NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 442

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *p*-NITROBENZOIC ACID

(CAS NO. 62-23-7)

IN F344/N 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.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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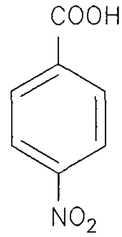
ABSTRACT



p-NITROBENZOIC ACID

CAS No. 62-23-7

Chemical Formula: $C_7H_5NO_4$ Molecular Weight: 167.12

Synonyms: 4-Nitrobenzoic acid; nitrodracylic acid; *p*-nitrobenzenecarboxylic acid; *p*-carboxynitrobenzene

p-Nitrobenzoic acid is produced in large volumes for organic synthesis and as an intermediate in the manufacture of pesticides, dyes, and industrial solvents. Groups of male and female F344/N rats and $B6C3F_1$ mice were exposed to *p*-nitrobenzoic acid (>99% pure) in feed for 14 days, 13 weeks, or 2 years for toxicity and carcinogenicity studies. Genetic toxicology studies were conducted in *in vitro* assays with *Salmonella typhimurium* and cultured Chinese hamster ovary cells, and in *in vivo* studies of erythrocyte micronucleus formation in mice in the 13-week study.

14-Day Study in Rats

Groups of five male and five female rats were given 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm *p*-nitrobenzoic acid in feed for 14 days. All rats survived until the end of the study. Male and female rats given 20,000 and 40,000 ppm lost weight. The final mean body weights of 10,000, 20,000, and 40,000 ppm males were 82%, 60%, or 52% that of the controls, and the final mean body weights of 10,000, 20,000, and 40,000 ppm females were 87%, 68%, and 65% that of the controls. There were no clinical findings that were characteristic of organ-specific toxicity. Absolute and relative spleen weights were significantly increased in rats exposed to 10,000, 20,000, and 40,000 ppm. There were decreases in erythrocyte count and hemoglobin and hematocrit values and increases in reticulocyte count, nucleated erythrocytes, and methemoglobin concentration that were most pronounced in the 20,000 and 40,000 ppm groups. Congestion of the spleen occurred in 10,000 ppm males and in 20,000 and 40,000 ppm females. Hypertrophy of the follicular epithelium of the thyroid gland was present in male and female rats exposed to 10,000, 20,000, or 40,000 ppm *p*-nitrobenzoic acid, while follicular hyperplasia was observed in the 40,000 ppm males and females. Atrophy of the testis was observed in 20,000 and 40,000 ppm males. Other lesions observed in 20,000 and 40,000 ppm rats included atrophy of the thymus in males and atrophy of the ovary, bone marrow, and thymus in females.

14-Day Study in Mice

Groups of five male and five female mice were given 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm *p*-nitrobenzoic acid in feed for 14 days. Three males and two females given 40,000 ppm died during the study. All other animals survived until the end of the

study. Male mice given 20,000 and 40,000 ppm and females given 20,000 ppm lost weight. Mean body weight gains of 20,000 and 40,000 ppm males and 10,000, 20,000, and 40,000 ppm females were significantly lower than those of the controls. There were no clinical findings related to organ-specific toxicity although lethargy and ataxia were observed in 40,000 ppm mice.

Relative liver weights were significantly increased in 20,000 and 40,000 ppm males and females and in 10,000 ppm females. Absolute and relative thymus weights of 20,000 and 40,000 ppm males and of 10,000, 20,000, and 40,000 ppm females were reduced. No significant differences in hematology parameters occurred in exposed mice. Testicular degeneration was observed in three 20,000 ppm and two 40,000 ppm males. Bone marrow hemorrhage and atrophy occurred in 40,000 ppm females.

13-Week Study in Rats

Groups of 10 male and 10 female rats were given 0, 630, 1,250, 2,500, 5,000, or 10,000 ppm *p*-nitrobenzoic acid in feed for 13 weeks resulting in approximate daily doses of 40, 70, 160, 310, or 660 mg/kg to males and 40, 80, 170, 340, or 680 mg/kg to females. All rats survived until the end of the study. Mean body weight gains and final mean body weights were significantly less than those of the controls in 2,500, 5,000, and 10,000 ppm males and in 5,000 and 10,000 ppm females. There were no clinical findings related to organ-specific toxicity.

Differences in spleen weights and hematology parameters characteristic of regenerative anemia were observed in males and females, primarily in groups given 10,000 ppm. The absolute and relative spleen weights were significantly increased in 10,000 ppm males and females and the relative spleen weights were significantly increased in 5,000 ppm males and females. Methemoglobin, Heinz bodies, and reticulocyte counts were increased and erythrocyte counts, hemoglobin, and hematocrit values were decreased in 10,000 ppm males and females.

Congestion, pigmentation, and accumulation of macrophages in the spleen and pigmentation in the kidney occurred in 2,500, 5,000, and 10,000 ppm males. Congestion and pigmentation of the spleen occurred in 10,000 ppm females. A yellowish brown pigment (hemosiderin) in the spleen and kidney was associated with hemolytic anemia. Mild cytoplasmic hyaline droplet accumulation was present in renal tubule epithelial cells in 10,000 ppm males while karyomegaly was present in male and female rats exposed to 2,500, 5,000, and 10,000 ppm *p*-nitrobenzoic acid. A chemical-related testicular lesion, consisting of atrophy of the seminiferous tubules, occurred in 10,000 ppm males.

13-Week Study in Mice

Groups of 10 male and 10 female mice were given 0, 1,250, 5,000, 10,000, or 20,000 ppm *p*-nitrobenzoic acid in feed for 13 weeks resulting in approximate daily doses of 170, 330, 670, 1,900, or 4,000 mg/kg body weight to males and 240, 460, 970, 2,500, or 4,900 mg/kg to females. All mice survived until the end of the study, except one 1,250 ppm female that was killed accidentally. Final mean body weights and mean body weight gains of all exposed males and of 5,000, 10,000, and 20,000 ppm females were significantly lower than those of the controls. No clinical findings or differences in organ weights or histopathology related to organ-specific toxicity were observed in exposed mice.

2-Year Study in Rats

Groups of 60 male and 60 female rats were given 0, 1,250, 2,500, or 5,000 ppm *p*-nitrobenzoic acid in feed for 2 years. Ten males and 10 females from each exposure group were evaluated at 15 months.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Two-year survival rates of 1,250 and 2,500 ppm males were similar to that of the controls. Two-year survival of 5,000 ppm males was marginally greater than that of the controls and was attributed in part to a decrease in the severity of nephropathy and a decrease in the incidence of mononuclear cell leukemia. Survival of exposed females was similar to that of the controls. Mean body weights of 5,000 ppm males were 2% to 8% lower than those of the controls through week 80. Final mean body weights of exposed males were similar to that of the controls. Mean body weights of 5,000 ppm females were 2% to 9% lower than those of the controls during the first year of the study and were 10% to 16% lower during the second year of the study. Final mean body weights of exposed females were 97% (1,250 ppm), 92% (2,500 ppm), and 84% (5,000 ppm) that of the controls. Feed consumption by exposed males and females was similar to that by the controls. Dietary levels of 1,250, 2,500, or 5,000 ppm *p*-nitrobenzoic acid delivered approximately 50, 100, or 210 mg/kg body weight per day to males and 60, 125, or 250 mg/kg per day to females. There were no clinical findings attributable to organ-specific toxicity.

Pathology Findings

There were increases in the incidences of clitoral gland adenoma and of clitoral gland adenoma or carcinoma (combined) (4/50, 14/49, 15/49, 15/50) in exposed females. The incidences of clitoral gland adenoma or carcinoma (combined) in the exposed groups (29% to 31%) exceeded the historical control mean incidence (11%) and range (2% to 21%) in female F344/N rats in recent 2-year NTP feed studies. The increased incidences of clitoral gland neoplasms were considered to be some evidence of carcinogenic activity in female rats exposed to *p*-nitrobenzoic acid. The incidences of hyperplasia of the clitoral gland in exposed females were marginally lower than that of the controls (10/50, 6/49, 6/49, 7/50).

There was a chemical-related decrease in the severity of nephropathy in male rats. Male rat kidneys were examined using both single and step-section analyses, and the incidences of renal tubule neoplasms were not statistically greater than those of the controls. Mild hyaline droplet accumulation was observed in renal tubule epithelial cells in 10,000 ppm males in the 13-week study, but this effect was not severe enough to lead to a chemical-related neoplastic response in the 2-year study as has been observed with other chemicals.

At the 15-month interim evaluation, hematologic parameters characteristic of a mild regenerative anemia and significant differences in spleen weights were noted in 5,000 ppm females. These differences included decreases in erythrocyte count, hemoglobin, and hematocrit, increases in spleen weights, and hemosiderin accumulation in splenic macrophages.

At 2 years, significant decreases in the incidences of mononuclear cell leukemia were observed in 5,000 ppm males and 2,500 and 5,000 ppm females (males: 29/50, 35/50, 26/50, 2/50; females: 17/50, 11/50, 3/50, 0/50). While the mechanism for this decrease is unknown, decreases in the incidence of mononuclear cell leukemia have also been observed in 2-year studies with other amine/nitro compounds.

2-Year Study in Mice

Groups of 60 male and 60 female mice were given 0, 1,250, 2,500, or 5,000 ppm *p*-nitrobenzoic acid in feed for 2 years. Ten males and 10 females from each exposure group were evaluated at 15 months.

Survival, Body Weights, Feed Consumption, and Clinical Findings

Two-year survival rates of exposed mice were similar to those of the controls. Mean body weights of 5,000 ppm males were 6% to 12% lower than those of the controls after week 17, and mean body weights of 5,000 ppm females were 12% to 24% lower than those of the controls after week 16. The final mean body weight of 5,000 ppm females was 19% less than that of the controls; final mean body weights of males were similar to that of the controls. Feed consumption by exposed mice was similar to that by the controls. Dietary levels of 1,250, 2,500, or 5,000 ppm *p*-nitrobenzoic acid delivered approximately 150, 300, or 675 mg/kg per day to males and 170, 365, or 905 mg/kg per day to females. There were no clinical findings of organ-specific toxicity. No chemical-related effects on hematology parameters were noted at the 15-month interim evaluation.

Pathology Findings

There were no increases or decreases in neoplasms in male or female mice that were considered to be related to chemical administration.

Genetic Toxicology

p-Nitrobenzoic acid was mutagenic in *Salmonella typhimurium* strain TA100 with and without S9. No mutagenic activity was noted in strains TA98, TA1535, or TA1537, with or without S9. *p*-Nitrobenzoic acid induced sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells in the absence of S9; with S9, results of both tests were negative. *In vivo*, no increase in micronuclei was observed in peripheral blood erythrocytes of male or female mice administered *p*-nitrobenzoic acid in dosed feed for 13 weeks.

Conclusions

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of *p*-nitrobenzoic acid in male F344/N rats exposed to 1,250, 2,500, or 5,000 ppm. There was *some evidence of carcinogenic activity* of *p*-nitrobenzoic acid in female F344/N rats based on increases in the incidences of clitoral gland adenoma and of clitoral gland adenoma or carcinoma (combined). There was *no evidence of carcinogenic activity* of *p*-nitrobenzoic acid in male or female $B6C3F_1$ mice exposed to 1,250, 2,500, or 5,000 ppm.

There were chemical-related decreases in the incidences of mononuclear cell leukemia in exposed male and female rats. *p*-Nitrobenzoic acid caused mild hematologic toxicity in female rats.

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

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

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 1,250, 2,500, or 5,000 ppm in feed (approximately 50, 100, or 210 mg/kg/day)	0, 1,250, 2,500, or 5,000 ppm in feed (approximately 60, 125, or 250 mg/kg/day)	0, 1,250, 2,500, or 5,000 ppm in feed (approximately 150, 300, or 675 mg/kg/day)	0, 1,250, 2,500, or 5,000 ppm in feed (approximately 170, 365, or 905 mg/kg/day)
Body weights	Dosed groups similar to control	High- and mid-dose groups lower than control	High-dose group lower than control	High-dose group lower than control
2-Year survival rates	12/50, 13/50, 13/50, 21/50	27/50, 23/50, 21/50, 21/50	39/50, 36/50, 39/50, 44/50	38/50, 36/49, 33/50, 30/50
Nonneoplastic effects	None	Mild hematologic toxicity	None	None
Neoplastic effects	None	Clitoral gland: adenoma (4/50, 12/49, 10/49, 12/50), carcinoma (1/50, 2/49, 5/49, 4/50), adenoma or carcinoma (combined) (4/50, 14/49, 15/49, 15/50)	None	None
Decreased incidences	Mononuclear cell leukemia (29/50, 35/50, 26/50, 2/50)	Mononuclear cell leukemia (17/50, 11/50, 3/50, 0/50)	None	None
Level of evidence of carcinogenic activity	No evidence	Some evidence	No evidence	No evidence

Genetic toxicology

Salmonella typhimurium gene mutation:	Positive in strain TA100 with and without S9; negative in strains TA98, TA1535, and TA1537, with and without S9
Sister chromatid exchanges	
Cultured Chinese hamster ovary cells *in vitro*:	Positive without S9; negative with S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Positive without S9; negative with S9
Micronuclei in mouse peripheral blood cells:	Negative at 13 weeks

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on *p*-nitrobenzoic acid on June 22, 1993, 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.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 22, 1993, the draft Technical Report on the toxicology and carcinogenesis studies of *p*-nitrobenzoic acid 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. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of *p*-nitrobenzoic acid by discussing the uses and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on chemical-related neoplastic lesions in female rats and nonneoplastic lesions in male (nephropathy) and female (hematologic toxicity) rats. Additional step-sections of the kidney were performed in male rats. The proposed conclusions were *no evidence of carcinogenic activity* in male F344/N rats, *some evidence of carcinogenic activity* in female F344/N rats, and *no evidence of carcinogenic activity* in male or female B6C3F$_1$ mice.

Dr. Brown, a principal reviewer, agreed with the proposed conclusions. He asked for comment on the seemingly paradoxical decrease in the incidence of mononuclear cell leukemia in exposed rats and the increased weight of the spleen. Dr. Ward noted that there was hematopoietic toxicity associated with the chemical and speculated that the stem cell in the bone marrow or spleen from which the leukemia derives may be one of the targets of the chemical resulting in an inhibition of leukemogenesis.

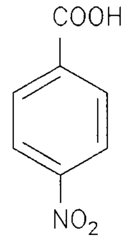
Dr. van Zwieten, the second principal reviewer, agreed with the proposed conclusions. He asked for substantiation of the conclusion that preputial gland and clitoral gland neoplasms were potentially lethal, because, in his experience, these neoplasms tend to be quite small and well circumscribed. Dr. S.L. Eustis, NIEHS, responded that the preputial gland neoplasms are not lethal in the sense of causing the animal's death, but as they get quite large with some becoming ulcerated, the animals are killed. Dr. J.K. Haseman, NIEHS, added that if a neoplasm were incidental, one would expect it to be more or less evenly distributed among the animals that died naturally and those that survived. However, in this study, the likelihood of observing a preputial gland neoplasm in an animal that died early was almost three times as high as in a surviving animal.

Dr. Ryan, the third principal reviewer, deferred her opinion of the proposed conclusions pending further discussion of exposure-related effects on clitoral gland and preputial gland lesions. She said there were inconsistencies in how body weight differences were discussed. For instance, decreased body weight in rats is offered as a possible explanation for the exposure-related decrease in leukemia. On the other hand, lack of an exposure-response for clitoral gland neoplasms was the main reason for some evidence rather than clear evidence for female rats, but was likely due, in her opinion, also to decreased body weight. Dr. Dunnick said the conclusion in female rats was based primarily on there being increases in neoplasms, mostly adenomas, at all three exposure levels. She agreed that body weight can affect the incidence of neoplasms, but the decrease in leukemia was believed to be more of a chemical effect than a body weight effect. Based on preputial gland neoplasms, Dr. Haseman said it was a close call between no evidence and equivocal evidence of carcinogenic activity in male rats. Dr. Eustis noted that the incidence of preputial gland carcinoma at the highest exposure level was within the historical control range.

Dr. Ward asked for comment on the presence of hyaline droplets in the kidneys of rats in subchronic studies and whether they were associated with $\alpha_{2\mu}$-globulin accumulation. Dr. Eustis said there was no evidence for accumulation of $\alpha_{2\mu}$-globulin in this study.

Dr. Brown moved that the Technical Report on *p*-nitrobenzoic acid be accepted with the revision discussed and with the conclusions as written for male rats and male and female mice, *no evidence of carcinogenic activity*, and for female rats, *some evidence of carcinogenic activity*. Dr. Taylor seconded the motion, which was accepted unanimously with ten votes.

INTRODUCTION



p-NITROBENZOIC ACID

CAS No. 62-23-7

Chemical Formula: $C_7H_5NO_4$ Molecular Weight: 167.12

Synonyms: 4-Nitrobenzoic acid; nitrodracylic acid; *p*-nitrobenzenecarboxylic acid; *p*-carboxynitrobenzene

Chemical and Physical Properties

p-Nitrobenzoic acid is a yellow-to-white crystalline material with no odor. It has a density of 1.61 at 20° C, and a melting point of 242° C. It is insoluble in water and petroleum ether; slightly soluble in acetone, benzene, and carbon disulfide; and soluble in methyl alcohol (1 g/110 mL) and ethanol (1 g/110 mL). The pK_a of *p*-nitrobenzoic acid is 3.4 (Sax, 1979; *Merck Index*, 1983; Lide, 1992).

