate	0/13 (0%)	0/1 (0%)	0/0 (0%)
First incidence (days)	–	423	–
Life table test	P=0.048	P=0.014	–
Cochran-Armitage test	P=0.299N		
Fisher exact test		P=0.090	–
All Organs: Benign Neoplasms			
Overall rate	21/21 (100%)	25/27 (93%)	30/34 (88%)
Adjusted rate	100.0%	100.0%	96.6%
Terminal rate	13/13 (100%)	1/1 (100%)	0/0 (0%)
First incidence (days)	410	305	210
Life table test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P=0.115N		
Fisher exact test		P=0.311N	P=0.136N

TABLE E3
Statistical Analysis of Primary Neoplasms in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
All Organs: Malignant Neoplasms			
Overall rate	15/21 (71%)	26/27 (96%)	34/34 (100%)
Adjusted rate	75.0%	100.0%	100.0%
Terminal rate	8/13 (62%)	1/1 (100%)	0/0 (0%)
First incidence (days)	564	207	158
Life table test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P=0.002		
Fisher exact test		P=0.021	P=0.002
All Organs: Benign or Malignant Neoplasms			
Overall rate	21/21 (100%)	27/27 (100%)	34/34 (100%)
Adjusted rate	100.0%	100.0%	100.0%
Terminal rate	13/13 (100%)	1/1 (100%)	0/0 (0%)
First incidence (days)	410	207	158
Life table test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	–		
Fisher exact test		P=1.000N	P=1.000N

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

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole[a]

	0 ppm	6,000 ppm	18,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
3-Month interim evaluation	10	10	10
6-Month interim evaluation	10	10	10
9-Month interim evaluation	10	10	6
15-Month interim evaluation	9	3	0
Early deaths			
Moribund	7	26	23
Natural deaths	1		11
Survivors			
Terminal sacrifice	13	1	0
Animals examined microscopically	60	60	60
3-Month Interim Evaluation			
Alimentary System			
Liver	(10)	(10)	(10)
Hematopoietic cell proliferation	1 (10%)		
Hepatodiaphragmatic nodule	2 (20%)		
Inflammation, granulomatous, multiple		1 (10%)	
Necrosis, focal	1 (10%)		
Hepatocyte, hypertrophy			10 (100%)
Hepatocyte, necrosis, multifocal			10 (100%)
Hepatocyte, necrosis, multiple	1 (10%)		
Hepatocyte, vacuolization cytoplasmic, multifocal			3 (30%)
Hepatocyte, Kupffer cell, pigmentation			10 (100%)
Cardiovascular System			
None			
Endocrine System			
None			
General Body System			
None			
Genital System			
Epididymis	(10)	(10)	(10)
Depletion			10 (100%)
Testes	(10)	(10)	(10)
Atrophy			9 (90%)
Degeneration			10 (100%)
Edema			7 (70%)

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
3-Month Interim Evaluation (continued)			
Hematopoietic System			
Spleen	(10)	(10)	(10)
Congestion		9 (90%)	10 (100%)
Depletion lymphoid			10 (100%)
Pigmentation	10 (100%)	10 (100%)	10 (100%)
Capsule, hypertrophy		10 (100%)	10 (100%)
Capsule, inflammation, chronic		1 (10%)	10 (100%)
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
None			
Special Senses System			
None			
Urinary System			
Kidney	(10)	(10)	(10)
Nephropathy	2 (20%)		
Nephropathy, chronic	2 (20%)	10 (100%)	7 (70%)
Pelvis, mineralization		9 (90%)	
Renal tubule, degeneration		10 (100%)	
Renal tubule, necrosis		10 (100%)	
Renal tubule, pigmentation		9 (90%)	10 (100%)
Urinary bladder	(9)	(9)	(10)
Inflammation, subacute			10 (100%)
Metaplasia, squamous			10 (100%)
Transitional epithelium, hyperplasia			9 (90%)
Wall, proliferation connective tissue			10 (100%)

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
6-Month Interim Evaluation			
Alimentary System			
Intestine large, colon			(3)
Epithelium, hyperplasia			1 (33%)
Liver	(10)	(10)	(10)
Inflammation, granulomatous, multiple			1 (10%)
Artery, inflammation, chronic, focal		1 (10%)	
Hepatocyte, hypertrophy			10 (100%)
Hepatocyte, necrosis, multifocal		1 (10%)	10 (100%)
Hepatocyte, vacuolization cytoplasmic		3 (30%)	6 (60%)
Hepatocyte, Kupffer cell, pigmentation		3 (30%)	10 (100%)
Cardiovascular System			
None			
Endocrine System			
None			
General Body System			
None			
Genital System			
Epididymis	(10)	(10)	(10)
Depletion			10 (100%)
Testes	(10)	(10)	(10)
Atrophy			10 (100%)
Degeneration			10 (100%)
Degeneration, focal	1 (10%)		
Hematopoietic System			
Spleen	(10)	(10)	(10)
Congestion		10 (100%)	10 (100%)
Depletion lymphoid			10 (100%)
Fibrosis			2 (20%)
Pigmentation		10 (100%)	8 (80%)
Capsule, hypertrophy		7 (70%)	10 (100%)
Capsule, inflammation, chronic			10 (100%)
Integumentary System			
None			
Musculoskeletal System			
None			

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
6-Month Interim Evaluation (continued)			
Nervous System			
None			
Respiratory System			
Lung		(2)	
Infiltration cellular, lymphocyte, multifocal		2 (100%)	
Inflammation		1 (50%)	
Inflammation, chronic		1 (50%)	
Special Senses System			
None			
Urinary System			
Kidney	(10)	(10)	(10)
Nephropathy, chronic	4 (40%)	10 (100%)	10 (100%)
Pigmentation		1 (10%)	1 (10%)
Pelvis, mineralization			1 (10%)
Renal tubule, mineralization		10 (100%)	1 (10%)
Renal tubule, pigmentation	2 (20%)	9 (90%)	9 (90%)
Renal tubule, regeneration		10 (100%)	10 (100%)
Transitional epithelium, hyperplasia			5 (50%)
Ureter	(10)	(10)	(9)
Transitional epithelium, hyperplasia			1 (11%)
Urinary bladder	(10)	(10)	(10)
Cyst, multiple			1 (10%)
Inflammation, subacute			7 (70%)
Metaplasia, squamous			10 (100%)
Transitional epithelium, hyperplasia		10 (100%)	
Wall, proliferation connective tissue		1 (10%)	9 (90%)
9-Month Interim Evaluation			
Alimentary System			
Intestine large, colon		(2)	(4)
Parasite metazoan			1 (25%)
Epithelium, hyperplasia			1 (25%)
Liver	(10)	(10)	(6)
Basophilic focus	1 (10%)	1 (10%)	
Cyst			1 (17%)
Hepatodiaphragmatic nodule	1 (10%)		
Inflammation, granulomatous, multifocal		1 (10%)	
Inflammation, granulomatous, multiple	3 (30%)	9 (90%)	6 (100%)
Vacuolization cytoplasmic		3 (30%)	
Bile duct, hyperplasia	6 (60%)		
Hepatocyte, Kupffer cell, pigmentation			5 (83%)
Mesentery	(1)		
Fat, necrosis, focal	1 (100%)		
Stomach, forestomach			(1)
Epithelium, hyperplasia			1 (100%)

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
9-Month Interim Evaluation (continued)			
Cardiovascular System			
None			
Endocrine System			
None			
General Body System			
None			
Genital System			
Epididymis	(10)	(10)	(6)
Depletion			1 (17%)
Preputial gland	(1)	(1)	
Hyperplasia		1 (100%)	
Testes	(10)	(10)	(6)
Interstitial cell, hyperplasia		2 (20%)	
Seminiferous tubule, atrophy			3 (50%)
Hematopoietic System			
Lymph node		(1)	
Pancreatic, hyperplasia		1 (100%)	
Spleen	(10)	(10)	(6)
Congestion		10 (100%)	5 (83%)
Hematopoietic cell proliferation		2 (20%)	5 (83%)
Pigmentation	10 (100%)	10 (100%)	1 (17%)
Capsule, hypertrophy		8 (80%)	6 (100%)
Capsule, inflammation, chronic		2 (20%)	6 (100%)
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
Lung		(2)	
Infiltration cellular, lymphocyte, multifocal		1 (50%)	

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
9-Month Interim Evaluation (continued)			
Special Senses System			
Eye	(1)	(1)	
Cataract	1 (100%)		
Cornea, edema		1 (100%)	
Urinary System			
Kidney	(10)	(10)	(6)
Fibrosis			1 (17%)
Hydronephrosis			2 (33%)
Nephropathy, chronic	10 (100%)	10 (100%)	6 (100%)
Pelvis, dilatation			1 (17%)
Pelvis, mineralization	4 (40%)	10 (100%)	2 (33%)
Renal tubule, pigmentation	10 (100%)	10 (100%)	6 (100%)
Renal tubule, regeneration			2 (33%)
Transitional epithelium, hyperplasia		7 (70%)	3 (50%)
Ureter	(10)	(10)	(6)
Dilatation	1 (10%)		1 (17%)
Transitional epithelium, hyperplasia			1 (17%)
Urinary bladder	(10)	(10)	(6)
Inflammation, subacute			3 (50%)
Inflammation, suppurative		1 (10%)	2 (33%)
Metaplasia, squamous			4 (67%)
Transitional epithelium, hyperplasia		9 (90%)	
Wall, proliferation connective tissue			4 (67%)
15-Month Interim Evaluation			
Alimentary System			
Liver	(9)	(3)	
Basophilic focus	3 (33%)		
Basophilic focus, multiple	1 (11%)		
Clear cell focus	1 (11%)		
Eosinophilic focus	1 (11%)		
Hepatodiaphragmatic nodule		1 (33%)	
Inflammation, granulomatous, multiple	6 (67%)	3 (100%)	
Vacuolization cytoplasmic	4 (44%)		
Bile duct, hyperplasia	9 (100%)		
Hepatocyte, Kupffer cell, pigmentation		1 (33%)	
Mesentery	(1)		
Fat, necrosis, focal	1 (100%)		
Cardiovascular System			
Heart	(1)		
Atrium, congestion	1 (100%)		
Endocrine System			
None			

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
15-Month Interim Evaluation (continued)			
General Body System			
None			
Genital System			
Testes	(9)	(3)	
Bilateral, interstitial cell, hyperplasia	1 (11%)		
Interstitial cell, hyperplasia	4 (44%)		
Hematopoietic System			
Lymph node	(1)	(1)	
Renal, angiectasis		1 (100%)	
Lymph node, mesenteric	(1)	(1)	
Hyperplasia, lymphoid	1 (100%)	1 (100%)	
Spleen	(9)	(3)	
Congestion	7 (78%)	1 (33%)	
Hematopoietic cell proliferation	4 (44%)	2 (67%)	
Pigmentation	6 (67%)	2 (67%)	
Capsule, hypertrophy		2 (67%)	
Capsule, inflammation, chronic		1 (33%)	
Integumentary System			
Skin	(2)		
Epidermis, fibrosis, focal	1 (50%)		
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
None			
Special Senses System			
None			
Urinary System			
Kidney	(9)	(3)	
Nephropathy, chronic	9 (100%)	3 (100%)	
Pelvis, dilatation		1 (33%)	
Pelvis, mineralization	3 (33%)	3 (100%)	
Renal tubule, pigmentation	9 (100%)	3 (100%)	
Renal tubule, regeneration		1 (33%)	
Transitional epithelium, hyperplasia		3 (100%)	

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
15-Month Interim Evaluation (continued)			
Urinary System (continued)			
Ureter	(9)	(3)	
Dilatation		1 (33%)	
Urinary bladder	(9)	(3)	
Transitional epithelium, hyperplasia		1 (33%)	
Wall, proliferation connective tissue		1 (33%)	
Stop-Exposure Study			
Alimentary System			
Intestine large, cecum	(1)	(21)	(28)
Dilatation			2 (7%)
Edema		2 (10%)	
Parasite metazoan		1 (5%)	
Submucosa, proliferation connective tissue		1 (5%)	
Intestine large, colon	(1)	(21)	(28)
Edema		1 (5%)	
Fibrosis		1 (5%)	
Hemorrhage		2 (10%)	4 (14%)
Intussusception			6 (21%)
Necrosis			1 (4%)
Parasite metazoan			1 (4%)
Epithelium, hyperplasia			9 (32%)
Serosa, inflammation, chronic		1 (5%)	1 (4%)
Wall, proliferation connective tissue			1 (4%)
Intestine large, rectum	(1)	(21)	(28)
Hemorrhage		1 (5%)	
Epithelium, hyperplasia			1 (4%)
Liver	(21)	(27)	(34)
Basophilic focus	1 (5%)	2 (7%)	
Basophilic focus, multiple	8 (38%)	3 (11%)	
Clear cell focus	1 (5%)	1 (4%)	
Clear cell focus, multiple	4 (19%)		
Degeneration, cystic	1 (5%)		
Eosinophilic focus	5 (24%)	2 (7%)	1 (3%)
Eosinophilic focus, multiple	2 (10%)	1 (4%)	1 (3%)
Hematopoietic cell proliferation		2 (7%)	1 (3%)
Hepatodiaphragmatic nodule	2 (10%)	1 (4%)	1 (3%)
Hyperplasia, nodular	5 (24%)		
Inflammation, granulomatous, multiple	5 (24%)	12 (44%)	15 (44%)
Mixed cell focus	1 (5%)	1 (4%)	
Mixed cell focus, multiple	1 (5%)		
Thrombosis		1 (4%)	
Vacuolization cytoplasmic	1 (5%)	2 (7%)	1 (3%)
Bile duct, hyperplasia	20 (95%)	7 (26%)	
Centrilobular, degeneration		1 (4%)	

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of o-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study (continued)			
Alimentary System (continued)			
Liver (continued)			
Hepatocyte, hypertrophy			6 (18%)
Hepatocyte, necrosis, multifocal			1 (3%)
Hepatocyte, necrosis, multiple		1 (4%)	
Hepatocyte, Kupffer cell, pigmentation		1 (4%)	30 (88%)
Serosa, fibrosis		1 (4%)	
Mesentery	(3)	(3)	(1)
Thrombosis		1 (33%)	
Fat, necrosis, focal	3 (100%)		
Pancreas	(1)	(4)	
Edema		1 (25%)	
Polyarteritis	1 (100%)		
Acinar cell, atrophy		1 (25%)	
Acinar cell, hyperplasia		1 (25%)	
Stomach, forestomach	(3)	(10)	(6)
Abscess		2 (20%)	
Edema		1 (10%)	
Inflammation, suppurative	1 (33%)		1 (17%)
Mineralization		1 (10%)	
Ulcer	2 (67%)		1 (17%)
Ulcer, multiple	1 (33%)		
Epithelium, hyperplasia	1 (33%)	4 (40%)	2 (33%)
Stomach, glandular	(3)	(10)	(6)
Erosion, multiple	1 (33%)		
Mineralization		2 (20%)	
Cardiovascular System			
Blood vessel		(1)	
Aorta, mineralization		1 (100%)	
Heart	(5)	(2)	
Inflammation, chronic	4 (80%)	2 (100%)	
Mineralization		1 (50%)	
Atrium, congestion	2 (40%)		
Atrium, dilatation	1 (20%)		
Atrium, thrombosis	2 (40%)	1 (50%)	
Endocrine System			
Adrenal gland, cortex	(2)	(2)	
Vacuolization cytoplasmic	1 (50%)		
Vacuolization cytoplasmic, focal		1 (50%)	
Parathyroid gland		(2)	
Hyperplasia		2 (100%)	
General Body System			
None			

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study (continued)			
Genital System			
Epididymis	(21)	(27)	(34)
Depletion cellular	17 (81%)	12 (44%)	9 (26%)
Preputial gland	(6)	(6)	
Atrophy	2 (33%)	3 (50%)	
Hyperplasia		1 (17%)	
Inflammation, suppurative	2 (33%)		
Necrosis	1 (17%)		
Duct, cyst	2 (33%)	4 (67%)	
Duct, cyst, multiple		1 (17%)	
Prostate		(4)	(5)
Inflammation, chronic		1 (25%)	
Inflammation, suppurative		1 (25%)	3 (60%)
Proliferation connective tissue			1 (20%)
Epithelium, hyperplasia			1 (20%)
Seminal vesicle	(2)	(1)	(2)
Atrophy	2 (100%)		
Adventitia, edema		1 (100%)	
Epithelium, hyperplasia			1 (50%)
Testes	(21)	(27)	(34)
Bilateral, interstitial cell, hyperplasia	1 (5%)	1 (4%)	
Interstitial cell, hyperplasia	2 (10%)	12 (44%)	
Seminiferous tubule, atrophy	20 (95%)	13 (48%)	21 (62%)
Hematopoietic System			
Lymph node	(14)	(16)	(6)
Bronchial, hyperplasia, lymphoid			1 (17%)
Deep cervical, angiectasis	1 (7%)		
Iliac, angiectasis		1 (6%)	
Iliac, hyperplasia, lymphoid		1 (6%)	1 (17%)
Mediastinal, angiectasis	2 (14%)	3 (19%)	
Mediastinal, congestion		1 (6%)	
Mediastinal, hemorrhage	2 (14%)		
Mediastinal, hyperplasia, lymphoid			2 (33%)
Mediastinal, pigmentation		3 (19%)	
Pancreatic, angiectasis	1 (7%)	1 (6%)	
Pancreatic, edema		1 (6%)	
Pancreatic, hemorrhage	1 (7%)		
Pancreatic, hyperplasia, lymphoid	1 (7%)	1 (6%)	2 (33%)
Renal, angiectasis	1 (7%)	1 (6%)	
Renal, inflammation, granulomatous		1 (6%)	
Lymph node, mandibular	(6)	(7)	
Hemorrhage	1 (17%)		
Hyperplasia, lymphoid	1 (17%)	3 (43%)	

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study (continued)			
Hematopoietic System (continued)			
Lymph node, mesenteric	(5)	(9)	(2)
Angiectasis		2 (22%)	
Congestion		1 (11%)	
Cyst		3 (33%)	
Edema		3 (33%)	
Fibrosis			1 (50%)
Hemorrhage	1 (20%)		
Hyperplasia, lymphoid	1 (20%)		
Spleen	(21)	(27)	(34)
Congestion	5 (24%)	15 (56%)	23 (68%)
Depletion lymphoid	1 (5%)		20 (59%)
Fibrosis	1 (5%)	1 (4%)	4 (12%)
Fibrosis, focal	1 (5%)		
Hematopoietic cell proliferation	9 (43%)	19 (70%)	12 (35%)
Hyperplasia, lymphoid		2 (7%)	
Inflammation, chronic			1 (3%)
Inflammation, granulomatous	1 (5%)		
Pigmentation	6 (29%)	14 (52%)	19 (56%)
Thrombosis			1 (3%)
Capsule, hypertrophy		15 (56%)	34 (100%)
Capsule, inflammation, chronic		5 (19%)	33 (97%)
Thymus	(1)		(2)
Atrophy			2 (100%)
Integumentary System			
Mammary gland	(1)	(1)	
Duct, cyst		1 (100%)	
Musculoskeletal System			
Bone	(1)	(1)	
Calvarium, hyperostosis		1 (100%)	
Nervous System			
Brain	(5)		
Compression	2 (40%)		
Hemorrhage, multiple	1 (20%)		
Respiratory System			
Lung	(7)	(3)	(2)
Congestion		2 (67%)	
Infiltration cellular, lymphocyte, multifocal			1 (50%)
Inflammation, granulomatous	1 (14%)		
Alveolar epithelium, hyperplasia	1 (14%)		
Alveolus, pigmentation	1 (14%)		
Nose	(1)		
Lumen, hyperkeratosis	1 (100%)		
Lumen, inflammation, suppurative	1 (100%)		

TABLE E4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study (continued)			
Special Senses System			
None			
Urinary System			
Kidney	(21)	(27)	(34)
Hydronephrosis			10 (29%)
Infarct			3 (9%)
Nephropathy, chronic	21 (100%)	27 (100%)	24 (71%)
Bilateral, hydronephrosis		2 (7%)	1 (3%)
Cortex, cyst		1 (4%)	
Papilla, necrosis			1 (3%)
Pelvis, dilatation			1 (3%)
Pelvis, inflammation, suppurative	1 (5%)		
Pelvis, mineralization	16 (76%)	27 (100%)	2 (59%)
Pelvis, necrosis			1 (3%)
Renal tubule, dilatation			1 (3%)
Renal tubule, hyperplasia		1 (4%)	
Renal tubule, mineralization		1 (4%)	3 (9%)
Renal tubule, necrosis			1 (3%)
Renal tubule, pigmentation	20 (95%)	26 (96%)	34 (100%)
Renal tubule, regeneration		2 (7%)	6 (18%)
Transitional epithelium, hemorrhage			1 (3%)
Transitional epithelium, hyperplasia	5 (24%)	24 (89%)	19 (56%)
Ureter	(19)	(25)	(34)
Dilatation		4 (16%)	14 (41%)
Hemorrhage			1 (3%)
Inflammation, chronic			1 (3%)
Transitional epithelium, hyperplasia		1 (4%)	
Urethra		(2)	(1)
Bulbourethral gland, cyst, multiple		1 (50%)	
Transitional epithelium, hyperplasia			1 (100%)
Urinary bladder	(21)	(27)	(34)
Hemorrhage		1 (4%)	6 (18%)
Inflammation, suppurative			4 (12%)
Metaplasia, squamous		3 (11%)	30 (88%)
Necrosis		1 (4%)	
Transitional epithelium, hyperplasia		9 (33%)	2 (6%)
Wall, proliferation connective tissue		1 (4%)	24 (71%)

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

APPENDIX F
SUMMARY OF LESIONS IN FEMALE RATS IN THE STOP-EXPOSURE FEED STUDY OF *o*-NITROANISOLE

TABLE F1
Summary of the Incidence of Neoplasms in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole[a]

	0 ppm	6,000 ppm	18,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
3-Month interim evaluation	10	10	10
6-Month interim evaluation	10	10	10
9-Month interim evaluation	10	10	6
15-Month interim evaluation	8	10	0
Early deaths			
Moribund	6	12	25
Natural deaths	2	4	9
Survivors			
Terminal sacrifice	14	4	0
Animals examined microscopically	60	60	60
***3-Month Interim Evaluation*[b]**			
***6-Month Interim Evaluation*[b]**			
Alimentary System			
Intestine large, colon		(1)	
Polyp adenomatous		1 (100%)	
Urinary System			
Urinary bladder	(10)	(10)	(10)
Transitional epithelium, carcinoma			10 (100%)
Neoplasm Summary			
Total animals with primary neoplasms[c]		1	10
Total primary neoplasms		1	10
Total animals with benign neoplasms		1	
Total benign neoplasms		1	
Total animals with malignant neoplasms			10
Total malignant neoplasms			10
***9-Month Interim Evaluation*[b]**			
Alimentary system			
Intestine large, colon			(1)
Polyp adenomatous, multiple			1 (100%)
Urinary System			
Urinary bladder	(10)	(9)	(6)
Sarcoma			2 (33%)
Transitional epithelium, carcinoma		1 (11%)	6 (100%)

TABLE F1
Summary of the Incidence of Neoplasms in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
9-Month Interim Evaluation (continued)			
Neoplasm Summary			
Total animals with primary neoplasms		1	6
Total primary neoplasms		1	9
Total animals with benign neoplasms			1
Total benign neoplasms			1
Total animals with malignant neoplasms		1	6
Total malignant neoplasms		1	8
15-Month Interim Evaluation			
Alimentary System			
Intestine large, colon		(2)	
Polyp adenomatous, multiple		2 (100%)	
Intestine large, rectum		(2)	
Polyp adenomatous		1 (50%)	
Cardiovascular System			
None			
Endocrine System			
Pituitary gland		(1)	
Pars distalis, adenoma		1 (100%)	
General Body System			
None			
Genital System			
Clitoral gland	(2)	(1)	
Adenoma	1 (50%)		
Uterus	(8)	(10)	
Polyp stromal	1 (13%)	1 (10%)	
Hematopoietic System			
None			
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			

TABLE F1
Summary of the Incidence of Neoplasms in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
15-Month Interim Evaluation (continued)			
Respiratory System			
None			
Special Senses System			
None			
Urinary System			
Urinary bladder	(8)	(10)	
Transitional epithelium, carcinoma		9 (90%)	
Transitional epithelium, papilloma		1 (10%)	
Neoplasm Summary			
Total animals with primary neoplasms	2	10	
Total primary neoplasms	2	15	
Total animals with benign neoplasms	2	3	
Total benign neoplasms	2	6	
Total animals with malignant neoplasms		9	
Total malignant neoplasms		9	
Stop-Exposure Study			
Alimentary System			
Intestine large, colon	(2)	(5)	(21)
Carcinoma			2 (10%)
Polyp adenomatous		3 (60%)	5 (24%)
Polyp adenomatous, multiple		1 (20%)	12 (57%)
Intestine large, rectum	(1)	(5)	(21)
Polyp adenomatous, multiple		1 (20%)	
Intestine small, ileum	(1)	(2)	
Intestine small, jejunum	(1)	(2)	
Liver	(22)	(20)	(34)
Squamous cell carcinoma, metastatic, urinary bladder			1 (3%)
Mesentery	(1)	(2)	(2)
Sarcoma, metastatic, multiple, urinary bladder			1 (50%)
Squamous cell carcinoma, metastatic, urinary bladder			1 (50%)
Pancreas	(1)		(4)
Sarcoma, metastatic, urinary bladder			1 (25%)
Squamous cell carcinoma, metastatic, urinary bladder			1 (25%)
Stomach, forestomach	(5)	(9)	(8)
Squamous cell carcinoma, metastatic, urinary bladder			1 (13%)
Squamous cell papilloma	1 (20%)	4 (44%)	4 (50%)
Stomach, glandular	(5)	(9)	(8)
Serosa, sarcoma, metastatic, urinary bladder			1 (13%)

TABLE F1
Summary of the Incidence of Neoplasms in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study (continued)			
Cardiovascular System			
None			
Endocrine System			
Adrenal gland, cortex	(2)		(1)
Squamous cell carcinoma, metastatic, urinary bladder			1 (100%)
Adrenal gland, medulla	(2)		(1)
Islets, pancreatic	(1)		
Carcinoma	1 (100%)		
Pituitary gland	(13)	(8)	
Pars distalis, adenoma	12 (92%)	4 (50%)	
Thyroid gland	(1)	(1)	
Follicular cell, carcinoma	1 (100%)	1 (100%)	
General Body System			
None			
Genital System			
Clitoral gland	(3)	(5)	(1)
Adenoma	1 (33%)		
Carcinoma	2 (67%)	1 (20%)	
Ovary	(1)		(1)
Squamous cell carcinoma, metastatic, urinary bladder			1 (100%)
Uterus	(21)	(20)	(34)
Polyp stromal	2 (10%)	2 (10%)	
Squamous cell carcinoma, metastatic, urinary bladder			1 (3%)
Cervix, carcinoma, metastatic, urinary bladder			1 (3%)
Cervix, leiomyosarcoma			1 (3%)
Hematopoietic System			
Lymph node	(14)	(16)	(12)
Iliac, squamous cell carcinoma, metastatic, urinary bladder			1 (8%)
Lymph node, mandibular	(7)	(2)	
Lymph node, mesenteric	(2)	(1)	(2)
Squamous cell carcinoma, metastatic, urinary bladder			1 (50%)
Spleen	(22)	(20)	(34)
Capsule, squamous cell carcinoma, metastatic, urinary bladder			1 (3%)
Thymus	(1)		(3)
Squamous cell carcinoma, metastatic, urinary bladder			1 (33%)