Use and Human Exposure

p-Nitrobenzoic acid is used in organic synthesis, in the manufacture of intermediates, and as a reagent for alkaloids and thorium (*Merck Index*, 1983). Nitrobenzoates are used in the manufacture of pesticides, dyes, explosives, and industrial solvents (Groenewegen *et al.*, 1992). Exposure to *p*-nitrobenzoic acid may occur through exposure to other chemicals that are metabolized or hydrolyzed to *p*-nitrobenzoic acid, including *p*-nitrobenzoyl chloride (Radding, 1977), *p*-nitrotoluene (Chism *et al.*, 1984), and 5-(4-nitrophenyl)-2,4-pentadienal (spy dust) (Burka *et al.*, 1987).

p-Nitrobenzoic acid was not found in a survey of 717 hazardous waste sites (USEPA, 1987). *p*-Nitrobenzoic acid is metabolized under aerobic and anaerobic conditions by bacteria, as well as when mixed with a representative municipal sewage sample, suggesting that under natural conditions bacteria would metabolize the chemical (Hallas and Alexander, 1983).

The U.S. International Trade Commission (USITC) did not report the production volume for *p*-nitrobenzoic acid or *p*-nitrobenzoyl chloride for 1988 (USITC, 1989). Other sources estimate the production of *p*-nitrobenzoic acid at 450 to 900 tons per year (4 to 8×10^6 kg/year), the production of *p*-aminobenzoic acid, a major metabolite of *p*-nitrobenzoic acid, at 250 tons/year (2×10^6 kg/year) (*Kirk-Othmer*, 1978), and the production of *p*-nitrobenzoyl chloride at 3×10^6 kg/year (NCI, 1980). The National Institute for Occupational Safety and Health (NIOSH) has estimated that there are 42,700 workers potentially exposed to *p*-nitrobenzoic acid in 16 different industries (NIOSH, 1993).

Absorption, Distribution, Metabolism, and Excretion

Experimental Animals

The metabolism of nitroaromatic compounds varies with species of animal and with the isomeric configuration of the chemical, as has been noted for some representative nitroaromatic chemicals such as nitrobenzene and *o*-, *m*-, and *p*-nitrotoluene (Rickert, 1987; NTP, 1992). One common pathway for metabolism of nitroaromatic compounds is reduction of the nitro groups (Rickert, 1987).

Nitroreductase activities are found both in mammalian tissues and in gastrointestinal microflora, and both can contribute to the eventual metabolism of nitroaromatic compounds (Zachariah and Juchau, 1974). In mammalian species, two nitro-reducing systems have been characterized in the liver, including one associated with the endoplasmic reticulum of the liver and one with the soluble cellular fractions (Carlson and Dubois, 1970; Mitchard, 1971). *Escherichia coli* and other bacteria contain various enzymes capable of reducing *p*-nitrobenzoic acid to *p*-aminobenzoic acid (Saz and Martinez, 1956; Thijssen and Henderson, 1973). Intestinal microbial flora appear to be responsible for at least some of the *in vivo* reduction of *p*-nitrobenzoic acid because the intestinal contents of rats receiving antibiotics indicated diminished reduction of *p*-nitrobenzoic acid (Zachariah and Juchau, 1974; Gardner and Renwick, 1978). Germ-free rats converted about 1% of *p*-nitrobenzoic acid to *p*-aminobenzoic acid, while conventional rats converted 25% to *p*-aminobenzoic acid (Wheeler *et al.*, 1975).

In addition to reduction of the nitro group, *p*-nitrobenzoic acid metabolism may occur by a number of pathways involving conjugation of the carboxylic acid group with glycine or glucuronic acid and reduction to *p*-aminobenzoic acid, which may then be conjugated at the carboxylic acid group or acetylated at the amino substituent (Williams, 1959).

Nitroaromatic compounds are characteristically toxic to the hematopoietic system (NTP, 1992). Aromatic and heterocyclic nitro compounds require reduction of the nitro group for the expression of these toxicologic activities (McCalla and Voutsinos, 1974; Wheeler *et al.*, 1975; Reddy *et al.*, 1976). A common feature of chemicals that cause hematopoietic toxicity characterized by methemoglobin formation is a free aromatic amine functional group. Hydroxylation of this aromatic amine group to a phenylhydroxylamine is thought to account for the formation of methemoglobinemia and the subsequent hematologic toxicity (Bus and Popp, 1987). This is supported by studies that show that hydroxylamino compounds produce methemoglobin *in vivo* and *in vitro*, and arylamines or nitrobenzenes themselves cannot oxidize hemoglobin *in vitro* (Facchini and Griffiths, 1981). Using liver homogenates from Wistar rats, Kato *et al.* (1969) identified *p*-hydroxylamino benzoic acid as a metabolite of *p*-nitrobenzoic acid, and a metabolic scheme (Figure 1) for *p*-nitrobenzoic acid has been proposed (Gillette *et al.*, 1968; Mitchard, 1971).

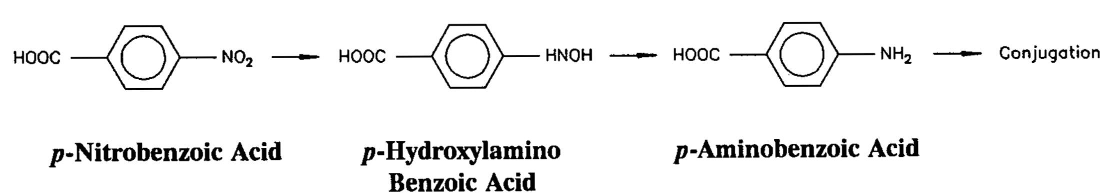


FIGURE 1
Metabolic Pathway of *p*-Nitrobenzoic Acid
[Proposed by Gillette *et al.* (1968) and Mitchard (1971)]

Quantitative information on pharmacokinetics, distribution, and elimination of metabolites of *p*-nitrobenzoic acid *in vivo* is limited. After an oral or intraperitoneal dose of 25 mg [^{14}C]-*p*-nitrobenzoic acid, female Wistar rats excreted 83% to 94% of the radiolabel in the urine within 24 hours. Urine metabolites were 2% free *p*-aminobenzoic acid, 18% conjugated aminobenzoic acid, 42% *p*-nitrobenzoic acid, and 13% conjugated *p*-nitrobenzoic acid (Gardner and Renwick, 1978). Studies to quantify the urinary metabolites of *p*-nitrobenzoic acid in the F344 rat and B6C3F$_1$ mouse have not been conducted.

Pharmacokinetic studies in marmosets receiving oral doses of 4-nitro[*carboxy*-^{14}C]benzoic acid (0.4 mmol/kg) found that peak blood levels were reached in 30 to 40 minutes and the terminal half-life of the chemical in the blood was estimated at 1 hour. Distribution and elimination of metabolites could not be determined from these studies (Kuzniar and James, 1981).

Humans

No information on the absorption, distribution, metabolism, or excretion of *p*-nitrobenzoic acid in humans was found in the literature.

Toxicity

Experimental Animals

Methemoglobin formation and hematopoietic toxicity are found after administration of aromatic nitro and amino compounds, and this toxicity is often more severe in rats than in mice (Beard and Noe, 1981; Rickert, 1987; NTP, 1992). For example, in studies of *o*-, *m*-, and *p*-nitrotoluene hematologic toxicity was characterized by increased methemoglobin, Heinz body formation, and hematopoiesis and by hemosiderin deposition and congestion in the spleen of rats.

p-Nitrobenzoic acid was reported to have LD$_{50}$ values of 1.47, 0.88, and 0.77 g/kg in female Swiss mice after oral, intraperitoneal, and intravenous administration, respectively. The oral LD$_{50}$ was 1.96 g/kg and the intravenous LD$_{50}$ was 1.21 g/kg in female Wistar rats. Rats receiving LD$_{50}$ levels of *p*-nitrobenzoic acid had liver infiltration with red blood cells and myeloid metaplasia of the red pulp of the spleen (Caujolle *et al.*, 1966).

Humans

No information on the toxicity of *p*-nitrobenzoic acid in humans was found in the literature.

Reproductive and Developmental Toxicity

Experimental Animals

Chapin *et al.* (1987) evaluated the effects of *p*-nitrobenzoic acid on sperm morphology and vaginal cytology in rats and mice exposed to 0, 630 (rats), 1,250, 2,500, 5,000, 10,000, or 20,000 (mice) ppm *p*-nitrobenzoic acid in feed for 13 weeks. Final body weights of 5,000 and 10,000 ppm male rats were 8% to 16% lower than that of the controls. The sperm count and right caudal, epididymal, and testis weights were reduced in 10,000 ppm male rats. Final body weights of 10,000 and 20,000 ppm male mice were 14% to 31% lower than those of the controls. In mice receiving 20,000 ppm, the right caudal, epididymal, and testis weights were reduced, but the sperm count was not significantly reduced. At lower exposure levels, there were no chemical-related effects in male rats and only minor effects in male mice. Significantly reduced body weights were observed in 10,000 ppm female rats and in 20,000 ppm female mice. Some of these females had prolonged estrous cycles that were apparently related to the reduced body weights (Chapin *et al.*, 1987).

Continuous breeding studies were conducted in Swiss (CD-1®) mice exposed to 7,500 or 15,000 ppm *p*-nitrobenzoic acid *ad libitum* in feed for a 7-day precohabitation period followed by a 98-day cohabitation period (Hope *et al.*, 1990). Final body weights of 15,000 ppm males and females were 93% and 88% that of the corresponding control groups, respectively. Feed consumption was similar between exposed and control groups. Pairs of mice exposed to 7,500 and 15,000 ppm had fewer litters and fewer live pups per litter and their pups weighed less than those of pairs receiving control feed. Crossover matings of exposed F$_1$ females to control males also resulted in fewer live pups per litter and lower pup weights, indicating that reproductive toxicity was primarily due to effects in females. Hope *et al.* (1990) concluded that the general toxic effects of *p*-nitrobenzoic acid (as measured by decreases in body weight of exposed animals) were not severe enough to cause impairment of fertility and reproduction, and the studies did not identify the mechanism responsible for this toxicity.

Humans
No information on reproductive and developmental toxicity of *p*-nitrobenzoic acid in humans was found in the literature.

Carcinogenicity
Experimental Animals
No studies describing the carcinogenic potential of *p*-nitrobenzoic acid in experimental animals were found in the literature.

Humans
No published information on carcinogenic potential of *p*-nitrobenzoic acid in humans is available.

Genetic Toxicity
p-Nitrobenzoic acid was positive, in the absence of S9 activation, in the *Bacillus subtilis* rec assay for growth inhibition due to DNA damage (Shimizu and Yano, 1986), and it induced gene mutations in *Salmonella typhimurium*, with and without S9 (Chiu *et al.*, 1978; Sundvall *et al.*, 1984; Shimizu and Yano, 1986; Zeiger *et al.*, 1987; Dellarco and Prival, 1989). No induction of unscheduled DNA synthesis was noted in rat hepatocytes treated *in vitro* with up to 1,000 nmol *p*-nitrobenzoic acid/mL (Probst *et al.*, 1981). Unpublished NTP data show that *p*-nitrobenzoic acid induces sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells. However, no increase in the frequency of micronucleated erythrocytes was observed in the peripheral blood of male and female mice administered *p*-nitrobenzoic acid in feed for 13 weeks (Appendix E).

The structural analogue, *m*-nitrobenzoic acid, was also positive in the *B. subtilis* rec assay (Shimizu and Yano, 1986) and *S. typhimurium* gene mutation assays (Chiu *et al.*, 1978; Sundvall *et al.*, 1984; Shimizu and Yano, 1986; Zeiger *et al.*, 1987). Unpublished NTP data show no induction of chromosomal aberrations or sister chromatid exchanges in cultured Chinese hamster ovary cells and no increase in the frequency of micronucleated erythrocytes in the blood of male or female mice receiving *m*-nitrobenzoic acid in feed for 13 weeks. *o*-Nitrobenzoic acid did not induce chromosomal aberrations in cultured Chinese hamster ovary cells, but it did induce sister chromatid exchanges (NTP, unpublished data) and, like the *p*- and *m*-isomers, it was mutagenic in the *S. typhimurium* assay (Zeiger *et al.*, 1987).

Study Rationale
p-Nitrobenzoic acid is a hydrolysis product of *p*-nitrobenzoyl chloride. *p*-Nitrobenzoyl chloride was originally nominated for testing by the National Cancer Institute because it is an acyl chloride and aromatic nitro compound with a large import volume (10,000 kg/year). However, because *p*-nitrobenzoyl chloride is unstable in feed and undergoes rapid hydrolysis to *p*-nitrobenzoic acid, *p*-nitrobenzoic acid was selected for study. *p*-Nitrobenzoic acid was selected because of workplace exposure through its use in manufacturing chemical intermediates, because it is a metabolite of other chemicals, and because of the lack of existing information on its chronic toxic and carcinogenic effects.

Interest in the potential carcinogenicity of *p*-nitrobenzoic acid is also based on its structure as a single, aromatic, nitro compound and the finding that other members of this chemical class are carcinogenic in rodents (Clayson and Garner, 1976; Ashby and Tennant, 1991).

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *p*-NITROBENZOIC ACID

p-Nitrobenzoic acid was obtained from E.I. du Pont de Nemours and Company, Inc. (Wilmington, DE), in one lot (40). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix H). Reports on the analyses performed in support of the *p*-nitrobenzoic acid studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a light yellow, crystalline solid, was identified as *p*-nitrobenzoic acid by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopies. Purity was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and high-performance liquid chromatography. Elemental analyses for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for *p*-nitrobenzoic acid. Karl Fischer analysis indicated 0.08% water. Functional group titration indicated a purity of 100.1%. Thin-layer chromatography using two systems detected one major spot and one trace impurity. No impurities with areas greater than 0.1% relative to the major peak area were observed using high-performance liquid chromatography. The overall purity was determined to be greater than 99%.

Stability studies performed using high-performance liquid chromatography indicated that *p*-nitrobenzoic acid was stable when stored in the dark for 2 weeks at temperatures up to 60° C. The study laboratory stored the bulk chemical in sealed containers, protected from light, at room temperature. Purity and stability were monitored during the 2-year study by high-performance liquid chromatography and functional group titration. No degradation of the bulk chemical was observed.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared once in the 14-day studies, every 2 weeks in the 13-week studies, and weekly in the 2-year studies by mixing *p*-nitrobenzoic acid and feed (Table H1). Homogeneity and stability studies of the 400 ppm concentration were performed by Midwest Research Institute using high-performance liquid chromatography. Homogeneity was confirmed, and the stability of the dose formulations when stored in the dark at room temperature was confirmed for at least 3 weeks. Dose formulations open to air and light were stable for 1 week.

Periodic analyses of the dose formulations of *p*-nitrobenzoic acid were conducted at the study laboratory and analytical chemistry laboratory using high-performance liquid chromatography. Dose formulations were analyzed once during the 14-day studies and were within 10% of the target concentrations (Table H2). Dose formulations for the 13-week studies were analyzed pre-study, during week 1, at study mid-point, and at the final mix (Table H3). During the 2-year studies, the dose formulations were analyzed approximately every two months (Table H4). All dose formulations were within 10% of the target concentrations during the 13-week studies; 95% (160/168) of the formulations were within 10% of the target concentrations during the 2-year studies. 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 H5).

14-DAY STUDIES

The 14-day studies were conducted to evaluate the cumulative toxic effects of repeated exposure to *p*-nitrobenzoic acid and to determine the appropriate doses to be used in the 13-week studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility

(Frederick, MD). At receipt, the animals were 4 weeks old. The rats were quarantined for 16 days before dosing began; the mice were quarantined for 15 days. Before the beginning of the studies, two male and two female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease.

Groups of five male and five female rats and mice received 0, 2,500, 5,000, 10,000, 20,000, or 40,000 ppm *p*-nitrobenzoic acid in feed for 14 days. Water and feed were available *ad libitum*. Feed consumption was measured twice weekly for rats and weekly for mice. Clinical observations were recorded twice daily. Animals were weighed at the beginning of the studies and weekly thereafter. Rats were housed five per cage; mice were housed individually.

At the end of the studies, blood was collected from the orbital sinus for hematology analyses. Automated hematologic determinations, except platelet counts, were performed using a Baker Series 7000 cell counter; platelet counts were determined using a Baker Series 810 whole blood platelet analyzer (Baker Instruments, Allentown, PA). Reagents were obtained from Baker Instruments. The clinical pathology parameters measured are listed in Table 1. The brain, heart, right kidney, liver, lungs, spleen, right testis, and thymus of all surviving animals were weighed. A necropsy was performed on all animals. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all controls and all 40,000 ppm animals at the end of the studies. Table 1 lists the tissues and organs routinely examined.

13-Week Studies

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

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories, Inc. (Gilroy, CA). At receipt, the animals were 3 to 4 weeks old. The rats were quarantined for 13 days before dosing began; the mice were quarantined for 11 days. Before the beginning of the studies, five male and five female rats and mice 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 male and five female control mice using the protocols of the NTP Sentinel Animal Program (Appendix K).

Groups of 10 male and 10 female rats received 0, 630, 1,250, 2,500, 5,000, or 10,000 ppm *p*-nitrobenzoic acid in feed for 13 weeks. Groups of 10 male and 10 female mice received 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm *p*-nitrobenzoic acid in feed for 13 weeks. The brain, heart, right kidney, liver, lungs, spleen, right testis, and thymus of all surviving animals were weighed.

Water and feed were available *ad libitum*. Feed consumption was measured weekly. Clinical observations were recorded twice daily. Animals were weighed at the beginning of the studies and weekly thereafter. Rats were housed five per cage; mice were housed individually.

Special study groups of 10 male and 10 female rats received 0, 630, 2,500, or 10,000 ppm *p*-nitrobenzoic acid for 13 weeks. On days 7, 30, 60, and 90, blood samples were collected from the orbital sinus for hematology and clinical chemistry analyses. Hematology analyses were performed as in the 14-day studies. Clinical chemistry parameters were measured using a Centrifichem-400 chemistry analyzer (Baker Instruments). Reagents were obtained from Baker Instruments or Sigma Diagnostics (St. Louis, MO). The clinical pathology parameters measured are listed in Table 1.

A necropsy was performed on all core study animals. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 6 μm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all controls, all animals dying before the end of the studies, and all 10,000 ppm rats and 20,000 ppm mice surviving to the end of the studies. Table 1 lists the tissues and organs routinely examined.

2-Year Studies

Study Design

Groups of 60 male and 60 female rats and mice received 0, 1,250, 2,500, or 5,000 ppm *p*-nitrobenzoic acid in feed for 103 weeks. Ten male and 10 female rats and mice from each group were evaluated at 15 months.

Source and Specification of Animals

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

Animal Maintenance

Rats were housed five per cage; mice were housed individually. Feed and water were available *ad libitum*. Feed consumption was measured every 4 weeks. Cages were rotated twice a week for rats and once a week for mice; racks were rotated every two weeks during the studies. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix J.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical observations and body weights were recorded at study initiation, weekly for 13 weeks, and monthly thereafter. Blood samples were collected from the retroorbital sinus at the 15-month interim evaluations for hematology analyses. Automated determinations were performed using an Ortho ELT-8 hematology analyzer (Ortho Instruments, Westwood, MA). Methemoglobin was measured using the Roche Cobas Fara (Roche Diagnostic Systems, Inc., Montclair, NJ). Reagents were obtained from the instrument manufacturer. The clinical pathology parameters measured are listed in Table 1. The right kidney, liver, and spleen were weighed at the 15-month interim evaluations.

A necropsy was performed on all animals. 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. Complete histopathologic examinations were performed on all animals. 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 microscope 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 pathology quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated by the quality assessment laboratory. The quality assessment pathologist microscopically reviewed the clitoral gland, kidney, liver, preputial gland, spleen, stomach, and uterus of all rats to confirm the incidences of neoplasms and nonneoplastic lesions. For mice, the quality assessment pathologist reviewed the forestomach, kidney, liver, lung, and thyroid gland to confirm the incidences of neoplasms and nonneoplastic lesions. In addition, each tissue with a neoplasm diagnosis from all rats and mice was microscopically reviewed.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed representative examples of potential chemical-related lesions including neoplasms of the clitoral gland, kidney, liver, preputial gland, spleen, and thyroid gland from rats; the forestomach, kidney, liver, lung, and thyroid gland from mice; and any other tissues when there was disagreement in diagnosis between the laboratory and quality assessment pathologist. Examples of disagreements in diagnoses between the laboratory and quality assessment pathologist 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 the tissues without knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent 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 found dead of other than natural causes or found to be missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A5, B1, B5, C1, C5, D1, and D5 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, and D3) and of all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Neoplasm Incidence

The majority of neoplasms in these studies were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was 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 the fit of the model was not significantly enhanced. 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, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods 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 included pairwise comparisons of each exposed group with controls, and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

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

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 Dunnett (1955) and Williams (1971, 1972). Hematology and clinical chemistry data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Dunn (1964) and Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related 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-related trend (Dunnett's or Dunn's test). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of lesion incidence in certain instances. Consequently, 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. Step-section historical data is taken from other NTP technical reports.

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, these studies 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 staff 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 discrepancies had been resolved or were otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicology of *p*-nitrobenzoic acid was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and the frequency of micronucleated erythrocytes in mouse peripheral blood. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of *p*-nitrobenzoic acid are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complimentarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests is not yet defined.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *p*-Nitrobenzoic Acid

14-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
Microbiological Associates, Inc. (Bethesda, MD)	Microbiological Associates, Inc. (Bethesda, MD)	Southern Research Institute (Birmingham, AL)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Frederick Cancer Research Facility (Frederick, MD)	Simonsen Laboratories, Inc. (Gilroy, CA)	Taconic Laboratory Animals and Services (Germantown, NY)
Size of Study Groups		
5 males and 5 females	Core study group: 10 male and 10 female rats and mice Special study group: 10 male and 10 female rats	60 males and 60 females
Time Held Before Studies		
Rats: 16 days Mice: 15 days	Rats: 13 days Mice: 11 days	12 days
Average Age When Studies Began		
6 weeks	5-6 weeks	44 days
Date of First Dose		
Rats: 13 December 1985 Mice: 12 December 1985	Rats: 22 May 1986 Mice: 20 May 1986	Rats: 11 May 1988 Mice: 25 May 1988
Duration of Dosing		
14 days	13 weeks	103 weeks
Date of Last Dose		
Rats: 26 December 1985 Mice: 25 December 1985	Rats: August 1986 Mice: August 1986	Rats: 1 May 1990 Mice: 15 May 1990
Method of Sacrifice		
CO_2 and exsanguination	CO_2 and exsanguination	CO_2 and exsanguination

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *p*-Nitrobenzoic Acid (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Necropsy Dates		
Rats: 27 December 1985 Mice: 26 December 1985	Rats: August 1986 Mice: August 1986	Rats: 9-10 May 1990 (males), 10-11 May 1990 (females) Mice: 23-24 May 1990 (males) 24-29 May 1990 (females)
Average Age at Necropsy		
8 weeks	18-19 weeks	772-778 days
Method of Animal Distribution		
Animals were randomized by weight with a computer randomization program.	Same as 14-day studies	Same as 14-day studies
Animals per Cage		
Rats: 5 Mice: 1	Rats: 5 Mice: 1	Rats: 5 Mice: 1
Method of Animal Identification		
Ear clip and toe clip	Ear clip and toe clip	Toe clip
Diet		
NIH-07 Open Formula Diet (powdered) (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 14-day studies	NIH-07 Open Formula Mash (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*
Maximum Storage Time for Feed		
120 days after milling	120 days after milling	120 days after milling
Feeders		
Rats: Stainless steel (Hahns Roofing and Sheet Metal Company, Birmingham, AL), changed twice weekly Mice: Stainless steel (Lab Products, Inc., Rochelle Park, NJ), changed weekly	Stainless steel (Hahns Roofing and Sheet Metal Company, Birmingham, AL), changed weekly	Stainless steel (Lab Products, Maywood, NY; Hoeltge, Inc., Cincinnati, OH; or Automated Precision, Madison, AL), changed weekly
Water		
Automatic watering system (Edstrom Industries, Inc., Waterford, WI), available *ad libitum*	Same as 14-day studies	Same as 14-day studies

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *p*-Nitrobenzoic Acid (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Cages		
Polycarbonate (Lab Products, Inc., Rochelle Park, NJ), changed weekly for rats and twice weekly for mice	Polycarbonate (Lab Products, Inc., Rochelle Park, NJ), changed twice weekly for rats and weekly for mice	Polycarbonate (Lab Products, Maywood, NJ), changed twice weekly for rats and weekly for mice
Bedding		
BetaChips® (Northeastern Product Corporation, Warrensburg, NY), changed weekly for rats and twice weekly for mice	BetaChips® (Northeastern Product Corporation, Warrensburg, NY), changed twice weekly for rats and weekly for mice	Sani-Chips (P.J. Murphy Forest Products Corporation, Montville, NJ), changed twice weekly for rats and weekly for mice
Cage Filters		
Spun-bonded polyester (Snow Filtration Company, Cincinnati, OH), changed once every 2 weeks	Same as 14-day studies	Remay® spun-bonded polyester (Andico, Birmingham, AL), changed every 2 weeks
Racks		
Stainless steel (Lab Products, Inc., Rochelle Park, NJ), changed once every 2 weeks	Same as 14-day studies	Stainless steel (Lab Products, Inc., Maywood, NJ), changed every 2 weeks
Animal Room Environment		
Average temperature: 22° C (rats), 21° C (mice) Relative humidity: 59% (rats), 45% (mice) Fluorescent light: 12 hours/day Room air changes: minimum of 12 changes/hour	Average temperature: 22° C Relative humidity: 71% (rats), 72% (mice) Fluorescent light: 12 hours/day Room air changes: minimum of 12 changes/hour	Average temperature: 22° C Relative humidity: 50%-51% Fluorescent light: 12 hours/day Room air changes: minimum of 10 changes/hour
Doses		
0, 2,500, 5,000, 10,000, 20,000, or 40,000 *p*-nitrobenzoic acid in feed, available *ad libitum*	Rats: 0, 630, 1,250, 2,500, 5,000, or 10,000 ppm *p*-nitrobenzoic acid in feed, available *ad libitum* Mice: 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm *p*-nitrobenzoic acid in feed, available *ad libitum*	0, 1,250, 2,500, or 5,000 ppm *p*-nitrobenzoic acid in feed, available *ad libitum*
Type and Frequency of Observation		
Animals were observed and clinical observations were recorded twice daily; animals were weighed on days 1, 8, and 15. Feed consumption was measured twice weekly for rats and once weekly for mice.	Animals were observed and clinical observations were recorded twice daily; animals were weighed initially and weekly thereafter. Feed consumption was measured weekly.	Animals were observed twice daily. Clinical observations and body weights were recorded initially, weekly during first 13 weeks, and monthly thereafter. Feed consumption was measured every 4 weeks.

TABLE 1
Experimental Design and Materials and Methods in the Feed Studies of *p*-Nitrobenzoic Acid (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Necropsy		
Necropsy was performed on all animals. Organs weighed were brain, heart, right kidney, liver, lungs, spleen, right testis, and thymus.	Necropsy was performed on all core animals. Organs weighed were brain, heart, right kidney, liver, lungs, spleen, right testis, and thymus.	Necropsy was performed on all animals. Organs weighed at 15 months were right kidney, liver, and spleen.
Clinical Pathology		
Blood samples were collected from the orbital sinus of all animals at necropsy. *Hematology:* hematocrit, hemoglobin, erythrocytes, reticulocytes, mean erythrocyte volume, leukocyte count and differential, and methemoglobin	Blood samples were collected from the orbital sinus of special study rats on days 7, 30, 60, and 90 at exposure levels of 0, 630, 2,500, and 10,000 ppm. *Hematology:* hematocrit, hemoglobin, erythrocytes, reticulocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, leukocyte count and differential, Heinz bodies, and methemoglobin *Clinical Chemistry:* alkaline phosphatase, alanine aminotransferase, and sorbitol dehydrogenase	Blood samples were collected from the retroorbital sinus of all animals at the 15-month interim evaluation. *Hematology:* hematocrit, hemoglobin, erythrocytes, mean erythrocyte volume, mean erythrocyte hemoglobin, mean erythrocyte hemoglobin concentration, platelets, reticulocytes, leukocyte count and differential, and methemoglobin
Histopathology		
Complete histopathologic examinations were performed on all controls and all 40,000 ppm animals at the end of the studies. In addition to gross lesions, the tissues examined included: adrenal gland, bone and marrow, brain, epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, salivary gland, seminal vesicle, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. Selected organs and gross lesions were examined in lower exposure groups until a no-effect level was observed. Selected organs were bone marrow, ovary (rats), testis, thymus (rats), thyroid gland (rats), and spleen (rats).	Except for special study rats, complete histopathologic examinations were performed on all controls, all animals dying before the end of the studies, and all 10,000 ppm rats and 20,000 ppm mice surviving to the end of the studies. In addition to gross lesions, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland (rats), epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland (rats), prostate gland, salivary gland, seminal vesicle, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.	Complete histopathologic examinations were performed on all animals. In addition to gross lesions, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, epididymis, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, seminal vesicle, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

14-Day Study

All rats survived to the end of the study (Table 2). Mean body weight gains were significantly reduced in males exposed to 10,000 ppm, and males and females exposed to 20,000 and 40,000 ppm lost weight. Males and females exposed to 10,000, 20,000, and 40,000 ppm had final mean body weights significantly lower than those of the controls. There were no clinical findings relating to organ-specific toxicity, although animals in the 40,000 ppm groups were lethargic during the second week on study. In most of the groups that lost weight, there was a reduction in feed consumption (Table 2). Feed spillage was not measured. Feed consumption by the other exposure groups was similar to that by the controls. Dietary levels of 2,500, 5,000, 10,000, 20,000, and 40,000 ppm *p*-nitrobenzoic acid resulted in average daily doses of 240, 450, 810, 1,170, and 2,260 mg/kg body weight to males and 230, 430, 840, 930, and 2,840 mg/kg to females. The estimate for 40,000 ppm females may exceed the actual value because of scattering of feed.

Table 2
Survival, Mean Body Weights, and Feed Consumption of Rats in the 14-Day Feed Study of *p*-Nitrobenzoic Acid

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	152 ± 5	210 ± 4	58 ± 4		16.3	16.4
2,500	5/5	145 ± 5	205 ± 6	60 ± 2	98	16.2	17.4
5,000	5/5	145 ± 3	198 ± 3	53 ± 2	94	14.6	16.0
10,000	5/5	148 ± 4	173 ± 4**	25 ± 2**	82	12.0	13.9
20,000	5/5	143 ± 4	127 ± 5**	−16 ± 2**	60	6.8	9.0
40,000	5/5	141 ± 5	110 ± 6**	−31 ± 4**	52	3.8	10.5
Female							
0	5/5	117 ± 3	140 ± 3	23 ± 1		10.8	11.6
2,500	5/5	116 ± 4	139 ± 4	24 ± 1	99	11.1	12.5
5,000	5/5	117 ± 2	134 ± 3	18 ± 1	96	10.1	11.4
10,000	5/5	102 ± 4**	123 ± 3**	21 ± 4	87	8.3	10.5
20,000	5/5	114 ± 3	95 ± 4**	−19 ± 2**	68	4.7	5.0
40,000	5/5	116 ± 3	91 ± 4**	−25 ± 4**	65	3.4	11.3

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption is expressed as grams of feed consumed per animal per day and was not corrected for feed spillage (scattering).

The absolute and relative thymus weights of 20,000 and 40,000 ppm males and females and the absolute thymus weights of 10,000 ppm males and females were significantly lower than those of the controls (Table F1). The thymus weight effects were considered to be related to lower body weight, lower feed intake, and stress. Decreases in absolute weights and increases in relative weights of other organs except the spleen were attributed to decreased body weights.

There were statistically significant increases in the absolute and relative spleen weights of 10,000, 20,000, and 40,000 ppm males and females and differences in the hematology parameters characteristic of a regenerative anemia, which was probably hemolytic in nature. There were statistically significant reductions in erythrocyte count, hemoglobin, and hematocrit values and statistically significant increases in reticulocyte count, nucleated erythrocytes, and methemoglobin concentrations (except in 10,000 ppm males) in the 10,000, 20,000, and 40,000 ppm groups (Table G1). Less pronounced differences in these parameters were observed in the other exposure groups. A significant leukocytosis with lymphocytes was present in 20,000 and 40,000 ppm males.

There were no gross lesions observed at necropsy that were considered to be related to chemical administration. Hypertrophy of the follicular epithelium of the thyroid gland was present in all male and female rats receiving 10,000, 20,000, and 40,000 ppm *p*-nitrobenzoic acid, while follicular cell hyperplasia was observed in four 40,000 ppm males and two 40,000 ppm females (Table 3). Atrophy (degeneration) of the testis was observed in 20,000 and 40,000 ppm males. Congestion of the spleen was observed in one 5,000 ppm male, in all 10,000 ppm males, and in all 20,000 and 40,000 ppm males and females. Other microscopic findings observed in the 20,000 and 40,000 ppm groups, including atrophy in the thymus of 20,000 and 40,000 ppm males and atrophy in the ovary, bone marrow, and thymus of 20,000 and 40,000 ppm females, were considered secondary to stress and inanition.

Hypertrophy of the follicular epithelium was diffuse and ranged from minimal to moderate in severity, in a dose-related manner, across exposure groups. Thyroid glands in exposed animals had a predominance of large follicles. The follicular epithelium was tall columnar to low cuboidal, the cytoplasm was slightly basophilic, nuclei were vesiculate, and the colloid was pale eosinophilic. Minimal thyroid follicular hyperplasia was characterized by focal stacking of epithelial cells that did not maintain contact with the basement membranes. Testicular atrophy was characterized by reduced seminiferous tubule size and fewer spermatogenic cells. Affected seminiferous tubules contained multinucleated giant cells that represented fused spermatid nuclei.

Based on the decreased mean body weights and clinical pathologic and histopathologic findings at 20,000 and 40,000 ppm, the high dose selected for the 13-week study was 10,000 ppm.