TABLE F1
Summary of the Incidence of Neoplasms in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study (continued)			
Integumentary System			
Mammary gland	(14)	(5)	
Adenoma		1 (20%)	
Fibroadenoma	7 (50%)	1 (20%)	
Fibroadenoma, multiple	1 (7%)	2 (40%)	
Skin	(1)		(1)
Head, squamous cell carcinoma, deep invasion	1 (100%)		
Musculoskeletal System			
Skeletal muscle	(1)		
Hindlimb, rhabdomyosarcoma	1 (100%)		
Nervous System			
Brain	(5)	(2)	
Ependymoma malignant		1 (50%)	
Glioma malignant	1 (20%)		
Respiratory System			
Lung	(3)	(1)	(2)
Squamous cell carcinoma, metastatic, urinary bladder			1 (50%)
Special Senses System			
None			
Urinary System			
Kidney	(22)	(20)	(34)
Squamous cell carcinoma, metastatic, urinary bladder			1 (3%)
Transitional epithelium, carcinoma			1 (3%)
Transitional epithelium, papilloma			1 (3%)
Urinary bladder	(20)	(20)	(34)
Fibrosarcoma			1 (3%)
Leiomyosarcoma		1 (5%)	2 (6%)
Sarcoma		1 (5%)	9 (26%)
Squamous cell carcinoma			1 (3%)
Squamous cell papilloma			2 (6%)
Squamous cell papilloma, multiple			2 (6%)
Transitional epithelium, carcinoma		18 (90%)	32 (94%)
Transitional epithelium, papilloma		1 (5%)	
Transitional epithelium, papilloma, multiple			1 (3%)
Systemic Lesions			
Multiple organs[d]	(22)	(20)	(34)
Leukemia mononuclear	3 (14%)		

TABLE F1
Summary of the Incidence of Neoplasms in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study (continued)			
Neoplasm Summary			
Total animals with primary neoplasms	20	20	32
Total primary neoplasms	34	43	76
Total animals with benign neoplasms	16	14	21
Total benign neoplasms	24	20	27
Total animals with malignant neoplasms	10	20	32
Total malignant neoplasms	10	23	49
Total animals with metastatic neoplasms			3
Total metastatic neoplasm			17

[a] Number of animals examined microscopically at site and number of animals with lesion.
[b] All organ systems listed in Table 1 (Materials and Methods) were evaluated, but neoplasms were found only in systems specified.
[c] Primary neoplasms: all neoplasms except metastatic neoplasms
[d] Number of animals with any tissue examined microscopically

TABLE F2a
Individual Animal Tumor Pathology of Female Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of o-Nitroanisole: 0 ppm

Number of Days on Study	0 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8 8 7 7 7 7 7 8 8 8 8 8	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 4 4 4 4 4 4 4 4 4 4 1 1 2 2 2 1 1 1 2 2 1 2 1 2 3 3 4 5 4 5	**Total Tissues/ Tumors**
Alimentary System		
Liver	+ + + + + + + + + +	10
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Uterus	+ + + + + + + + + +	10
Hematopoietic System		
Spleen	+ + + + + + + + + +	10
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		

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

TABLE F2a
Individual Animal Tumor Pathology of Female Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	0 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8 8 7 7 7 7 7 8 8 8 8 8	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 4 4 4 4 4 4 4 4 4 4 1 1 2 2 2 1 1 1 2 2 1 2 1 2 3 3 4 5 4 5	**Total Tissues/ Tumors**
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + + + + + + + + +	10
Urinary bladder	+ + + + + + + + + +	10
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE F2a
Individual Animal Tumor Pathology of Female Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm

Number of Days on Study	0 8 7	0 8 7	0 8 7	0 8 7	0 8 7	0 8 8	0 8 8	0 8 8	0 8 8	0 8 8	
Carcass ID Number	0 6 5 1	0 6 5 2	0 6 5 3	0 6 6 1	0 6 6 2	0 6 5 4	0 6 5 5	0 6 6 3	0 6 6 4	0 6 6 5	**Total Tissues/ Tumors**
Alimentary System											
Liver	+	+	+	+	+	+	+	+	+	+	10
Cardiovascular System											
None											
Endocrine System											
None											
General Body System											
None											
Genital System											
Uterus	+	+	+	+	+	+	+	+	+	+	10
Hematopoietic System											
Spleen	+	+	+	+	+	+	+	+	+	+	10
Integumentary System											
None											
Musculoskeletal System											
None											
Nervous System											
None											
Respiratory System											
None											
Special Senses System											
None											

TABLE F2a
Individual Animal Tumor Pathology of Female Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	0 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8 8 7 7 7 7 7 8 8 8 8 8	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 6 6 6 6 6 6 6 6 6 6 5 5 5 6 6 5 5 6 6 6 1 2 3 1 2 4 5 3 4 5	**Total Tissues/ Tumors**
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + + + + + + + + +	10
Urinary bladder	+ + + + + + + + + +	10
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE F2a
Individual Animal Tumor Pathology of Female Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm

Number of Days on Study	0 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8 8 7 7 7 7 7 7 7 8 8 8	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 5 5 5 5 5 5 5 5 5 5 3 3 3 3 3 4 4 4 4 4 1 2 3 4 5 1 2 3 4 5	**Total Tissues/ Tumors**
Alimentary System		
Liver	+ + + + + + + + + +	10
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Uterus	+ + + + + + + + + +	10
Hematopoietic System		
Spleen	+ + + + + + + + + +	10
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		
Special Senses System		
None		

TABLE F2a
Individual Animal Tumor Pathology of Female Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	0 0 0 0 0 0 0 0 0 0 8 8 8 8 8 8 8 8 8 8 7 7 7 7 7 7 7 8 8 8	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 5 5 5 5 5 5 5 5 5 5 3 3 3 3 3 4 4 4 4 4 1 2 3 4 5 1 2 3 4 5	**Total Tissues/ Tumors**
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + + + + + + + + +	10
Urinary bladder	+ + + + + + + + + +	10
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE F2b
Individual Animal Tumor Pathology of Female Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm

Number of Days on Study	1 1 1 1 1 1 1 1 1 1 9 9 9 9 9 9 9 9 9 9 0 0 0 0 0 0 0 1 1 1	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 4 4 4 4 4 4 4 4 4 4 3 3 3 3 4 4 4 3 4 4 1 2 3 4 1 2 3 5 4 5	**Total Tissues/ Tumors**
Alimentary System		
Liver	+ + + + + + + + + +	10
Mesentery	+	1
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Uterus	+ + + + + + + + + +	10
Hematopoietic System		
Spleen	+ + + + + + + + + +	10
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		

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

TABLE F2b
Individual Animal Tumor Pathology of Female Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	1 1 1 1 1 1 1 1 1 1 9 9 9 9 9 9 9 9 9 9 0 0 0 0 0 0 0 1 1 1	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 4 4 4 4 4 4 4 4 4 4 3 3 3 3 4 4 4 3 4 4 1 2 3 4 1 2 3 5 4 5	Total Tissues/ Tumors
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + M + + + + + + +	9
Urinary bladder	+ + + + + + + + + +	10
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE F2b
Individual Animal Tumor Pathology of Female Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm

Number of Days on Study	1 9 0	1 9 0	1 9 1	1 9 1	1 9 1	1 9 1	1 9 1	1 9 1	1 9 1	1 9 1	
Carcass ID Number	0 6 7 1	0 6 7 2	0 6 7 3	0 6 7 4	0 6 7 5	0 6 8 1	0 6 8 2	0 6 8 3	0 6 8 4	0 6 8 5	**Total Tissues/ Tumors**
Alimentary System											
Intestine large									+		1
Intestine large, cecum									+		1
Intestine large, colon									+		1
Polyp adenomatous									X		1
Intestine large, rectum									+		1
Liver	+	+	+	+	+	+	+	+	+	+	10
Cardiovascular System											
None											
Endocrine System											
None											
General Body System											
None											
Genital System											
Ovary						+					1
Uterus	+	+	+	+	+	+	+	+	+	+	10
Hematopoietic System											
Spleen	+	+	+	+	+	+	+	+	+	+	10
Integumentary System											
None											
Musculoskeletal System											
None											
Nervous System											
None											

TABLE F2b
Individual Animal Tumor Pathology of Female Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	1 1 1 1 1 1 1 1 1 1 9 9 9 9 9 9 9 9 9 9 0 0 1 1 1 1 1 1 1 1	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 6 6 6 6 6 6 6 6 6 6 7 7 7 7 7 8 8 8 8 8 1 2 3 4 5 1 2 3 4 5	Total Tissues/ Tumors
Respiratory System		
Lung	+ +	2
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + + + + + + + + +	10
Urinary bladder	+ + + + + + + + + +	10
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE F2b
Individual Animal Tumor Pathology of Female Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm

Number of Days on Study	1 1 1 1 1 1 1 1 1 1 9 9 9 9 9 9 9 9 9 9 0 0 0 0 0 0 0 1 1 1	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 1 2 3 4 5 1 2 3 4 5	**Total Tissues/ Tumors**
Alimentary System		
Liver	+ + + + + + + + + +	10
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Uterus	+ + + + + + + + + +	10
Hematopoietic System		
Spleen	+ + + + + + + + + +	10
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		
Special Senses System		
None		

TABLE F2b
Individual Animal Tumor Pathology of Female Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	1 1 1 1 1 1 1 1 1 1 9 9 9 9 9 9 9 9 9 9 0 0 0 0 0 0 0 1 1 1	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6 1 2 3 4 5 1 2 3 4 5	**Total Tissues/ Tumors**
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + + + + + + + + +	10
Urinary bladder	+ + + + + + + + + +	10
Transitional epithelium, carcinoma	X X X X X X X X X X	10
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE F2c
Individual Animal Tumor Pathology of Female Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm

Number of Days on Study	2 2 2 2 2 2 2 2 2 2 7 7 7 7 7 7 7 7 7 7 4 4 4 4 4 5 5 5 5 5	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 4 4 4 4 4 4 4 4 4 4 5 5 5 6 6 5 5 6 6 6 1 2 3 1 2 4 5 3 4 5	**Total Tissues/ Tumors**
Alimentary System		
Liver	+ + + + + + + + + +	10
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Ovary	+	1
Uterus	+ + + + + + + + + +	10
Hematopoietic System		
Spleen	+ + + + + + + + + +	10
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		

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

TABLE F2c
Individual Animal Tumor Pathology of Female Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	2 7 4	2 7 4	2 7 4	2 7 4	2 7 4	2 7 5	2 7 5	2 7 5	2 7 5	2 7 5	
Carcass ID Number	0 4 5 1	0 4 5 2	0 4 5 3	0 4 6 1	0 4 6 2	0 4 5 4	0 4 5 5	0 4 6 3	0 4 6 4	0 4 6 5	Total Tissues/ Tumors
Special Senses System											
None											
Urinary System											
Kidney	+	+	+	+	+	+	+	+	+	+	10
Ureter	+	+	+	+	+	+	+	+	+	+	10
Urinary bladder	+	+	+	+	+	+	+	+	+	+	10
Systemic Lesions											
Multiple organs	+	+	+	+	+	+	+	+	+	+	10

TABLE F2c
Individual Animal Tumor Pathology of Female Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm

Number of Days on Study	2 2 2 2 2 2 2 2 2 2 7 7 7 7 7 7 7 7 7 7 4 4 4 4 5 5 5 5 5 5	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 6 7 7 7 6 6 6 6 7 7 9 0 0 0 9 9 9 9 0 0 1 1 2 3 2 3 4 5 4 5	**Total Tissues/ Tumors**
Alimentary System		
Liver	+ + + + + + + + + +	10
Mesentery	+	1
Stomach	+	1
Stomach, forestomach	+	1
Stomach, glandular	+	1
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Uterus	+ + + + + + + + + +	10
Hematopoietic System		
Spleen	+ + + + + + + + + +	10
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		
Respiratory System		
None		

TABLE F2c
Individual Animal Tumor Pathology of Female Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	2 2 2 2 2 2 2 2 2 2 7 7 7 7 7 7 7 7 7 7 4 4 4 4 5 5 5 5 5 5	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 6 7 7 7 6 6 6 6 7 7 9 0 0 0 9 9 9 9 0 0 1 1 2 3 2 3 4 5 4 5	Total Tissues/ Tumors
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + + + + + + + + +	10
Urinary bladder	+ + + + + + M + + +	9
Transitional epithelium, carcinoma	X	1
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE F2c
Individual Animal Tumor Pathology of Female Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm

Number of Days on Study	2 7 4	2 7 4	2 7 5	2 7 5	2 7 5	2 7 5	
Carcass ID Number	0 5 7 1	0 5 7 2	0 5 7 3	0 5 7 4	0 5 7 5	0 5 8 5	**Total Tissues/ Tumors**
Alimentary System							
Intestine large	+						1
Intestine large, cecum	+						1
Intestine large, colon	+						1
Polyp adenomatous, multiple	X						1
Intestine large, rectum	+						1
Liver	+	+	+	+	+	+	6
Cardiovascular System							
None							
Endocrine System							
None							
General Body System							
None							
Genital System							
Uterus	+	+	+	+	+	+	6
Hematopoietic System							
Lymph node	+						1
Spleen	+	+	+	+	+	+	6
Integumentary System							
None							
Musculoskeletal System							
None							
Nervous System							
None							

TABLE F2c
Individual Animal Tumor Pathology of Female Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	2 7 4	2 7 4	2 7 5	2 7 5	2 7 5	2 7 5	
Carcass ID Number	0 5 7 1	0 5 7 2	0 5 7 3	0 5 7 4	0 5 7 5	0 5 8 5	Total Tissues/ Tumors
Respiratory System							
None							
Special Senses System							
None							
Urinary System							
Kidney	+	+	+	+	+	+	6
Ureter	+	+	+	+	+	+	6
Urinary bladder	+	+	+	+	+	+	6
Sarcoma				X		X	2
Transitional epithelium, carcinoma	X	X	X	X	X	X	6
Systemic Lesions							
Multiple organs	+	+	+	+	+	+	6

TABLE F2d
Individual Animal Tumor Pathology of Female Rats at the 15-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm

Number of Days on Study	4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6	
Carcass ID Number	0 0 0 0 0 0 0 0 4 4 4 4 4 4 4 4 7 7 7 8 8 7 7 8 1 2 3 3 4 4 5 5	**Total Tissues/ Tumors**
Alimentary System		
Liver	+ + + + + + + +	8
Mesentery	+ +	2
Cardiovascular System		
None		
Endocrine System		
None		
General Body System		
None		
Genital System		
Clitoral gland	+ +	2
Adenoma	X	1
Ovary	+	1
Uterus	+ + + + + + + +	8
Polyp stromal	X	1
Hematopoietic System		
Spleen	+ + + + + + + +	8
Integumentary System		
None		
Musculoskeletal System		
None		
Nervous System		
None		

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

TABLE F2d
Individual Animal Tumor Pathology of Female Rats at the 15-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6	
Carcass ID Number	0 0 0 0 0 0 0 0 4 4 4 4 4 4 4 4 7 7 7 8 8 7 7 8 1 2 3 3 4 4 5 5	**Total Tissues/ Tumors**
Respiratory System		
None		
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + + + +	8
Ureter	M + + + + + + +	7
Urinary bladder	+ + + + + + + +	8
Systemic Lesions		
Multiple organs	+ + + + + + + +	8

TABLE F2d
Individual Animal Tumor Pathology of Female Rats at the 15-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm

Number of Days on Study	4 5 5	4 5 5	4 5 5	4 5 5	4 5 5	4 5 6	4 5 6	4 5 6	4 5 6	4 5 6	
Carcass ID Number	0 7 1 1	0 7 1 2	0 7 1 3	0 7 2 1	0 7 2 2	0 7 1 4	0 7 1 5	0 7 2 3	0 7 2 4	0 7 2 5	**Total Tissues/ Tumors**
Alimentary System											
Intestine large			+						+		2
Intestine large, cecum			+						+		2
Intestine large, colon			+						+		2
Polyp adenomatous, multiple			X						X		2
Intestine large, rectum			+						+		2
Polyp adenomatous			X								1
Liver	+	+	M	+	+	+	+	+	+	+	9
Mesentery	+		+	+				+		+	5
Cardiovascular System											
None											
Endocrine System											
Pituitary gland			+								1
Pars distalis, adenoma			X								1
General Body System											
None											
Genital System											
Clitoral gland		+									1
Oviduct				+							1
Uterus	+	+	+	+	+	+	+	+	+	+	10
Polyp stromal						X					1
Hematopoietic System											
Lymph node			+				+				2
Spleen	+	+	+	+	+	+	+	+	+	+	10
Integumentary System											
None											
Musculoskeletal System											
None											

TABLE F2d
Individual Animal Tumor Pathology of Female Rats at the 15-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	4 4 4 4 4 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 6 6 6 6 6	
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 7 7 7 7 7 7 7 7 7 7 1 1 1 2 2 1 1 2 2 2 1 2 3 1 2 4 5 3 4 5	**Total Tissues/ Tumors**
Nervous System		
None		
Respiratory System		
None		
Special Senses System		
None		
Urinary System		
Kidney	+ + + + + + + + + +	10
Ureter	+ + + + + + + + + +	10
Urinary bladder	+ + + + + + + + + +	10
Transitional epithelium, carcinoma	X X X X X X X X X	9
Transitional epithelium, papilloma	X	1
Systemic Lesions		
Multiple organs	+ + + + + + + + + +	10

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm

Number of Days on Study	1 0 3	4 0 8	4 1 3	4 2 1	5 9 0	6 4 8	6 6 2	6 7 9	7 2 8	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	
Carcass ID Number	0 3 8 1	0 4 8 1	0 4 8 2	0 3 7 1	0 4 0 1	0 3 9 1	0 3 9 2	0 3 7 2	0 3 7 3	0 3 7 4	0 3 7 5	0 3 8 2	0 3 8 3	0 3 8 4	0 3 8 5	0 3 9 3	0 3 9 4	0 3 9 5	0 4 0 2	0 4 0 3	0 4 0 4	0 4 0 5	**Total Tissues/ Tumors**	
Alimentary System																								
Intestine large	+								+														2	
Intestine large, cecum	A								+														1	
Intestine large, colon	+								+														2	
Intestine large, rectum	A								+														1	
Intestine small	+								+														2	
Intestine small, duodenum	+								+														2	
Intestine small, ileum	A								+														1	
Intestine small, jejunum	A								+														1	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22	
Mesentery																						+	1	
Pancreas					+																		1	
Stomach					+			+	+				+								+		5	
Stomach, forestomach					+			+	+				+								+		5	
Squamous cell papilloma													X										1	
Stomach, glandular					+			+	+				+								+		5	
Tongue			+																				1	
Cardiovascular System																								
None																								
Endocrine System																								
Adrenal gland								+	+														2	
Adrenal gland, cortex								+	+														2	
Adrenal gland, medulla								+	+														2	
Islets, pancreatic													+										1	
Carcinoma													X										1	
Pituitary gland		+				+	+	+	+	+	+	+		+	+	+			+	+			13	
Pars distalis, adenoma						X	X	X	X	X	X	X		X	X	X			X	X			12	
Thyroid gland																		+					1	
Follicular cell, carcinoma																		X					1	
General Body System																								
None																								

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

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole:
0 ppm (continued)

Number of Days on Study	1 0 3	4 0 8	4 1 3	4 2 1	5 9 0	6 4 8	6 6 2	6 7 9	7 2 8	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 3 8 1	0 4 8 1	0 4 8 2	0 3 7 1	0 4 0 1	0 3 9 1	0 3 9 2	0 3 7 2	0 3 7 3	0 3 7 4	0 3 7 5	0 3 8 2	0 3 8 3	0 3 8 4	0 3 8 5	0 3 9 3	0 3 9 4	0 3 9 5	0 4 0 2	0 4 0 3	0 4 0 4	0 4 0 5	**Total Tissues/ Tumors**
Genital System																							
Clitoral gland											+									+	+		3
Adenoma																				X			1
Carcinoma											X										X		2
Ovary				+																			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	21
Polyp stromal																	X				X		2
Hematopoietic System																							
Lymph node						+	+	+	+	+		+	+	+	+	+	+	+	+		+		14
Lymph node, mandibular						+			+				+	+	+		+	+					7
Lymph node, mesenteric								+	+														2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Thymus									+														1
Integumentary System																							
Mammary gland			+			+	+	+	+	+	+		+	+	+	+	+		+		+		14
Fibroadenoma			X				X		X		X		X			X	X						7
Fibroadenoma, multiple										X													1
Skin					+																		1
Head, squamous cell carcinoma, deep invasion					X																		1
Musculoskeletal System																							
Bone					+				+														2
Skeletal muscle		+																					1
Hindlimb, rhabdomyosarcoma		X																					1
Nervous System																							
Brain				+		+		+	+							+							5
Glioma malignant				X																			1
Respiratory System																							
Lung	+	+																			+		3
Special Senses System																							
Eye							+																1

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 0 ppm (continued)

Number of Days on Study	1 0 3	4 0 8	4 1 3	4 2 1	5 9 0	6 4 8	6 6 2	6 7 9	7 2 8	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 3 8 1	0 4 8 1	0 4 8 2	0 3 7 1	0 4 0 1	0 3 9 1	0 3 9 2	0 3 7 2	0 3 7 3	0 3 7 4	0 3 7 5	0 3 8 2	0 3 8 3	0 3 8 4	0 3 8 5	0 3 9 3	0 3 9 4	0 3 9 5	0 4 0 2	0 4 0 3	0 4 0 4	0 4 0 5	**Total Tissues/ Tumors**
Urinary System																							
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Ureter	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	20
Systemic Lesions																							
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	22
Leukemia mononuclear								X	X					X									3

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm

Number of Days on Study	3 1 1	3 5 1	4 2 1	4 2 1	4 2 4	4 5 2	4 7 6	4 7 7	5 0 4	5 5 2	6 0 1	6 3 2	6 3 9	6 3 9	6 6 2	6 6 8	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 6 1 1	0 6 1 2	0 6 1 3	0 6 4 1	0 6 3 1	0 6 3 2	0 6 2 1	0 6 2 2	0 6 4 2	0 6 4 3	0 6 4 4	0 6 3 3	0 6 1 4	0 6 3 4	0 6 1 5	0 6 2 3	0 6 2 4	0 6 2 5	0 6 3 5	0 6 4 5	**Total Tissues/ Tumors**
Alimentary System																					
Intestine large	+							+		+					+	+					5
Intestine large, cecum	+							+		+					+	+					5
Intestine large, colon	+							+		+					+	+					5
Polyp adenomatous	X							X							X						3
Polyp adenomatous, multiple																X					1
Intestine large, rectum	+							+		+					+	+					5
Polyp adenomatous, multiple										X											1
Intestine small								+								+					2
Intestine small, duodenum								+								+					2
Intestine small, ileum								+								+					2
Intestine small, jejunum								+								+					2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Mesentery									+						+						2
Stomach	+		+		+			+			+	+	+			+	+				9
Stomach, forestomach	+		+		+			+			+	+	+			+	+				9
Squamous cell papilloma					X						X					X	X				4
Stomach, glandular	+		+		+			+			+	+	+			+	+				9
Cardiovascular System																					
Heart			+				+														2
Endocrine System																					
Pituitary gland					+	+							+		+	+	+	+		+	8
Pars distalis, adenoma													X		X			X		X	4
Thyroid gland																				+	1
Follicular cell, carcinoma																				X	1
General Body System																					
None																					
Genital System																					
Clitoral gland				+		+			+								+			+	5
Carcinoma																				X	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Polyp stromal							X							X							2

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	3 1 1	3 5 9	4 2 1	4 2 1	4 2 4	4 5 2	4 7 6	4 7 7	5 0 4	5 5 2	6 0 1	6 3 2	6 3 9	6 3 9	6 6 2	6 6 8	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 6 1 1	0 6 1 2	0 6 1 3	0 6 4 1	0 6 3 1	0 6 3 2	0 6 2 1	0 6 2 2	0 6 4 2	0 6 4 3	0 6 4 4	0 6 3 3	0 6 1 4	0 6 3 4	0 6 1 5	0 6 2 3	0 6 2 4	0 6 2 5	0 6 3 5	0 6 4 5	**Total Tissues/ Tumors**
Hematopoietic System																					
Lymph node		+		+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	16
Lymph node, mandibular								+												+	2
Lymph node, mesenteric								+													1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Integumentary System																					
Mammary gland									+		+			+			+		+	+	5
Adenoma																				X	1
Fibroadenoma																		X			1
Fibroadenoma, multiple															X					X	2
Musculoskeletal System																					
Bone									+								+	+			3
Nervous System																					
Brain	+		+																		2
Ependymoma malignant	X																				1
Respiratory System																					
Lung																	+				1
Special Senses System																					
None																					
Urinary System																					
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Ureter	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	17
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20
Leiomyosarcoma							X														1
Sarcoma									X												1
Transitional epithelium, carcinoma		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	18
Transitional epithelium, papilloma									X												1

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 6,000 ppm (continued)

Number of Days on Study	3 1 1	3 5 9	4 2 1	4 2 1	4 2 4	4 5 2	4 7 6	4 7 7	5 0 4	5 5 2	6 0 1	6 3 2	6 3 9	6 3 9	6 6 2	6 6 8	7 2 9	7 2 9	7 2 9	7 2 9	
Carcass ID Number	0 6 1 1	0 6 1 2	0 6 1 3	0 6 4 1	0 6 3 1	0 6 3 2	0 6 2 1	0 6 2 2	0 6 4 2	0 6 4 3	0 6 4 4	0 6 3 3	0 6 1 4	0 6 3 4	0 6 1 5	0 6 2 3	0 6 2 4	0 6 2 5	0 6 3 5	0 6 4 5	Total Tissues/ Tumors
Systemic Lesions																					
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm

Number of Days on Study	0 4 8	0 8 4	2 1 9	2 2 1	2 3 3	2 3 9	2 4 5	2 4 7	2 4 7	2 4 8	2 6 2	2 6 5	2 6 8	2 6 8	2 8 1	2 8 4	2 9 8	3 0 3	3 0 7	3 0 7	3 0 9	3 0 9	3 1 7	3 2 4	3 2 7
Carcass ID Number	0 5 1 1	0 6 0 1	0 5 1 2	0 5 1 3	0 5 8 1	0 5 1 4	0 5 8 2	0 4 9 1	0 5 8 3	0 5 2 1	0 5 8 4	0 5 9 1	0 5 2 2	0 5 2 3	0 6 0 2	0 5 2 4	0 6 0 3	0 5 2 5	0 5 2 1	0 5 1 5	0 4 9 2	0 6 0 4	0 5 9 2	0 4 9 3	0 5 0 2
Alimentary System																									
Intestine large					+				+	+		+		+	+		+	+	+	+		+	+	+	
Intestine large, cecum					+				+	+		+		+	+		+	+	+	+		+	+	+	
Intestine large, colon					+				+	+		+		+	+		+	+	+	+		+	+	+	
Carcinoma																							X		
Polyp adenomatous										X							X		X			X	X		
Polyp adenomatous, multiple					X									X				X						X	
Intestine large, rectum					+				+	+		+		+	+		+	+	+	+		+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, urinary bladder																								X	
Mesentery																				+			+		
Sarcoma, metastatic, multiple, urinary bladder																				X					
Squamous cell carcinoma, metastatic, urinary bladder																								X	
Pancreas																+				+			+		
Sarcoma, metastatic, urinary bladder																				X					
Squamous cell carcinoma, metastatic, urinary bladder																								X	
Stomach							+												+	+			+	+	
Stomach, forestomach							+												+	+			+	+	
Squamous cell carcinoma, metastatic, urinary bladder																								X	
Squamous cell papilloma							X																		X
Stomach, glandular							+												+	+			+	+	
Serosa, sarcoma, metastatic, urinary bladder																				X					
Cardiovascular System																									
None																									
Endocrine System																									
Adrenal gland																							+		
Adrenal gland, cortex																							+		
Squamous cell carcinoma, metastatic, urinary bladder																							X		
Adrenal gland, medulla																							+		

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	3 3 3 3 3 3 3 4 4 3 3 3 4 4 4 4 0 2 3 6 6 0 5 5 6 8 5	
Carcass ID Number	0 0 0 0 0 0 0 0 0 4 5 6 4 5 5 5 5 5 9 0 0 9 9 9 9 0 0 4 3 5 5 3 4 5 4 5	**Total Tissues/ Tumors**
Alimentary System		
Intestine large	+ + + + + + + +	21
Intestine large, cecum	+ + + + + + + +	21
Intestine large, colon	+ + + + + + + +	21
Carcinoma	X	2
Polyp adenomatous		5
Polyp adenomatous, multiple	X X X X X X X X	12
Intestine large, rectum	+ + + + + + + +	21
Liver	+ + + + + + + + +	34
Squamous cell carcinoma, metastatic, urinary bladder		1
Mesentery		2
Sarcoma, metastatic, multiple, urinary bladder		1
Squamous cell carcinoma, metastatic, urinary bladder		1
Pancreas	+	4
Sarcoma, metastatic, urinary bladder		1
Squamous cell carcinoma, metastatic, urinary bladder		1
Stomach	+ + +	8
Stomach, forestomach	+ + +	8
Squamous cell carcinoma, metastatic, urinary bladder		1
Squamous cell papilloma	X X	4
Stomach, glandular	+ + +	8
Serosa, sarcoma, metastatic, urinary bladder		1
Cardiovascular System		
None		
Endocrine System		
Adrenal gland		1
Adrenal gland, cortex		1
Squamous cell carcinoma, metastatic, urinary bladder		1
Adrenal gland, medulla		1