Table 3
Incidences of Selected Nonneoplastic Lesions in Rats in the 14-Day Feed Study of *p*-Nitrobenzoic Acid

Dose (ppm)	0	2,500	5,000	10,000	20,000	40,000
Male						
Thyroid Gland[a]	5	–[b]	–	5	5	5
Hypertrophy, Follicular Epithelium[c]	0	–	–	5** (1.0)[d]	5** (1.5)	5** (2.5)
Hyperplasia, Follicular Epithelium	0	–	–	0	0	4*
Testis	5	–	–	5	5	5
Atrophy, Germinal Epithelium	0	–	–	0	1	4*
Spleen	5	5	5	5	5	5
Congestion	0	0	1	5**	5**	5**
Thymus	5	–	–	5	5	5
Atrophy, Cortex	0	–	–	0	2	2
Bone Marrow	5	–	–	–	–	5
Atrophy	0	–	–	–	–	0
Female						
Thyroid Gland	5	–	–	5	5	5
Hypertrophy, Follicular Epithelium	0	–	–	5** (1.0)	5** (1.5)	5** (2.5)
Hyperplasia, Follicular Epithelium	0	–	–	0	0	2
Spleen	5	–	–	5	5	5
Congestion	0	–	–	0	5**	5**
Thymus	5	–	–	5	5	5
Atrophy, Cortex	0	–	–	0	1	4*
Bone Marrow	5	–	–	5	5	5
Atrophy	0	–	–	0	1	5**
Ovary	5	–	–	5	5	5
Atrophy	0	–	–	0	2	4*

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
a Number of animals with organ examined microscopically
b Organ not examined in this exposure group
c Number of animals with lesion
d Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe

13-Week Study

All rats in the 13-week study survived until the end of the study (Table 4). Mean body weight gain and final mean body weights were significantly lower than those of the controls in 2,500 ppm males and in 5,000 and 10,000 ppm males and females. There were no clinical findings that could be clearly related to *p*-nitrobenzoic acid exposure. Feed consumption by males and females was similar to that by the controls. Dietary levels of 630, 1,250, 2,500, 5,000, or 10,000 ppm *p*-nitrobenzoic acid delivered average daily doses of 40, 70, 160, 210, or 660 mg/kg to males and 40, 80, 170, 340, or 680 mg/kg to females.

The absolute and relative spleen weights were significantly increased in males and females exposed to 10,000 ppm, and the relative spleen weights were significantly increased in males and females exposed to 5,000 ppm (Table F2). These differences were probably a result of a hemolytic anemia. Differences in the absolute and relative weights of other organs were considered to be related to decreased body weights.

Table 4
Survival, Mean Body Weights, and Feed Consumption of Rats in the 13-Week Feed Study of *p*-Nitrobenzoic Acid

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 13
Male							
0	10/10	116 ± 4	354 ± 6	238 ± 5		11.8	15.6
630	10/10	119 ± 4	358 ± 5	239 ± 5	101	12.3	16.8
1,250	10/10	114 ± 4	341 ± 6	227 ± 5	96	10.5	15.3
2,500	10/10	114 ± 3	335 ± 4*	221 ± 4*	95	11.1	16.8
5,000	10/10	107 ± 5	322 ± 6**	216 ± 4**	91	10.4	15.8
10,000	10/10	117 ± 4	261 ± 3**	144 ± 3**	74	10.3	14.6
Female							
0	10/10	97 ± 2	204 ± 4	106 ± 4		9.5	10.0
630	10/10	100 ± 3	202 ± 3	102 ± 3	99	9.7	9.7
1,250	10/10	97 ± 2	200 ± 3	103 ± 3	98	9.0	10.0
2,500	10/10	98 ± 3	195 ± 3	98 ± 2	96	9.5	10.3
5,000	10/10	95 ± 2	182 ± 2**	87 ± 3**	89	8.6	10.0
10,000	10/10	99 ± 2	169 ± 2**	70 ± 2**	83	8.5	9.8

* Significantly different ($P \leq 0.05$) from the control group by Williams' test
** $P \leq 0.01$
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.

Differences in hematology and clinical chemistry parameters were observed primarily in the 10,000 ppm rats (Table G2). These differences included increases in methemoglobin and Heinz bodies as early as day 7 and increased reticulocyte counts, decreased erythrocyte counts, and decreased hemoglobin and hematocrit values as early as day 30 of the study. In addition, slight increases in mean erythrocyte hemoglobin at days 30 and 60 in male rats and increases in mean erythrocyte volume in male and female rats at days 30 and 60 were supportive of a regenerative anemia. The slight increases in leukocyte count in 10,000 ppm females at days 7 and 30 may have been associated with a hemolytic anemia. Slight increases in alanine aminotransferase were present in 10,000 ppm males and females at days 7 and 30.

Chemical-related histopathologic lesions were observed in the testis, spleen, and kidney. As in the 14-day study, the testicular lesion in 10,000 ppm males consisted of atrophy of the seminiferous tubules characterized by mild to severe depletion of spermatogenic cells and by pyknotic cells and multinucleated cells in the lumen of the seminiferous tubules.

Yellow-brown pigmentation of the red pulp was present in the spleen of 2,500, 5,000, and 10,000 ppm males and females, and congestion was observed in the spleen of 2,500, 5,000, and 10,000 ppm males and 10,000 ppm females (Table 5). Splenic sinusoids were ectatic, and macrophages contained yellow-brown pigment consistent with hemosiderin. Mild pigmentation was also present in the kidney of 5,000 and 10,000 ppm males. The pigmentation was present in the cytoplasm of renal tubule epithelial cells. The yellow-brown pigment, consistent with hemosiderin, in the spleen and kidney was associated with the hemolytic anemia.

Mild karyomegaly of renal tubule epithelial cells was observed in the kidney of 5,000 ppm females and 10,000 ppm males and females. The mild karyomegaly was more prominent in the outer cortex and was scattered in renal tubule epithelial cells. Karyomegaly was characterized by nuclei that were 4 to 6 times larger than normal. Occasional nuclei were pleomorphic and contained two prominent nucleoli.

Male rats exposed to 10,000 ppm had mild cytoplasmic hyaline droplet accumulation in renal tubule epithelial cells within the outer renal cortex. Multiple hyaline droplets were most commonly present within the cytoplasm of cells, but the droplets were also observed protruding from the cell, and were often observed within renal tubule lumens. Hyaline droplets were eosinophilic, crystalline-shaped or amorphous to spherical, and variable in size. The droplets were more frequent and larger than the smaller, more uniform protein "reabsorption droplets" typically present in the kidney of male control rats. Minimal hyaline droplet accumulation was also observed in 630, 1,250, 2,500, and 5,000 ppm males. Using the Mallory-Heidenhain stain for proteins, the cytoplasmic hyaline droplets appeared intensely eosinophilic, similar to the staining observed for the protein "reabsorption droplets." There was no degeneration or necrosis of the renal tubule epithelial cells and no mineralization or granular casts was observed.

Dose Selection Rationale: Based on lower mean body weights and increased severity of splenic lesions, dietary levels of *p*-nitrobenzoic acid selected for the 2-year feed study in rats were 0, 1,250, 2,500, and 5,000 ppm.

TABLE 5
Incidences of Selected Nonneoplastic Lesions in Rats in the 13-Week Feed Study of *p*-Nitrobenzoic Acid

Dose (ppm)	0	630	1,250	2,500	5,000	10,000
Male						
Spleen[a]	10	–[b]	10	10	10	10
Congestion[c]	0	–	0	2 (1.0)[d]	10** (1.0)	10** (1.5)
Pigmentation	0	–	0	6** (1.0)	10** (1.0)	10** (1.6)
Kidney	10	10	10	10	10	10
Pigmentation	0	0	0	10** (1.0)	10** (2.0)	10** (2.0)
Cytoplasmic Hyaline Droplet Accumulation[e]	0	10** (1.0)	10** (1.0)	10** (1.0)	10** (1.0)	10** (2.0)
Karyomegaly	0	0	0	6** (1.0)	10** (1.0)	10** (2.0)
Female						
Spleen	10	–	10	10	10	10
Congestion	0	–	0	0	0	10** (1.5)
Pigmentation	0	–	0	10** (1.0)	10** (1.2)	10** (1.5)
Kidney	10	10	10	10	10	10
Karyomegaly	0	0	0	10** (1.0)	10** (2.0)	10** (2.0)

** Significantly different ($P \leq 0.01$) from the control group by the Fisher exact test
[a] Number of animals with organ examined microscopically
[b] Organ not examined in this exposure group
[c] Number of animals with lesion
[d] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe
[e] Diagnosed as cytoplasmic change by the study pathologist

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. Two-year survival of males receiving 1,250 and 2,500 ppm was similar to that of the controls at the end of the study. The survival of 5,000 ppm males was marginally greater than that of the controls, which was attributed to a decrease in the severity of nephropathy and a decrease in the incidence of mononuclear cell leukemia in this exposure group. Survival of exposed females was similar to that of the controls.

Body Weights, Feed Consumption, and Clinical Findings

The mean body weights of 5,000 ppm males were 2% to 8% lower than those of the controls through week 80 (Table 7 and Figure 3). Final mean body weights of exposed males were similar to that of the controls. The mean body weights of 5,000 ppm females were 2% to 9% lower than those of the controls during the first year of the study and 10% to 16% lower during the second year of the study (Table 8 and Figure 3). Feed consumption by exposed groups was similar to that by the controls (Tables I1 and I2). Dietary levels of 1,250, 2,500, or 5,000 ppm *p*-nitrobenzoic acid delivered approximately 50, 100, or 210 mg/kg body weight per day to males and 60, 125, or 250 mg/kg per day to females. There were no clinical findings attributable to organ-specific toxicity.

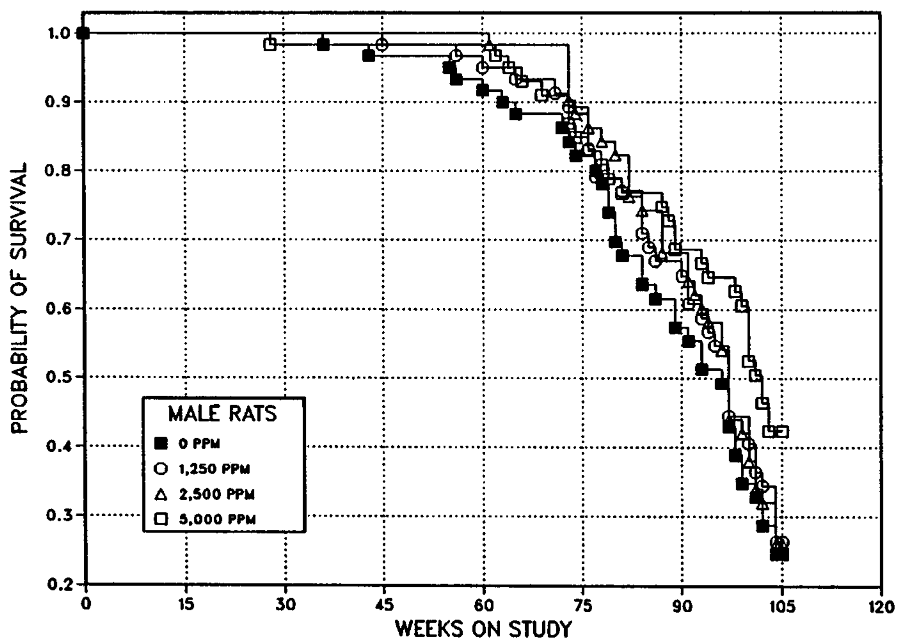
Hematology

Marginal differences were noted between the hematologic profile of 5,000 ppm females and that of the controls. These differences did not appear to affect the well-being of the animals. At the 15-month interim evaluation, leukocyte count was significantly increased in 5,000 ppm males and females (Table G3). In 5,000 ppm females, erythrocyte count, hemoglobin, hematocrit, mean erythrocyte hemoglobin, and mean erythrocyte hemoglobin concentration values were significantly lower than those of the controls. Nucleated erythrocyte, segmented neutrophil, lymphocyte, and platelet values were significantly greater than those of the controls in 5,000 ppm females.

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

Dose (ppm)	0	1,250	2,500	5,000
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Moribund	32	34	34	25
Natural deaths	6	3	3	4
Animals surviving to study termination	12	13	13	21
Percent probability of survival at end of study[b]	25	26	26	42
Mean survival (days)[c]	587	607	618	618
Survival analyses[d]	P=0.038N	P=0.651N	P=0.563N	P=0.053N
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Moribund	21	23	27	26
Natural deaths	2	4	2	3
Animals surviving to study termination	27	23	21	21
Percent probability of survival at end of study	54	46	43	42
Mean survival (days)	659	633	616	635
Survival analyses	P=0.250	P=0.400	P=0.137	P=0.231

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on first day of terminal sacrifice
[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 exposure columns. A negative trend or a lower mortality in an exposure group is indicated by N.



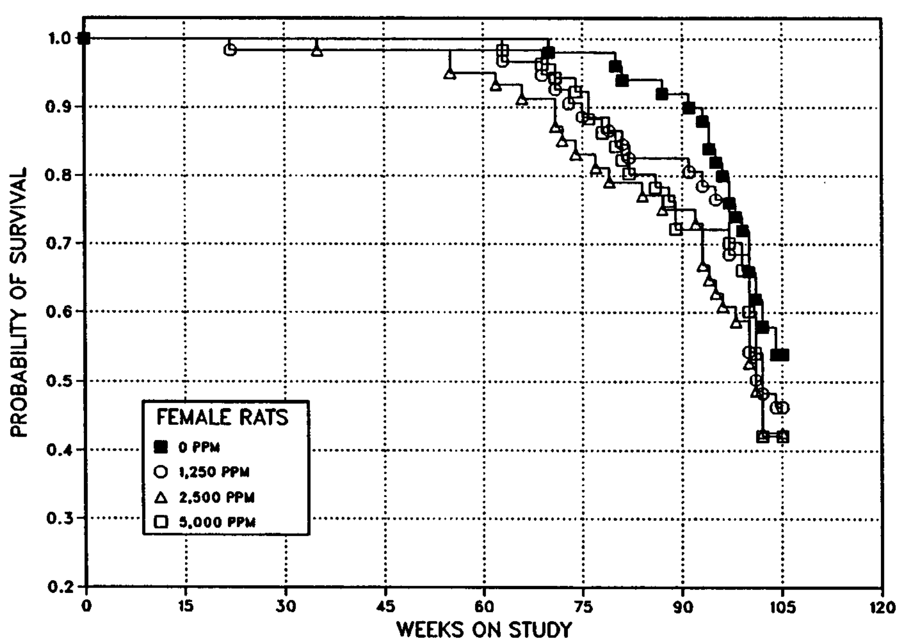


Figure 2
Kaplan-Meier Survival Curves for Rats Administered *p*-Nitrobenzoic Acid in Feed for 2 Years

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

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	1,250 ppm Av. Wt. (g)	1,250 ppm Wt. (% of controls)	1,250 ppm No. of Survivors	2,500 ppm Av. Wt. (g)	2,500 ppm Wt. (% of controls)	2,500 ppm No. of Survivors	5,000 ppm Av. Wt. (g)	5,000 ppm Wt. (% of controls)	5,000 ppm No. of Survivors
1	128	60	126	98	60	124	96	60	126	98	60
2	169	60	168	100	60	166	98	60	164	97	60
3	207	60	206	99	60	200	97	60	198	96	60
4	235	60	231	99	60	227	97	60	221	94	60
5	262	60	259	99	60	258	99	60	240	92	60
6	283	60	281	100	60	280	99	60	262	93	60
7	300	60	299	100	60	298	99	60	278	93	60
8	313	60	310	99	60	311	99	60	294	94	60
9	321	60	320	100	60	322	100	60	304	94	60
10	338	60	337	100	60	337	100	60	315	93	60
11	347	60	350	101	60	350	101	60	329	95	60
12	352	60	355	101	60	356	101	60	334	95	60
13	362	60	360	99	60	359	99	60	338	93	60
17	387	60	381	99	60	391	101	60	366	95	60
21	409	60	409	100	60	412	101	60	389	95	60
25	426	60	421	99	60	427	100	60	400	94	60
28	435	60	431	99	60	435	100	60	410	94	59
33	450	60	450	100	60	447	99	60	426	95	59
37	460	59	461	100	60	464	101	60	442	96	59
41	469	59	470	100	60	466	99	60	446	95	59
45	475	58	475	100	60	480	101	60	459	97	59
49	478	58	485	102	59	484	101	60	464	97	59
53	480	58	488	102	59	485	101	60	463	97	59
57	482	56	491	102	58	486	101	60	464	96	59
61	484	55	484	100	57	480	99	60	461	95	59
65	483	54	487	101	57	486	101	59	465	96	57
69[a]	482	43	490	102	46	485	101	49	466	97	46
73	474	42	478	101	45	472	99	49	458	97	45
77	475	40	480	101	41	474	100	43	465	98	41
80	472	34	471	100	39	469	99	41	458	97	39
85	463	31	463	100	35	469	101	37	459	99	38
89	462	30	468	101	33	473	102	34	462	100	36
93	455	27	458	101	30	470	103	31	457	101	34
97	442	24	447	101	27	451	102	26	447	101	32
101	449	17	441	98	20	460	102	19	444	99	26
Mean for weeks											
1-13	278		277	100		276	99		262	94	
14-52	443		443	100		445	100		422	95	
53-101	469		473	101		474	101		459	98	

[a] Interim evaluation occurred during week 66.