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	0 4 8	0 8 4	2 1 9	2 2 1	2 3 3	2 3 9	2 4 5	2 4 7	2 4 7	2 4 8	2 6 2	2 6 5	2 6 8	2 6 8	2 8 1	2 8 4	2 9 8	3 0 3	3 0 7	3 0 7	3 0 9	3 0 9	3 1 7	3 2 4	3 2 7
Carcass ID Number	0 5 1 1	0 6 0 1	0 5 1 2	0 5 1 3	0 5 8 1	0 5 1 4	0 5 8 2	0 4 9 1	0 5 8 3	0 5 2 1	0 5 8 4	0 5 9 1	0 5 2 2	0 5 2 3	0 6 0 2	0 5 2 4	0 6 0 3	0 5 2 5	0 5 0 1	0 5 1 5	0 4 9 2	0 6 0 4	0 5 9 2	0 4 9 3	0 5 0 2
General Body System																									
None																									
Genital System																									
Clitoral gland																									
Ovary																								+	
Squamous cell carcinoma, metastatic, urinary bladder																								X	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, urinary bladder																								X	
Cervix, carcinoma, metastatic, urinary bladder						X																			
Cervix, leiomyosarcoma												X													
Hematopoietic System																									
Lymph node			+		+			+		+	+				+		+							+	
Iliac, squamous cell carcinoma, metastatic, urinary bladder																								X	
Lymph node, mesenteric																								+	
Squamous cell carcinoma, metastatic, urinary bladder																								X	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, squamous cell carcinoma, metastatic, urinary bladder																								X	
Thymus					+		+																	+	
Squamous cell carcinoma, metastatic, urinary bladder																								X	
Integumentary System																									
Skin																									
Musculoskeletal System																									
None																									
Nervous System																									
None																									

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	3 3 3 3 3 3 3 4 4 3 3 3 4 4 4 4 0 2 3 6 6 0 5 5 6 8 5	
Carcass ID Number	0 0 0 0 0 0 0 0 0 4 5 6 4 5 5 5 5 5 9 0 0 9 9 9 9 0 0 4 3 5 5 3 4 5 4 5	Total Tissues/ Tumors
General Body System		
None		
Genital System		
Clitoral gland	+	1
Ovary		1
Squamous cell carcinoma, metastatic, urinary bladder		1
Uterus	+ + + + + + + + +	34
Squamous cell carcinoma, metastatic, urinary bladder		1
Cervix, carcinoma, metastatic, urinary bladder		1
Cervix, leiomyosarcoma		1
Hematopoietic System		
Lymph node	+ + + +	12
Iliac, squamous cell carcinoma, metastatic, urinary bladder		1
Lymph node, mesenteric	+	2
Squamous cell carcinoma, metastatic, urinary bladder		1
Spleen	+ + + + + + + + +	34
Capsule, squamous cell carcinoma, metastatic, urinary bladder		1
Thymus		3
Squamous cell carcinoma, metastatic, urinary bladder		1
Integumentary System		
Skin	+	1
Musculoskeletal System		
None		
Nervous System		
None		

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	0 4 8	0 8 4	2 1 9	2 2 1	2 3 3	2 3 9	2 4 5	2 4 7	2 4 7	2 4 8	2 6 2	2 6 5	2 6 8	2 6 8	2 8 1	2 8 4	2 9 8	3 0 3	3 0 7	3 0 7	3 0 9	3 0 9	3 1 7	3 2 4	3 2 7
Carcass ID Number	0 5 1 1	0 6 0 1	0 5 1 2	0 5 1 3	0 5 8 1	0 5 1 4	0 5 8 2	0 4 9 1	0 5 8 3	0 5 2 1	0 5 8 1	0 5 9 4	0 5 2 1	0 5 2 3	0 6 2 2	0 5 0 4	0 6 2 4	0 5 0 3	0 5 2 5	0 5 0 1	0 5 1 5	0 4 9 2	0 6 0 4	0 5 9 2	0 4 9 3	0 5 0 2
Respiratory System																									
Lung																								+	
Squamous cell carcinoma, metastatic, urinary bladder																								X	
Special Senses System																									
Eye												+													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, urinary bladder																								X	
Transitional epithelium, carcinoma																				X					
Transitional epithelium, papilloma																									
Ureter	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																						X			
Leiomyosarcoma																									
Sarcoma									X	X			X	X		X					X				
Squamous cell carcinoma																								X	
Squamous cell papilloma				X																					
Squamous cell papilloma, multiple												X													
Transitional epithelium, carcinoma			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transitional epithelium, papilloma, multiple												X													
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE F2e
Individual Animal Tumor Pathology of Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole: 18,000 ppm (continued)

Number of Days on Study	3 3 3 3 3 3 3 4 4 3 3 3 4 4 4 4 0 2 3 6 6 0 5 5 6 8 5	
Carcass ID Number	0 0 0 0 0 0 0 0 0 4 5 6 4 5 5 5 5 5 9 0 0 9 9 9 9 0 0 4 3 5 5 3 4 5 4 5	**Total Tissues/ Tumors**
Respiratory System		
Lung	+	2
Squamous cell carcinoma, metastatic, urinary bladder		1
Special Senses System		
Eye		1
Urinary System		
Kidney	+ + + + + + + + +	34
Squamous cell carcinoma, metastatic, urinary bladder		1
Transitional epithelium, carcinoma		1
Transitional epithelium, papilloma	X	1
Ureter	+ + + + + + + + +	33
Urinary bladder	+ + + + + + + + +	34
Fibrosarcoma		1
Leiomyosarcoma	X X	2
Sarcoma	X X X	9
Squamous cell carcinoma		1
Squamous cell papilloma	X	2
Squamous cell papilloma, multiple	X	2
Transitional epithelium, carcinoma	X X X X X X X X X	32
Transitional epithelium, papilloma, multiple		1
Systemic Lesions		
Multiple organs	+ + + + + + + + +	34

TABLE F3
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole

	0 ppm	6,000 ppm	18,000 ppm
Clitoral Gland: Carcinoma			
Overall rate[a]	2/3 (67%)	1/5 (20%)	0/1 (0%)
Adjusted rate[b]	66.7%	50.0%	0.0%
Terminal rate[c]	2/3 (67%)	1/2 (50%)	0/0 (0%)
First incidence (days)	728 (T)	728 (T)	–[e]
Life table test[d]	P=0.909N	P=0.691N	–
Logistic regression test[d]	P=0.909N	P=0.691N	–
Cochran-Armitage test[d]	P=0.295N		
Fisher exact test[d]		P=0.286N	P=0.500N
Clitoral Gland: Adenoma or Carcinoma			
Overall rate	3/3 (100%)	1/5 (20%)	0/1 (0%)
Adjusted rate	100.0%	50.0%	0.0%
Terminal rate	3/3 (100%)	1/2 (50%)	0/0 (0%)
First incidence (days)	728 (T)	728 (T)	–
Life table test	P=0.793N	P=0.419N	–
Logistic regression test	P=0.793N	P=0.419N	–
Cochran-Armitage test	P=0.116N		
Fisher exact test		P=0.071N	P=0.250N
Intestine Large (Colon): Carcinoma			
Overall rate	0/22 (0%)	0/20 (0%)	2/34 (6%)
Adjusted rate	0.0%	0.0%	19.8%
Terminal rate	0/14 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	–	–	317
Life table test	P=0.025	–	P=0.095
Logistic regression test	P=0.354	–	P=0.565
Cochran-Armitage test	P=0.164		
Fisher exact test		–	P=0.364
Intestine Large (Colon): Adenomatous Polyp			
Overall rate	0/22 (0%)	4/20 (20%)	17/34 (50%)
Adjusted rate	0.0%	41.5%	100.0%
Terminal rate	0/14 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	–	311	233
Life table test	P<0.001	P=0.014	P<0.001
Logistic regression test	P=0.002	P=0.064	P=0.002
Cochran-Armitage test	P<0.001		
Fisher exact test		P=0.043	P<0.001
Intestine Large (Rectum): Adenomatous Polyp			
Overall rate	0/22 (0%)	1/20 (5%)	0/34 (0%)
Adjusted rate	0.0%	9.1%	0.0%
Terminal rate	0/14 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	–	552	–
Life table test	P=0.783	P=0.402	–
Logistic regression test	P=0.907N	P=0.508	–
Cochran-Armitage test	P=0.619N		
Fisher exact test		P=0.476	–

TABLE F3
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Mammary Gland: Fibroadenoma or Adenoma			
Overall rate	8/22 (36%)	3/20 (15%)	0/34 (0%)
Adjusted rate	49.1%	58.3%	0.0%
Terminal rate	6/14 (43%)	2/4 (50%)	0/0 (0%)
First incidence (days)	413	662	–
Life table test	P=0.753	P=0.598	P=0.983N
Logistic regression test	P=0.362N	P=0.361N	P=0.364N
Cochran-Armitage test	P<0.001N		
Fisher exact test		P=0.110N	P<0.001N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rate	12/13 (92%)	4/8 (50%)	0/0 (0%)
Adjusted rate	100.0%	76.2%	0.0%
Terminal rate	9/9 (100%)	2/3 (67%)	0/0 (0%)
First incidence (days)	648	639	–
Life table test	P=0.812N	P=0.661N	–
Logistic regression test	P=0.296N	P=0.097N	–
Cochran-Armitage test	P=0.124N		
Fisher exact test		P=0.047N	P=1.000N
Skin: Squamous Cell Carcinoma			
Overall rate	1/22 (5%)	0/20 (0%)	0/34 (0%)
Adjusted rate	5.6%	0.0%	0.0%
Terminal rate	0/14 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	590	–	–
Life table test	P=0.910N	P=0.617N	–
Logistic regression test	P=0.555N	P=0.512N	P=0.897N
Cochran-Armitage test	P=0.321N		
Fisher exact test		P=0.524N	P=0.393N
Stomach (Forestomach): Squamous Cell Papilloma			
Overall rate	1/22 (5%)	4/20 (20%)	4/34 (12%)
Adjusted rate	7.1%	49.4%	100.0%
Terminal rate	1/14 (7%)	1/4 (25%)	0/0 (0%)
First incidence (days)	728 (T)	424	245
Life table test	P<0.001	P=0.024	P=0.003
Logistic regression test	P=0.129	P=0.099	P=0.279
Cochran-Armitage test	P=0.440		
Fisher exact test		P=0.144	P=0.340
Urinary Bladder (Transitional Epithelium): Papilloma			
Overall rate	0/20 (0%)	1/20 (5%)	1/34 (3%)
Adjusted rate	0.0%	8.3%	4.3%
Terminal rate	0/12 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	–	504	265
Life table test	P=0.187	P=0.419	P=0.518
Logistic regression test	P=0.791	P=0.530	P=0.871
Cochran-Armitage test	P=0.565		
Fisher exact test		P=0.500	P=0.630

TABLE F3
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Urinary Bladder (Transitional Epithelium): Carcinoma			
Overall rate	0/20 (0%)	18/20 (90%)	32/34 (94%)
Adjusted rate	0.0%	100.0%	100.0%
Terminal rate	0/12 (0%)	4/4 (100%)	0/0 (0%)
First incidence (days)	–	359	219
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
Urinary Bladder: Leiomyosarcoma			
Overall rate	0/20 (0%)	1/20 (5%)	2/34 (6%)
Adjusted rate	0.0%	7.1%	22.2%
Terminal rate	0/12 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	–	476	333
Life table test	P=0.009	P=0.450	P=0.074
Logistic regression test	P=0.506	P=0.529	P=0.546
Cochran-Armitage test	P=0.316		
Fisher exact test		P=0.500	P=0.392
Urinary Bladder: Sarcoma			
Overall rate	0/20 (0%)	1/20 (5%)	9/34 (26%)
Adjusted rate	0.0%	8.3%	100.0%
Terminal rate	0/12 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	–	504	248
Life table test	P<0.001	P=0.419	P<0.001
Logistic regression test	P=0.044	P=0.530	P=0.079
Cochran-Armitage test	P=0.003		
Fisher exact test		P=0.500	P=0.010
Urinary Bladder: Squamous Cell Papilloma			
Overall rate	0/20 (0%)	0/20 (0%)	4/34 (12%)
Adjusted rate	0.0%	0.0%	35.2%
Terminal rate	0/12 (0%)	0/4 (0%)	0/0 (0%)
First incidence (days)	–	–	221
Life table test	P=0.003	–	P=0.019
Logistic regression test	P=0.223	–	P=0.407
Cochran-Armitage test	P=0.041		
Fisher exact test		–	P=0.147
Uterus: Stromal Polyp			
Overall rate	2/22 (9%)	2/20 (10%)	0/34 (0%)
Adjusted rate	14.3%	18.8%	0.0%
Terminal rate	2/14 (14%)	0/4 (0%)	0/0 (0%)
First incidence (days)	728 (T)	476	–
Life table test	P=0.590	P=0.369	–
Logistic regression test	P=0.667N	P=0.599	–
Cochran-Armitage test	P=0.090N		
Fisher exact test		P=0.659	P=0.150N

TABLE F3
Statistical Analysis of Primary Neoplasms in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
All Organs: Mononuclear Cell Leukemia			
Overall rate	3/22 (14%)	0/20 (0%)	0/34 (0%)
Adjusted rate	20.0%	0.0%	0.0%
Terminal rate	2/14 (14%)	0/4 (0%)	0/0 (0%)
First incidence (days)	679	–	–
Life table test	P=0.689N	P=0.413N	–
Logistic regression test	P=0.565N	P=0.300N	P=1.000N
Cochran-Armitage test	P=0.043N		
Fisher exact test		P=0.134N	P=0.056N
All Organs: Benign Neoplasms			
Overall rate	18/22 (82%)	14/20 (70%)	22/34 (65%)
Adjusted rate	89.9%	92.8%	100.0%
Terminal rate	12/14 (86%)	3/4 (75%)	0/0 (0%)
First incidence (days)	408	311	221
Life table test	P<0.001	P=0.030	P<0.001
Logistic regression test	P=0.198	P=0.473N	P=0.329
Cochran-Armitage test	P=0.136N		
Fisher exact test		P=0.296N	P=0.139N
All Organs: Malignant Neoplasms			
Overall rate	10/22 (45%)	20/20 (100%)	32/34 (94%)
Adjusted rate	54.6%	100.0%	100.0%
Terminal rate	6/14 (43%)	4/4 (100%)	0/0 (0%)
First incidence (days)	408	311	219
Life table test	P<0.001	P<0.001	P<0.001
Logistic regression test	P<0.001	P<0.001	P<0.001
Cochran-Armitage test	P<0.001		
Fisher exact test		P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms			
Overall rate	20/22 (91%)	20/20 (100%)	32/34 (94%)
Adjusted rate	95.2%	100.0%	100.0%
Terminal rate	13/14 (93%)	4/4 (100%)	0/0 (0%)
First incidence (days)	408	311	219
Life table test	P<0.001	P=0.002	P<0.001
Logistic regression test	P=0.041	P=0.205	P=0.037
Cochran-Armitage test	P=0.590		
Fisher exact test		P=0.268	P=0.515

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

TABLE F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Feed Study of o-Nitroanisole[a]

	0 ppm	6,000 ppm	18,000 ppm
Disposition Summary			
Animals initially in study	60	60	60
3-Month interim evaluation	10	10	10
6-Month interim evaluation	10	10	10
9-Month interim evaluation	10	10	6
15-Month interim evaluation	8	10	0
Early deaths			
Moribund	6	12	25
Natural deaths	2	4	9
Survivors			
Terminal sacrifice	14	4	0
Animals examined microscopically	60	60	60
3-Month Interim Evaluation			
Alimentary System			
Liver	(10)	(10)	(10)
Hepatodiaphragmatic nodule	1 (10%)		1 (10%)
Vacuolization cytoplasmic	1 (10%)		1 (10%)
Hepatocyte, hypertrophy			10 (100%)
Hepatocyte, necrosis, multifocal	1 (10%)	3 (30%)	10 (100%)
Hepatocyte, vacuolization cytoplasmic			1 (10%)
Hepatocyte, vacuolization cytoplasmic, multifocal			1 (10%)
Hepatocyte, Kupffer cell, pigmentation			10 (100%)
Kupffer cell, pigmentation, multifocal		1 (10%)	
Cardiovascular System			
None			
Endocrine System			
None			
General Body System			
None			
Genital System			
Uterus	(10)	(10)	(10)
Atrophy		10 (100%)	10 (100%)

TABLE F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
3-Month Interim Evaluation (continued)			
Hematopoietic System			
Spleen	(10)	(10)	(10)
Congestion		10 (100%)	10 (100%)
Depletion lymphoid			10 (100%)
Pigmentation	10 (100%)	10 (100%)	10 (100%)
Capsule, hypertrophy		10 (100%)	10 (100%)
Capsule, inflammation, chronic		6 (60%)	9 (90%)
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
None			
Special Senses System			
None			
Urinary System			
Kidney	(10)	(10)	(10)
Corticomedullary junction, mineralization	9 (90%)	9 (90%)	9 (90%)
Renal tubule, pigmentation		10 (100%)	10 (100%)
Urinary bladder	(10)	(10)	(10)
Inflammation, subacute			8 (80%)
Metaplasia, squamous			10 (100%)
Transitional epithelium, hyperplasia		8 (80%)	10 (100%)
Wall, proliferation connective tissue			6 (60%)
6-Month Interim Evaluation			
Alimentary System			
Liver	(10)	(10)	(10)
Hepatodiaphragmatic nodule		1 (10%)	
Inflammation, granulomatous, multifocal	1 (10%)		
Inflammation, granulomatous, multiple	4 (40%)		5 (50%)
Hepatocyte, hypertrophy			10 (100%)
Hepatocyte, necrosis, multifocal			10 (100%)
Hepatocyte, vacuolization cytoplasmic			1 (10%)
Hepatocyte, Kupffer cell, pigmentation		9 (90%)	10 (100%)
Mesentery	(1)		
Fat, necrosis, focal	1 (100%)		

TABLE F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Feed Study of o-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
6-Month Interim Evaluation (continued)			
Cardiovascular System			
None			
Endocrine System			
None			
General Body System			
None			
Genital System			
Ovary		(1)	
Cyst		1 (100%)	
Uterus	(10)	(10)	(10)
Atrophy		10 (100%)	10 (100%)
Cervix, cyst		1 (10%)	
Hematopoietic System			
Spleen	(10)	(10)	(10)
Congestion		10 (100%)	10 (100%)
Depletion lymphoid			10 (100%)
Pigmentation	5 (50%)	10 (100%)	9 (90%)
Capsule, hypertrophy		10 (100%)	10 (100%)
Capsule, inflammation, chronic		2 (20%)	10 (100%)
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
Lung		(2)	
Infiltration cellular, lymphocyte, multifocal		2 (100%)	
Inflammation, chronic, multifocal		2 (100%)	
Special Senses System			
None			

TABLE F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
6-Month Interim Evaluation (continued)			
Urinary System			
Kidney	(10)	(10)	(10)
Corticomedullary junction, mineralization	2 (20%)		2 (20%)
Renal tubule, mineralization	3 (30%)	4 (40%)	
Renal tubule, pigmentation		10 (100%)	10 (100%)
Transitional epithelium, hyperplasia			2 (20%)
Urinary bladder	(10)	(10)	(10)
Inflammation, subacute		5 (50%)	10 (100%)
Metaplasia, squamous			10 (100%)
Transitional epithelium, hyperplasia		10 (100%)	
Transitional epithelium, metaplasia, squamous		1 (10%)	
Wall, proliferation connective tissue		2 (20%)	10 (100%)
9-Month Interim Evaluation			
Alimentary System			
Intestine large, colon			(1)
Parasite metazoan			1 (100%)
Liver	(10)	(10)	(6)
Basophilic focus	5 (50%)	2 (20%)	
Hepatodiaphragmatic nodule			1 (17%)
Inflammation, granulomatous, multiple	5 (50%)	5 (50%)	6 (100%)
Hepatocyte, Kupffer cell, pigmentation	1 (10%)	7 (70%)	6 (100%)
Mesentery		(1)	
Fat, necrosis, focal		1 (100%)	
Stomach, forestomach		(1)	
Epithelium, hyperplasia		1 (100%)	
Cardiovascular System			
None			
Endocrine System			
None			
General Body System			
None			
Genital System			
Ovary	(1)		
Cyst	1 (100%)		
Uterus	(10)	(10)	(6)
Atrophy			3 (50%)
Dilatation	1 (10%)	3 (30%)	1 (17%)

TABLE F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
9-Month Interim Evaluation (continued)			
Hematopoietic System			
Lymph node			(1)
Pancreatic, hyperplasia, lymphoid			1 (100%)
Spleen	(10)	(10)	(6)
Congestion	3 (30%)	10 (100%)	5 (83%)
Hematopoietic cell proliferation	1 (10%)	1 (10%)	5 (83%)
Hypertrophy		1 (10%)	
Pigmentation	5 (50%)	10 (100%)	4 (67%)
Capsule, hypertrophy		8 (80%)	6 (100%)
Capsule, inflammation, chronic			6 (100%)
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
None			
Special Senses System			
None			
Urinary System			
Kidney	(10)	(10)	(6)
Nephropathy, chronic	5 (50%)	3 (30%)	3 (50%)
Pelvis, inflammation, suppurative		1 (10%)	
Pelvis, mineralization	1 (10%)	1 (10%)	2 (33%)
Renal tubule, mineralization	9 (90%)	8 (80%)	4 (67%)
Renal tubule, pigmentation	6 (60%)	10 (100%)	6 (100%)
Renal tubule, regeneration		1 (10%)	
Transitional epithelium, hyperplasia		1 (10%)	1 (17%)
Ureter	(10)	(10)	(6)
Dilatation			2 (33%)
Urinary bladder	(10)	(9)	(6)
Inflammation, subacute			1 (17%)
Inflammation, suppurative			2 (33%)
Metaplasia, squamous			4 (67%)
Transitional epithelium, hyperplasia		9 (100%)	
Wall, proliferation connective tissue		1 (11%)	4 (67%)

TABLE F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
15-Month Interim Evaluation			
Alimentary System			
Liver	(8)	(9)	
Basophilic focus		1 (11%)	
Basophilic focus, multiple	6 (75%)	2 (22%)	
Inflammation, granulomatous, multiple	1 (13%)	4 (44%)	
Bile duct, hyperplasia	2 (25%)		
Hepatocyte, hypertrophy	1 (13%)		
Hepatocyte, Kupffer cell, pigmentation		2 (22%)	
Mesentery	(2)	(5)	
Fat, inflammation, chronic		4 (80%)	
Fat, necrosis, focal	2 (100%)	1 (20%)	
Cardiovascular System			
None			
Endocrine System			
None			
General Body System			
None			
Genital System			
Clitoral gland	(2)	(1)	
Duct, cyst		1 (100%)	
Ovary	(1)		
Cyst	1 (100%)		
Oviduct		(1)	
Cyst		1 (100%)	
Uterus	(8)	(10)	
Dilatation	1 (13%)	1 (10%)	
Endometrium, hyperplasia, cystic		1 (10%)	
Epithelium, hyperplasia, focal		1 (10%)	
Hematopoietic System			
Lymph node		(2)	
Mediastinal, angiectasis		1 (50%)	
Mediastinal, hyperplasia, lymphoid		1 (50%)	
Mediastinal, pigmentation		1 (50%)	
Spleen	(8)	(10)	
Congestion	4 (50%)	3 (30%)	
Hematopoietic cell proliferation	2 (25%)	8 (80%)	
Pigmentation	5 (63%)	7 (70%)	
Capsule, hypertrophy		9 (90%)	
Capsule, inflammation, chronic		1 (10%)	

TABLE F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
15-Month Interim Evaluation (continued)			
Integumentary System			
None			
Musculoskeletal System			
None			
Nervous System			
None			
Respiratory System			
None			
Special Senses System			
None			
Urinary System			
Kidney	(8)	(10)	
Nephropathy, chronic	5 (63%)	5 (50%)	
Pelvis, mineralization	1 (13%)	2 (20%)	
Proximal convoluted renal tubule, degeneration, hyaline		1 (10%)	
Renal tubule, mineralization	8 (100%)	9 (90%)	
Renal tubule, pigmentation	7 (88%)	10 (100%)	
Ureter	(7)	(10)	
Dilatation		1 (10%)	
Urinary bladder	(8)	(10)	
Inflammation, suppurative		1 (10%)	
Metaplasia, squamous		2 (20%)	
Necrosis		1 (10%)	
Transitional epithelium, hyperplasia		3 (30%)	
Wall, proliferation connective tissue		6 (60%)	
Stop-Exposure Study			
Alimentary System			
Intestine large, cecum	(1)	(5)	(21)
Ulcer			1 (5%)
Intestine large, colon	(2)	(5)	(21)
Autolysis			1 (5%)
Intussusception			1 (5%)
Necrosis			1 (5%)
Parasite metazoan			1 (5%)
Proliferation connective tissue			1 (5%)
Epithelium, hyperplasia			5 (24%)

TABLE F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study (continued)			
Alimentary System (continued)			
Intestine large, rectum	(1)	(5)	(21)
Autolysis			1 (5%)
Parasite metazoan		1 (20%)	
Liver	(22)	(20)	(34)
Basophilic focus	1 (5%)	2 (10%)	
Basophilic focus, multiple	15 (68%)	9 (45%)	
Eosinophilic focus	4 (18%)	1 (5%)	
Eosinophilic focus, multiple	1 (5%)	1 (5%)	
Hematopoietic cell proliferation	1 (5%)		
Hepatodiaphragmatic nodule	2 (9%)	3 (15%)	2 (6%)
Inflammation, granulomatous, multiple	15 (68%)	10 (50%)	28 (82%)
Mixed cell focus	4 (18%)	1 (5%)	
Vacuolization cytoplasmic	3 (14%)		
Bile duct, hyperplasia	5 (23%)	1 (5%)	1 (3%)
Hepatocyte, hypertrophy	2 (9%)	2 (10%)	2 (6%)
Hepatocyte, mitotic alteration	1 (5%)		
Hepatocyte, necrosis, multifocal			1 (3%)
Hepatocyte, Kupffer cell, pigmentation	9 (41%)	2 (10%)	34 (100%)
Mesentery	(1)	(2)	(2)
Fat, necrosis, focal	1 (100%)	2 (100%)	
Pancreas	(1)		(4)
Ectopic tissue			1 (25%)
Acinus, atrophy			1 (25%)
Stomach, forestomach	(5)	(9)	(8)
Diverticulum	1 (20%)		
Edema	1 (20%)	1 (11%)	
Ulcer	1 (20%)		
Epithelium, hyperplasia	2 (40%)	4 (44%)	1 (13%)
Stomach, glandular	(5)	(9)	(8)
Mineralization			1 (13%)
Cardiovascular System			
Heart		(2)	
Inflammation, chronic		1 (50%)	
Mineralization, multifocal		1 (50%)	
Endocrine System			
Adrenal gland, cortex	(2)		(1)
Bilateral, vacuolization cytoplasmic	1 (50%)		
Pituitary gland	(13)	(8)	
Pars distalis, cyst		1 (13%)	
Pars distalis, hemorrhage	3 (23%)		
Pars distalis, hyperplasia, focal		2 (25%)	
Thyroid gland	(1)	(1)	
C-cell, hyperplasia		1 (100%)	
General Body System			
None			