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

Weeks on Study	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	105	60	106	101	60	103	98	60	103	98	60
2	125	60	125	100	60	125	100	60	122	98	60
3	137	60	137	100	60	134	98	60	131	96	60
4	149	60	149	100	60	146	99	60	143	96	60
5	156	60	157	100	60	154	99	60	150	96	60
6	166	60	168	101	60	164	99	60	160	97	60
7	173	60	174	101	60	170	98	60	167	97	60
8	175	60	177	101	60	173	99	60	171	98	60
9	178	60	179	101	60	176	99	60	172	97	60
10	184	60	185	101	60	183	100	60	179	98	60
11	190	60	191	101	60	188	99	60	183	96	60
12	191	60	193	101	60	191	100	60	187	98	60
13	192	60	192	100	60	188	98	60	184	96	60
17	203	60	205	101	60	193	95	60	199	98	60
21	211	60	211	100	60	207	98	60	203	96	60
25	218	60	218	100	59	212	97	60	206	95	60
29	217	60	220	102	59	216	100	60	208	96	60
33	228	60	226	99	59	221	97	60	212	93	60
37	236	60	235	100	59	227	97	59	219	93	60
41	242	60	243	101	59	234	97	59	224	93	60
45	249	60	249	100	59	242	97	59	230	92	60
50	262	60	261	100	59	254	97	59	237	91	60
53	271	60	269	99	59	262	97	59	243	90	60
57	280	60	276	99	59	267	95	57	245	87	60
61	290	60	282	97	59	273	94	57	253	87	60
65	298	60	289	97	58	280	94	56	257	86	59
69[a]	306	50	297	97	48	286	94	45	267	87	49
73	308	49	299	97	46	290	94	42	264	86	47
77	316	49	304	96	44	292	92	41	270	86	44
81	321	48	308	96	43	298	93	39	274	86	42
85	324	47	313	97	41	296	92	38	270	84	40
89	334	46	323	97	41	306	92	37	282	85	38
93	332	45	324	98	40	305	92	36	283	85	36
97	337	40	327	97	35	316	94	30	289	86	35
101	341	31	331	97	25	314	92	24	288	84	28
Mean for weeks											
1-13	163		164	101		161	99		158	97	
14-52	230		230	100		223	97		215	93	
53-101	312		303	97		291	93		268	86	

[a] Interim evaluation occurred during week 66.

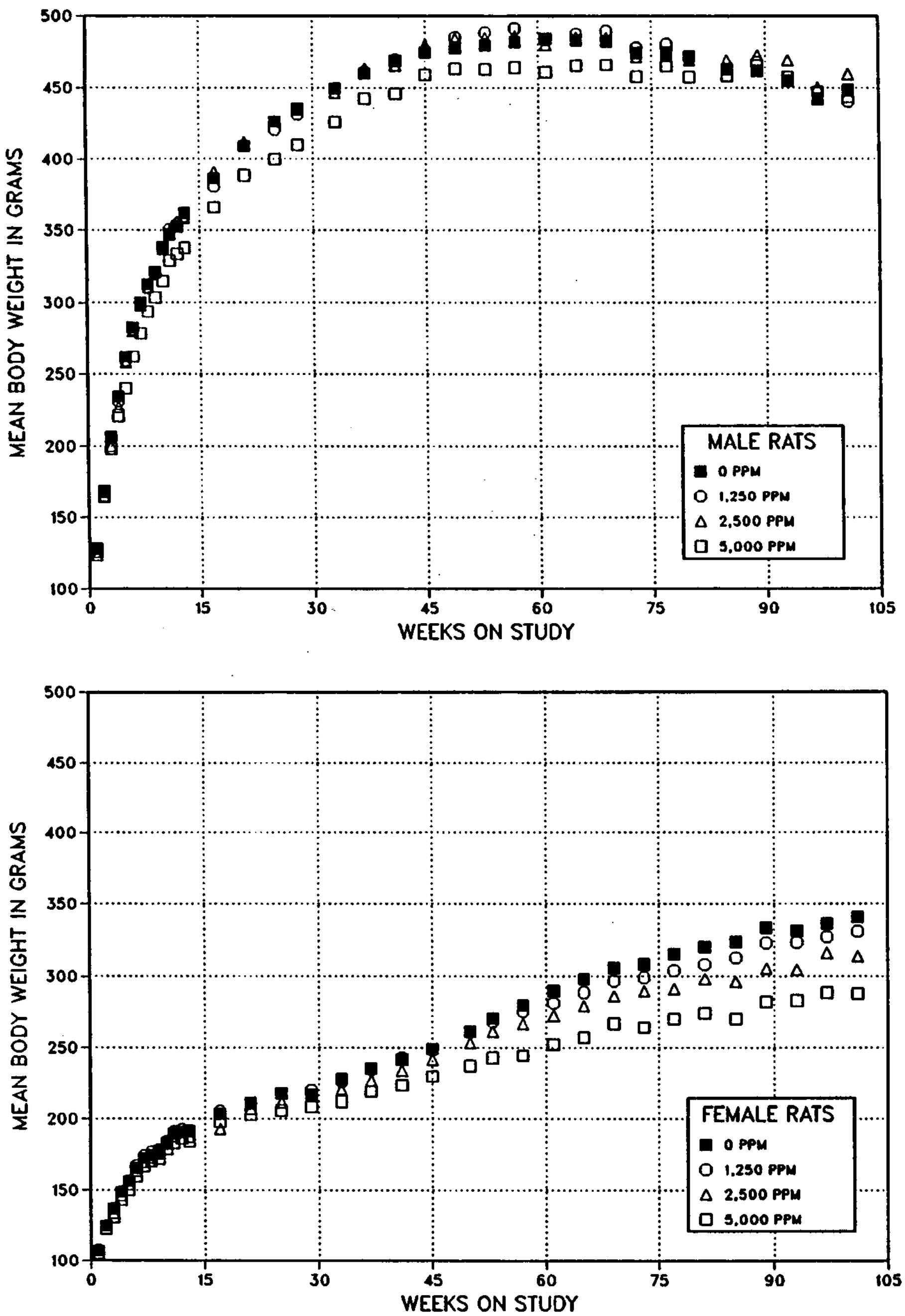


FIGURE 3
Growth Curves for Rats Administered *p*-Nitrobenzoic Acid in Feed for 2 Years

Pathology and Statistical Evaluation

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

Preputial/Clitoral gland: The incidence of preputial gland carcinoma in 5,000 ppm males was significantly greater than that of the controls by the logistic regression test but not by the life table test. However, the incidences of preputial gland adenoma and of preputial gland adenoma or carcinoma (combined) in exposed males were not statistically different from those of the controls (Table 9). Twenty-one of the 25 preputial gland neoplasms occurred in animals sacrificed in a moribund condition prior to the end of the study, suggesting that these were generally lethal neoplasms. Thus, the most appropriate test for these neoplasms is life table analysis rather than logistic regression. These preputial gland neoplasms were observed on gross pathology examination and the average diameter of the preputial gland carcinomas was 31 mm. No preputial gland hyperplasia was observed and few preputial gland adenomas were observed at 15 months.

At the end of the study, all exposed female groups had incidences of clitoral gland adenoma and adenoma or carcinoma (combined) that were significantly greater than those of the controls (Tables 10 and B3). The incidences of clitoral gland adenoma and of clitoral gland adenoma or carcinoma (combined) in groups exposed to *p*-nitrobenzoic acid exceeded the historical control ranges in female F344/N rats in recent 2-year NTP feed studies (Table B4a). Clitoral gland hyperplasia was not observed at the 15-month interim evaluation, and the incidences of hyperplasia in exposed females were marginally lower than that of the controls at 2 years (Tables 10 and B5). Because there was no dose response for clitoral gland neoplasms and the time to neoplasm occurrence was similar (approximately 700 days) in control and exposed groups, and because there was no increase in the incidence of clitoral gland hyperplasia, the increased incidences of clitoral gland neoplasms were considered to be only some evidence of carcinogenic activity in female rats exposed to *p*-nitrobenzoic acid.

Preputial and clitoral gland adenomas were generally circumscribed and sometimes caused compression of the surrounding tissue. The neoplastic cells formed acini and clusters, which were spherical to elongated in shape and varied in size. Many of the neoplastic cells had discrete borders and granular cytoplasm. Foci of cellular debris, necrosis, and cysts were often present. Carcinomas were generally larger masses and less circumscribed than adenomas and often infiltrated the adjacent normal tissue.

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Preputial Gland in Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid

Dose (ppm)	0	1,250	2,500	5,000
15-Month Interim Evaluation				
Preputial Gland[a]	10	10	10	10
Adenoma[b]	1	0	1	1
2-Year Study				
Preputial Gland	50	50	49	50
Hyperplasia	4 (2.0)[c]	0	1 (2.0)	3 (1.3)
Adenoma				
Overall rate[d]	3/50 (6%)	3/50 (6%)	4/49 (8%)	3/50 (6%)
Adjusted rate[e]	21.1%	13.6%	16.5%	10.4%
Terminal rate[f]	2/12 (17%)	0/13 (0%)	1/13 (8%)	1/21 (5%)
First incidence (days)	689	588	532	617
Life table test[g]	P=0.382N	P=0.603N	P=0.555	P=0.434N
Logistic regression test[g]	P=0.522N	P=0.611N	P=0.560	P=0.554N
Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	4/49 (8%)	6/50 (12%)
Adjusted rate	2.7%	2.9%	15.9%	15.0%
Terminal rate	0/12 (0%)	0/13 (0%)	0/13 (0%)	0/21 (0%)
First incidence (days)	548	602	651	518
Life table test	P=0.031	P=0.744N	P=0.234	P=0.094
Logistic regression test	P=0.002	P=0.743	P=0.192	P=0.009
Adenoma or Carcinoma[h]				
Overall rate	4/50 (8%)	4/50 (8%)	8/49 (16%)	9/50 (18%)
Adjusted rate	23.2%	16.1%	29.8%	23.8%
Terminal rate	2/12 (17%)	0/13 (0%)	1/13 (8%)	1/21 (5%)
First incidence (days)	548	588	532	518
Life table test	P=0.176	P=0.579N	P=0.254	P=0.278
Logistic regression test	P=0.024	P=0.607N	P=0.219	P=0.055

[a] Number of animals with preputial gland examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Number of animals with neoplasm per number of animals examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test regards neoplasms in animals dying prior to terminal sacrifice as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.
[h] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 139/1,169 (11.9% ± 7.8%), range 2%-30%

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Clitoral Gland in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid

Dose (ppm)	0	1,250	2,500	5,000
Clitoral Gland[a]	50	49	49	50
Hyperplasia[b]	10 (2.0)[c]	6 (1.8)	6 (2.2)	7 (2.3)
Adenoma				
Overall rate[d]	4/50 (8%)	12/49 (24%)	10/49 (20%)	12/50 (24%)
Adjusted rate[e]	11.9%	42.5%	33.7%	42.1%
Terminal rate[f]	2/27 (7%)	7/22 (32%)	4/20 (20%)	7/21 (33%)
First incidence (days)	653	665	496	483
Life table test[g]	P=0.034	P=0.013	P=0.030	P=0.013
Logistic regression test[g]	P=0.046	P=0.013	P=0.050	P=0.023
Carcinoma				
Overall rate	1/50 (2%)	2/49 (4%)	5/49 (10%)	4/50 (8%)
Adjusted rate	3.7%	6.0%	19.3%	11.7%
Terminal rate	1/27 (4%)	0/22 (0%)	3/20 (15%)	0/21 (0%)
First incidence (days)	730 (T)	694	499	528
Life table test	P=0.085	P=0.460	P=0.056	P=0.139
Logistic regression test	P=0.117	P=0.459	P=0.084	P=0.224
Adenoma or Carcinoma[h]				
Overall rate	4/50 (8%)	14/49 (29%)	15/49 (31%)	15/50 (30%)
Adjusted rate	11.9%	45.9%	48.9%	47.7%
Terminal rate	2/27 (7%)	7/22 (32%)	7/20 (35%)	7/21 (33%)
First incidence (days)	653	665	496	483
Life table test	P=0.008	P=0.005	P=0.001	P=0.002
Logistic regression test	P=0.011	P=0.004	P=0.003	P=0.004

(T)Terminal sacrifice
[a] Number of animals with clitoral gland examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Number of animals with neoplasm per number of animals examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test regards neoplasms in animals dying prior to terminal sacrifice as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal.
[h] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 120/1,096 (10.9% ± 5.3%), range 2%-21%

Kidney: The severity of nephropathy was decreased at 15 months in males exposed to 2,500 and 5,000 ppm *p*-nitrobenzoic acid. At 2 years, the incidences of nephropathy for all groups of rats were 98% to 100% (Tables 11, A5, and B5); however, the severity decreased as exposure level increased in males and females. Nephropathy was less severe in females than in males, consistent with differences normally seen between aging male and female rats. Nephropathy was characterized by glomerulosclerosis, thickening of renal tubule basement membrane, degeneration and atrophy of tubule epithelium, dilatation of tubule lumens by pale pink acellular material (hyaline casts), interstitial fibrosis, and chronic inflammation. Regeneration of the renal tubule epithelium was also observed and the extent and severity of this process paralleled the overall severity of the degenerative changes. Few hyaline droplets were observed in renal tubule epithelial cells of male rats at the end of the 2-year study. It was difficult to further evaluate karyomegaly of renal tubule cells in males and females at 2 years because the karyomegaly could not be differentiated from regenerative changes associated with nephropathy.

There was an increase in the severity of pigmentation of renal tubule epithelial cells at the 15-month interim evaluation and at 2 years (Table 11). The pigment was primarily in the cytoplasm of proximal convoluted renal tubule epithelial cells and was variably brown to light brown or golden. Representative sections of kidney were stained for iron by Perls' method. Positive ferric iron staining was characterized by a distinct medium to dark blue coloration primarily in very small granules, most were 1 micron or less in size. These granules were irregularly distributed, primarily in proximal convoluted renal tubule epithelial cells in the outer cortex. The positive staining indicated the presence of ferric iron, a form compatible with that present in hemosiderin. The severity of the pigment stained by Perls' method was similar in almost all instances to the severity of yellowish brown pigment deposition detected in the hematoxylin and eosin slides.

Proliferative lesions and neoplasms were also present in the kidneys of males. In the 2,500 ppm group, one male had a renal tubule adenoma and one male had a renal tubule carcinoma (Tables 11 and A1). Renal tubule hyperplasia, a possible precursor of adenomas, occurred in three 1,250 ppm males, one 2,500 ppm male, and one 5,000 ppm male. Oncocytic hyperplasia of renal tubules was also present in one control male, one 2,500 ppm male, and five 5,000 ppm males. One 1,250 ppm female and five 5,000 ppm females had oncocytic hyperplasia; however, there were no renal tubule adenomas or carcinomas in females.

Initially, a single hematoxylin and eosin-stained section of each kidney was prepared. Primarily because of the increased incidence of renal tubule hyperplasia in exposed males, because of the adenoma and carcinoma observed in 2,500 ppm males, and because of the unusual occurrence of oncocytic hyperplasia in 5,000 ppm males, additional step sections of kidney were prepared from the remaining formalin-fixed tissues. Six to eight additional kidney sections taken at 1 mm intervals were prepared for each male. Additional males with focal hyperplasia or adenoma were identified. The incidences of these proliferative lesions in the step sections and in the single and step sections combined are shown in Table 11. There were no significant increases in the incidence of renal tubule neoplasms.

Renal tubule hyperplasia, as defined in this study, was distinguished from regenerative epithelial changes commonly seen as a part of nephropathy and was considered a preneoplastic lesion. Renal tubule hyperplasia, adenoma, and carcinoma are part of a morphologic continuum. Hyperplasia was generally a focal, minimal to mild lesion consisting of tubules that were dilated to 1.5 to 2 times normal diameter and were lined by increased numbers of tubule epithelial cells, which partially or totally filled the tubule lumen. Cells within hyperplastic lesions varied slightly in size and sometimes stained more basophilic than normal cells but otherwise appeared similar to normal tubule epithelial cells. Renal tubule adenomas were larger discrete lesions, ranging from greater than five tubule diameters to 1 mm or more in size. Cells within adenomas were mildly to moderately pleomorphic, sometimes had vacuolated cytoplasm, and tended to form complex patterns, particularly microtubular structures. A few adenomas contained varying amounts of hyaline basement membrane material that divided the epithelial cells into small irregular clusters.