TABLE F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Feed Study of o-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study (continued)			
Genital System			
Clitoral gland	(3)	(5)	(1)
Inflammation, suppurative	1 (33%)		
Duct, cyst		5 (100%)	1 (100%)
Ovary	(1)		(1)
Cyst	1 (100%)		
Uterus	(21)	(20)	(34)
Atrophy		1 (5%)	28 (82%)
Dilatation	3 (14%)	2 (10%)	2 (6%)
Fibrosis, focal	1 (5%)		
Inflammation, suppurative	2 (10%)		
Cervix, cyst	1 (5%)		
Cervix, myometrium, hypertrophy	1 (5%)	2 (10%)	
Endometrium, hyperplasia, cystic	3 (14%)	2 (10%)	
Hematopoietic System			
Lymph node	(14)	(16)	(12)
Deep cervical, angiectasis	1 (7%)		
Iliac, hyperplasia, lymphoid		1 (6%)	7 (58%)
Mediastinal, angiectasis	2 (14%)	9 (56%)	
Mediastinal, hyperplasia, lymphoid	1 (7%)	1 (6%)	1 (8%)
Mediastinal, pigmentation	3 (21%)	2 (13%)	
Pancreatic, angiectasis	2 (14%)		
Pancreatic, pigmentation		1 (6%)	
Lymph node, mandibular	(7)	(2)	
Cyst	1 (14%)	1 (50%)	
Cyst, multiple	1 (14%)		
Hyperplasia, lymphoid	2 (29%)		
Lymph node, mesenteric	(2)	(1)	(2)
Angiectasis			1 (50%)
Spleen	(22)	(20)	(34)
Atrophy		2 (10%)	1 (3%)
Congestion	12 (55%)	7 (35%)	24 (71%)
Depletion lymphoid	4 (18%)	5 (25%)	16 (47%)
Hematopoietic cell proliferation	17 (77%)	12 (60%)	20 (59%)
Hyperplasia, histiocytic, lymphoid	1 (5%)	1 (5%)	
Hyperplasia, lymphoid		1 (5%)	1 (3%)
Pigmentation	16 (73%)	12 (60%)	15 (44%)
Capsule, hypertrophy		9 (45%)	33 (97%)
Capsule, inflammation, chronic			30 (88%)
Thymus	(1)		(3)
Atrophy			1 (33%)
Congestion			1 (33%)
Integumentary System			
Mammary gland	(14)	(5)	
Hyperplasia, lobular	8 (57%)	1 (20%)	
Duct, cyst	9 (64%)	3 (60%)	

TABLE F4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole (continued)

	0 ppm	6,000 ppm	18,000 ppm
Stop-Exposure Study (continued)			
Musculoskeletal System			
Bone	(2)	(3)	
Calvarium, hyperostosis	2 (100%)	3 (100%)	
Nervous system			
Brain	(5)	(2)	
Compression	4 (80%)		
Hydrocephalus		1 (50%)	
Respiratory System			
Lung	(3)	(1)	(2)
Congestion	1 (33%)		
Infiltration cellular, histiocyte	1 (33%)		
Alveolar epithelium, hyperplasia		1 (100%)	
Special Senses System			
Eye	(1)		(1)
Cataract	1 (100%)		
Cornea, edema			1 (100%)
Retina, degeneration	1 (100%)		
Urinary System			
Kidney	(22)	(20)	(34)
Hydronephrosis		2 (10%)	15 (44%)
Inflammation, suppurative		1 (5%)	
Nephropathy, chronic	19 (86%)	12 (60%)	3 (9%)
Bilateral, hydronephrosis		1 (5%)	3 (9%)
Papilla, necrosis		2 (10%)	2 (6%)
Pelvis, dilatation			2 (6%)
Pelvis, hemorrhage		1 (5%)	
Pelvis, inflammation, suppurative		1 (5%)	
Pelvis, mineralization	6 (27%)	4 (20%)	13 (38%)
Pelvis, necrosis			2 (6%)
Renal tubule, mineralization	17 (77%)	9 (45%)	17 (50%)
Renal tubule, pigmentation	20 (91%)	20 (100%)	34 (100%)
Renal tubule, regeneration		2 (10%)	3 (9%)
Transitional epithelium, hyperplasia		5 (25%)	16 (47%)
Ureter	(20)	(17)	(33)
Dilatation		5 (29%)	19 (58%)
Transitional epithelium, hyperplasia			2 (6%)
Urinary bladder	(20)	(20)	(34)
Hemorrhage		2 (10%)	5 (15%)
Inflammation, subacute			1 (3%)
Inflammation, suppurative		1 (5%)	8 (24%)
Metaplasia, squamous		6 (30%)	25 (74%)
Necrosis		3 (15%)	1 (3%)
Transitional epithelium, hyperplasia		4 (20%)	1 (3%)
Wall, infiltration cellular, lipocyte		3 (15%)	2 (6%)
Wall, proliferation connective tissue		11 (55%)	20 (59%)

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

APPENDIX G
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). *o*-Nitroanisole was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA100, TA1535, TA1537, TA98, and TA97) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation continued for an additional 48 hours.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of *o*-nitroanisole. High dose was limited by toxicity. All positive assays were repeated under the conditions which elicited the positive response.

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 which was not dose related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A negative response was obtained when no increase in revertant colonies was observed following chemical treatment.

CHINESE HAMSTER OVARY CYTOGENETICS ASSAYS

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

In the SCE test without S9, CHO cells were incubated for 26 hours with *o*-nitroanisole in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing *o*-nitroanisole was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 1.5 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 *o*-nitroanisole, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no *o*-nitroanisole and incubation proceeded for an additional 25.5 hours, with Colcemid present for the final 2 to 3 hours. Harvesting and staining was the same as for cells treated without S9.

In the chromosomal Abs test without S9, cells were incubated in McCoy's 5A medium with *o*-nitroanisole for 8 hours; Colcemid was added and incubation continued for 2 to 3 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with *o*-nitroanisole and S9 for 2 hours, after which the treatment medium was removed and the cells incubated for 9 hours in fresh medium, with Colcemid present for the final 2 to 3 hours. Cells were harvested in the same manner as for the treatment without S9.

For the SCE test, because significant chemical-induced cell cycle delay was seen at some dose levels, incubation time was lengthened at these dose levels to ensure a sufficient number of scorable cells.

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

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

Mouse Lymphoma Protocol

The experimental protocol is presented in detail by Myhr *et al.* (1985) *o*-Nitroanisole was supplied as a coded aliquot by Radian Corporation (Austin, TX). The highest dose of *o*-nitroanisole was determined by solubility or toxicity. Mouse L5178Y lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with *l*-glutamine, sodium pyruvate, pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (TFT)-resistant cells, subcultures were exposed once to medium containing THMG (thymidine, hypoxanthine, methotrexate, glycine) for 1 day, to THG for 1 day, and to normal medium for 3 to 5 days. For cloning, 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 6×10^6 cells. Incubation with *o*-nitroanisole continued for 4 hours, at which time the medium plus *o*-nitroanisole 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, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothimydine for selection of TFT-resistant cells ($TK^{-/-}$), and 600 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. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P<0.05$) for *o*-nitroanisole to be considered capable of inducing TFT resistance; a single significant response led to a "questionable" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call. An inconclusive test was one in which no significant response was observed at any of the doses tested, but, based on the relative total growth (RTG) values, it was apparent that higher doses could have been used.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr *et al.* (1985). This assay is initially performed without S9; because a clearly positive response was obtained, *o*-nitroanisole was not tested with S9.

RESULTS

o-Nitroanisole was tested in a preincubation protocol in two laboratories for induction of gene mutations in four strains of *Salmonella typhimurium* in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Table G1). In the first study (Haworth *et al.*, 1983), concentrations of 33 to 2,150 μg/plate were tested in strains TA100, TA1535, TA1537, and TA98; positive responses were observed only in strain TA100, with and without S9. In the second study, strains TA100, TA1535, TA97, and TA98 were tested (top dose, 3,333 μg/plate); positive responses were again noted for TA100, with and without S9, and also for TA1535, without S9. Both these strains mutate via base-substitution. In cytogenetic tests with CHO cells, *o*-nitroanisole induced SCEs with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table G2; Galloway *et al.*, 1987); at higher doses (above 123 μg/mL without S9, and above 811 μg/mL with S9), delayed harvest was used to offset *o*-nitroanisole-induced cell cycle delay and allow for accumulation of sufficient metaphases for analysis. In the CHO cell chromosomal Abs test (Table G3; Galloway *et al.*, 1987), *o*-nitroanisole induced a significant increase in Abs at the highest dose (1,060 μg/mL) tested in the presence of S9 activation; this response was due mainly to an increase in breaks which occurred in the long arm of the X chromosome. No increase in Abs was observed in either of the two trials conducted without S9. *o*-Nitroanisole was positive in the mouse lymphoma L5178Y cell assay for induction of TFT resistance in the absence of S9 activation; it was not tested with S9 (Table G4). The first of three trials was considered inconclusive because a negative response was obtained at the highest nonlethal dose tested, but the relative total growth was not markedly decreased. In the remaining two trials, a dose-related increase in TFT-resistant colonies was observed and significant responses occurred at doses where the relative total growth was depressed below 50%.

TABLE G1
Mutagenicity of *o*-Nitroanisole 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
Study performed at EG&G Mason Research Institute							
TA100	0	163 ± 8.5	132 ± 6.3	135 ± 6.1	139 ± 9.8	146 ± 16.1	138 ± 2.1
	33	162 ± 9.3	129 ± 3.8	168 ± 10.7	151 ± 8.4	153 ± 11.1	144 ± 14.3
	100	176 ± 7.2	152 ± 3.3	194 ± 5.0	221 ± 3.5	143 ± 6.3	144 ± 6.1
	333	233 ± 15.0	205 ± 6.1	296 ± 4.7	318 ± 22.5	219 ± 15.0	196 ± 13.7
	666		319 ± 5.5		401 ± 9.5		299 ± 5.5
	1,000	371 ± 6.7	340 ± 17.7	276 ± 47.4	314 ± 21.7	310 ± 7.2	310 ± 9.3
	1,200		Toxic		98 ± 27.3[c]		295 ± 19.5[c]
	1,500		Toxic		50 ± 3.5[c]		262 ± 14.5[c]
	2,150	Toxic		Toxic		Toxic	
Trial summary		Weakly Positive	Positive	Weakly Positive	Positive	Weakly Positive	Positive
Positive control[d]		1,196 ± 18.3	1,159 ± 33.4	1,245 ± 33.5	1,428 ± 64.4	1,114 ± 28.3	1,372 ± 70.4

Strain	Dose (μg/plate)	Revertants/plate -S9	+10% hamster S9	+10% rat S9
TA1535	0	39 ± 3.0	15 ± 3.2	11 ± 2.4
	33	34 ± 6.1	13 ± 0.9	12 ± 1.8
	100	33 ± 5.0	11 ± 1.2	9 ± 1.8
	333	43 ± 6.4	17 ± 0.9	13 ± 1.2
	1,000	56 ± 4.4	9 ± 0.6	20 ± 4.5
	2,150	Toxic	Toxic	Toxic
Trial summary		Negative	Negative	Negative
Positive control		919 ± 13.0	75 ± 5.5	69 ± 2.6
TA1537	0	7 ± 0.9	12 ± 2.8	10 ± 2.2
	33	7 ± 0.0	7 ± 2.6	13 ± 2.3
	100	8 ± 0.3	6 ± 1.7	7 ± 1.5
	333	7 ± 1.5	9 ± 2.5	7 ± 0.9
	1,000	5 ± 1.0	4 ± 0.7	8 ± 1.8
	2,150	Toxic	Toxic	Toxic
Trial summary		Negative	Negative	Negative
Positive control		376 ± 48.1	80 ± 7.0	80 ± 4.1
TA98	0	19 ± 2.2	32 ± 1.2	33 ± 4.3
	33	22 ± 2.3	35 ± 2.3	32 ± 6.7
	100	20 ± 4.3	34 ± 3.6	31 ± 1.9
	333	22 ± 2.0	44 ± 1.8	31 ± 0.3
	1,000	31 ± 4.5	44 ± 2.6	35 ± 1.2
	2,150	Toxic	Toxic	24 ± 0.3[c]
Trial summary		Negative	Negative	Negative
Positive control		1,484 ± 36.7	944 ± 39.0	929 ± 26.5

TABLE G1
Mutagenicity of *o*-Nitroanisole in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -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
Study performed at SRI, International							
TA100	0	128 ± 12.0	127 ± 5.1	128 ± 11.8	126 ± 5.2	134 ± 3.5	112 ± 14.4
	10			128 ± 11.0	121 ± 8.8		
	33	133 ± 21.5	127 ± 8.9	159 ± 4.6	158 ± 13.3	122 ± 28.9	148 ± 5.5
	100	125 ± 25.4	129 ± 15.4	227 ± 17.6	197 ± 17.8	147 ± 1.8	153 ± 11.1
	166				268 ± 15.4		
	333	189 ± 15.7	182 ± 15.8	122 ± 12.0	113 ± 18.8	233 ± 3.5	247 ± 18.5
	1,000	331 ± 9.1	336 ± 4.5	53 ± 51.5		386 ± 35.7	263 ± 2.9
	1,666		519 ± 27.6				117 ± 16.2
	3,333	297 ± 32.2[c]				35 ± 16.8[c]	
Trial summary		Positive	Positive	Equivocal	Positive	Positive	Positive
Positive control		584 ± 3.0	625 ± 16.8	2,032 ± 10.1	1,711 ± 7.8	810 ± 20.5	1,951 ± 28.9
TA1535	0	34 ± 2.5	22 ± 4.1	9 ± 2.0	10 ± 1.2	10 ± 3.6	10 ± 2.3
	10			7 ± 2.3	7 ± 0.9		
	33	36 ± 8.7		8 ± 2.3	7 ± 1.2	7 ± 0.7	
	100	32 ± 1.5	24 ± 2.6	11 ± 2.3	8 ± 0.0	8 ± 1.2	8 ± 1.2
	333	42 ± 0.9	24 ± 2.2	8 ± 1.0	6 ± 1.2	11 ± 1.5	10 ± 1.5
	1,000	58 ± 2.9	36 ± 3.5	6 ± 4.2	1 ± 0.7	13 ± 1.3	8 ± 3.6
	1,666		51 ± 4.1				7 ± 0.7
	3,333	66 ± 7.8	33 ± 4.6			3 ± 2.2	2 ± 1.2
Trial summary		Weakly Positive	Weakly Positive	Negative	Negative	Negative	Negative
Positive control		459 ± 20.4	694 ± 8.6	486 ± 54.7	704 ± 35.4	193 ± 8.9	540 ± 12.0

Strain	Dose (μg/plate)	Revertants/plate -S9	+10% hamster S9	+10% rat S9
TA97	0	185 ± 5.8	185 ± 11.7	186 ± 12.0
	10		191 ± 4.7	
	33	167 ± 11.8	199 ± 10.0	183 ± 9.1
	100	178 ± 12.0	193 ± 10.9	190 ± 4.0
	333	188 ± 9.3	217 ± 13.3	206 ± 1.0
	1,000	218 ± 5.3	227 ± 12.3	203 ± 4.9
	3,333	116 ± 40.2		179 ± 4.9
Trial summary		Negative	Negative	Negative
Positive control		2,023 ± 223.0	1,241 ± 77.4	1,751 ± 209.0

TABLE G1
Mutagenicity of *o*-Nitroanisole in *Salmonella typhimurium* (continued)

Strain	Dose (μg/plate)	Revertants/plate -S9	Revertants/plate +10% hamster S9	Revertants/plate +10% rat S9
Study performed at SRI, International				
TA98	0	22 ± 5.0	32 ± 2.5	35 ± 4.6
	10		25 ± 6.1	
	33	16 ± 3.5	25 ± 3.9	21 ± 2.4
	100	17 ± 0.7	33 ± 6.0	25 ± 3.0
	333	24 ± 4.5	31 ± 2.7	32 ± 3.5
	1,000	24 ± 1.2	6 ± 2.3	31 ± 4.4
	3,333	0 ± 0.0[c]		7 ± 1.5[c]
Trial summary		Negative	Negative	Negative
Positive control		860 ± 80.3	1,088 ± 14.9	367 ± 14.4

[a] The detailed protocol as well as the data from the EG&G Mason Research Institute study are presented in Haworth *et al.* (1983). Cells and *o*-nitroanisole or solvent (dimethylsulfoxide) were incubated in the absence of exogenous metabolic activation (-S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague-Dawley rat liver. The high dose was limited by toxicity; 0 μg/plate dose is the solvent control.

[b] Revertants are presented as mean ± standard error from three plates.

[c] Slight toxicity

[d] 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE G2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *o*-Nitroanisole[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9[c]								
Trial 1								
Summary: Weak positive								
Dimethylsulfoxide		50	1,034	487	0.47	9.7	25.5	
Mitomycin-C	0.005	50	1,046	1,819	1.73	36.4	25.5	269.23
o-Nitroanisole	12.300	50	1,044	544	0.52	10.9	25.5	10.64
	41.200	50	1,033	544	0.52	10.9	25.5	11.81
	123.000	50	1,027	667	0.64	13.3	25.5	37.90*
								P<0.001[d]
Trial 2								
Summary: Positive								
Dimethylsulfoxide		50	1,046	461	0.44	9.2	26.0	
Mitomycin-C	0.005	50	1,040	1,922	1.84	38.4	26.0	319.33
o-Nitroanisole	202.000	50	1,043	541	0.51	10.8	32.5[e]	17.69
	251.000	50	1,028	565	0.54	11.3	32.5[e]	24.71*
	301.000	50	1,042	567	0.54	11.3	32.5[e]	23.47*
	350.000	0						
								P<0.001
+S9[f]								
Trial 1								
Summary: Positive								
Dimethylsulfoxide		50	1,033	388	0.37	7.8	25.5	
Cyclophosphamide	1.500	50	1,040	1,860	1.78	37.2	25.5	376.16
o-Nitroanisole[g]	608.000	50	1,033	516	0.49	10.3	25.5	32.99*
	811.000	50	1,023	540	0.52	10.8	25.5	40.54*
	1,010.000	50	1,026	543	0.52	10.9	32.0[e]	40.90*
								P<0.001

TABLE G2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *o*-Nitroanisole (continued)

° Positive (>20% increase over solvent control)
[a] Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol and these data are presented in Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with *o*-nitroanisole or solvent (dimethylsulfoxide) as described in [c] and [f] below, and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
[b] SCEs/chromosome of culture exposed to *o*-nitroanisole relative to those of culture exposed to solvent.
[c] In the absence of S9, cells were incubated with *o*-nitroanisole or solvent for 2 hours at 37° C. Then BrdU was added and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and Colcemid was added, and incubation was continued for 1.5 hours.
[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose
[e] Because *o*-nitroanisole-induced cell cycle delay was observed, harvest time was extended to maximize the proportion of second division cells available for analysis.
[f] In the presence of S9, cells were incubated with *o*-nitroanisole or solvent for 2 hours at 37° C. The cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 25.5 hours, with Colcemid present for the final 2 to 3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.
[g] Precipitate formed at all dose levels in this trial.

TABLE G3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by *o*-Nitroanisole[a]

-S9[b]					+S9[c]				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1 – Harvest time: 11.0 hours Summary: Negative					**Trial 1** – Harvest time: 11.0 hours Summary: Weak positive				
Dimethylsulfoxide					Dimethylsulfoxide				
	100	3	0.03	3.0		100	5	0.05	5.0
						100	6	0.06	5.0
Mitomycin-C					Cyclophosphamide				
0.5	100	30	0.30	23.0	25.0	100	33	0.33	26.0
o-Nitroanisole					*o*-Nitroanisole				
216.3	100	1	0.01	1.0	519.0	100	5	0.05	5.0
432.6	100	1	0.01	1.0	742.0	100	12	0.12	11.0
618.0	100	1	0.01	1.0	1,060.0	100	55	0.55	49.0*
				P=0.868[d]					P<0.001
Trial 2 – Harvest time: 10.5 hours Summary: Negative									
Dimethylsulfoxide									
	100	3	0.03	3.0					
Mitomycin-C									
0.5	100	21	0.21	17.0					
o-Nitroanisole[e]									
655.1	100	0	0.00	0.0					
722.7	50	1	0.02	2.0					
803.4	100	1	0.01	1.0					
				P=0.366					

* Positive (P<0.05)

[a] Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations and these data are found in Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with *o*-nitroanisole or solvent (dimethylsulfoxide) as indicated in [b] and [c]. Cells were arrested in first metaphase by addition of Colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.

[b] In the absence of S9, cells were incubated with *o*-nitroanisole or solvent for 8 hours at 37° C. Cells were then washed and fresh medium containing Colcemid was added for an additional 2 to 3 hours followed by harvest.

[c] In the presence of S9, cells were incubated with *o*-nitroanisole or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 9 hours. Colcemid was added for the last 2 to 3 hours of incubation before harvest. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

[d] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

[e] Precipitate formed at all dose levels in this trial.

TABLE G4
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by *o*-Nitroanisole[a]

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction
-S9						
Trial 1						
Ethanol						
		100	94	225	75	
		115	103	198	58	
		99	103	219	74	69
Ethylmethane sulfonate (μg/mL)						
	250	88	70	819	311	
		73	50	920	420	
		103	70	1,101	356	362[c]
o-Nitroanisole (μL/mL)						
	0.0125	94	114	158	56	
		111	101	171	52	
		116	127	136	39	49
	0.025	114	124	135	39	
		79	83	106	45	
		101	99	173	57	47
	0.05	99	117	158	53	
		92	96	171	62	
		105	102	145	46	54
	0.1	114	116	179	52	
	0.2	88	73	195	74	
	0.3	92	42	219	79	
		94	59	229	81	
		108	62	261	81	81
	0.5	Lethal				
		Lethal				
		Lethal				

TABLE G4
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by o-Nitroanisole (continued)

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
Trial 2						
Ethanol						
		61	78	90	49	
		72	109	77	36	
		68	108	64	32	
		82	105	90	36	38
Ethyl methanesulfonate (μg/mL)						
	250	84	68	847	336	
		70	58	783	373	
		73	76	669	305	338[c]
o-Nitroanisole (μL/mL)						
	0.025	58	80	62	36	
		74	99	52	23	
		72	85	45	21	27
	0.05	74	88	57	26	
		66	78	45	23	
		78	76	86	37	28
	0.1	56	57	91	54	
		66	56	80	41	
		65	70	80	41	45
	0.15	89	45	191	71	
		54	50	92	57	
		72	43	133	62	63[c]
	0.2	69	43	126	61	
		77	40	183	80	
		71	42	141	67	69[c]
	0.3	63	10	346	184	
		49	10	181	123	
		67	13	297	149	152[c]
	0.4	Lethal				
		Lethal				
		Lethal				

TABLE G4
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by *o*-Nitroanisole (continued)

Compound	Concentration	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
Trial 3						
Ethanol		79	92	94	40	
		88	80	95	36	
		114	121	104	30	
		106	107	123	39	36
Ethylmethanesulfonate (μg/mL)						
	250	57	37	857	506	
		73	62	865	395	
		56	43	616	370	424[c]
o-Nitroanisole (μL/mL)						
	0.025	49	59	56	38	
		65	72	58	30	34
	0.05	62	62	46	25	
		59	65	77	43	
		79	75	105	44	37
	0.1	68	42	124	61	
		60	47	75	42	
		69	68	70	34	45
	0.15	84	52	103	41	
		70	62	86	41	
		94	50	140	50	44
	0.2	56	29	105	63	
		67	24	188	94	
		77	41	139	60	72[c]
	0.3	68	24	193	95	
		61	34	146	79	
		82	29	196	80	85[c]
	0.4[d]	Lethal				
		Lethal				
		Lethal				

[a] Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr *et al.* (1985). The highest dose of *o*-nitroanisole is determined by solubility or toxicity. All doses are tested in triplicate; the average of the three tests is presented in the table. Cells (6×10^5/mL) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

[b] Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/10^6 cells treated).

[c] Significant positive response ($P<0.05$)

[d] Precipitation

APPENDIX H
ORGAN WEIGHTS
AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Day Feed Study of o-Nitroanisole[a]

	0 ppm	583 ppm	1,166 ppm	2,332 ppm	4,665 ppm	9,330 ppm
Male						
n	5	5	5	5	5	5
Necropsy body wt	237 ± 3	243 ± 3	243 ± 5	240 ± 4	229 ± 5	212 ± 2**
Brain						
Absolute	1.810 ± 0.028	1.868 ± 0.029	1.840 ± 0.022	1.874 ± 0.020	1.856 ± 0.014	1.828 ± 0.015
Relative	7.64 ± 0.04	7.70 ± 0.10	7.59 ± 0.17	7.83 ± 0.11	8.11 ± 0.13**	8.62 ± 0.07**
Heart						
Absolute	0.833 ± 0.033	0.855 ± 0.016	0.864 ± 0.016	0.866 ± 0.044	0.835 ± 0.018	0.789 ± 0.015
Relative	3.51 ± 0.12	3.53 ± 0.05	3.56 ± 0.04	3.61 ± 0.13	3.65 ± 0.09	3.72 ± 0.06
R. Kidney						
Absolute	0.941 ± 0.039	1.024 ± 0.060	0.987 ± 0.029	1.021 ± 0.039	0.982 ± 0.033	0.985 ± 0.033
Relative	3.97 ± 0.13	4.21 ± 0.21	4.08 ± 0.18	4.26 ± 0.12	4.28 ± 0.09	4.64 ± 0.15**
Liver						
Absolute	13.060 ± 0.533	12.540 ± 0.468	14.600 ± 0.207*	14.380 ± 0.334	14.060 ± 0.412	13.100 ± 0.170
Relative	55.05 ± 1.71	51.64 ± 1.37	60.17 ± 0.61**	60.00 ± 0.63**	61.34 ± 1.25**	61.74 ± 0.71**
Lungs						
Absolute	1.220 ± 0.098	1.314 ± 0.074	1.220 ± 0.096[b]	1.100 ± 0.055	1.172 ± 0.065	0.998 ± 0.149
Relative	5.13 ± 0.35	5.43 ± 0.34	5.04 ± 0.29[b]	4.59 ± 0.23	5.12 ± 0.27	4.70 ± 0.70
R. Testis						
Absolute	1.220 ± 0.030	1.310 ± 0.018*	1.276 ± 0.007	1.292 ± 0.011	1.264 ± 0.027	1.250 ± 0.023
Relative	5.14 ± 0.07	5.40 ± 0.11	5.26 ± 0.08	5.40 ± 0.07	5.51 ± 0.04**	5.89 ± 0.13**
Thymus						
Absolute	0.567 ± 0.037	0.595 ± 0.022	0.587 ± 0.019	0.616 ± 0.033	0.570 ± 0.029	0.541 ± 0.016
Relative	2.39 ± 0.13	2.45 ± 0.07	2.42 ± 0.10	2.57 ± 0.13	2.48 ± 0.11	2.55 ± 0.09
Trachea						
Absolute	0.703 ± 0.266	0.927 ± 0.207	0.813 ± 0.329[b]	0.802 ± 0.244	1.052 ± 0.300	1.032 ± 0.321
Relative	2.92 ± 1.08	3.86 ± 0.89	3.32 ± 1.34[b]	3.37 ± 1.04	4.60 ± 1.32	4.88 ± 1.53

TABLE H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Day Feed Study of *o*-Nitroanisole (continued)

	0 ppm	583 ppm	1,166 ppm	2,332 ppm	4,665 ppm	9,330 ppm
Female						
n	5	5	5	5	5	5
Necropsy body wt	151 ± 1	154 ± 2	152 ± 2	150 ± 2	145 ± 1	148 ± 2
Brain						
Absolute	1.704 ± 0.066	1.750 ± 0.025	1.738 ± 0.034	1.740 ± 0.022	1.672 ± 0.007	1.684 ± 0.048
Relative	11.29 ± 0.46	11.38 ± 0.07	11.45 ± 0.21	11.60 ± 0.12	11.55 ± 0.11	11.43 ± 0.45
Heart						
Absolute	0.620 ± 0.016	0.620 ± 0.029	0.594 ± 0.021	0.595 ± 0.012	0.565 ± 0.017	0.603 ± 0.011
Relative	4.11 ± 0.12	4.03 ± 0.15	3.91 ± 0.08	3.96 ± 0.07	3.91 ± 0.13	4.09 ± 0.08
R. Kidney						
Absolute	0.592 ± 0.018	0.636 ± 0.021	0.641 ± 0.034	0.648 ± 0.026	0.641 ± 0.032	0.650 ± 0.024
Relative	3.92 ± 0.13	4.14 ± 0.10	4.23 ± 0.23	4.31 ± 0.13	4.42 ± 0.20°	4.40 ± 0.11°
Liver						
Absolute	6.196 ± 0.162	6.896 ± 0.213°	6.792 ± 0.223°	7.422 ± 0.205°°	7.040 ± 0.207°°	7.916 ± 0.128°°
Relative	41.06 ± 1.23	44.81 ± 0.89°	44.73 ± 1.18°	49.48 ± 1.29°°	48.65 ± 1.62°°	53.63 ± 0.54°°
Lungs						
Absolute	0.924 ± 0.044	0.962 ± 0.062	1.108 ± 0.066	0.966 ± 0.066	1.004 ± 0.149	0.952 ± 0.048
Relative	6.12 ± 0.27	6.28 ± 0.48	7.30 ± 0.44	6.45 ± 0.48	6.94 ± 1.05	6.45 ± 0.31
Thymus						
Absolute	0.484 ± 0.024	0.427 ± 0.020	0.427 ± 0.006	0.442 ± 0.019	0.476 ± 0.039	0.484 ± 0.042
Relative	3.20 ± 0.16	2.78 ± 0.14	2.82 ± 0.08	2.95 ± 0.13	3.28 ± 0.26	3.27 ± 0.25
Trachea						
Absolute	0.817 ± 0.242	0.650 ± 0.252	0.831 ± 0.214	0.579 ± 0.189	0.850 ± 0.242	0.829 ± 0.270
Relative	5.38 ± 1.59	4.29 ± 1.69	5.49 ± 1.41	3.91 ± 1.31	5.89 ± 1.69	5.66 ± 1.87

° Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
°° P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=4

TABLE H2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of o-Nitroanisole[a]

	0 ppm	200 ppm	600 ppm	2,000 ppm	6,000 ppm	18,000 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	360 ± 13	373 ± 7	380 ± 7	363 ± 4	311 ± 5**	173 ± 7**
Brain						
Absolute	1.999 ± 0.027	2.050 ± 0.027	2.034 ± 0.025	1.878 ± 0.090	1.968 ± 0.020	1.808 ± 0.026**
Relative	5.61 ± 0.19	5.50 ± 0.09	5.37 ± 0.12	5.18 ± 0.26	6.34 ± 0.10*	10.59 ± 0.37**
Heart						
Absolute	1.123 ± 0.031	1.110 ± 0.030	1.141 ± 0.022	1.087 ± 0.025	0.988 ± 0.018**	0.645 ± 0.022**
Relative	3.14 ± 0.08	2.97 ± 0.06	3.01 ± 0.05	3.00 ± 0.07	3.18 ± 0.05	3.76 ± 0.13**
R. Kidney						
Absolute	1.151 ± 0.036	1.240 ± 0.035	1.365 ± 0.026**	1.312 ± 0.024**	1.466 ± 0.047**	0.904 ± 0.020**
Relative	3.21 ± 0.08	3.32 ± 0.07	3.60 ± 0.06*	3.62 ± 0.07**	4.71 ± 0.12**	5.28 ± 0.17**
Liver						
Absolute	12.120 ± 0.611	13.920 ± 0.367**	15.520 ± 0.461**	17.280 ± 0.306**	17.050 ± 0.449**	10.970 ± 0.274**
Relative	33.51 ± 0.95	37.27 ± 0.56*	40.83 ± 0.77**	47.67 ± 1.23**	54.78 ± 0.95**	63.94 ± 1.59**
Lungs						
Absolute	1.996 ± 0.041	2.038 ± 0.066	2.249 ± 0.067	1.965 ± 0.050	1.840 ± 0.076	1.271 ± 0.040**
Relative	5.59 ± 0.20	5.47 ± 0.20	5.93 ± 0.19	5.42 ± 0.17	5.91 ± 0.21	7.39 ± 0.18**
Spleen						
Absolute	0.750 ± 0.036[b]	0.802 ± 0.016[b]	0.834 ± 0.016	0.834 ± 0.013	1.132 ± 0.029**	1.297 ± 0.057**
Relative	2.06 ± 0.04[b]	2.15 ± 0.05[b]	2.20 ± 0.02	2.30 ± 0.03	3.64 ± 0.08**	7.57 ± 0.33**
R. Testis						
Absolute	1.544 ± 0.024	1.570 ± 0.034	1.555 ± 0.018	1.502 ± 0.059	1.578 ± 0.022	0.663 ± 0.085**
Relative	4.32 ± 0.12	4.22 ± 0.11	4.10 ± 0.08	4.14 ± 0.16	5.08 ± 0.06*	3.77 ± 0.38
Thymus						
Absolute	0.311 ± 0.027	0.378 ± 0.020	0.335 ± 0.023	0.346 ± 0.025	0.312 ± 0.018	0.162 ± 0.015**[b]
Relative	0.86 ± 0.07	1.01 ± 0.05	0.88 ± 0.05	0.95 ± 0.07	1.01 ± 0.06	0.95 ± 0.07[b]

TABLE H2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of *o*-Nitroanisole (continued)

	0 ppm	200 ppm	600 ppm	2,000 ppm	6,000 ppm	18,000 ppm
Female						
n	10	10	10	9	10	10
Necropsy body wt	213 ± 3	217 ± 3	211 ± 2	208 ± 3	183 ± 2**	137 ± 2**
Brain						
Absolute	1.862 ± 0.036	1.827 ± 0.008	1.873 ± 0.024	1.836 ± 0.023	1.772 ± 0.027*	1.628 ± 0.019**
Relative	8.77 ± 0.20	8.43 ± 0.12	8.90 ± 0.14	8.84 ± 0.12	9.70 ± 0.15**	11.89 ± 0.15**
Heart						
Absolute	0.765 ± 0.012	0.735 ± 0.015	0.779 ± 0.018	0.732 ± 0.022	0.653 ± 0.005**	0.507 ± 0.012**
Relative	3.60 ± 0.08	3.39 ± 0.08	3.70 ± 0.10	3.52 ± 0.08	3.58 ± 0.04	3.70 ± 0.08
R. Kidney						
Absolute	0.721 ± 0.011	0.730 ± 0.011	0.746 ± 0.008	0.742 ± 0.019	0.715 ± 0.020	0.698 ± 0.022
Relative	3.40 ± 0.07	3.37 ± 0.07	3.54 ± 0.06	3.58 ± 0.09	3.91 ± 0.11**	5.09 ± 0.13**
Liver						
Absolute	6.720 ± 0.080	7.370 ± 0.092**	7.810 ± 0.123**	8.900 ± 0.153**	9.400 ± 0.193**	9.100 ± 0.143**
Relative	31.62 ± 0.33	33.99 ± 0.47**	37.06 ± 0.46**	42.85 ± 0.55**	51.43 ± 0.95**	66.41 ± 0.75**
Lungs						
Absolute	1.400 ± 0.046	1.465 ± 0.046	1.503 ± 0.024[b]	1.444 ± 0.032	1.346 ± 0.043	1.026 ± 0.030**
Relative	6.58 ± 0.20	6.77 ± 0.26	7.16 ± 0.10[b]	6.96 ± 0.13	7.35 ± 0.17**	7.48 ± 0.16**
Spleen						
Absolute	0.532 ± 0.011	0.537 ± 0.009	0.544 ± 0.010	0.542 ± 0.013	0.778 ± 0.024**[b]	1.327 ± 0.032**[b]
Relative	2.50 ± 0.06	2.48 ± 0.05	2.58 ± 0.04	2.61 ± 0.05	4.25 ± 0.13**[b]	9.66 ± 0.22**[b]
Thymus						
Absolute	0.306 ± 0.013	0.304 ± 0.008	0.269 ± 0.009	0.279 ± 0.007	0.276 ± 0.020	0.155 ± 0.013**
Relative	1.44 ± 0.06	1.40 ± 0.04	1.28 ± 0.04	1.35 ± 0.04	1.52 ± 0.12	1.13 ± 0.09**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=9

TABLE H3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of o-Nitroanisole[a]

	0 ppm	222 ppm	666 ppm	2,000 ppm
Male				
n	10	10	10	9
Necropsy body wt	455 ± 9	445 ± 7	441 ± 7	437 ± 6
Brain				
Absolute	2.118 ± 0.017	2.057 ± 0.017*	2.085 ± 0.012	2.088 ± 0.021
Relative	4.67 ± 0.07	4.63 ± 0.07	4.74 ± 0.06	4.79 ± 0.06
R. Kidney				
Absolute	1.419 ± 0.049	1.387 ± 0.043	1.408 ± 0.037	1.513 ± 0.027
Relative	3.12 ± 0.05	3.11 ± 0.08	3.19 ± 0.06	3.47 ± 0.05**
Liver				
Absolute	14.909 ± 0.250	14.911 ± 0.353	15.535 ± 0.491	17.932 ± 0.273**
Relative	32.82 ± 0.17	33.47 ± 0.59	35.22 ± 0.82**	41.09 ± 0.57**
Spleen				
Absolute	1.002 ± 0.066	0.880 ± 0.031[b]	1.029 ± 0.079	1.171 ± 0.096[c]
Relative	2.21 ± 0.16	1.98 ± 0.07[b]	2.34 ± 0.19	2.69 ± 0.20[c]
R. Testis				
Absolute	1.644 ± 0.024	1.576 ± 0.018	1.497 ± 0.087[b]	1.749 ± 0.054[d]
Relative	3.63 ± 0.07	3.55 ± 0.07	3.37 ± 0.17[b]	3.98 ± 0.11[d]
Female				
n	10	10	10	9
Necropsy body wt	267 ± 8	273 ± 10	272 ± 11	260 ± 9
Brain				
Absolute	1.856 ± 0.030	1.837 ± 0.026	1.857 ± 0.030	1.847 ± 0.029
Relative	6.98 ± 0.15	6.79 ± 0.21	6.91 ± 0.24	7.15 ± 0.19
R. Kidney				
Absolute	0.833 ± 0.023	0.832 ± 0.031	0.849 ± 0.035	0.809 ± 0.028
Relative	3.12 ± 0.06	3.05 ± 0.05	3.12 ± 0.03	3.12 ± 0.07
Liver				
Absolute	7.642 ± 0.276	8.193 ± 0.309	8.866 ± 0.418*	9.723 ± 0.431**
Relative	28.58 ± 0.54	30.01 ± 0.44	32.53 ± 0.51**	37.32 ± 1.05**
Spleen				
Absolute	0.497 ± 0.019	0.493 ± 0.028	0.538 ± 0.035	0.561 ± 0.034
Relative	1.86 ± 0.06	1.80 ± 0.06	1.96 ± 0.09	2.14 ± 0.08*

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=9
[c] n=8
[d] n=7

TABLE H4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole[a]

	0 ppm	6,000 ppm	18,000 ppm
Male			
n	10	10	10
Necropsy body wt	308 ± 4	249 ± 4**	145 ± 3**
R. Kidney			
Absolute	0.963 ± 0.012	1.063 ± 0.017	0.706 ± 0.024**
Relative	3.13 ± 0.02	4.27 ± 0.02**	4.88 ± 0.12**
Liver			
Absolute	8.097 ± 0.093	10.553 ± 0.307**	8.131 ± 0.284
Relative	26.31 ± 0.33	42.30 ± 0.56**	56.06 ± 1.08**
Spleen			
Absolute	0.588 ± 0.008	0.776 ± 0.018**[b]	1.151 ± 0.064**
Relative	1.91 ± 0.02	3.11 ± 0.06**[b]	7.93 ± 0.35**
R. Testis			
Absolute	1.408 ± 0.017	1.447 ± 0.023	0.524 ± 0.031**
Relative	4.57 ± 0.04	5.81 ± 0.07**	3.67 ± 0.29**
Urinary Bladder			
Absolute	0.094 ± 0.007	0.101 ± 0.007	0.185 ± 0.023**
Relative	0.31 ± 0.02	0.41 ± 0.03	1.28 ± 0.16**
Female			
n	10	10	10
Necropsy body wt	167 ± 2	155 ± 2**	100 ± 3**
R. Kidney			
Absolute	0.587 ± 0.013	0.569 ± 0.012	0.530 ± 0.020*
Relative	3.52 ± 0.09	3.68 ± 0.06	5.30 ± 0.11**
Liver			
Absolute	4.069 ± 0.061	5.676 ± 0.091**	5.173 ± 0.269**
Relative	24.39 ± 0.35	36.71 ± 0.29**	51.58 ± 1.69**
Spleen			
Absolute	0.412 ± 0.008	0.523 ± 0.016**	0.770 ± 0.041**
Relative	2.47 ± 0.04	3.39 ± 0.12**	7.70 ± 0.37**
Urinary Bladder			
Absolute	0.062 ± 0.003	0.066 ± 0.003	0.163 ± 0.009**
Relative	0.37 ± 0.02	0.43 ± 0.02	1.64 ± 0.09**
Uterus			
Absolute	0.368 ± 0.016	0.240 ± 0.022**	0.132 ± 0.043**
Relative	2.21 ± 0.11	1.56 ± 0.15	1.39 ± 0.51

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=9

TABLE H5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole[a]

	0 ppm	6,000 ppm	18,000 ppm
Male			
n	10	10	10
Necropsy body wt	383 ± 9	289 ± 6**	166 ± 2**
R. Kidney			
Absolute	1.216 ± 0.037	1.189 ± 0.015	0.837 ± 0.014**
Relative	3.17 ± 0.07	4.12 ± 0.05**	5.05 ± 0.07**
Liver			
Absolute	9.552 ± 0.345	11.767 ± 0.299**	9.154 ± 0.232
Relative	24.89 ± 0.58	40.69 ± 0.51**	55.22 ± 1.29**
Spleen			
Absolute	0.748 ± 0.037	0.899 ± 0.017	1.758 ± 0.109**
Relative	1.94 ± 0.06	3.12 ± 0.07*	10.58 ± 0.61**
R. Testis			
Absolute	1.512 ± 0.029	1.530 ± 0.038	0.473 ± 0.030**
Relative	3.97 ± 0.15	5.29 ± 0.10**	2.85 ± 0.18**
Urinary Bladder			
Absolute	0.167 ± 0.019	0.119 ± 0.013	1.333 ± 0.482**
Relative	0.44 ± 0.05	0.41 ± 0.04	8.02 ± 2.87**
Female			
n	10	10	10
Necropsy body wt	197 ± 2	169 ± 3**	114 ± 4**
R. Kidney			
Absolute	0.655 ± 0.013	0.614 ± 0.010*	0.594 ± 0.016**[b]
Relative	3.34 ± 0.07	3.65 ± 0.03**	5.25 ± 0.10**[b]
Liver			
Absolute	4.753 ± 0.082	5.871 ± 0.154**	6.205 ± 0.284**
Relative	24.20 ± 0.45	34.81 ± 0.36**	54.05 ± 1.11**
Spleen			
Absolute	0.456 ± 0.012	0.696 ± 0.015**	1.304 ± 0.083**
Relative	2.32 ± 0.05	4.13 ± 0.06**	11.33 ± 0.53**
Urinary Bladder			
Absolute	0.073 ± 0.006	0.079 ± 0.004	0.490 ± 0.070**
Relative	0.37 ± 0.03	0.47 ± 0.03	4.25 ± 0.60**
Uterus			
Absolute	0.620 ± 0.030	0.262 ± 0.019**	0.104 ± 0.013**[b]
Relative	3.15 ± 0.14	1.56 ± 0.11**	0.92 ± 0.12**[b]

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=9

TABLE H6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole[a]

	0 ppm	6,000 ppm	18,000 ppm
Male			
n	10	10	6
Necropsy body wt	458 ± 8	403 ± 5**	290 ± 7**
R. Kidney			
Absolute	1.416 ± 0.030	1.306 ± 0.021	1.237 ± 0.148
Relative	3.10 ± 0.09	3.24 ± 0.04	4.26 ± 0.49**
Liver			
Absolute	15.565 ± 0.392	14.888 ± 0.386	10.352 ± 0.552**
Relative	34.05 ± 0.80	36.88 ± 0.53*	35.63 ± 1.31
Spleen			
Absolute	0.827 ± 0.026	0.868 ± 0.028	1.213 ± 0.102**
Relative	1.81 ± 0.05	2.15 ± 0.06*	4.17 ± 0.29**
R. Testis			
Absolute	1.563 ± 0.020	1.528 ± 0.022	1.177 ± 0.060**
Relative	3.42 ± 0.05	3.79 ± 0.05*	4.07 ± 0.24**
Urinary Bladder			
Absolute	0.141 ± 0.018	0.232 ± 0.052	3.455 ± 0.660**
Relative	0.31 ± 0.05	0.57 ± 0.12	11.97 ± 2.31**
Female			
n	10	10	6
Necropsy body wt	232 ± 6	211 ± 2**	177 ± 5**
R. Kidney			
Absolute	0.714 ± 0.016[b]	0.720 ± 0.014	0.728 ± 0.022
Relative	3.09 ± 0.07[b]	3.42 ± 0.06*	4.12 ± 0.17**
Liver			
Absolute	7.019 ± 0.260	6.940 ± 0.130	6.347 ± 0.247
Relative	30.28 ± 0.60	32.92 ± 0.52*	35.83 ± 1.19**
Spleen			
Absolute	0.446 ± 0.019	0.514 ± 0.014	0.912 ± 0.071**
Relative	1.93 ± 0.06	2.44 ± 0.07	5.20 ± 0.53**
Urinary Bladder			
Absolute	0.066 ± 0.003	0.084 ± 0.007	3.363 ± 0.728**
Relative	0.29 ± 0.02	0.40 ± 0.03	19.51 ± 4.62**
Uterus			
Absolute	0.845 ± 0.063	0.862 ± 0.131	0.502 ± 0.102*
Relative	3.66 ± 0.24	4.07 ± 0.59	2.76 ± 0.52

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=9

TABLE H7
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole[a]

	0 ppm	6,000 ppm
Male		
n	9	3
Necropsy body wt	455 ± 10	441 ± 16
R. Kidney		
Absolute	1.806 ± 0.071	1.975 ± 0.052
Relative	3.96 ± 0.11	4.50 ± 0.24*
Liver		
Absolute	17.815 ± 0.635	17.322 ± 0.482
Relative	39.08 ± 0.72	39.39 ± 1.31
Spleen		
Absolute	0.906 ± 0.021	1.028 ± 0.060*
Relative	2.00 ± 0.05	2.35 ± 0.21*
R. Testis		
Absolute	1.687 ± 0.115	1.734 ± 0.028
Relative	3.73 ± 0.30	3.95 ± 0.17
Urinary Bladder		
Absolute	0.107 ± 0.004	0.813 ± 0.322**
Relative	0.23 ± 0.01	1.82 ± 0.70**
Female		
n	8	10
Necropsy body wt	291 ± 5	237 ± 6**
R. Kidney		
Absolute	1.062 ± 0.020	0.996 ± 0.023
Relative	3.66 ± 0.06	4.22 ± 0.08**
Liver		
Absolute	9.453 ± 0.161	8.891 ± 0.349
Relative	32.60 ± 0.87	37.56 ± 0.92**
Spleen		
Absolute	0.549 ± 0.016	0.532 ± 0.015
Relative	1.89 ± 0.07	2.27 ± 0.11*
Urinary Bladder		
Absolute	0.089 ± 0.005	1.595 ± 0.755
Relative	0.31 ± 0.01	6.99 ± 3.29
Uterus		
Absolute	0.767 ± 0.031	0.818 ± 0.061
Relative	2.64 ± 0.10	3.52 ± 0.34*

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

TABLE H8
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Day Feed Study of *o*-Nitroanisole[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm
Male						
n	5	5	5	5	5	5
Necropsy body wt	27.4 ± 0.9	24.8 ± 0.6°	25.8 ± 0.4°	25.6 ± 0.2°	23.6 ± 0.5°°	19.0 ± 0.6°°
Brain						
Absolute	0.158 ± 0.006	0.146 ± 0.014	0.149 ± 0.004	0.131 ± 0.005°	0.126 ± 0.006°°	0.113 ± 0.005°°
Relative	5.78 ± 0.22	5.87 ± 0.46	5.79 ± 0.17	5.11 ± 0.23	5.36 ± 0.24	5.96 ± 0.10
Heart						
Absolute	0.461 ± 0.013	0.462 ± 0.012	0.475 ± 0.016	0.482 ± 0.012	0.445 ± 0.011	0.444 ± 0.010
Relative	16.88 ± 0.68	18.67 ± 0.64	18.41 ± 0.63	18.83 ± 0.61	18.94 ± 0.83	23.44 ± 0.74°°
R. Kidney						
Absolute	0.274 ± 0.015	0.242 ± 0.005	0.251 ± 0.010	0.246 ± 0.013	0.205 ± 0.010°°	0.165 ± 0.004°°
Relative	9.98 ± 0.23	9.76 ± 0.19	9.70 ± 0.32	9.62 ± 0.55	8.70 ± 0.37°	8.72 ± 0.27°
Liver						
Absolute	1.760 ± 0.106	1.494 ± 0.024°	1.542 ± 0.078°	1.630 ± 0.055°	1.424 ± 0.057°°	1.128 ± 0.046°°
Relative	64.17 ± 2.92	60.30 ± 0.77	59.67 ± 2.26	63.65 ± 1.93	60.36 ± 2.15	59.46 ± 2.31
Lungs						
Absolute	0.150 ± 0.030	0.183 ± 0.018	0.222 ± 0.014	0.203 ± 0.014	0.154 ± 0.023	0.156 ± 0.017
Relative	5.47 ± 1.00	7.45 ± 0.83	8.58 ± 0.49	7.91 ± 0.51	6.45 ± 0.89	8.33 ± 1.09
R. Testis						
Absolute	0.129 ± 0.021[b]	0.106 ± 0.004	0.120 ± 0.011	0.128 ± 0.010	0.102 ± 0.004	0.111 ± 0.009
Relative	4.61 ± 0.61[b]	4.26 ± 0.13	4.66 ± 0.46	5.00 ± 0.41	4.31 ± 0.12	5.90 ± 0.64
Thymus						
Absolute	0.052 ± 0.005	0.053 ± 0.006	0.054 ± 0.007	0.059 ± 0.012	0.049 ± 0.005	0.022 ± 0.006°°
Relative	1.89 ± 0.17	2.10 ± 0.21	2.12 ± 0.28	2.30 ± 0.50	2.08 ± 0.24	1.12 ± 0.28
Trachea						
Absolute	0.268 ± 0.024[b]	0.240 ± 0.026	0.219 ± 0.023	0.245 ± 0.021	0.229 ± 0.017	0.212 ± 0.004
Relative	9.69 ± 0.88[b]	9.62 ± 0.86	8.52 ± 1.00	9.56 ± 0.81	9.73 ± 0.83	11.17 ± 0.27

TABLE H8
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Day Feed Study of *o*-Nitroanisole (continued)

	0 ppm	250 ppm	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm
Female						
n	5	5	5	5	5	5
Necropsy body wt	19.2 ± 0.2	20.4 ± 0.5	19.0 ± 0.3	20.0 ± 0.3	18.0 ± 0.8	15.6 ± 0.9**
Brain						
Absolute	0.108 ± 0.004	0.118 ± 0.005	0.114 ± 0.004	0.116 ± 0.007	0.103 ± 0.005	0.093 ± 0.003
Relative	5.63 ± 0.24	5.83 ± 0.35	6.00 ± 0.22	5.79 ± 0.35	5.75 ± 0.36	6.05 ± 0.35
Heart						
Absolute	0.455 ± 0.010	0.478 ± 0.010	0.440 ± 0.023	0.463 ± 0.009	0.435 ± 0.018	0.432 ± 0.013
Relative	23.67 ± 0.41	23.44 ± 0.54	23.11 ± 0.93	23.16 ± 0.26	24.23 ± 0.49	27.93 ± 1.43**
R. Kidney						
Absolute	0.164 ± 0.012	0.181 ± 0.005	0.155 ± 0.008	0.176 ± 0.009	0.138 ± 0.006*	0.117 ± 0.007**
Relative	8.55 ± 0.68	8.87 ± 0.17	8.19 ± 0.46	8.80 ± 0.46	7.71 ± 0.27	7.57 ± 0.56
Liver						
Absolute	1.004 ± 0.011	1.246 ± 0.052	1.028 ± 0.034	1.298 ± 0.023*	1.152 ± 0.095	1.002 ± 0.119
Relative	52.30 ± 0.49	60.98 ± 1.02	54.08 ± 1.25	64.94 ± 1.19**	63.57 ± 2.55**	63.44 ± 3.64**
Lungs						
Absolute	0.157 ± 0.008	0.194 ± 0.035	0.156 ± 0.019	0.163 ± 0.020	0.150 ± 0.010	0.146 ± 0.009
Relative	8.19 ± 0.48	9.42 ± 1.56	8.23 ± 1.01	8.19 ± 1.09	8.34 ± 0.44	9.37 ± 0.50
Thymus						
Absolute	0.064 ± 0.007	0.092 ± 0.015	0.068 ± 0.003	0.083 ± 0.005	0.036 ± 0.010*	0.019 ± 0.003**
Relative	3.35 ± 0.37	4.46 ± 0.63	3.60 ± 0.18	4.14 ± 0.27	1.92 ± 0.45*	1.20 ± 0.16**
Trachea						
Absolute	0.231 ± 0.011	0.203 ± 0.034	0.226 ± 0.013	0.239 ± 0.017	0.214 ± 0.009	0.173 ± 0.017*
Relative	12.03 ± 0.60	9.99 ± 1.68	11.92 ± 0.67	11.98 ± 0.83	12.00 ± 0.71	11.23 ± 1.35

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=4

TABLE H9
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of *o*-Nitroanisole[a]

	0 ppm	60 ppm	200 ppm	600 ppm	2,000 ppm	6,000 ppm
Male						
n	10	10	7	9	10	10
Necropsy body wt	33.4 ± 0.5	31.8 ± 0.4	30.9 ± 2.0	33.2 ± 0.8	33.5 ± 0.6	26.1 ± 0.4**
Brain						
Absolute	0.489 ± 0.006	0.486 ± 0.010	0.477 ± 0.008[b]	0.479 ± 0.007	0.468 ± 0.004	0.473 ± 0.005
Relative	14.66 ± 0.32	15.27 ± 0.33	16.25 ± 1.40[b]	14.47 ± 0.29	14.02 ± 0.21	18.18 ± 0.26**
Heart						
Absolute	0.191 ± 0.006	0.182 ± 0.005	0.182 ± 0.011	0.181 ± 0.004	0.171 ± 0.005*	0.147 ± 0.006**
Relative	5.70 ± 0.13	5.72 ± 0.18	5.98 ± 0.36	5.46 ± 0.12	5.12 ± 0.12	5.61 ± 0.19
R. Kidney						
Absolute	0.343 ± 0.009	0.318 ± 0.012	0.315 ± 0.012[b]	0.318 ± 0.008	0.336 ± 0.015	0.238 ± 0.009**
Relative	10.28 ± 0.33	9.99 ± 0.36	10.61 ± 0.58[b]	9.58 ± 0.22	10.01 ± 0.38	9.15 ± 0.36*
Liver						
Absolute	1.873 ± 0.082	1.725 ± 0.037	1.654 ± 0.202	2.059 ± 0.109	2.192 ± 0.051	1.804 ± 0.058
Relative	56.07 ± 2.37	54.15 ± 0.71	52.21 ± 3.71	61.74 ± 2.23	65.50 ± 1.09**	69.18 ± 1.59**
Lungs						
Absolute	0.264 ± 0.010	0.254 ± 0.008	0.255 ± 0.011[b]	0.276 ± 0.010	0.274 ± 0.010	0.223 ± 0.007**
Relative	7.88 ± 0.27	7.97 ± 0.25	8.57 ± 0.49[b]	8.31 ± 0.32	8.19 ± 0.25	8.55 ± 0.29
Spleen						
Absolute	0.112 ± 0.005	0.122 ± 0.009	0.098 ± 0.014	0.096 ± 0.007	0.113 ± 0.007	0.076 ± 0.003**[c]
Relative	3.36 ± 0.13	3.81 ± 0.27	3.08 ± 0.33	2.88 ± 0.18	3.38 ± 0.20	2.92 ± 0.09[c]
R. Testis						
Absolute	0.120 ± 0.003	0.124 ± 0.003	0.120 ± 0.004[b]	0.114 ± 0.004	0.129 ± 0.004	0.121 ± 0.003
Relative	3.59 ± 0.10	3.89 ± 0.13	4.03 ± 0.21[b]	3.44 ± 0.17	3.86 ± 0.12	4.66 ± 0.17**
Thymus						
Absolute	0.040 ± 0.004	0.048 ± 0.003	0.042 ± 0.007	0.043 ± 0.003	0.038 ± 0.003	0.044 ± 0.002
Relative	1.19 ± 0.11	1.51 ± 0.11	1.33 ± 0.18	1.30 ± 0.12	1.15 ± 0.09	1.69 ± 0.10*