Oncocytic hyperplasia was characterized by individual tubules or small clusters of tubules, which were somewhat dilated and totally filled by large polygonal

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid

Dose (ppm)	0	1,250	2,500	5,000
Male				
15-Month Interim Evaluation				
Kidney[a]	10	10	10	10
Pigmentation[b]	10 (1.0)[c]	10 (1.1)	10 (1.9)**	10 (2.4)**
Nephropathy	10 (2.0)	10 (2.0)	10 (1.8)	10 (1.7)
Renal Tubule Hyperplasia	0	0	1 (2.0)	0
2-Year Study				
Single Sections (Standard Evaluation)				
Kidney	50	50	50	50
Pigmentation	50 (1.8)	50 (2.3)**	50 (2.4)**	50 (2.6)**
Nephropathy	50 (2.7)	50 (2.5)	50 (1.9)**	50 (1.6)**
Oncocytic Hyperplasia	1 (2.0)	0	1 (1.0)	5 (1.6)
Renal Tubule Hyperplasia	0	3 (1.7)	1 (1.0)	1 (2.0)
Renal Tubule Adenoma	0	0	1	0
Renal Tubule Carcinoma	0	0	1	0
Renal Tubule Adenoma or Carcinoma[d]	0	0	2	0
Step Sections (Extended Evaluation)				
Oncocytic Hyperplasia	0	0	0	5
Renal Tubule Hyperplasia	1	4	4	4
Renal Tubule Adenoma	1	1	1	3
Single and Step Sections Combined				
Oncocytic Hyperplasia	1	0	1	10*
Renal Tubule Hyperplasia	1	7*	5	4
Renal Tubule Adenoma	1	1	2	3
Renal Tubule Carcinoma	0	0	1	0
Renal Tubule Adenoma or Carcinoma[e]	1	1	3	3

(continued)

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

Dose (ppm)	0	1,250	2,500	5,000
Female				
15-Month Interim Evaluation				
Kidney	10	10	10	10
Pigmentation	10 (1.1)	10 (2.2)**	10 (2.9)**	10 (2.9)**
Nephropathy	10 (1.4)	10 (1.0)	9 (1.1)	9 (1.3)
2-Year Study				
Kidney	50	50	50	50
Pigmentation	50 (1.8)	50 (2.1)	50 (2.4)**	50 (2.7)**
Nephropathy	50 (1.9)	49 (1.6)	49 (1.3)**	49 (1.2)**
Oncocytic Hyperplasia	0	1 (1.0)	0	5* (1.2)
Renal Tubule Hyperplasia	0	0	1 (1.0)	0

* Significantly different ($P \leq 0.05$) from the control group by logistic regression test
** Significantly different ($P \leq 0.01$) from the control group by the Mann-Whitney U test
[a] Number of animals with kidney examined microscopically
[b] Number of animals with lesion
[c] Average severity of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[d] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 15/1,251 (1.2% ± 1.7%), range 0%-6%
[e] Historical incidence for 2-year NTP feed, gavage, and inhalation studies with untreated control groups: 22/608 (3.6% ± 2.7%), range 0%-8%

cells with abundant brightly eosinophilic granular cytoplasm and small, often centrally located, basophilic nuclei (oncocytes). These lesions are thought to arise from the distal tubule epithelium.

Spleen: There were significant increases in absolute and relative spleen weights of females, but not of males, at 15 months (Table F3). Associated with the increases in splenic weight were increases in yellow-brown pigment in the red pulp consistent with the accumulation of hemosiderin in splenic macrophages at 15 months (Tables A5 and B5). The severity of pigmentation generally increased as the exposure level increased (severity in males: 1.0, 1.0, 1.5, and 1.9; females: 2.0, 1.9, 2.3, and 3.0). At the end of 2 years, it was difficult to evaluate the severity of splenic pigmentation because rats with mononuclear cell leukemia usually had greatly distended spleens that were packed with leukemia cells. Due to obliteration of the spleen with mononuclear cell leukemia, the Pathology Working Group could not confirm a chemical-related effect for splenic pigmentation at the end of the 2-year study. As with splenic pigmentation, it was difficult to assess extramedullary hematopoiesis because of the mononuclear cell leukemia. The incidences of bone marrow hypercellularity were not supportive of any chemical-related effect on hematopoietic cell proliferation. Furthermore, the majority of animals with increased hematopoietic cell proliferation had complicating neoplasms or inflammatory lesions, which probably accounted for increased hematopoietic cell proliferation.

Mononuclear cell leukemia: There were significant dose-related trends in the incidences of mononuclear cell leukemia in males and females (Table 12). The incidences of mononuclear cell leukemia in 5,000 ppm males (29/50, 35/50, 26/50, 2/50; Table A3) and in 2,500 and 5,000 ppm females (17/50, 11/50, 3/50, 0/50; Table B3) were significantly lower than those of the controls. The incidences in controls (males, 58%; females, 34%), while within the range of historical controls (males, 32% to 62%, Table A4c; females, 14% to 52%, Table B4b), were greater than the mean historical rates. The decrease in the incidences of total malignant neoplasms in 5,000 ppm males and females and increased survival of 5,000 ppm males were attributed to the decreased incidences of mononuclear cell leukemia in these groups.

Liver: The incidences of fatty cellular change (males: 15/49, 13/50, 11/50, 7/50; females: 14/50, 13/50, 7/50, 7/50), multifocal hyperplasia (males: 13/49, 12/50, 13/50, 4/50; females: 9/50, 10/50, 3/50, 2/50), and centrilobular atrophy (males: 22/49, 27/50, 23/50, 5/50; females: 14/50, 11/50, 4/50, 2/50) (Tables A5 and B5) in 5,000 ppm rats were generally lower than those of the controls. The fatty change, focal hyperplasia, and centrilobular atrophy were secondary to the mononuclear cell leukemia, and the lower incidences of these lesions parallel those of mononuclear cell leukemia.

Thyroid gland: The incidence of thyroid gland C-cell adenoma in 5,000 ppm females was marginally lower than that of the controls (9/50, 5/49, 4/50, 2/50; Table B3). No chemical-related differences in the incidences of C-cell carcinoma or C-cell hyperplasia were observed. C-cell adenomas are common lesions of aging F344 rats. C-cell adenomas may be single, multiple, or bilateral. They occur as discrete focal masses of C-cells but may contain widely separated, isolated follicles. The neoplasm is usually well demarcated and causes some compression of the surrounding parenchyma. There were no chemical-related decreased incidences of thyroid gland C-cell neoplasms in male rats.

TABLE 12
Incidences of Mononuclear Cell Leukemia in Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid

Dose (ppm)	0	1,250	2,500	5,000
Male				
15-Month Interim Evaluation				
Mononuclear Cell Leukemia[a]	0/10	1/10	0/10	0/10
2-Year Study				
Mononuclear Cell Leukemia[b]				
Overall rate	29/50 (58%)	35/50 (70%)	26/50 (52%)	2/50 (4%)
Adjusted rate[c]	76.2%	79.9%	76.3%	4.9%
Terminal rate[d]	4/12 (33%)	5/13 (38%)	7/13 (54%)	0/21 (0%)
First incidence (days)	503	415	506	445
Life table test[e]	P<0.001N	P=0.424	P=0.215N	P<0.001N
Logistic regression test[e]	P<0.001N	P=0.177	P=0.127N	P<0.001N
Female				
15-Month Interim Evaluation				
Mononuclear Cell Leukemia	0/10	1/10	0/10	0/10
2-Year Study				
Mononuclear Cell Leukemia[f]				
Overall rate	17/50 (34%)	11/50 (22%)	3/50 (6%)	0/50 (0%)
Adjusted rate	38.6%	32.5%	8.5%	0.0%
Terminal rate	3/27 (11%)	4/23 (17%)	0/21 (0%)	0/21 (0%)
First incidence (days)	490	566	492	—[g]
Life table test	P<0.001N	P=0.272N	P=0.008N	P<0.001N
Logistic regression test	P<0.001N	P=0.159N	P<0.001N	P<0.001N

[a] Number of animals with neoplasm per number of animals necropsied
[b] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 603/1,253 (48.1% ± 8.7%), range 32%-62%
[c] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[d] Observed incidence in animals surviving until the end of the study
[e] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test regards neoplasms in animals dying prior to terminal sacrifice as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. A negative trend or a lower incidence in an exposure group is indicated by N.
[f] Historical incidence: 324/1,251 (25.9% ± 8.6%), range 14%-52%
[g] Not applicable; no neoplasms in animal group

MICE

14-Day Study

Three males and two females receiving 40,000 ppm died during days 5 through 8 of the study. All other animals survived until the end of the study (Table 13). Males exposed to 20,000 and 40,000 ppm *p*-nitrobenzoic acid and females exposed to 20,000 ppm lost weight. Mean body weight gains of 20,000 and 40,000 ppm males and of 10,000, 20,000, and 40,000 ppm females were significantly lower than those of the controls. There were no clinical findings relating to organ-specific toxicity, although lethargy and ataxia were observed in 40,000 ppm mice. Feed consumption by males and females was similar to that by the controls, although the feed consumption data varied. Scattering of feed by these mice might have contributed to the variability in the data. Dietary levels of 2,500, 5,000, 10,000, 20,000, or 40,000 ppm *p*-nitrobenzoic acid delivered average daily doses of 1,000, 2,000, 3,500, 8,500, or 14,000 mg/kg body weight to males and 1,000, 2,000, 4,000, 9,500, or 21,500 mg/kg to females.

Table 13
Survival, Mean Body Weights, and Feed Consumption of Mice in the 14-Day Feed Study of *p*-Nitrobenzoic Acid

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	18.2 ± 1.0	19.5 ± 0.9	1.3 ± 0.2		5.4	5.7
2,500	5/5	18.3 ± 0.6	19.1 ± 0.7	0.8 ± 0.3	98	8.0	6.8
5,000	5/5	17.8 ± 0.5	18.4 ± 0.5	0.5 ± 0.2	94	6.2	8.3
10,000	5/5	18.4 ± 0.4	19.0 ± 0.4	0.7 ± 0.4	98	5.3	7.9
20,000	5/5	18.4 ± 0.3	17.9 ± 0.5	-0.5 ± 0.4**	92	6.4	8.6
40,000	2/5[d]	18.2 ± 0.8	18.0 ± 0.4	-0.7 ± 0.4**	92	4.0	8.5
Female							
0	5/5	15.5 ± 0.7	16.8 ± 0.7	1.3 ± 0.5		6.3	7.1
2,500	5/5	15.6 ± 0.3	16.5 ± 0.4	0.8 ± 0.4	98	6.8	8.3
5,000	5/5	15.7 ± 0.6	15.9 ± 0.4	0.2 ± 0.3	95	5.8	7.6
10,000	5/5	15.4 ± 0.2	15.3 ± 0.2*	-0.1 ± 0.1*	91	5.0	8.0
20,000	5/5	15.2 ± 0.6	14.6 ± 0.3**	-0.6 ± 0.3*	87	6.9	7.3
40,000	3/5[e]	15.1 ± 0.7	15.3 ± 0.7*	0.8 ± 0.9*	91	8.8	7.5

* Significantly different (P≤0.05) from the control group by Williams' test
** P≤0.01
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.
[d] Day of death: 5, 5, 6
[e] Day of death: 7, 8

Absolute and relative thymus weights of 20,000 ppm males and 10,000, 20,000, and 40,000 ppm females were significantly less than those of the controls (Table F4). Relative liver weights of 20,000 and 40,000 ppm males and females and of 10,000 ppm females were significantly greater than those of the controls (Table F4). Differences in the absolute and relative weights of other organs were related to decreased body weights. No biologically significant differences in hematology parameters occurred in exposed males or females (Table G4).

There were no gross lesions observed at necropsy that were considered to be related to chemical administration. Degeneration of the germinal epithelium of the testis was observed in 20,000 and 40,000 ppm males (Table 14). Microscopically, testicular degeneration was characterized by multinucleated giant cells, pyknosis, and cytoplasmic vacuolization of germinal cells. Bone marrow hemorrhage and bone marrow atrophy occurred in the 40,000 ppm female mice that died early. It was uncertain if these effects were due to the reduced body weight or if they were a chemical effect. Other lesions, including bone marrow atrophy and hemorrhage in males, were considered secondary to stress and inanition.

Based on mortality and reduced mean body weights at 40,000 ppm, the high concentration selected for the 13-week feed study in mice was 20,000 ppm.

TABLE 14
Incidences of Selected Nonneoplastic Lesions in Mice in the 14-Day Feed Study of *p*-Nitrobenzoic Acid

Dose (ppm)	0	2,500	5,000	10,000	20,000	40,000
Male						
Bone Marrow[a]	5	–[b]	–	–	5	5
Atrophy[c]	0	–	–	–	0	2
Hemorrhage	0	–	–	–	0	3
Testis	5	–	–	5	5	5
Degeneration, Germinal Epithelium	0	–	–	0	3	2
Female						
Bone Marrow	5	–	–	–	5	5
Atrophy	0	–	–	–	0	3
Hemorrhage	0	–	–	–	0	2

a Number of animals with organ examined microscopically
b Organ not examined in this exposure group
c Number of animals with lesion

13-Week Study

One female exposed to 1,250 ppm was accidentally killed during week 3 of the study. All other mice survived until the end of the study (Table 15). Final mean body weights and mean body weight gains of all exposed males and of females exposed to 5,000, 10,000, and 20,000 ppm were significantly lower than those of controls. No chemical-related clinical findings were observed. Feed consumption by exposed groups was similar to or greater than that by the controls throughout the study. Dietary levels of 1,250, 2,500, 5,000, 10,000, or 20,000 ppm *p*-nitrobenzoic acid delivered average daily doses of 170, 330, 670, 1,900, or 4,000 mg/kg body weight to males and 240, 460, 970, 2,500, or 4,900 mg/kg to females.

Differences in absolute and relative organ weights in exposed mice were considered to be related to lower body weights (Table F5). Microscopically, minimal degeneration of the germinal epithelium of the seminiferous tubules was observed in the testis of six 20,000 ppm males. Testicular degeneration was considered to be related to the reduced body weight effect of *p*-nitrobenzoic acid exposure.

Dose Selection Rationale: Based on lower final mean body weights, the dietary levels of *p*-nitrobenzoic acid selected for the 2-year feed study in mice were 0, 1,250, 2,500, and 5,000 ppm.

Table 15
Survival, Mean Body Weights, and Feed Consumption of Mice in the 13-Week Feed Study of *p*-Nitrobenzoic Acid

Dose (ppm)	Survival[a]	Mean Body Weight[b] (g) Initial	Final	Change	Final Weight Relative to Controls (%)	Feed Consumption[c] Week 1	Week 13
Male							
0	10/10	21.5 ± 0.4	33.8 ± 0.6	12.4 ± 0.6		3.5	3.8
1,250	10/10	21.6 ± 0.6	31.5 ± 0.7**	9.9 ± 0.7*	93	3.5	3.8
2,500	10/10	21.9 ± 0.4	31.6 ± 0.7**	9.7 ± 0.6**	93	3.7	3.4
5,000	10/10	22.0 ± 0.4	29.6 ± 0.7**	7.6 ± 0.7**	88	3.3	3.6
10,000	10/10	21.8 ± 0.6	26.8 ± 0.3**	4.9 ± 0.3**	79	4.0	5.3
20,000	10/10	21.9 ± 0.6	23.4 ± 0.4**	1.6 ± 0.9**	69	4.6	5.0
Female							
0	10/10	17.5 ± 0.2	26.3 ± 0.5	8.8 ± 0.4		3.6	4.2
1,250	9/10[d]	17.6 ± 0.2	25.3 ± 0.5	7.7 ± 0.5	96	3.9	4.4
2,500	10/10	17.6 ± 0.2	26.0 ± 0.3	8.4 ± 0.3	99	3.7	4.4
5,000	10/10	17.6 ± 0.4	24.7 ± 0.3**	7.1 ± 0.3**	94	3.6	4.6
10,000	10/10	17.6 ± 0.3	22.6 ± 0.3**	5.0 ± 0.3**	86	4.2	5.8
20,000	10/10	17.5 ± 0.2	20.1 ± 0.4**	2.6 ± 0.5**	76	4.3	4.8

* Significantly different ($P \leq 0.05$) from the control group by Williams' test
** $P \leq 0.01$
[a] Number of animals surviving/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Feed consumption is expressed as grams of feed consumed per animal per day.
[d] Week of death: 3 (accidental)

2-Year Study

Survival

Estimates of survival probabilities for male and female mice are presented in Table 16 and in the Kaplan-Meier curves in Figure 4. Two-year survival rates of exposed mice were similar to those of the controls.

Body Weights, Feed Consumption, and Clinical Findings

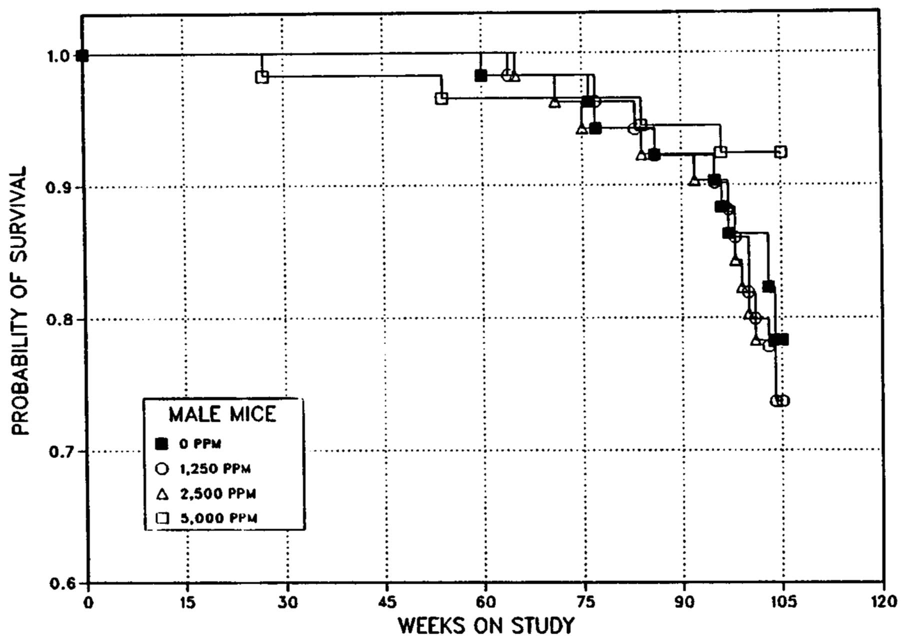
Mean body weights of 5,000 ppm males were 6% to 12% lower than those of the controls after week 17 of the study (Table 17 and Figure 5). Mean body weights of 5,000 ppm females were 12% to 24% lower than those of the controls after week 16 (Table 18 and Figure 5). The final mean body weight of 5,000 ppm males was 90% that of the controls, and the final mean body weight of 5,000 ppm females was 81% that of the controls. Mean body weights of the other exposure groups were similar to those of the controls.

Feed consumption by exposed groups was similar to that by the control groups (Tables I3 and I4). Dietary levels of 1,250, 2,500, or 5,000 ppm *p*-nitrobenzoic acid delivered 150, 300, or 675 mg/kg body weight per day to males and 170, 365, or 905 mg/kg per day to females. There were no clinical findings of organ-specific toxicity in mice.

Table 16
Survival of Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid

Dose (ppm)	0	1,250	2,500	5,000
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]		1		2
Moribund	9	4	10	2
Natural deaths	2	9	1	2
Animals surviving to study termination	39	36	39	44
Percent probability of survival at end of study[b]	78	74	78	92
Mean survival (days)[c]	666	654	664	641
Survival analyses[d]	P=0.077N	P=0.764	P=1.000	P=0.125N
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Accidental deaths[a]			1	2
Moribund	9	8	12	10
Natural deaths	3	5	4	8
Animals surviving to study termination	38	36	33	30
Missing[a]		1		
Percent probability of survival at end of study	77	74	67	63
Mean survival (days)	660	658	649	625
Survival analyses	P=0.118	P=0.925	P=0.465	P=0.194

[a] Censored from survival analyses
[b] Kaplan-Meier determinations based on the number of animals alive on first day of terminal sacrifice
[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 exposure columns. A negative trend or a lower mortality in an exposure group is indicated by N.



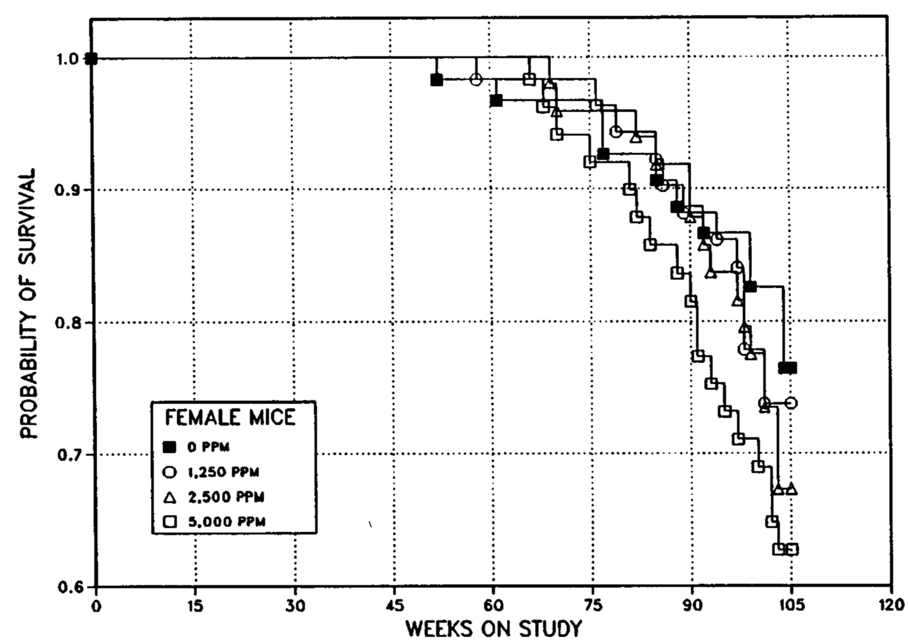


FIGURE 4
Kaplan-Meier Survival Curves for Mice Administered *p*-Nitrobenzoic Acid in Feed for 2 Years

TABLE 17
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid

Weeks on Study	0 ppm Av. Wt. (g)	0 ppm No. of Survivors	1,250 ppm Av. Wt. (g)	1,250 ppm Wt. (% of controls)	1,250 ppm No. of Survivors	2,500 ppm Av. Wt. (g)	2,500 ppm Wt. (% of controls)	2,500 ppm No. of Survivors	5,000 ppm Av. Wt. (g)	5,000 ppm Wt. (% of controls)	5,000 ppm No. of Survivors
1	23.7	60	22.7	96	60	23.0	97	60	22.9	97	60
2	24.8	60	24.3	98	59	24.4	98	60	23.9	96	58
3	26.0	60	25.4	98	59	25.7	99	60	25.1	97	58
4	26.8	60	26.5	99	59	26.4	99	60	25.9	97	58
5	27.5	60	27.3	99	59	27.4	100	60	26.8	98	58
6	28.1	60	27.9	99	59	27.9	99	60	27.3	97	58
7	28.6	60	28.0	98	59	28.4	99	60	27.5	96	58
8	29.3	60	28.8	98	59	29.3	100	60	28.3	97	58
9	30.5	60	29.9	98	59	30.2	99	60	29.3	96	58
10	31.1	60	30.1	97	59	30.8	99	60	29.5	95	58
11	32.0	60	31.2	98	59	31.7	99	60	30.3	95	58
12	31.7	60	31.8	100	59	31.5	99	60	30.7	97	58
13	33.1	60	32.8	99	59	33.1	100	60	31.7	96	58
17	35.4	60	34.9	99	59	34.9	99	60	33.2	94	58
21	37.2	60	36.5	98	59	36.4	98	60	34.5	93	58
25	38.4	60	38.0	99	59	37.8	98	60	35.3	92	58
29	40.8	60	40.2	99	59	39.8	98	60	37.5	92	57
33	41.9	60	41.9	100	59	41.6	99	60	38.7	92	57
37	43.4	60	43.5	100	59	43.3	100	60	40.8	94	57
41	45.5	60	45.1	99	59	44.8	99	60	41.8	92	57
45	46.1	60	45.4	99	59	45.4	99	60	41.9	91	57
49	47.5	60	46.9	99	59	46.7	98	60	43.3	91	57
53	47.4	60	47.3	100	59	46.7	99	60	43.7	92	57
57	47.6	60	46.8	98	59	46.3	97	60	42.9	90	56
61	47.3	59	46.5	98	59	46.0	97	60	42.8	91	56
65	47.9	59	47.5	99	58	46.2	97	60	43.5	91	56
69[a]	47.8	49	48.0	100	48	46.3	97	49	42.8	90	46
73	49.5	49	48.9	99	48	48.2	97	48	44.4	90	46
77	49.2	48	48.8	99	48	48.2	98	47	44.7	91	46
81	49.2	47	48.1	98	47	47.1	96	47	43.5	88	46
85	48.0	47	48.4	101	46	47.3	99	46	43.6	91	45
89	48.9	46	48.8	100	45	47.4	97	46	43.3	89	45
93	48.0	46	49.0	102	45	47.5	99	45	43.1	90	45
97	46.5	43	47.5	102	44	46.6	100	44	41.8	90	44
101	45.9	43	47.7	104	39	46.4	101	40	41.4	90	44
Mean for weeks											
1-13	28.7		28.2	98		28.4	99		27.6	96	
14-52	41.8		41.4	99		41.2	99		38.6	92	
53-101	47.9		47.9	100		46.9	98		43.2	90	

[a] Interim evaluation occurred during week 66.

Table 18
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid

Weeks on Study	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	17.9	60	18.0	101	60	17.7	99	60	17.8	99	60
2	20.4	60	20.2	99	60	20.1	99	59	19.8	97	58
3	22.4	60	22.3	100	60	22.1	99	59	21.5	96	58
4	23.1	60	23.0	100	60	22.7	98	59	21.9	95	58
5	24.1	60	24.1	100	60	23.6	98	59	22.7	94	58
6	24.3	60	24.5	101	60	24.2	100	59	23.3	96	58
7	25.2	60	25.5	101	60	24.9	99	59	23.9	95	58
8	25.4	60	25.8	102	60	25.3	100	59	24.5	97	58
9	25.9	60	25.8	100	60	25.4	98	59	24.5	95	58
10	27.1	60	27.0	100	60	26.1	96	59	25.3	93	58
11	28.2	60	28.0	99	60	27.1	96	59	26.0	92	58
12	28.8	60	28.5	99	60	27.6	96	59	26.4	92	58
16	31.2	60	30.2	97	60	29.7	95	59	27.4	88	58
20	33.4	60	32.3	97	60	31.5	94	59	28.9	87	58
24	34.3	60	33.7	98	60	32.1	94	59	29.7	87	58
28	36.8	60	35.7	97	60	34.8	95	59	31.1	85	58
32	39.2	60	38.1	97	60	37.2	95	59	32.9	84	58
36	40.4	60	39.7	98	60	38.6	96	59	34.1	84	58
40	42.6	60	42.6	100	60	41.0	96	59	35.6	84	58
44	44.6	60	44.1	99	60	42.5	95	59	36.4	82	58
48	46.0	60	45.7	99	60	44.0	96	59	38.1	83	58
52	47.0	60	46.3	99	60	45.0	96	59	38.5	82	58
56	46.3	59	45.8	99	60	43.8	95	59	37.0	80	58
60	47.0	59	46.9	100	59	44.5	95	59	37.2	79	58
64	48.8	58	48.0	98	59	44.7	92	59	37.6	77	58
68[a]	48.5	48	48.7	100	49	45.9	95	49	38.0	78	46
72	49.7	48	49.5	100	49	47.2	95	47	39.0	79	45
76	51.2	48	51.4	100	47	49.0	96	47	40.0	78	44
80	52.1	46	51.0	98	46	48.2	93	47	39.9	77	44
84	51.2	46	51.0	100	46	48.2	94	46	40.5	79	41
88	52.0	44	50.6	97	44	48.1	93	45	39.6	76	41
93	50.6	43	49.5	98	43	47.4	94	42	38.5	76	37
96	49.9	43	48.5	97	42	46.5	93	41	39.3	79	35
100	49.8	41	48.6	98	38	46.2	93	38	38.8	78	33
104	48.2	38	47.7	99	36	45.2	94	33	38.8	81	30
Mean for weeks											
1-13	24.4		24.4	100		23.9	98		23.1	95	
14-52	39.6		38.8	98		37.6	95		33.3	84	
53-104	49.6		49.0	99		46.5	94		38.8	78	

[a] Interim evaluation occurred during week 66.

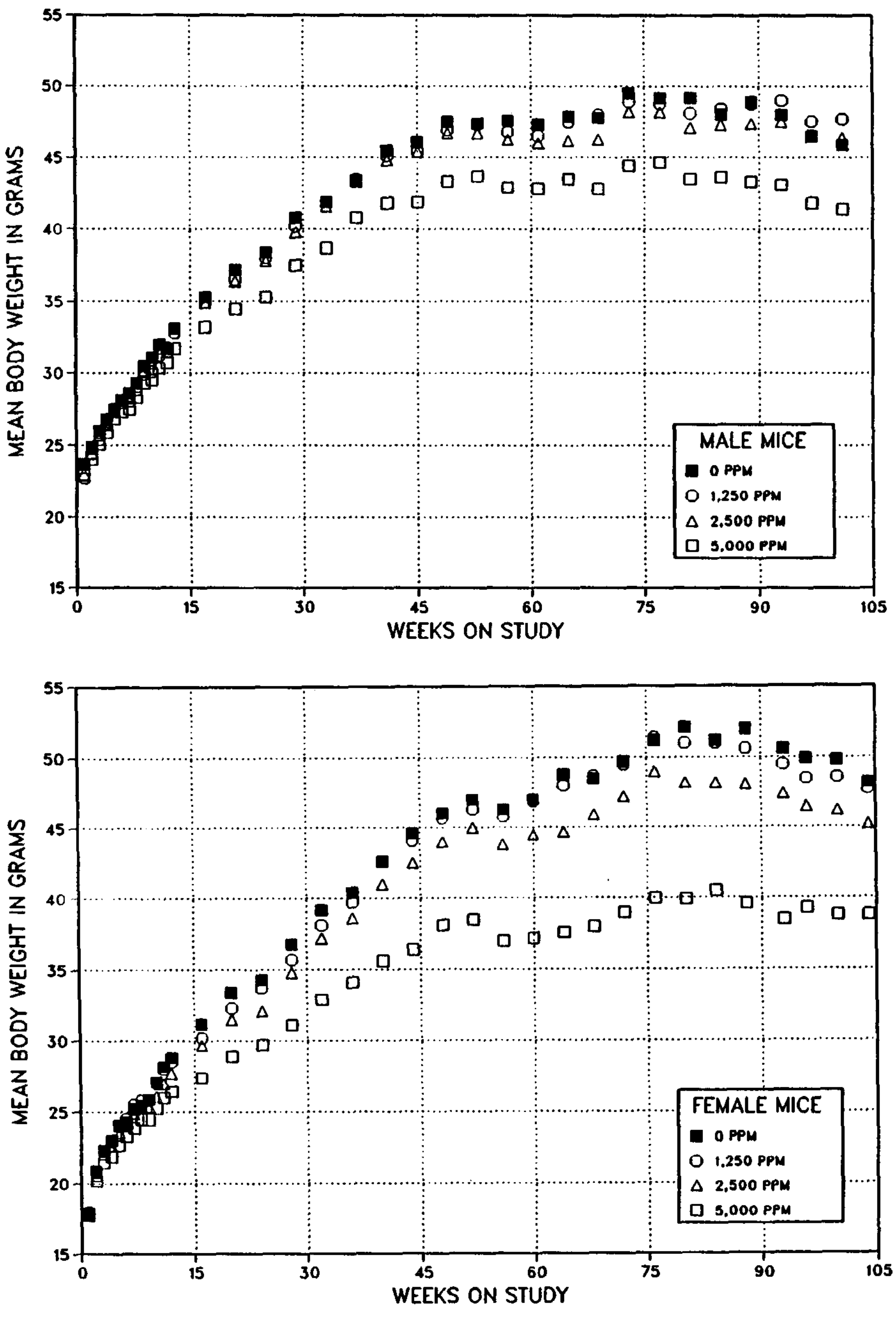


FIGURE 5
Growth Curves for Mice Administered *p*-Nitrobenzoic Acid in Feed for 2 Years

Hematology

The results of hematology evaluations are shown in Table G5. No chemical-related effects on hematology parameters were observed at 15 months.

Pathology and Statistical Evaluation

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

Lung: The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in 1,250 and 5,000 ppm females were significantly greater than that of the controls by pairwise comparisons but not by the trend statistics, and the highest incidence in these groups (20%) fell within the historical control range of 2% to 26% (Tables 19, D3, and D4). The historical incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in control female B6C3F_1 mice from recent NTP studies is 106/1,371 (7.7%). At the 15-month interim evaluation, no hyperplasia or neoplasms were observed in females. At 2 years, the incidences of alveolar epithelial hyperplasia in exposed females were similar to that of the controls.

At the 15-month interim evaluation, a few alveolar/bronchiolar adenomas were observed in exposed male mice. In addition, alveolar epithelial hyperplasia was observed in one 1,250 ppm and one 2,500 ppm male but not in controls. At 2 years, incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in exposed groups of male mice were not significantly different than that of the controls (Tables 19 and C3). The incidence of alveolar epithelial hyperplasia in 5,000 ppm males was greater than that of the controls.

Alveolar epithelial hyperplasia is considered a precursor lesion of alveolar/bronchiolar adenoma and carcinoma. Hyperplasia consists of a focal increase in cellularity of the alveolar epithelium with retention of the alveolar architecture. In contrast, alveolar/bronchiolar adenomas are discrete expansile masses that compress adjacent tissue. Adenomas lack normal architecture and consist of somewhat pleomorphic to columnar cells arranged in regular or papillary patterns. Alveolar/bronchiolar carcinomas are similar but consist of heterogenous cell populations with varying degrees of cellular pleomorphism and atypia. Adenocarcinomas are larger, highly anaplastic neoplasms, often containing areas of hemorrhage or necrosis.

Kidney: The relative kidney weight of females exposed to 5,000 ppm was significantly greater than that of the controls at 15 months (Table F6); however, this effect was considered to be related to the lower mean body weight in this exposure group. The incidence of mineralization of the kidney was lower than that of the controls in 5,000 ppm females (15/50, 7/49, 7/50, 5/50; Table D5). The mineralization was minimal in severity (1.0, 1.0, 1.0, 1.2) and was not considered to be chemical related. The incidences of mineralization in males exposed to 2,500 and 5,000 ppm were also lower than that of the controls (41/50, 33/49, 23/50, 31/48; Table C5). At 15 months and 2 years, there were marginal decreases in the incidence of renal tubule regeneration in male and female mice. In addition, at 2 years, there were marginal decreases in the incidence of cortical cysts in male mice.