TABLE H9
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of o-Nitroanisole (continued)

	0 ppm	60 ppm	200 ppm	600 ppm	2,000 ppm	6,000 ppm
Female						
n	10	10	10	10	10	10
Necropsy body wt	26.4 ± 0.6	26.0 ± 0.3	25.7 ± 0.5	26.3 ± 0.4	25.0 ± 0.3*	20.9 ± 0.6**
Brain						
Absolute	0.511 ± 0.007[c]	0.482 ± 0.010	0.491 ± 0.013[c]	0.513 ± 0.015	0.502 ± 0.012	0.461 ± 0.015*
Relative	19.27 ± 0.45[c]	18.54 ± 0.39	18.82 ± 0.55[c]	19.54 ± 0.60	20.15 ± 0.57	22.11 ± 0.74**
Heart						
Absolute	0.154 ± 0.007	0.160 ± 0.007	0.159 ± 0.007[c]	0.152 ± 0.004	0.147 ± 0.005	0.131 ± 0.008*
Relative	5.82 ± 0.20	6.14 ± 0.26	6.08 ± 0.25[c]	5.78 ± 0.14	5.91 ± 0.21	6.23 ± 0.31
R. Kidney						
Absolute	0.221 ± 0.008	0.213 ± 0.007	0.226 ± 0.010	0.224 ± 0.007	0.224 ± 0.019	0.175 ± 0.007**
Relative	8.39 ± 0.29	8.18 ± 0.27	8.79 ± 0.36	8.54 ± 0.30	9.00 ± 0.84	8.32 ± 0.15
Liver						
Absolute	1.366 ± 0.059	1.367 ± 0.024	1.346 ± 0.042	1.568 ± 0.040*	1.613 ± 0.033*	1.532 ± 0.096*
Relative	51.74 ± 1.57	52.53 ± 0.61	52.32 ± 1.16	59.75 ± 1.53**	64.74 ± 1.66**	72.85 ± 3.18**
Lungs						
Absolute	0.224 ± 0.011	0.241 ± 0.008	0.243 ± 0.010	0.266 ± 0.013	0.228 ± 0.008	0.199 ± 0.005
Relative	8.51 ± 0.42	9.28 ± 0.28	9.42 ± 0.25	10.12 ± 0.44**	9.11 ± 0.27	9.54 ± 0.36
Spleen						
Absolute	0.103 ± 0.005	0.111 ± 0.005	0.109 ± 0.005	0.122 ± 0.006	0.105 ± 0.004	0.089 ± 0.007**
Relative	3.93 ± 0.23	4.28 ± 0.15	4.23 ± 0.15	4.66 ± 0.25	4.20 ± 0.15	4.21 ± 0.27
Thymus						
Absolute	0.055 ± 0.007	0.049 ± 0.003	0.057 ± 0.004	0.060 ± 0.006	0.064 ± 0.004	0.051 ± 0.004
Relative	2.13 ± 0.28	1.89 ± 0.12	2.23 ± 0.15	2.30 ± 0.24	2.55 ± 0.16	2.43 ± 0.19

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)
[b] n=6
[c] n=9

TABLE H10
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of *o*-Nitroanisole[a]

	0 ppm	666 ppm	2,000 ppm	6,000 ppm
Male				
n	10	10	9	10
Necropsy body wt	46.1 ± 1.4	43.8 ± 2.8	46.1 ± 2.0	31.1 ± 0.6**
Brain				
Absolute	0.472 ± 0.006	0.462 ± 0.008	0.468 ± 0.007	0.451 ± 0.005*
Relative	10.31 ± 0.28	10.94 ± 0.69	10.26 ± 0.37	14.56 ± 0.37**
R. Kidney				
Absolute	0.385 ± 0.009	0.404 ± 0.020	0.426 ± 0.018	0.288 ± 0.008**
Relative	8.40 ± 0.23	9.36 ± 0.32*	9.26 ± 0.25*	9.27 ± 0.24*
Liver				
Absolute	1.885 ± 0.102	2.077 ± 0.168	2.463 ± 0.113**	2.001 ± 0.079
Relative	40.77 ± 1.33	47.35 ± 1.99**	53.51 ± 1.31**	64.27 ± 1.81**
Spleen				
Absolute	0.068 ± 0.006	0.065 ± 0.005	0.068 ± 0.005	0.062 ± 0.006
Relative	1.46 ± 0.09	1.49 ± 0.08	1.48 ± 0.12	1.99 ± 0.18**
R. Testis				
Absolute	0.121 ± 0.004	0.113 ± 0.005	0.127 ± 0.005	0.120 ± 0.001
Relative	2.63 ± 0.08	2.66 ± 0.16	2.76 ± 0.10	3.88 ± 0.10**
Female				
n	10	10	10	10
Necropsy body wt	46.2 ± 1.8	50.7 ± 2.1	41.6 ± 1.6	25.3 ± 0.4**
Brain				
Absolute	0.489 ± 0.004	0.487 ± 0.003	0.487 ± 0.005	0.468 ± 0.004**
Relative	10.72 ± 0.38	9.77 ± 0.43	11.86 ± 0.45	18.54 ± 0.24**
R. Kidney				
Absolute	0.260 ± 0.008	0.276 ± 0.009	0.263 ± 0.010	0.187 ± 0.005**
Relative	5.68 ± 0.19	5.49 ± 0.17	6.35 ± 0.19	7.40 ± 0.18**
Liver				
Absolute	1.685 ± 0.044	2.065 ± 0.084	1.931 ± 0.110	1.433 ± 0.053*
Relative	36.87 ± 1.43	40.87 ± 0.97	46.21 ± 1.52**	56.60 ± 1.66**
Spleen				
Absolute	0.101 ± 0.010	0.099 ± 0.006	0.091 ± 0.006	0.065 ± 0.003**
Relative	2.32 ± 0.33	1.99 ± 0.16	2.18 ± 0.09	2.57 ± 0.13

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error)

APPENDIX I
HEMATOLOGY, CLINICAL CHEMISTRY, AND URINALYSIS RESULTS

TABLE I1
Hematology, Clinical Chemistry, and Urinalysis Data for Male Rats in the 14-Day Feed Study of o-Nitroanisole[a]

	0 ppm	583 ppm	1,166 ppm	2,332 ppm	4,665 ppm	9,330 ppm
n	5	5	5	5	5	5
Hematology						
Hematocrit (%)	44.0 ± 0.4	41.9 ± 0.2**	41.9 ± 0.3**	39.8 ± 0.2**	38.2 ± 0.2**	32.4 ± 1.7**
Hemoglobin (g/dL)	15.5 ± 0.1	14.8 ± 0.0**	14.9 ± 0.1*	14.1 ± 0.1**	13.6 ± 0.1**	11.9 ± 0.6**
Erythrocytes ($10^6/\mu L$)	7.54 ± 0.07	7.20 ± 0.03**	7.24 ± 0.05**	6.92 ± 0.05**	6.71 ± 0.06**	5.57 ± 0.27**
Reticulocytes ($10^6/\mu L$)	0.10 ± 0.01	0.14 ± 0.02	0.18 ± 0.02*	0.17 ± 0.02*	0.26 ± 0.02**	0.59 ± 0.06**
Leukocytes ($10^3/\mu L$)	5.80 ± 0.17	5.33 ± 0.17	5.74 ± 0.16	5.49 ± 0.31	5.07 ± 0.34	5.86 ± 0.37
Segmented neutrophils ($10^3/\mu L$)	0.69 ± 0.02	0.80 ± 0.07	0.85 ± 0.06	1.23 ± 0.09**	1.51 ± 0.34**	1.35 ± 0.25**
Lymphocytes ($10^3/\mu L$)	5.03 ± 0.14	4.40 ± 0.13*	4.83 ± 0.19	4.09 ± 0.29**	3.47 ± 0.17**	4.43 ± 0.33**
Monocytes ($10^3/\mu L$)	0.04 ± 0.02	0.10 ± 0.02	0.05 ± 0.01	0.12 ± 0.03	0.06 ± 0.02	0.06 ± 0.03
Eosinophils ($10^3/\mu L$)	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.04 ± 0.01	0.03 ± 0.02	0.02 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.01 ± 0.01	0.03 ± 0.02	0.00 ± 0.00	0.01 ± 0.01	0.03 ± 0.01	0.11 ± 0.03**
Total bone marrow cellularity (10^6/femur)	9.65 ± 0.46	10.58 ± 0.49	11.37 ± 0.67	11.08 ± 0.46	9.99 ± 0.18	10.84 ± 0.42
Clinical Chemistry						
Methemoglobin (g/dL)	1.75 ± 0.20	2.15 ± 0.05	2.43 ± 0.06**	2.44 ± 0.13**	3.19 ± 0.13**	8.01 ± 0.42**
Urinalysis						
Specific gravity	1.022 ± 0.001	1.027 ± 0.002	1.023 ± 0.009	1.023 ± 0.002	1.026 ± 0.005	1.016 ± 0.002

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error

TABLE I2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of *o*-Nitroanisole[a]

	0 ppm	200 ppm	600 ppm	2,000 ppm	6,000 ppm	18,000 ppm
Male						
Hematology						
n	10	10	10	10	10	10
Hematocrit (%)	45.0 ± 0.7	44.5 ± 0.3	44.4 ± 0.4	42.8 ± 0.5*	39.5 ± 0.4**	39.4 ± 0.4**
Hemoglobin (g/dL)	15.7 ± 0.3	15.4 ± 0.1	15.3 ± 0.1	14.6 ± 0.2**	13.5 ± 0.1**	14.6 ± 0.2**
Erythrocytes ($10^6/\mu L$)	8.17 ± 0.12	8.11 ± 0.04	8.16 ± 0.07	8.05 ± 0.10	6.97 ± 0.08**	6.02 ± 0.11**
Mean cell volume (fL)	55.0 ± 0.3	54.8 ± 0.2	54.4 ± 0.2	53.2 ± 0.1	56.7 ± 0.2*	65.6 ± 0.9**
Mean cell hemoglobin (pg)	19.2 ± 0.1	19.0 ± 0.1	18.7 ± 0.1	18.1 ± 0.1	19.4 ± 0.1	24.4 ± 0.4**
Mean cell hemoglobin concentration (g/dL)	34.9 ± 0.1	34.7 ± 0.2	34.4 ± 0.2	34.0 ± 0.2*	34.2 ± 0.1	37.1 ± 0.3
Reticulocytes ($10^6/\mu L$)	0.76 ± 0.18	1.40 ± 0.14*	1.47 ± 0.18**	1.54 ± 0.20*	4.56 ± 0.50**	8.04 ± 1.19**[b]
Leukocytes ($10^3/\mu L$)	5.51 ± 0.32	5.65 ± 0.20	6.37 ± 0.25*	6.63 ± 0.22**	8.29 ± 0.27**	10.31 ± 0.77**
Segmented neutrophils ($10^3/\mu L$)	0.99 ± 0.20	1.09 ± 0.12	1.09 ± 0.10	0.85 ± 0.11	0.98 ± 0.19	1.21 ± 0.21
Lymphocytes ($10^3/\mu L$)	4.40 ± 0.17	4.45 ± 0.18	5.15 ± 0.25*	5.66 ± 0.17**	7.17 ± 0.14**	8.98 ± 0.63**
Monocytes ($10^3/\mu L$)	0.08 ± 0.01	0.09 ± 0.03	0.09 ± 0.03	0.07 ± 0.02	0.10 ± 0.04	0.10 ± 0.04
Eosinophils ($10^3/\mu L$)	0.05 ± 0.02	0.03 ± 0.01	0.04 ± 0.02	0.05 ± 0.02	0.05 ± 0.03	0.02 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.20 ± 0.13	0.50 ± 0.22	0.10 ± 0.10	0.20 ± 0.13	2.00 ± 0.47**	5.67 ± 1.41**[b]
Clinical Chemistry						
n	10	9	10	10	10	10
Methemoglobin (g/dL)	5.16 ± 0.58	5.81 ± 0.32	5.16 ± 0.26	5.15 ± 0.21	10.28 ± 0.63**	16.23 ± 0.74**
Urinalysis						
n	10	10	10	10	10	10
Specific gravity	1.030 ± 0.004	1.022 ± 0.003	1.034 ± 0.005	1.029 ± 0.003	1.032 ± 0.001	1.040 ± 0.004*

TABLE I2
Hematology, Clinical Chemistry, and Urinalysis Data for Rats in the 13-Week Feed Study of o-Nitroanisole (continued)

	0 ppm	200 ppm	600 ppm	2,000 ppm	6,000 ppm	18,000 ppm
Female						
Hematology						
n	10	10	10	9	10	10
Hematocrit (%)	44.9 ± 0.2	45.3 ± 0.4	45.5 ± 0.4	43.7 ± 0.2*	39.3 ± 0.2**	39.5 ± 0.2**
Hemoglobin (g/dL)	15.4 ± 0.1	15.3 ± 0.2	15.2 ± 0.1	14.5 ± 0.1**	13.0 ± 0.1**	14.2 ± 0.1**
Erythrocytes ($10^6/\mu L$)	7.45 ± 0.03	7.50 ± 0.08	7.54 ± 0.06	7.27 ± 0.03*	6.40 ± 0.05**	5.89 ± 0.05**
Mean cell volume (fL)	60.3 ± 0.2	60.4 ± 0.3	60.2 ± 0.1	60.1 ± 0.1	61.5 ± 0.2**	67.2 ± 0.4**
Mean cell hemoglobin (pg)	20.6 ± 0.1	20.4 ± 0.1	20.1 ± 0.1	20.0 ± 0.1**	20.3 ± 0.1	24.1 ± 0.2
Mean cell hemoglobin concentration (g/dL)	34.2 ± 0.2	33.8 ± 0.2	33.4 ± 0.2	33.3 ± 0.2*	33.1 ± 0.2*	36.0 ± 0.2
Reticulocytes ($10^6/\mu L$)	0.92 ± 0.27	0.79 ± 0.18	1.26 ± 0.18	2.36 ± 0.17**	4.36 ± 0.44**	11.01 ± 1.15**
Leukocytes ($10^3/\mu L$)	4.84 ± 0.35	4.48 ± 0.18	5.16 ± 0.29	4.83 ± 0.22	6.97 ± 0.26**	9.96 ± 0.68**
Segmented neutrophils ($10^3/\mu L$)	0.81 ± 0.12	0.70 ± 0.09	0.88 ± 0.08	0.61 ± 0.08	0.79 ± 0.07	1.15 ± 0.16
Lymphocytes ($10^3/\mu L$)	3.97 ± 0.32	3.72 ± 0.16	4.18 ± 0.24	4.19 ± 0.15	6.13 ± 0.26**	8.69 ± 0.59**
Monocytes ($10^3/\mu L$)	0.04 ± 0.02	0.02 ± 0.01	0.07 ± 0.02	0.01 ± 0.01	0.02 ± 0.01	0.15 ± 0.03*
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.04 ± 0.01	0.04 ± 0.01	0.03 ± 0.02	0.03 ± 0.01	0.01 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.20 ± 0.13	0.30 ± 0.15	0.30 ± 0.21	0.56 ± 0.34	1.60 ± 0.97	8.40 ± 1.71**
Clinical Chemistry						
n	10	10	10	9	10	10
Methemoglobin (g/dL)	2.56 ± 0.44	1.83 ± 0.07	2.23 ± 0.07	2.51 ± 0.09*	6.70 ± 0.24**	16.46 ± 0.41**
Urinalysis						
n	10	10	8	9	9	10
Specific gravity	1.034 ± 0.005	1.026 ± 0.005	1.034 ± 0.006	1.027 ± 0.002	1.046 ± 0.006	1.035 ± 0.003

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=9

TABLE I3
Hematology and Clinical Chemistry Data for Rats at the 3-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole[a]

	0 ppm	6,000 ppm	18,000 ppm
Male			
Hematology			
n	10	10	10
Hematocrit (%)	45.3 ± 0.5	38.9 ± 0.5**	36.9 ± 0.4**
Hemoglobin (g/dL)	16.4 ± 0.2	13.6 ± 0.3**	13.6 ± 0.2**
Erythrocytes ($10^6/\mu L$)	9.61 ± 0.07	8.19 ± 0.09**	6.46 ± 0.07**
Mean cell volume (fL)	47.0 ± 0.2	47.4 ± 0.2	57.0 ± 0.5**
Mean cell hemoglobin (pg)	16.9 ± 0.1	16.6 ± 0.3	21.1 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	36.1 ± 0.2	34.9 ± 0.6	37.0 ± 0.3
Platelets ($10^3/\mu L$)	5.3 ± 0.1	7.0 ± 0.1**	4.7 ± 0.2
Reticulocytes ($10^6/\mu L$)	1.99 ± 0.13	4.86 ± 0.45**	11.38 ± 1.05**
Leukocytes ($10^3/\mu L$)	3.48 ± 0.22	3.99 ± 0.33	3.39 ± 0.10
Segmented neutrophils ($10^3/\mu L$)	0.65 ± 0.05	0.75 ± 0.07	0.57 ± 0.06
Lymphocytes ($10^3/\mu L$)	2.76 ± 0.20	3.20 ± 0.35	2.73 ± 0.12
Atypical lymphocytes ($10^3/\mu L$)	0.06 ± 0.01	0.03 ± 0.01	0.08 ± 0.02
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Clinical Chemistry			
n	9	10	10
Methemoglobin (g/dL)	0.27 ± 0.07	0.60 ± 0.08*	1.17 ± 0.17**
Female			
Hematology			
n	9	9	8
Hematocrit (%)	45.0 ± 1.1	38.1 ± 0.5**	34.7 ± 0.8**
Hemoglobin (g/dL)	15.8 ± 0.4	13.4 ± 0.2**	12.5 ± 0.6**
Erythrocytes ($10^6/\mu L$)	8.79 ± 0.19	7.45 ± 0.08**	6.29 ± 0.15**
Mean cell volume (fl)	51.2 ± 0.2	51.1 ± 0.4	55.4 ± 0.4**
Mean cell hemoglobin (pg)	18.0 ± 0.1	18.0 ± 0.1	19.8 ± 0.5**
Mean cell hemoglobin concentration (g/dL)	35.1 ± 0.2	35.3 ± 0.2	35.9 ± 1.0**
Platelets ($10^3/\mu L$)	5.7 ± 0.2	7.1 ± 0.2*	4.4 ± 0.2
Reticulocytes ($10^6/\mu L$)	2.27 ± 0.39	4.82 ± 0.42**	9.50 ± 0.90**
Leukocytes ($10^3/\mu L$)	3.20 ± 0.30	2.86 ± 0.21	2.96 ± 0.13
Segmented neutrophils ($10^3/\mu L$)	0.81 ± 0.08	0.55 ± 0.08*	0.44 ± 0.05**
Lymphocytes ($10^3/\mu L$)	2.28 ± 0.28	2.26 ± 0.18	2.44 ± 0.09
Atypical lymphocytes ($10^3/\mu L$)	0.08 ± 0.01	0.03 ± 0.02*	0.07 ± 0.01
Monocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.03 ± 0.02	0.02 ± 0.01	0.01 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.11 ± 0.11	0.67 ± 0.44	4.13 ± 0.79**
Clinical Chemistry			
n	9	10	8
Methemoglobin (g/dL)	0.31 ± 0.08	0.58 ± 0.05*	1.16 ± 0.12**

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error

TABLE I4
Hematology and Clinical Chemistry Data for Rats at the 6-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole[a]

	0 ppm	6,000 ppm	18,000 ppm
Male			
Hematology			
n	9	10	9
Hematocrit (%)	45.6 ± 0.7[b]	39.0 ± 0.5**	40.8 ± 0.7**[b]
Hemoglobin (g/dL)	14.6 ± 0.5	12.7 ± 0.1**	13.0 ± 0.2**
Erythrocytes (10^6/μL)	8.50 ± 0.33	7.39 ± 0.05**	6.66 ± 0.11**
Mean cell volume (fL)	54.2 ± 2.3	52.7 ± 0.6	61.2 ± 1.3**
Mean cell hemoglobin (pg)	17.2 ± 0.2	17.2 ± 0.1	19.6 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	32.0 ± 0.9	32.6 ± 0.5	32.2 ± 0.6
Platelets (10^3/μL)	5.9 ± 0.7	7.7 ± 0.1	3.9 ± 0.2*
Reticulocytes (10^6/μL)	2.34 ± 0.78[b]	3.06 ± 0.37	9.13 ± 1.21**[b]
Leukocytes (10^3/μL)	4.50 ± 0.29	5.49 ± 0.23	3.62 ± 0.21*
Segmented neutrophils (10^3/μL)	1.13 ± 0.12	1.29 ± 0.15	1.06 ± 0.21
Lymphocytes (10^3/μL)	3.19 ± 0.30	4.02 ± 0.30	2.50 ± 0.09
Atypical lymphocytes (10^3/μL)	0.06 ± 0.02	0.03 ± 0.02	0.03 ± 0.01
Monocytes (10^3/μL)	0.03 ± 0.01	0.07 ± 0.02	0.01 ± 0.01
Eosinophils (10^3/μL)	0.07 ± 0.02	0.05 ± 0.01	0.02 ± 0.01*
Clinical Chemistry			
n	10	10	10
Methemoglobin (g/dL)	0.64 ± 0.22	1.80 ± 0.36**	1.93 ± 0.25**
Female			
Hematology			
n	9	8	9
Hematocrit (%)	42.6 ± 1.0	37.6 ± 0.9**[c]	38.4 ± 0.4**
Hemoglobin (g/dL)	14.1 ± 0.2	12.5 ± 0.2**	12.1 ± 0.1**
Erythrocytes (10^6/μL)	7.56 ± 0.11	6.62 ± 0.08**	6.21 ± 0.11**
Mean cell volume (fL)	56.2 ± 1.4	56.8 ± 1.4	62.2 ± 1.5*
Mean cell hemoglobin (pg)	18.6 ± 0.1	18.9 ± 0.1*	19.5 ± 0.2**
Mean cell hemoglobin concentration (g/dL)	33.1 ± 0.8	33.4 ± 0.8	31.5 ± 0.5
Platelets (10^3/μL)	5.4 ± 0.1	6.2 ± 0.2	3.4 ± 0.1**
Reticulocytes (10^6/μL)	1.18 ± 0.16	4.22 ± 0.55**[c]	12.29 ± 1.41**
Leukocytes (10^3/μL)	2.52 ± 0.13	3.48 ± 0.22**	3.07 ± 0.13**
Segmented neutrophils (10^3/μL)	0.59 ± 0.05	0.71 ± 0.08	0.62 ± 0.09
Lymphocytes (10^3/μL)	1.8 ± 0.1	2.7 ± 0.2**	2.4 ± 0.1**
Atypical lymphocytes (10^3/μL)	0.03 ± 0.01	0.05 ± 0.02	0.03 ± 0.03
Monocytes (10^3/μL)	0.03 ± 0.02	0.01 ± 0.01	0.03 ± 0.01
Eosinophils (10^3/μL)	0.03 ± 0.01	0.01 ± 0.01	0.00 ± 0.00**
Nucleated erythrocytes (10^3/μL)	2.00 ± 0.96	2.78 ± 0.78[c]	7.67 ± 1.52**
Clinical Chemistry			
n	9	9	9
Methemoglobin (g/dL)	0.75 ± 0.23	1.85 ± 0.59	2.98 ± 0.48**

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
** P≤0.01
[a] Mean ± standard error [b] n=10 [c] n=9

TABLE I5
Hematology and Clinical Chemistry Data for Rats at the 9-Month Interim Evaluation in the Stop-Exposure Feed Study of *o*-Nitroanisole[a]

	0 ppm	6,000 ppm	18,000 ppm
Male			
Hematology			
n	10	10	6
Hematocrit (%)	37.8 ± 0.6	36.5 ± 0.3°	33.7 ± 2.4
Hemoglobin (g/dL)	14.4 ± 0.1	14.0 ± 0.1°	12.9 ± 0.8°
Erythrocytes ($10^6/\mu L$)	8.91 ± 0.12	8.36 ± 0.08°°	7.82 ± 0.63°
Mean cell volume (fL)	42.3 ± 0.5	43.6 ± 0.3	43.2 ± 0.7
Mean cell hemoglobin (pg)	16.2 ± 0.2	16.8 ± 0.1	16.6 ± 0.4
Mean cell hemoglobin concentration (g/dL)	38.3 ± 0.5	38.5 ± 0.3	38.4 ± 0.7
Platelets ($10^3/\mu L$)	4.7 ± 0.2	5.4 ± 0.1°	5.1 ± 0.3
Reticulocytes ($10^6/\mu L$)	1.40 ± 0.27	1.67 ± 0.26	5.45 ± 1.61°°
Leukocytes ($10^3/\mu L$)	3.10 ± 0.14	3.54 ± 0.25	4.93 ± 0.62°°
Segmented neutrophils ($10^3/\mu L$)	0.79 ± 0.12	0.96 ± 0.10°	2.56 ± 0.45°°
Lymphocytes ($10^3/\mu L$)	2.20 ± 0.10	2.47 ± 0.18	2.33 ± 0.25
Atypical lymphocytes ($10^3/\mu L$)	0.04 ± 0.01	0.03 ± 0.01	0.01 ± 0.01
Monocytes ($10^3/\mu L$)	0.04 ± 0.01	0.05 ± 0.01	0.03 ± 0.02
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.03 ± 0.01	0.01 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.20 ± 0.13	0.40 ± 0.16	0.83 ± 0.54
Clinical Chemistry			
n	4	6	2
Methemoglobin (g/dL)	0.21 ± 0.07	0.22 ± 0.02	0.25 ± 0.03
Female			
Hematology			
n	9	10	6
Hematocrit (%)	34.7 ± 0.6	37.3 ± 0.6	32.0 ± 2.5
Hemoglobin (g/dL)	14.0 ± 0.2	14.7 ± 0.2	12.3 ± 1.1
Erythrocytes ($10^6/\mu L$)	7.76 ± 0.09	8.08 ± 0.15	6.76 ± 0.58
Mean cell volume (fL)	44.9 ± 0.4	46.1 ± 0.5	47.7 ± 0.8°°
Mean cell hemoglobin (pg)	18.0 ± 0.1	18.3 ± 0.1	18.2 ± 0.4
Mean cell hemoglobin concentration (g/dL)	40.2 ± 0.5	39.6 ± 0.4	38.2 ± 0.5°
Platelets ($10^3/\mu L$)	4.3 ± 0.2	4.4 ± 0.2	4.7 ± 0.4
Reticulocytes ($10^6/\mu L$)	1.56 ± 0.18	1.53 ± 0.18	9.20 ± 3.85°
Leukocytes ($10^3/\mu L$)	1.49 ± 0.08	1.96 ± 0.10°°	4.40 ± 0.32°°
Segmented neutrophils ($10^3/\mu L$)	0.29 ± 0.02	0.36 ± 0.04	1.86 ± 0.27°°
Lymphocytes ($10^3/\mu L$)	1.15 ± 0.08	1.55 ± 0.09°	2.40 ± 0.18°°
Atypical lymphocytes ($10^3/\mu L$)	0.02 ± 0.01	0.02 ± 0.01	0.04 ± 0.02
Monocytes ($10^3/\mu L$)	0.01 ± 0.00	0.01 ± 0.01	0.07 ± 0.02°
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.02 ± 0.00	0.03 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.44 ± 0.24	0.20 ± 0.13	1.00 ± 0.52
Clinical Chemistry			
n	5	6	4
Methemoglobin (g/dL)	0.22 ± 0.07	0.28 ± 0.10	0.31 ± 0.07

° Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
°° $P \leq 0.01$
[a] Mean ± standard error

TABLE I6
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of o-Nitroanisole[a]

	0 ppm	60 ppm	200 ppm	600 ppm	2,000 ppm	6,000 ppm
Male						
Hematology						
n	10	10	7	8	10	10
Hematocrit (%)	44.4 ± 0.7	41.7 ± 0.9*	45.7 ± 1.3	42.1 ± 0.4*	41.1 ± 0.9*	41.5 ± 0.2**
Hemoglobin (g/dL)	14.6 ± 0.2	13.8 ± 0.3*	15.2 ± 0.5	14.0 ± 0.1*	13.5 ± 0.3*	13.6 ± 0.1**
Erythrocytes ($10^6/\mu L$)	8.32 ± 0.14	7.68 ± 0.24	8.54 ± 0.36	7.94 ± 0.11	7.92 ± 0.14	8.08 ± 0.06
Mean cell volume (fL)	53.3 ± 0.3	54.5 ± 0.9	53.9 ± 1.5	53.1 ± 0.4	51.9 ± 0.2**	51.3 ± 0.2**
Mean cell hemoglobin (pg)	17.6 ± 0.1	18.0 ± 0.2	17.9 ± 0.4	17.6 ± 0.1	17.1 ± 0.1*	16.9 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	33.0 ± 0.2	33.0 ± 0.2	33.3 ± 0.3	33.2 ± 0.2	33.0 ± 0.2	32.9 ± 0.2
Reticulocytes ($10^6/\mu L$)	1.52 ± 0.22[b]	2.98 ± 0.36*[b]	2.51 ± 0.85	2.21 ± 0.43	2.91 ± 0.20**	2.28 ± 0.16
Leukocytes ($10^3/\mu L$)	4.38 ± 0.53	4.39 ± 0.48	5.26 ± 1.08	4.18 ± 0.43	4.74 ± 0.52	3.08 ± 0.17
Segmented neutrophils ($10^3/\mu L$)	1.60 ± 0.48	2.13 ± 0.29	2.67 ± 0.75	2.75 ± 0.35	2.37 ± 0.45	0.52 ± 0.06[b]
Lymphocytes ($10^3/\mu L$)	2.73 ± 0.15	2.22 ± 0.32	2.51 ± 0.51	1.35 ± 0.16**	2.32 ± 0.39	2.37 ± 0.17
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.03 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.02 ± 0.01	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.04 ± 0.02	0.01 ± 0.01	0.04 ± 0.02	0.04 ± 0.01	0.04 ± 0.01	0.07 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.10 ± 0.10	0.00 ± 0.00	0.00 ± 0.00	0.13 ± 0.13	0.10 ± 0.10	0.10 ± 0.10
Clinical Chemistry						
n	10	10	7	7	10	9
Methemoglobin (g/dL)	2.80 ± 0.16	2.74 ± 0.35	2.00 ± 0.23	2.51 ± 0.18	2.73 ± 0.18	3.94 ± 0.22**
Urinalysis						
n	3	7	2	8	5	8
Specific gravity	1.050 ± 0.015	1.043 ± 0.011	1.031 ± 0.002	1.027 ± 0.005	1.031 ± 0.007	1.023 ± 0.006

TABLE I6
Hematology, Clinical Chemistry, and Urinalysis Data for Mice in the 13-Week Feed Study of *o*-Nitroanisole (continued)

	0 ppm	60 ppm	200 ppm	600 ppm	2,000 ppm	6,000 ppm
Female						
Hematology						
n	10	10	10	10	10	10
Hematocrit (%)	47.6 ± 0.5	48.8 ± 0.3	48.5 ± 0.4	47.7 ± 0.3	46.6 ± 0.5	43.2 ± 0.2**
Hemoglobin (g/dL)	15.5 ± 0.2	15.7 ± 0.1	15.7 ± 0.1	15.4 ± 0.1	15.0 ± 0.1*	14.1 ± 0.1**
Erythrocytes ($10^6/\mu L$)	8.76 ± 0.10	9.03 ± 0.07	8.95 ± 0.07	8.77 ± 0.07	8.57 ± 0.08	8.22 ± 0.09**
Mean cell volume (fL)	54.3 ± 0.3	54.1 ± 0.1	54.3 ± 0.2	53.4 ± 0.9	54.4 ± 0.4	52.5 ± 0.5**
Mean cell hemoglobin (pg)	17.7 ± 0.1	17.4 ± 0.1*	17.5 ± 0.1	17.6 ± 0.1	17.5 ± 0.1	17.2 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.6 ± 0.2	32.2 ± 0.1	32.4 ± 0.2	32.3 ± 0.1	32.2 ± 0.2	32.8 ± 0.1
Reticulocytes ($10^6/\mu L$)	2.46 ± 0.38	2.91 ± 0.30	2.09 ± 0.25	2.51 ± 0.38	1.93 ± 0.09	3.07 ± 0.31
Leukocytes ($10^3/\mu L$)	2.75 ± 0.12	2.88 ± 0.28	2.91 ± 0.30	2.24 ± 0.18[b]	1.98 ± 0.13*	3.15 ± 0.28
Segmented neutrophils ($10^3/\mu L$)	0.50 ± 0.07	0.66 ± 0.10	1.01 ± 0.25	0.48 ± 0.07[b]	0.47 ± 0.11	0.47 ± 0.05
Lymphocytes ($10^3/\mu L$)	2.19 ± 0.10	2.17 ± 0.21	1.86 ± 0.15	1.72 ± 0.14[b]	1.47 ± 0.10**	2.61 ± 0.26
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00[b]	0.02 ± 0.01	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.06 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.01[b]	0.03 ± 0.01	0.06 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.10 ± 0.10	0.00 ± 0.00	0.00 ± 0.00
Clinical chemistry						
n	10	10	9	10	10	10
Methemoglobin (g/dL)	1.86 ± 0.26	2.39 ± 0.16	2.33 ± 0.12	0.93 ± 0.34	0.69 ± 0.22	2.66 ± 0.48
Urinalysis						
n	6	10	6	7	9	10
Specific gravity	1.018 ± 0.003	1.020 ± 0.002	1.025 ± 0.002	1.019 ± 0.003	1.016 ± 0.001	1.020 ± 0.003

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=9

APPENDIX J
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF *o*-NITROANISOLE

o-Nitroanisole was obtained from Aldrich Chemical Company (Milwaukee, WI) in three lots (lot TE061197, lot 2712DL, and lot 1517AM). Lot TE061197 was used throughout the 14-day and 13-week studies in rats and mice and in a portion of the stop-exposure and 2-year studies in rats. Lot 2712DL was used in a portion of the stop-exposure study in rats and the 2-year studies in rats and mice; lot 1517AM was used in a portion of the 2-year studies in rats and mice. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (MRI; Kansas City, MO). MRI reports on analyses performed in support of the *o*-nitroanisole studies are on file at the National Institute of Environmental Health Sciences.

All three lots of the chemical, a clear yellow liquid, were identified as *o*-nitroanisole by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra of *o*-nitroanisole (*Sadtler Standard Spectra*), as shown in Figures J1 and J2.

The purity of all lots was determined by Karl Fischer water analysis, elemental analyses, titration, thin-layer chromatography (TLC), and gas chromatography. Titration was performed by reducing the nitro group with titanous chloride in a glacial acetic acid:hydrochloric acid:hydrofluoric acid medium followed by back-titration of the excess titanous chloride with 0.25 N ferric ammonium sulfate. Titration was monitored potentiometrically with a platinum foil indicator electrode versus a silver/silver chloride reference electrode. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) toluene and 2) methylene chloride. Plates were examined under shortwave (254 nm) and longwave (366 nm) ultraviolet light and a spray of 5% titanous chloride. Gas chromatographic analysis was performed with a flame ionization detector (FID) with a nitrogen carrier gas at a flow rate of 70 mL/minute. Two systems were used: A) 10% SP-2100 on 80/100 Supelcoport, with an oven temperature program of 50° C for 5 minutes, then 50° to 250° C at 10° C per minute, and B) 10% Carbowax 20M/TPA on 80/100 Chromosorb W(AW) with an oven temperature program of 60° C for 6 minutes, then 60° to 200° C at 10° C per minute.

Elemental analyses of lot TE061197 for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for *o*-nitroanisole. Karl Fischer water analysis indicated 0.238 ± 0.008% water. Titration indicated a purity of at least 97%. Each TLC system indicated only a major spot. Gas chromatography using the first system indicated a major peak and one impurity with a total area of less than 0.3% relative to the major peak. A major peak with no impurities with areas greater than or equal to 0.1% of the major peak area was observed with the second column. The overall purity was determined to be approximately 99%.

Lot 2712DL was received in two shipments, which were analyzed separately. For the first batch, elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for *o*-nitroanisole. Karl Fischer water analysis indicated 0.091 ± 0.003% water. Titration indicated a purity of at least 97%. Each TLC system indicated only a major spot. Gas chromatography using the first system indicated a major peak and three impurities with a total area of 0.4% relative to the major peak. A major peak and two impurities with a total area of 0.3% relative to the major peak was observed with the second system. For the second batch, elemental analyses for carbon were slightly low, while values for hydrogen and nitrogen were in agreement with the theoretical values for *o*-nitroanisole. Titration indicated a purity of at least 96%. Each TLC system indicated only a major spot. Gas chromatography using both systems indicated a major peak and two impurities with a total area of 0.3% relative to the major peak. A concomitant analysis of lot TE061197 using gas chromatography indicated a major peak and one impurity

with an area of 0.1% relative to the major peak by system A. The second system indicated a major peak and one impurity with an area of 0.1% relative to the major peak. The overall purity of this batch of lot 2712DL was determined to be approximately 99%, which is consistent with lot TE061197.

Elemental analyses of lot 1517AM for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for *o*-nitroanisole. Karl Fischer water analysis indicated 0.037 ± 0.002% water. Titration indicated a purity of at least 98%. Each TLC system indicated one major spot and no impurities. Gas chromatography using system A indicated a major peak and three impurities with a total area of 0.67% relative to the major peak. A major peak and three impurities with a total area of 0.56% relative to the major peak was observed with system B as described above, but with an oven temperature program of 60° C for 6 minutes, then 60° to 225° C at 10° C per minute. A concomitant analysis of lot TE061197 with lot 1517AM by gas chromatography using system A, but with an oven temperature of 180° C, and with pentadecane added as an internal standard, gave a relative purity of approximately 100% for lot 1517AM relative to lot TE061197.

Stability studies were performed by the analytical chemistry laboratory on lot TE061197. Gas chromatography was performed using system A described above, but with *n*-pentadecane added as an internal standard and an oven temperature of 180° C. These studies indicated that *o*-nitroanisole was stable as a bulk chemical for at least 2 weeks at temperatures up to 60° C. The stability of the bulk chemical was monitored periodically at the study laboratory with infrared and ultraviolet/visible spectroscopy and gas chromatography methods similar to those described above. No degradation of the bulk chemical was observed.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared by mixing the appropriate amounts of *o*-nitroanisole and feed in a blender (Patterson-Kelley Twin Shell with intensifier bar) for 15 minutes (Table J1). Studies to determine homogeneity and stability of the dosed feed preparations were conducted by the analytical chemistry laboratory. For homogeneity analyses, feed samples were extracted with 100 mL of acetonitrile, centrifuged, and further diluted with acetonitrile. The absorbance of the samples was measured versus acetonitrile by ultraviolet spectroscopy at 325 nm. For the stability studies, feed samples were extracted with 100 mL of 0.25 N hydrochloric acid in acetonitrile, centrifuged, and further diluted with acetonitrile. The samples were then injected into a high-performance liquid chromatographic system equipped with a μBondpak C_{18} column. The mobile phase was a mixture of water:acetonitrile at a ratio of 60:40 and a flow rate of 1 mL/minute. Ultraviolet detection was at 254 nm. Homogeneity was confirmed and the stability of the dose formulations was established for at least 2 weeks when stored in the dark at temperatures up to 25° C and for 1 week when stored open to air and light.

Periodic analyses of the dose formulations of *o*-nitroanisole were conducted at the study laboratory and the analytical chemistry laboratory using an ultraviolet spectroscopic method as well as two HPLC methods. During the 14-day studies, the dose formulations were analyzed at the beginning of the studies (Table J2). During the 13-week studies, the dose formulations were analyzed at the initiation, midpoint, and termination of the studies (Table J3). In both the 14-day and 13-week studies, an ultraviolet spectroscopic method that required an acetonitrile extraction was used.

During the 2-year studies, the dose formulations were analyzed at least once every 8 weeks using two HPLC methods (Table J4). The two methods differed primarily in the extraction and clean-up procedures. The earlier subchronic studies had demonstrated that *o*-nitroanisole binds strongly to feed; it was also observed that the analytical recovery was time dependent so that the longer the chemical stayed in contact with the feed, the lower the recovery. The first method used to overcome this problem involved an elaborate extraction and clean-up procedure. The feed formulations were first digested with approximately 8 N hydrochloric acid, diluted with ethanol, and then extracted with petroleum ether:ethyl ether (1:1). After evaporation to dryness, the oily residue was dissolved in corn oil, and the corn oil solution was then

extracted with acetonitrile. Prior to the injection into the HPLC, the acetonitrile extract was diluted with water and filtered. The complexity of the first method contributed to periodic analysis problems. During the second year of the 2-year study, the extraction and clean-up method was simplified. In the modified procedure, the untreated feed formulations were extracted directly with 0.25 N hydrochloric acid in acetonitrile; the extracts were then neutralized with sodium hydroxide and injected into the HPLC. The method was limited by the requirement that the analyses had to be conducted immediately after the dose formulations were prepared. The change was worthwhile because during the remainder of the studies only three formulations were outside of the specifications. While the analytical recovery problem was overcome by the immediate analysis of the feed formulations, there was concern that the bioavailability of *o*-nitroanisole would be affected by the physical binding to feed. In a subsequent separate study, it was demonstrated that the physical binding of *o*-nitroanisole to feed did not affect its bioavailability (Yuan *et al.*, 1991).

In the stop-exposure and 2-year studies, 85% (141/166) of the dose formulations were within ± 10% of the target concentrations. Results of the periodic referee analyses performed by the analytical chemistry laboratory were in good agreement with the results obtained by the study laboratory (Table J5).

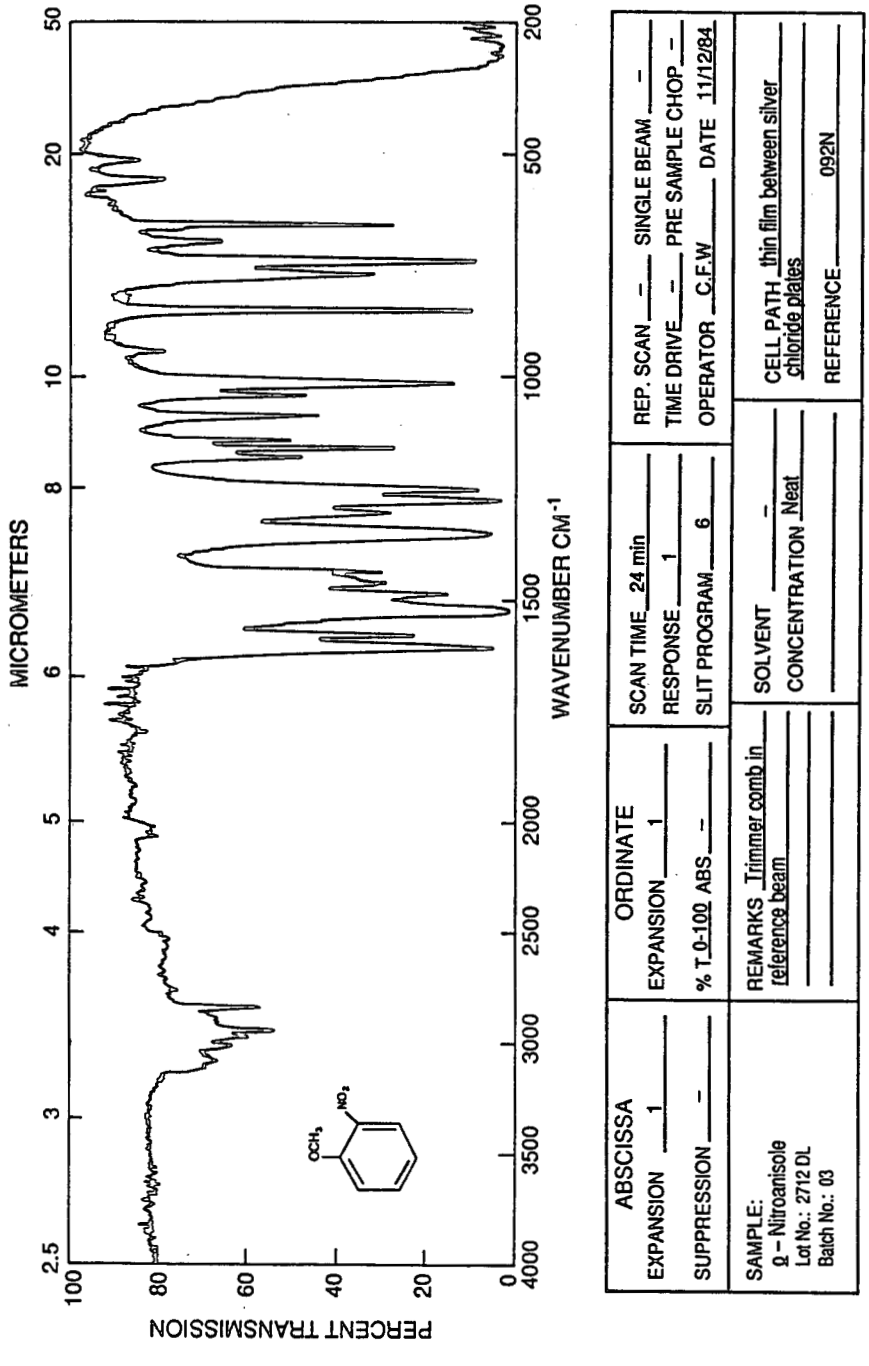


FIGURE J1
Infrared Absorption Spectrum of *o*-Nitroanisole

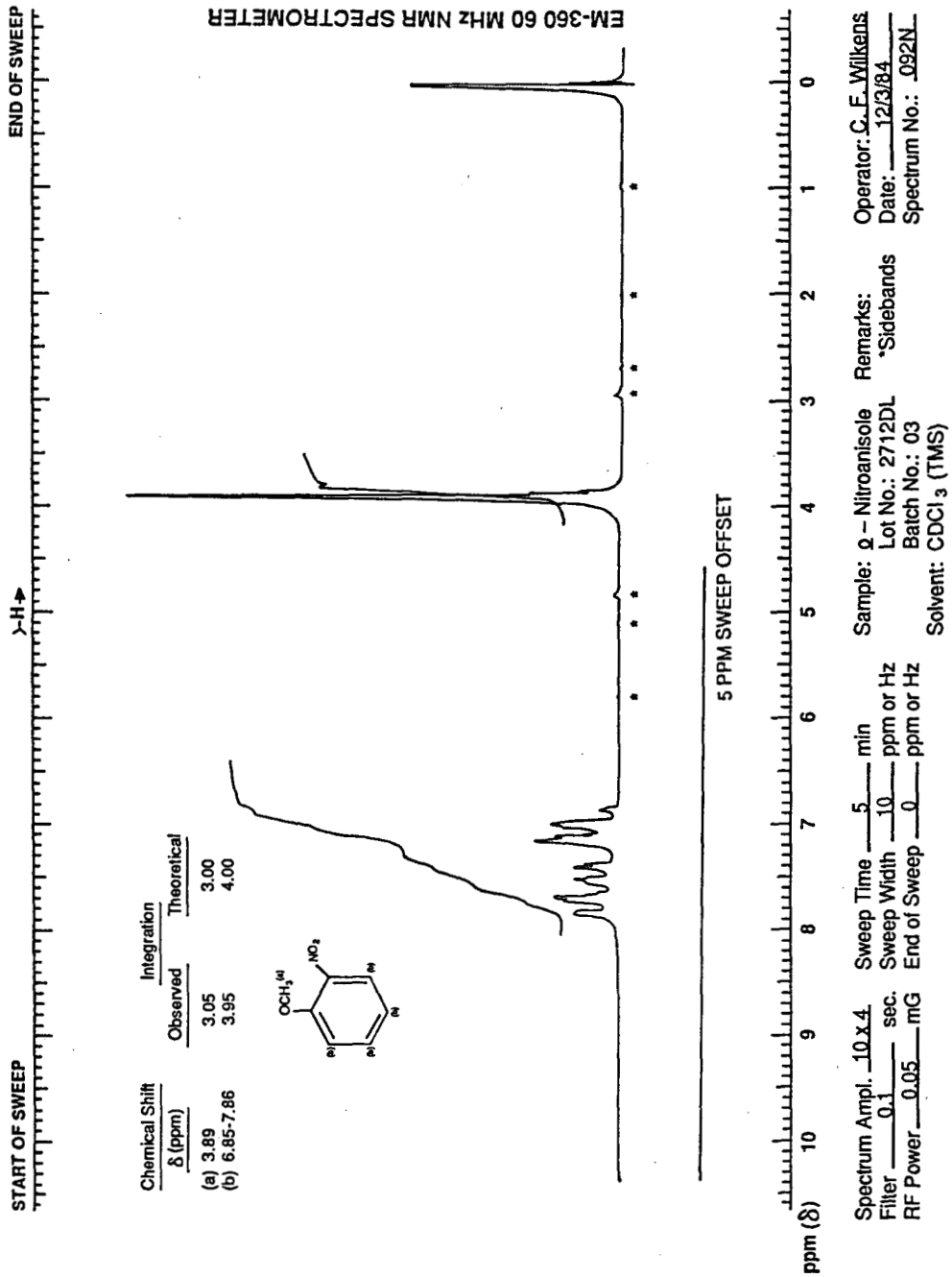


FIGURE J2
Nuclear Magnetic Resonance Spectrum of *o*-Nitroanisole

TABLE J1
Preparation and Storage of Dose Formulations in the Feed Studies of *o*-Nitroanisole

14-Day Studies	13-Week Studies	2-Year Studies
Preparation		
Dose formulations were prepared at the beginning of the studies. Premix was prepared by mixing feed and *o*-nitroanisole; premix and remaining feed were layered in a blender with an intensifier bar and mixed for 15 minutes.	Same as 14-day studies except that dose formulations were prepared weekly.	Same as 14-day studies except that dose formulations were prepared weekly. For the 666 ppm dose groups, feed was placed in a sieve and shaken to obtain feed flour. The premix was prepared by mixing *o*-nitroanisole and feed flour; premix and remaining feed were placed in a blender with an intensifier bar and mixed for 15 minutes.
Lot Number		
TE061197	TE061197	TE061197, 2712DL, and 1517AM
Maximum Storage Time		
14 days	Same as 14-day studies	Same as 14-day studies
Storage		
Room temperature, in glass jugs	Same as 14-day studies	Same as 14-day studies
Study Laboratory		
Hazleton Raltech, Inc., Madison, WI	Same as 14-day studies	Southern Research Institute, Birmingham, AL
Analytical Chemistry Laboratory		
Midwest Research Institute, Kansas City, MO	Same as 14-day studies	Same as 14-day studies

TABLE J2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 14-Day Feed Studies of *o*-Nitroanisole

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
Rats				
31 March 1982	31 March 1982	583	320	–45
		1,166	891	–24
		2,332	1,742	–25
		4,665	4,056	–13
		9,330	7,470	–20
7 April 1982	7 April 1982	250	206[b]	–18
Mice				
31 March 1982	31 March 1982	250	57	–76
		500	278	–44
		1,000	894	–11
		2,000	1,502	–25
		4,000	3,146	–22
7 April 1982	7 April 1982	250	206	–18

[a] Results of duplicate analyses
[b] Result of seven analyses. Excludes one outlier value of 370 ppm.

TABLE J3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of *o*-Nitroanisole

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
5 May 1982	5 May 1982	60	52.7[b]	–12
		60	46.2[b]	–23
		60	59.1[b]	–2
		60	57.9[b]	–4
		60	40.7[b]	–32
		60	37.9[b]	–37
		200	158	–21[c]
		600	654	+9
		2,000	2,110	+6
		6,000	5,300	–12[c]
		18,000	17,570[b]	–2
		18,000	17,720[b]	–2
		18,000	17,730[b]	–2
		18,000	17,670[b]	–2
		18,000	17,920[b]	0
		18,000	17,930[b]	0
10 May 1982[d]	10 May 1982	200	164	–18[c]
		6,000	5,305	–12[c]
12 May 1982[d]	12 May 1982	200	209	+4
		6,000	5925	–1
17 June 1982	17 June 1982	60	22.7[b]	–62
		60	15.1[b]	–75
		60	20.4[b]	–66
		60	13.9[b]	–77
		60	15.0[b]	–75
		60	19.7[b]	–67
		200	146[e]	–27[c]
		600	459[e]	–23[c]
		2,000	1,750[e]	–12[c]
		6,000	5,442[e]	–9
		18,000	17,200[e]	–4
21 June 1982[d]	21 June 1982	60	35.3[b]	–41
		60	44.9[b]	–25
		60	37.8[b]	–37
		60	39.9[b]	–34
		60	31.6[b]	–47
		60	40.1[b]	–33
		200	225[e]	+13[c]
		600	478[e]	–20[c]
		2,000	1,704	–15
21 June 1982[f]	21 June 1982	60	66.7	+11
		200	302	+51
		600	442	–26

TABLE J3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of *o*-Nitroanisole (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
1 July 1982	1 July 1982	60	55.4	–8
		200	174	–13
		600	517	–14
		2,000	1,671	–16
		6,000	5,171	–14
		18,000	16,300	–9
5 August 1982	5 August 1982	60	58.3	–3
		200	182	–9
		600	540	–10
		2,000	2,445	+22
		6,000	6,490	+8
		18,000	18,260	+1

[a] Results of duplicate analyses unless otherwise noted
[b] Results of homogeneity analyses
[c] Sample remixed
[d] Results of remix
[e] Results of quadruple analyses
[f] Results of remix; analyzed using modified method

TABLE J4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *o*-Nitroanisole[a]

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[b] (ppm)	Difference from Target (%)
3 September 1984	4-11 September 19840	222	155[c]	–30
		222	173[c]	–22
		222	199[c]	–10
		222	192	–14
		222	196	–12
		666	628	–6
		666	638	–4
		666	628	–6
		2,000	2,060[c]	+3
		2,000	1,970[c]	–2
		2,000	2,060[c]	+3
		2,000	1,940	–3
		2,000	1,960	–2
10 September 1984	11-17 September 1984	222	218	–2
		222	243	+9
		222	214	–4
		6,000	5,200[c]	–13
		6,000	5,520[c]	–8
		6,000	5,720[c]	–5
		18,000	17,900[c]	–1
		18,000	18,500[c]	+3
		18,000	19,400[c]	+8
17 September 1984	17-19 September 1984	222	204	–8
		222	208[c]	–6
		222	211[c]	–5
		222	198[c]	–11
		222	234	+5
15 October 1984	15-20 October 1984	666	657[c]	–1
		666	692[c]	+4
		666	636[c]	–5
		666	675	+1
		666	675	+1
		666	638	–4
		2,000	1,560	–22
		2,000	1,640	–18
		2,000	1,680	–16
		2,000	1,840	–8
		6,000	5,400[c]	–10
		6,000	5,720[c]	–5
		6,000	6,260[c]	+4
		6,000	5,740	–4
		6,000	5,400	–10
		6,000	5,440	–9
	23-29 October 1984[d]	6,000	6,050	+1

TABLE J4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of o-Nitroanisole (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
22 October 1984[e]	23-29 October 1984	2,000	1,900	-5
		2,000	1,910	-5
		2,000	2,120	+6
		2,000	2,000	0
5 November 1984	5-10 November 1984	222	227	+2
		666	680	+2
		666	724	+9
		666	674	+1
		2,000	1,820	-9
		2,000	1,890	-6
		2,000	1,820	-9
		2,000	1,950	-3
		6,000	6,200	+3
		6,000	6,010	0
		6,000	6,230	+4
		6,000	5,340	-11
		18,000	17,700	-2
		18,000	17,600	-2
		18,000	18,000	0
3 December 1984	3-6 December 1984	666	616	-8
		666	603	-9
		666	636	-5
		666	581	-13
		2,000	1,960	-2
		2,000	1,980	-1
		2,000	1,920	-4
		2,000	1,900	-5
		6,000	5,660	-6
		6,000	5,760	-4
		6,000	5,700	-5
		6,000	5,270	-12
7 December 1984[e]	10 December 1984	666	704	+6
		6,000	5,880	-2
14 January 1985	14-17 January 1984	222	214	-4
		222	226	+2
		666	625	-6
		666	701	+5
		2,000	1,980	-1
		2,000	1,980	-1
		6,000	5,480	-9
		6,000	6,040	+1
		18,000	17,800	-1
		18,000	16,300	-9

TABLE J4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *o*-Nitroanisole (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
11 March 1985	11-14 March 1985	222	70	-68[f]
		222	34	-85[f]
		666	502	-25[f]
		666	509	-24[f]
		2,000	1,900	-5[f]
		2,000	2,010	+1[f]
		6,000	5,350	-11[f]
		6,000	5,630	-6[f]
		18,000	15,100	-16[f]
		18,000	18,700	+4[f]
15 March 1985[e]	15-17 March 1985	222	224	+10
		222	303	+36
		666	836	+26
		666	812	+22
		2,000	2,280	+14
		2,000	2,100	+5
		6,000	5,540	-8
		6,000	5,570	-7
		18,000	18,500	+3
		18,000	18,500	+3
6-7 May 1985	6-8 May 1985	222	248	+12[g]
		222	266	+20[g]
		666	659	-1
		666	723	+9
		2,000	1,840	-8
		2,000	1,860	-7
		6,000	5,480	-9
		6,000	5,400	-10
23-24 September 1985	23 September -11 October 1985	222	211	-5
		222	225	+1
		666	666	0
		666	676	+2
		2,000	2,040	+2
		2,000	1,940	-3
		6,000	5,710	-5
		6,000	5,580	-7
2 December 1985	2-5 December 1985	222	170	-23[f]
		222	180	-19[f]
		666	594	-11[f]
		666	656	-2
		2,000	1,940	-3
		2,000	1,980	-1
		6,000	5,740	-4
		6,000	4,900	-18[f]

TABLE J4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *o*-Nitroanisole (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
6 December 1985	6 December 1985	222	223[e]	0
		222	214[e]	–4
		666	663[e]	0
		6,000	6,000	0
13-14 January 1986	13-15 January 1986	222	242	+9
		222	242	+9
		666	632	–5
		666	650	–2
		2,000	1,800	–10
		2,000	1,860	–7
		6,000	6,020	0
		6,000	6,110	+2
24 February 1986	24-27 February 1986	222	228	+3
		222	227	+2
		666	652	–2
		666	636	–5
		2,000	2,000	0
		2,000	1,980	–1
		6,000	5,800	–3
		6,000	5,710	–5
21 April 1986	21-23 April 1986	222	202	–9
		222	207	–7
		666	614	–8
		666	630	–5
		2,000	2,000	0
		2,000	1,990	0
		6,000	5,890	–2
		6,000	5,960	–1
23-24 June 1986	23-25 June 1986	222	208	–6
		222	202	–9
		666	631	–5
		666	606	–9
		2,000	1,930	–4
		2,000	1,980	–1
		6,000	5,740	–4
		6,000	5,860	–2
11-12 August 1986	11 August 1986	222	203	–9
		222	205	–8
		666	647	–3
		666	609	–9
		2,000	1,990	–1
		2,000	1,860	–7
		6,000	5,930	–1
		6,000	5,760	–4

TABLE J4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *o*-Nitroanisole (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration (ppm)	Difference from Target (%)
22 September 1986	22-23 September 1986	666	616	–8
		666	637	–4
		2,000	2,120	+6
		2,000	2,090	+4
		6,000	5,880	–2
		6,000	5,900	–2

[a] Dose formulations for rats: 222, 666, and 2,000 ppm; dose formulations for mice: 666, 2,000, and 6,000 ppm; dose formulations for stop study rats: 6,000 and 18,000 ppm.
[b] Results of duplicate analyses
[c] Homogeneity analysis results (top left, top right, and bottom ports of blender)
[d] Results of reanalysis
[e] Results of remix
[f] Sample remixed
[g] Used for dosing; high results believed due to analytical, not mixing, procedure.

TABLE J5
Results of Referee Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *o*-Nitroanisole

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory[a]	Referee Laboratory[b]
Rats			
3 September 1984	2,000	1,940	2,030
11 March 1985	666	502	643
15 March 1985	222	303	225
	666	836	685
	2,000	2,280	1,950
2 December 1985	666	656	655
23 June 1986	222	208	222
Mice			
3 December 1984	666	603	600
	666	580	614
	2,000	1,920	1,900
	2,000	1,900	1,890
	6,000	5,660	5,600
	6,000	5,270	5,680
11 March 1985	666	502	643
15 March 1985	666	836	685
	666	812	652
	2,000	2,280	1,950
23-24 September 1985	6,000	5,710	5,760
2-3 December 1985	655	656	655
22 September 1986	2,000	2,090	1,920

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

APPENDIX K
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES

TABLE K1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of *o*-Nitroanisole

Week	0 ppm		222 ppm			666 ppm			2,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	13.7	109	14.8	108	30	14.0	106	88	13.2	107	246
5	16.0	245	16.5	258	14	16.3	255	43	17.0	259	131
9	16.1	302	15.0	302	11	15.9	301	35	16.2	301	108
12	16.5	331	16.1	326	11	16.6	324	34	16.8	324	104
16	16.6	364	16.5	360	10	16.5	357	31	16.9	353	96
21	15.5	380	15.4	375	9	15.7	373	28	16.0	371	86
24	16.0	403	15.6	389	9	15.6	392	27	15.7	391	80
28	15.2	408	15.1	401	8	15.5	400	26	16.0	399	80
32	16.2	421	16.4	413	9	16.8	413	27	16.3	412	79
36	16.2	428	16.2	420	9	16.5	421	26	15.5	421	74
40	16.5	438	17.6	424	9	15.9	432	24	16.5	429	77
44	16.0	444	16.4	437	8	16.3	438	25	16.5	435	76
48	15.0	450	15.5	439	8	15.5	440	23	15.7	438	72
52	15.1	441	14.6	437	7	15.6	440	24	16.2	437	74
56	15.2	447	15.2	441	8	15.2	441	23	15.6	435	72
60	14.7	445	14.8	437	8	15.1	441	23	15.3	436	70
64	14.7	447	15.1	438	8	15.1	442	23	13.4	430	62
68	14.3	446	14.9	435	8	15.1	441	23	14.1	427	66
72	15.1	443	14.6	436	7	15.2	443	23	14.7	420	70
76	14.4	441	14.3	433	7	14.7	438	22	14.8	415	71
80	14.7	440	14.3	434	7	14.6	439	22	14.5	411	70
84	13.5	435	14.1	427	7	13.8	430	21	13.9	389	71
88	13.9	430	13.3	426	7	13.7	430	21	13.8	395	70
92	14.1	428	14.3	419	8	13.6	415	22	14.6	378	77
96	13.3	418	14.2	411	8	13.0	412	21	14.8	368	80
100	15.1	417	14.8	407	8	14.5	402	24	15.7	351	89
Mean for weeks											
1-13	15.6	247	15.6	249	17	15.7	246	50	15.8	248	147
14-52	15.8	418	15.9	409	9	16.0	411	26	16.1	409	79
52-100	14.4	437	14.5	429	8	14.5	431	22	14.6	405	72

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

TABLE K2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of *o*-Nitroanisole

Week	0 ppm		222 ppm			666 ppm			2,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
1	10.8	92	10.9	90	27	11.1	90	82	10.6	92	230
5	9.9	143	10.3	160	14	10.6	160	44	10.8	152	142
9	10.4	175	9.9	174	13	10.0	172	39	9.6	174	111
12	9.7	184	10.0	179	12	10.0	179	37	9.8	179	109
16	10.2	196	10.1	190	12	10.1	191	35	10.0	190	105
21	9.9	201	9.7	196	11	9.6	197	32	9.4	194	97
24	9.8	203	9.4	200	10	10.3	201	34	9.7	200	97
28	9.3	211	9.8	207	11	9.5	207	31	9.2	204	91
32	10.3	217	10.3	213	11	10.2	214	32	10.0	209	95
36	10.4	221	10.3	217	11	10.6	218	32	9.8	216	91
40	10.5	232	11.3	226	11	10.9	228	32	10.9	221	99
44	10.4	238	10.4	233	10	11.5	234	33	10.5	227	92
48	10.2	246	10.3	240	10	10.5	242	29	10.4	234	89
52	10.7	255	10.8	245	10	11.1	249	30	10.9	240	91
56	11.0	261	10.7	253	9	11.3	259	29	10.9	248	88
60	10.5	268	10.7	262	9	11.1	266	28	10.7	256	84
64	11.1	275	11.0	266	9	10.8	273	26	9.8	262	75
68	10.7	282	11.2	272	9	11.2	279	27	10.9	266	82
72	11.4	289	11.1	279	9	11.2	284	26	11.3	273	82
76	11.5	298	11.1	284	9	11.4	289	26	11.4	279	82
80	11.3	304	11.8	293	9	10.8	294	25	11.2	285	78
84	11.6	306	11.8	294	9	11.8	294	27	11.4	286	80
88	11.7	313	11.1	309	8	11.2	302	25	10.5	295	71
92	11.1	316	11.2	305	8	11.2	305	24	11.4	293	78
96	11.2	315	11.2	308	8	11.8	304	26	11.7	291	81
100	11.2	317	11.9	304	9	12.5	304	27	12.1	289	84
Mean for weeks											
1-13	10.2	148	10.3	151	17	10.4	151	50	10.2	149	148
14-52	10.1	222	10.2	217	11	10.4	218	32	10.1	214	95
52-100	11.2	295	11.2	286	9	11.4	288	26	11.1	277	80

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

TABLE K3
Feed and Compound Consumption by Male Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole

Week	0 ppm		6,000 ppm			18,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	15.7	160	14.5	146	596	7.3	102	1,287
6	16.3	264	15.0	229	343	9.1	135	1,215
10	16.4	315	11.8	237	299	9.0	150	1,080
13	16.8	339	14.8	271	328	9.5	158	1,082
17	15.7	371	14.0	294	286	9.8	164	1,071
21	15.4	382	14.2	305	280	10.1	174	1,040
25	16.3	398	14.9	318	282	9.8	179	980
29	16.0	411	15.2	341		13.1	217	
33	15.5	417	17.4	363		13.2	255	
37	16.6	437	16.5	386		12.5	277	
41	16.3	437	16.2	393		10.7	279	
45	17.0	447	15.4	406		15.6	273	
49	15.7	447	16.0	414		–[c]	–	
53	15.3	444	16.3	410				
57	15.8	444	15.9	415				
61	16.1	450	16.0	413				
65	15.6	443	14.3	405				
69	14.9	452	15.0	403				
73	15.3	444	14.3	398				
77	14.4	444	15.7	402				
81	15.0	435	17.4	390				
85	15.1	439	16.6	369				
89	14.6	436	14.7	369				
93	14.9	427	13.8	381				
97	12.8	420	24.1	296				
101	11.5	404	18.7	354				
Mean for weeks								
1-13	16.4	269	14.1	221	405	8.7	136	1,166
14-52	16.1	416	15.6	358	282	11.8	227	1,030
52-101	14.7	437	16.4	385		–	–	–

[a] Grams of feed consumed per animal per day
[b] Milligrams of *o*-nitroanisole consumed per day per kilogram body weight
[c] No measurements taken due to 100% mortality

TABLE K4
Feed and Compound Consumption by Female Rats in the Stop-Exposure Feed Study of *o*-Nitroanisole

Week	0 ppm		6,000 ppm			18,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
2	11.5	120	10.5	112	560	6.1	86	1,279
6	10.7	163	9.7	149	390	6.2	101	1,105
10	10.1	179	7.5	154	292	6.3	109	1,048
13	10.8	185	8.8	166	318	7.2	113	1,160
17	9.7	198	8.5	176	289	6.6	120	993
21	9.3	204	8.1	175	277	6.7	124	979
25	10.0	208	9.4	180	312	7.2	127	1,014
29	9.9	214	9.4	193		10.4	150	
33	11.0	219	10.5	196		10.6	166	
37	10.9	230	10.7	205		8.9	173	
41	11.0	237	10.2	208		9.9	175	
45	10.1	246	10.2	216		10.1	185	
49	10.9	254	10.4	220		10.7	189	
53	10.9	261	10.3	224		9.2	187	
57	11.1	273	11.0	230		7.3	192	
61	11.7	279	10.8	233		–[c]	–	
65	11.2	287	10.1	236				
69	11.3	294	10.8	246				
73	11.2	299	11.1	249				
77	11.6	305	11.9	252				
81	11.4	307	11.7	253				
85	12.2	317	12.3	254				
89	11.9	320	11.5	258				
93	11.9	321	10.8	271				
97	12.1	321	12.4	268				
101	12.7	324	11.3	269				
Mean for weeks								
1-13	10.8	162	9.2	145	393	6.5	102	1,148
14-52	10.3	223	9.7	197	292	9.0	156	995
52-101	11.6	301	11.2	249		8.3	190	

[a] Grams of feed consumed per animal per day
[b] Milligrams of *o*-nitroanisole consumed per day per kilogram body weight
[c] No measurements taken due to 100% mortality

TABLE K5
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of *o*-Nitroanisole

Week	0 ppm		666 ppm			2,000 ppm			6,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)[a]	Body Weight (g)	Dose/ Day (mg/kg/day)
2	4.7	25.1	4.5	24.7	122	4.4	24.7	354	3.6	21.2	1,017
6	4.6	29.1	4.6	28.7	107	4.3	28.3	306	4.3	24.8	1,033
10	4.5	31.1	4.7	30.7	102	4.5	30.6	296	4.7	25.9	1,090
13	4.4	32.7	4.5	32.5	91	4.0	31.9	252	4.1	27.3	898
17	4.6	35.1	4.4	34.5	85	4.5	34.0	263	3.9	27.6	843
21	4.2	37.8	4.2	37.3	75	4.3	36.5	234	4.0	28.0	862
25	5.1	39.6	5.6	38.4	97	5.6	37.7	297	4.6	28.9	952
29	5.0	41.6	5.1	40.3	84	5.1	39.5	258	4.2	29.1	861
33	5.1	43.7	5.1	42.3	80	5.1	41.7	244	4.6	30.1	911
37	5.0	44.5	5.2	43.2	80	5.1	42.4	238	4.2	30.1	834
41	4.8	45.0	4.8	44.2	73	4.6	42.7	216	3.4	30.4	666
45	5.1	45.0	5.2	43.8	79	5.1	43.1	238	4.1	30.0	817
49	5.0	45.7	5.2	44.1	79	5.1	43.7	234	4.0	29.9	811
53	4.9	46.7	5.2	45.2	77	4.9	44.7	218	4.4	30.5	862
57	5.0	46.9	5.3	45.9	76	5.0	45.3	219	4.3	31.0	824
61	4.8	47.8	4.8	46.5	69	4.8	45.6	209	4.0	30.9	773
65	4.9	48.0	5.0	47.6	70	4.6	46.6	199	3.6	31.5	693
69	5.4	49.2	5.2	48.0	73	5.2	47.2	221	4.3	31.7	812
73	5.1	49.0	5.0	48.2	69	4.9	47.2	208	3.9	31.8	737
77	5.4	48.7	5.3	48.3	73	5.3	47.4	224	4.0	31.9	746
81	5.2	48.9	5.3	47.9	73	5.1	46.9	216	4.0	31.8	761
85	5.4	48.4	5.4	47.4	75	5.0	46.3	217	3.9	31.8	742
89	5.2	47.9	5.2	47.6	73	5.0	45.8	219	3.9	31.8	727
93	5.3	47.7	5.4	46.5	77	5.2	44.8	232	4.0	31.7	755
97	4.9	48.0	5.1	46.6	72	5.3	43.8	244	4.2	31.6	795
101	5.4	47.6	5.4	46.1	78	5.3	42.2	250	4.2	32.0	793
Mean for weeks											
1-13	4.5	29.5	4.6	29.2	106	4.3	28.9	302	4.2	24.8	1,009
14-52	4.9	42.0	5.0	40.9	81	4.9	40.1	247	4.1	29.3	840
52-101	5.1	48.1	5.2	47.1	74	5.0	45.7	221	4.0	31.5	771

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

TABLE K6
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of *o*-Nitroanisole

Week	0 ppm		666 ppm			2,000 ppm			6,000 ppm		
	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)	Feed (g/day)	Body Weight (g)	Dose/ Day (mg/kg/day)
4	5.9	23.0	5.9	23.2	170	5.5	22.3	490	4.1	19.2	1,296
8	5.2	25.6	5.6	25.8	146	5.5	24.6	445	4.0	21.2	1,128
12	5.3	27.1	5.2	27.5	126	4.9	26.2	375	3.6	21.4	998
17	6.1	29.7	5.7	30.2	127	5.9	27.9	420	4.7	22.2	1,272
21	5.6	32.7	5.9	33.3	117	5.6	30.2	368	5.0	23.4	1,291
25	5.3	34.1	5.7	34.7	109	5.4	30.9	352	5.2	23.4	1,332
29	6.4	36.7	6.1	37.3	108	6.2	32.9	378	6.4	24.4	1,581
33	5.9	38.8	6.3	39.0	108	6.0	34.8	346	5.6	24.7	1,370
37	5.9	39.0	6.7	39.9	112	6.4	35.6	360	5.1	24.5	1,240
41	5.7	40.4	5.8	41.2	94	5.4	35.9	300	4.3	25.0	1,028
45	5.6	40.9	5.6	41.1	92	5.5	36.3	304	4.8	25.0	1,146
49	6.1	42.5	6.1	42.2	97	5.6	37.4	299	5.5	24.7	1,344
53	5.5	43.7	5.9	43.5	91	5.2	37.9	274	4.7	25.1	1,120
57	6.0	44.9	6.3	44.6	94	5.8	39.0	299	6.1	25.4	1,435
61	5.8	47.4	5.9	46.3	84	5.4	40.3	269	4.5	25.4	1,053
65	5.7	48.1	5.8	47.7	80	5.4	41.2	261	4.8	25.6	1,119
69	5.7	49.6	5.9	47.4	82	5.4	42.1	257	4.2	26.1	969
73	5.5	49.6	5.6	47.1	79	5.2	42.1	246	4.2	26.1	967
77	6.1	51.0	6.0	48.0	83	5.7	42.2	271	4.9	26.7	1,098
81	6.1	51.1	6.5	47.9	91	5.7	42.3	271	5.3	26.6	1,194
85	6.0	51.7	6.3	48.2	86	5.8	42.1	275	5.0	26.7	1,133
89	5.9	51.1	5.9	48.0	82	5.4	42.7	253	4.5	27.1	992
93	5.9	49.8	6.3	46.3	90	5.8	41.7	276	4.6	26.7	1,026
97	6.4	49.6	6.0	45.6	88	5.9	41.7	281	4.9	27.0	1,087
101	6.4	48.0	6.7	44.6	101	5.8	39.2	294	5.6	27.2	1,238
Mean for weeks											
1-13	5.5	25.2	5.6	25.5	147	5.3	24.4	437	3.9	20.6	1,141
14-52	5.9	37.2	6.0	37.7	107	5.8	33.5	347	5.2	24.1	1,289
52-101	5.9	48.9	6.1	46.6	87	5.6	41.1	271	4.9	26.3	1,110

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

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

TABLE L1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE L2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

TABLE L3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.32 ± 0.57	21.2–23.2	25
Crude fat (% by weight)	5.60 ± 0.44	4.6–6.4	25
Crude fiber (% by weight)	3.54 ± 0.54	2.8–5.4	25
Ash (% by weight)	6.62 ± 0.44	6.0–7.9	25
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.060	1.210–1.390	8
Cystine	0.306 ± 0.084	0.181–0.400	8
Glycine	1.150 ± 0.047	1.060–1.210	8
Histidine	0.576 ± 0.024	0.531–0.607	8
Isoleucine	0.917 ± 0.029	0.881–0.944	8
Leucine	1.946 ± 0.055	1.850–2.040	8
Lysine	1.270 ± 0.058	1.200–1.370	8
Methionine	0.448 ± 0.128	0.306–0.699	8
Phenylalinine	0.987 ± 0.140	0.665–1.110	8
Threonine	0.877 ± 0.042	0.824–0.940	8
Tryptophan	0.236 ± 0.176	0.107–0.671	8
Tyrosine	0.676 ± 0.105	0.564–0.794	8
Valine	1.103 ± 0.040	1.050–1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830–2.570	7
Linolenic	0.280 ± 0.040	0.210–0.320	7
Vitamins			
Vitamin A (IU/kg)	9,212 ± 4,047	4,500–19,000	25
Vitamin D (IU/kg)	4,450 ± 1,382	3,000–6,300	4
α-Tocopherol (ppm)	37.95 ± 9.406	22.50–48.90	8
Thiamine (ppm)	21.76 ± 3.41	19.0–37.0	25
Riboflavin (ppm)	7.92 ± 0.87	6.10–9.00	8
Niacin (ppm)	103.38 ± 26.59	65.0–150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0–34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60–14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80–3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19–0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6–65.0	8
Choline (ppm)	3,089 ± 328.69	2,400–3,430	8
Minerals			
Calcium (%)	1.12 ± 0.13	0.87–1.40	25
Phosphorus (%)	0.93 ± 0.06	0.81–1.00	25
Potassium (%)	0.883 ± 0.078	0.772–0.971	6
Chloride (%)	0.526 ± 0.092	0.380–0.635	8
Sodium (%)	0.313 ± 0.390	0.258–0.371	8
Magnesium (%)	0.168 ± 0.010	0.151–0.181	8
Sulfur (%)	0.280 ± 0.064	0.208–0.420	8
Iron (ppm)	360.54 ± 100	255.0–523.0	8
Manganese (ppm)	91.97 ± 6.01	81.70–99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10–64.50	8
Copper (ppm)	11.06 ± 2.50	8.090–15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52–4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04–2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490–0.780	4

TABLE L4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.74 ± 0.16	0.22–0.98	25
Cadmium (ppm)	0.10 ± 0.20	<0.10–0.20	25
Lead (ppm)	0.47 ± 0.20	0.05–0.87	25
Mercury (ppm)[b]	0.05 ± 0.01	0.05–0.08	25
Selenium (ppm)	0.34 ± 0.08	0.17–0.48	25
Aflatoxins (ppb)	<5.0		25
Nitrate nitrogen (ppm)	15.41 ± 5.02	2.90–22.0	25
Nitrite nitrogen (ppm)	0.25 ± 0.43	<0.10–2.10	25
BHA (ppm)[c]	2.36 ± 0.81	<2.00–5.00	25
BHT (ppm)[c]	1.88 ± 1.17	<1.00–5.00	25
Aerobic plate count (CFU/g)[d]	117,596 ± 151,945	3,900–570,000	25
Coliform (MPN/g)[e]	248 ± 513	<3.00–2,400	25
E. coli (MPN/g)[f]	10.9 ± 30.07	<3.00–150.0	25
E. coli (MPN/g)[g]	5.2 ± 8.17	<3.00–43.00	24
Total nitrosoamines (ppb)[h]	6.61 ± 2.50	3.30–13.30	25
N-Nitrosodimethylamine (ppb)[h]	5.95 ± 2.35	3.00–13.00	25
N-Nitrosopyrrolidine (ppb)[h]	0.66 ± 0.78	0.30–4.00	25
Pesticides			
α-BHC[i]	<0.01		25
ß-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.1		25
Estimated PCBs	<0.2		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.1		25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion[j]	0.23 ± 0.63	0.05–3.20	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

TABLE L4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given as the mean.
[b] Mean, standard deviation, and range include one value of 0.08 ppm. All other values are less than 0.05 ppm.
[c] Sources of contamination - soy oil and fish meal.
[d] CFU = colony forming units.
[e] MPN = most probable number.
[f] Mean, standard deviation, and range include one large value of 150 MPN/g obtained in batch milled 17 October 1984.
[g] Mean, standard deviation, and range include value given in [f].
[h] All values were corrected for percent recovery.
[i] BHC = hexachlorocyclohexane or benzene hexachloride
[j] Ten lots contained more than 0.05 ppm, including one with 3.20 ppm milled 7 May 1985.

APPENDIX M
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. The sentinel animals come from the same production source and weanling groups as animals used for the studies of chemical compounds, and these animals and the study animals are subject to identical environmental conditions.

Serum samples were collected from randomly selected rats and mice during the 14-day, 13-week, and 2-year studies, and rats during the stop-exposure study. Blood from each animal was collected from the orbital sinus, allowed to clot, and the serum separated. The serum was cooled and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated blow; the times during the studies at which blood was collected for serological testing are also listed.

Test and Method	Time of Analysis
Rats	
14-Day Studies	
Hemagglutination Inhibition	
PVM (pneumonis virus of mice)	Study termination
Sendai	Study termination
KRV (Kilham rat virus)	Study termination
H-1 (Toolan's H-1 virus)	Study termination
Polyoma virus	Study termination
Complement Fixation	
RCV (rat coronavirus)	Study termination
13-Week Studies	
Hemagglutination Inhibition	
PVM	Study termination
KRV	Study termination
H-1	Study termination
Complement Fixation	
Sendai	Study termination
RCV	Study termination
2-Year Studies	
Hemagglutination Inhibition	
KRV	6, 12, 18, and 24 months
H-1	6, 12, 18, and 24 months
ELISA	
Mycoplasma pulmonis	6, 12, 18, and 24 months
Mycoplasma arthritidis	6, 12, 18, and 24 months
PVM	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	6, 12, 18, and 24 months
CARB	24 months

Test and Method (continued)	Time of Analysis (continued)
Rats (continued)	
Stop-Exposure Study	
Hemagglutination Inhibition	
KRV	6, 12, 18, and 24 months
H-1	6, 12, 18, and 24 months
ELISA	
Mycoplasma arthritidis	6, 12, 18, and 24 months
Mycoplasma pulmonis	6, 12, 18, and 24 months
PVM	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
RCV/SDA	6, 12, 18, and 24 months
CARB	24 months
Mice	
14-Day Studies	
Hemagglutination Inhibition	
PVM	Study termination
Reovirus 3	Study termination
GDVII	Study termination
Sendai	Study termination
MVM	Study termination
Ectromelia virus	Study termination
Complement Fixation	
Mouse adenoma virus	Study termination
LCM	Study termination
RCV	Study termination
ELISA	
MHV	Study termination
13-Week Studies	
Hemagglutination Inhibition	
PVM	Study termination
Reovirus 3	Study termination
GDVII	Study termination
MVM	Study termination
Ectromelia virus	Study termination
Complement Fixation	
Sendai	Study termination
Mouse adenoma virus	Study termination
MHV	Study termination
LCM	Study termination

Test and Method (continued)	Time of Analysis (continued)
Mice (continued)	
2-Year Studies	
Hemagglutination Inhibition	
K (papovirus)	6, 12, 18, and 24 months
MVM	6, 12, 18, and 24 months
Complement Fixation	
LCM	6, 12, and 18 months
ELISA	
Mycoplasma pulmonis	6, 12, 18, and 24 months
Mycoplasma arthritidis	6, 12, 18, and 24 months
PVM	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
MHV	6, 12, 18, and 24 months
Ectromelia virus	6, 12, 18, and 24 months
GDVII	6, 12, 18, and 24 months
Reovirus 3	6, 12, 18, and 24 months
Mouse adenoma virus	6, 12, 18, and 24 months
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	6, 12, 18, and 24 months
LCM	24 months

RESULTS

The serology results for sentinel animals are presented in Table M1.

TABLE M1
Murine Virus Antibody Determinations for Rats and Mice
in the 14-Day, 13-Week, 2-Year, and Stop-Exposure Feed Studies of *o*-Nitroanisole

	Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
14-Day Studies			
Rats	14 days	0/10	None positive
Mice	14 days	0/10	None positive
13-Week Studies			
Rats	13 weeks	0/10	None positive
Mice	13 weeks	0/10	None positive
2-Year Studies			
Rats	6 months	1/10	Possible *M. arthritidis*
	12 months	1/10	Possible *M. arthritidis*
	18 months	0/9	None positive
	24 months	0/10	None positive
Mice	6 months	0/10	None positive
	12 months	1/9	Possible *M. arthritidis*
	18 months	1/8	Possible *M. arthritidis*
	24 months	0/10	None positive
Stop-Exposure Study			
	6 months	1/9	Possible *M. arthritidis*
	12 months	1/10	Possible *M. arthritidis*
	18 months	1/10	Possible *M. arthritidis*
	24 months	1/10	Possible *M. arthritidis*

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PRINTED AS OF MAY 1993

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

☆ U.S. GOVERNMENT PRINTING OFFICE: 1993 342-280/80012

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

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

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

DEPARTMENT OF
HEALTH & HUMAN SERVICES

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

Official Business
Penalty for Private Use - $300

NIH Publication No. 93-3147
May 1993