TABLE 19
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid

Dose (ppm)	0	1,250	2,500	5,000
Male				
15-Month Interim Evaluation				
Lung[a]	10	10	10	10
Alveolar Epithelial Hyperplasia[b]	0	1	1	0
Alveolar/bronchiolar Adenoma	0	1	2	1
2-Year Study				
Lung	50	50	50	50
Alveolar Epithelial Hyperplasia	2	7	7	8*
Alveolar/bronchiolar Adenoma				
Overall rate[c]	6/50 (12%)	12/50 (24%)	8/50 (16%)	9/50 (18%)
Adjusted rate[d]	15.4%	29.2%	20.5%	20.5%
Terminal rate[e]	6/39 (15%)	8/36 (22%)	8/39 (21%)	9/44 (20%)
First incidence (days)	729 (T)	537	729 (T)	729 (T)
Life table test[f]	P=0.545	P=0.077	P=0.385	P=0.378
Logistic regression test[f]	P=0.393	P=0.091	P=0.385	P=0.378
Alveolar/bronchiolar Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	5/50 (10%)
Adjusted rate	2.6%	8.0%	5.1%	11.4%
Terminal rate	1/39 (3%)	2/36 (6%)	2/39 (5%)	5/44 (11%)
First incidence (days)	729 (T)	725	729 (T)	729 (T)
Life table test	P=0.116	P=0.279	P=0.500	P=0.133
Logistic regression test	P=0.095	P=0.279	P=0.500	P=0.133
Alveolar/bronchiolar Adenoma or Carcinoma[g]				
Overall rate	7/50 (14%)	14/50 (28%)	10/50 (20%)	13/50 (26%)
Adjusted rate	17.9%	34.2%	25.6%	29.5%
Terminal rate	7/39 (18%)	10/36 (28%)	10/39 (26%)	13/44 (30%)
First incidence (days)	729 (T)	537	729 (T)	729 (T)
Life table test	P=0.303	P=0.053	P=0.293	P=0.166
Logistic regression test	P=0.165	P=0.064	P=0.293	P=0.166

(continued)

TABLE 19
Incidences of Neoplasms and Nonneoplastic Lesions of the Lung in Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

Dose (ppm)	0	1,250	2,500	5,000
Female				
Lung	50	49	50	50
Alveolar Epithelial Hyperplasia	3	3	0	1
Alveolar/bronchiolar Adenoma				
Overall rate	3/50 (6%)	5/49 (10%)	3/50 (6%)	8/50 (16%)
Adjusted rate	7.5%	12.9%	8.7%	24.3%
Terminal rate	2/38 (5%)	3/36 (8%)	2/33 (6%)	6/30 (20%)
First incidence (days)	689	685	715	570
Life table test	P=0.035	P=0.324	P=0.599	P=0.050
Logistic regression test	P=0.052	P=0.343	P=0.643	P=0.071
Alveolar/bronchiolar Carcinoma				
Overall rate	0/50 (0%)	5/49 (10%)	1/50 (2%)	1/50 (2%)
Adjusted rate	0.0%	13.9%	2.9%	3.3%
Terminal rate	0/38 (0%)	5/36 (14%)	0/33 (0%)	1/30 (3%)
First incidence (days)	–[h]	730 (T)	720	730 (T)
Life table test	P=0.572N	P=0.029	P=0.468	P=0.453
Logistic regression test	P=0.568N	P=0.029	P=0.491	P=0.453
Alveolar/bronchiolar Adenoma or Carcinoma[i]				
Overall rate	3/50 (6%)	10/49 (20%)	4/50 (8%)	9/50 (18%)
Adjusted rate	7.5%	26.1%	11.3%	27.5%
Terminal rate	2/38 (5%)	8/36 (22%)	2/33 (6%)	7/30 (23%)
First incidence (days)	689	685	715	570
Life table test	P=0.063	P=0.031	P=0.428	P=0.027
Logistic regression test	P=0.088	P=0.031	P=0.475	P=0.039

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression test
(T)Terminal sacrifice
[a] Number of animals with lung examined microscopically
[b] Number of animals with lesion
[c] Number of animals with neoplasm per number of animals examined microscopically
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals surviving until the end of the study
[f] In the control column are the P values associated with the trend test. In the exposure group columns are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test 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. A negative trend in an exposure group is indicated by N.
[g] Historical incidence for 2-year NTP feed studies with untreated control groups (mean ± standard deviation): 242/1,369 (17.7% ± 7.3%), range 4%-30%
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence: 106/1,371 (7.7% ± 5.0%), range 2%-26%

Genetic Toxicology

p-Nitrobenzoic acid, tested in a preincubation protocol at concentrations of 1 to 3,333 μg/plate, with and without induced rat or hamster S9, was mutagenic in strain TA100 (Table E1; Zeiger *et al.*, 1987). No mutagenicity was detected in strains TA98, TA1535, or TA1537, with or without S9.

In cytogenetic tests with cultured Chinese hamster ovary cells, *p*-nitrobenzoic acid induced significant increases in sister chromatid exchanges (Table E2; Zeiger *et al.*, 1987) and chromosomal aberrations (Table E3; Zeiger *et al.*, 1987) at dose levels which induced cell cycle delay in the absence of S9; no increases in either endpoint were observed in the presence of S9. In the sister chromatid exchange test without S9, doses ranging from 498 to 1,000 μg/mL produced positive responses, induced cell cycle delay, and required use of an extended harvest protocol to allow accumulation of sufficient cells for metaphase analysis. Doses producing positive responses in the chromosomal aberrations assay without S9 ranged from 875 to 1,750 μg/mL *p*-nitrobenzoic acid. As with the sister chromatid exchange test, cell harvest was delayed to permit a sufficient number of cells to progress to metaphase for analysis.

Despite the positive results obtained in the *in vitro* studies, results of a single NTP *in vivo* genotoxicity study were negative. In this study, the frequencies of micronucleated normochromatic erythrocytes in the peripheral blood of male and female mice were unaffected by exposure to *p*-nitrobenzoic acid in feed for 13 weeks (Table E4).

DISCUSSION AND CONCLUSIONS

p-Nitrobenzoic acid is produced in large volumes for organic synthesis and as an intermediate in the manufacture of pesticides, dyes, and industrial solvents. *p*-Nitrobenzoic acid is also a hydrolysis product or metabolite of other high-volume production chemicals including *p*-nitrobenzoyl chloride and *o*-nitrotoluene. Despite the widespread use and occurrence of *p*-nitrobenzoic acid, there is little information on the toxic and carcinogenic effects of this chemical after long-term exposure. These toxicity and carcinogenicity rodent studies were conducted to provide this information.

Many nitroaromatic compounds are toxic to the hematopoietic system (Beard and Noe, 1981; Beutler, 1985; Bus and Popp, 1987). Generalized toxicity to the hematopoietic system of the rat was observed in studies of the nitroaromatic compounds *o*-, *m*-, and *p*-nitrotoluene (NTP, 1992), *p*-chloroaniline (NCI, 1979a), and *o*-nitroanisole (NTP, 1993). The mechanism of the anemia is thought to involve oxidative damage to hemoglobin leading to Heinz body formation and decreased erythrocyte survival, followed by macrophage ingestion of the injured erythrocytes and removal of macrophages by the spleen resulting in splenic congestion and hemosiderin accumulation. The characteristic hematologic toxicity induced by amine/nitroaromatic compounds is attributed to the formation of a hydroxylamino compound (Facchini and Griffiths, 1981), and it has been observed in a variety of animals, including rodents, dogs, and cats, exposed to nitroaromatic compounds (Kiese, 1966) and in humans exposed to aniline and nitroaromatic compounds (Finch, 1948; Smith, 1991). *p*-Nitrobenzoic acid was toxic to the hematopoietic system of rats in the current studies.

In the 14-day rat study, there were decreases in erythrocyte count and hemoglobin and hematocrit values, and increases in nucleated erythrocytes, reticulocyte counts, and methemoglobin concentration, which were most pronounced in the 20,000 and 40,000 ppm groups. Hypertrophy of the follicular epithelium of the thyroid gland was observed in rats at doses of 10,000 ppm and greater in the 14-day studies, but this change was not seen in the 13-week or 2-year studies, probably because lower doses were used and rats were able to adapt to this effect. In the 13-week rat study, a mild hemolytic (regenerative) anemia was characterized by decreases in hematocrit and hemoglobin values and increases in methemoglobin concentration, reticulocyte counts, and Heinz body formation in 10,000 ppm rats. Hemosiderin accumulation in the spleen was present in 2,500, 5,000, and 10,000 ppm male and female rats, and congestion was observed in 2,500 and 5,000 ppm males and 10,000 ppm males and females. There were increased incidences of renal tubule pigmentation (hemosiderin) in 5,000 and 10,000 ppm males. Increases in absolute and relative spleen weights were observed in 10,000 ppm rats in the 13-week study. At the 15-month interim evaluation in the 2-year rat study, there were decreases in erythrocyte count, hemoglobin, and hematocrit levels, and increases in nucleated erythrocytes that were most pronounced in 5,000 ppm females. In exposed males and females, increased severity of pigmentation (hemosiderin) of renal tubule epithelial cells was also supportive of this hemolytic anemia.

Hematologic toxicity was not observed in mice in these studies. In studies of other nitroaromatic compounds (e.g., nitrotoluenes, *p*-chloroaniline, and *p*-nitroanisole) the hematologic toxicity was also less severe in mice than in rats. Studies with *p*-chloroaniline hydrochloride (NTP, 1989a) and aniline hydrochloride (NCI, 1978) suggest that these chemicals are cleared from blood more quickly in mice than in rats (McCarthy *et al.*, 1985). Species differences in clearance of *p*-nitrobenzoic acid and its metabolites from blood may also account for the fact that mice are less susceptible to hematologic toxicity than rats. Methemoglobin can be reduced to hemoglobin in mammalian species by NADH-dependent methemoglobin reductase located in erythrocytes. Mice have higher levels of this reductase than rats (Smith, 1991), and species differences in the ability to reduce methemoglobin may be another reason why mice are less susceptible than rats to the hematologic toxicity of *p*-nitrobenzoic acid.

Because of the hematologic toxicity in rats and decreased body weights of 10,000, 20,000, and 40,000 ppm rats and mice in the 14-day studies and 10,000 ppm rats and mice in the 13-week studies, the highest exposure level selected for the 2-year studies was 5,000 ppm. While there were no chemical-related decreases in survival of exposed groups in the 2-year studies, the mean body weights of 5,000 ppm female rats, 5,000 ppm male mice, and 5,000 ppm female mice were consistently lower than those of the respective control groups. The 2-year studies were considered to be adequate assessments of the carcinogenic potential of *p*-nitrobenzoic acid in the F344/N rat and B6C3F$_1$ mouse.

In the 2-year study, the incidences of mononuclear cell leukemia were decreased in exposed groups of male and female rats. The incidences of mononuclear cell leukemia in 5,000 ppm male rats (4%) and 2,500 (6%) and 5,000 ppm (0%) female rats were below the historical control ranges from recent NTP 2-year feed studies (males: range 32% to 62%, 603/1,253, mean 48%; females: range 14% to 52%, 324/1,251, mean 26%). While the mechanism for this decrease is unknown, a decrease in the incidence of mononuclear cell leukemia has also been observed with other amine/nitro compounds including aniline hydrochloride (NCI, 1978) and *p*-chloroaniline (NCI, 1979a). Injury to splenic cells associated with hematologic toxicity may decrease the chance for the development of mononuclear cell leukemia, which arises from splenic cells in the Fischer rat (Losco and Ward, 1984; Stromberg, 1985). The splenic toxicity appears to be less severe with *p*-nitrobenzoic acid than with aniline hydrochloride or *p*-chloroaniline (Stefanski *et al.*, 1990). In studies of aniline hydrochloride (NCI, 1978), *p*-chloroaniline (NCI, 1979a), *o*-toluidine (NCI, 1979b), and D&C Red No. 9 (NTP, 1982a) splenic damage was more extensive and led to fibrosis and the development of sarcomas of the spleen (Goodman *et al.*, 1984; Weinberger *et al.*, 1985).

While decreased incidences of mononuclear cell leukemia have been observed in rats treated with amine/nitro compounds (Table 17), not all chemicals of this class produced this effect [e.g., *o*-nitroanisole (NTP, 1993)]. Decreased incidences of mononuclear cell leukemia have also been observed with aromatic compounds that do not contain the amine/nitro substitution [e.g., 4-hexylresorcinol (NTP, 1988a) and α-methylbenzyl alcohol (NTP, 1990)]. Some of the chemicals that caused decreased incidences of mononuclear cell leukemia [nitrobenzoic acid (King and Henschel, 1941; Rosenthal and Bauer, 1941) and 4-hexylresorcinol (NTP, 1988a; Burnens and Vurma-Pupp, 1989; Collins and Levett, 1989)] share an antibacteriostatic activity, but studies to determine if this activity is related to inhibition of nucleic acid synthesis or cell proliferation/growth have not been reported. It has previously been reported (Rao *et al.*, 1987) that decreased incidences of naturally occurring neoplasms (e.g., neoplasms of the liver or mammary gland) may occur when a chemical causes a decrease in body weight. In the present 2-year studies of *p*-nitrobenzoic acid, there were decreases in body weights in exposed groups of rats where there were also decreases in the incidences of mononuclear cell leukemia. Further studies are needed to explain the relationship between body weight and neoplasm occurrence in rodents and to determine if body weight was a factor in the decreased incidences of mononuclear cell leukemia in rats exposed to *p*-nitrobenzoic acid.

In the 13-week rat study, chemical-related effects on the kidney included hyaline droplet accumulation in males and karyomegaly in males and females. In the 2-year rat study, chemical-related effects included tubule epithelial cell hyperplasia in 1,250 ppm males and oncocytic hyperplasia in 5,000 ppm males and females. Also at 2 years, nephropathy severity decreased with increasing dose in both males and females. However, the association between hyaline droplet accumulation ($\alpha_{2\mu}$-globulin-associated nephrotoxicity) and kidney neoplasms was not observed in the 2-year study. Chemicals that cause protein droplet accumulation have been found to bind to $\alpha_{2\mu}$-globulin (Dietrich and Swenberg, 1991). Evidence suggests that the chemical binding is responsible for the accumulation of this protein. Chemical-mediated accumulation of $\alpha_{2\mu}$-globulin is thought to be responsible for cell death, which in turn stimulates cell division as the kidney attempts to repair itself. With prolonged chemical exposure, repeated cycles of cytotoxicity and reparative replication are proposed to be responsible for the observed tumorigenic response (USEPA, 1991). In the present studies, the typical cytotoxicity associated with hyaline droplet ($\alpha_{2\mu}$-globulin-associated) nephrotoxicity (such as single cell necrosis of the P2 segment epithelium, accumulation of granular casts, linear mineralization

TABLE 17
Results of Carcinogenicity Tests of Selected Chemicals Causing Decreased Incidences of Mononuclear Cell Leukemia in Male and Female Fisher Rats

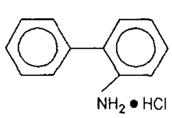
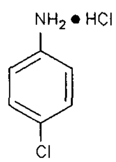
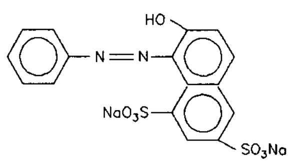
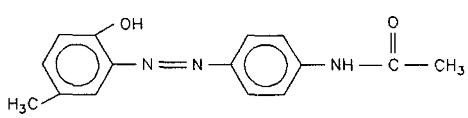
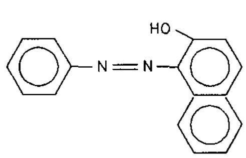
Chemical	Incidences of Leukemia[a]		Carcinogenicity[b]				*Salmonella*
	Male Rats	Female Rats	♂ Rat	♀ Rat	♂ Mouse	♀ Mouse	Test Result
2-Biphenylamine Hydrochloride NTP TR 233 	15/50, 1/50, 4/50	5/50, 1/49, 3/50	–	–	+ He	–	
***p*-Chloroaniline Hydrochloride NTP TR 351** 	21/49, 3/50, 2/50, 3/50	10/50, 2/50, 1/50, 1/50	+ S	–	+ L,He	–	+
C.I. Acid Orange 10 NTP TR 211 	22/90, 4/50, 3/50	16/88, 2/50, 0/50	–	–	–	–	–
C.I. Disperse Yellow 3 NTP TR 222 	13/50, 2/50, 1/50	8/50, 2/50, 1/50	+ L	–	–	+ L	+
C.I. Solvent Yellow 14 NTP TR 226 	25/50, 2/50, 4/50	11/50, 2/49, 0/49	+ L	+ L	–	–	+

TABLE 17
Results of Carcinogenicity Tests of Selected Chemicals Causing Decreased Incidences of Mononuclear Cell Leukemia in Male and Female Fisher Rats (continued)

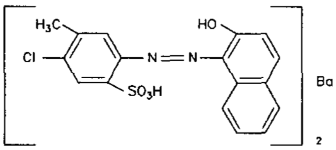
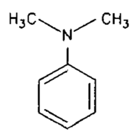
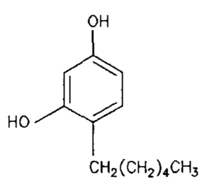
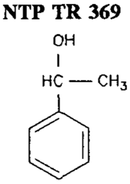
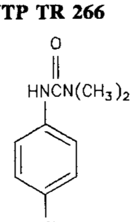
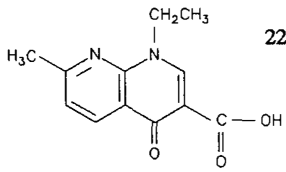
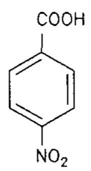
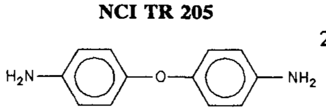
	Incidences of Leukemia		Carcinogenicity				*Salmonella*
Chemical	Male Rats	Female Rats	♂ Rat	♀ Rat	♂ Mouse	♀ Mouse	Test Result
D & C Red 9 **NTP TR 225** 	12/50, 4/50, 3/50	11/50, 5/50, 3/50	+ S,L	–	–	–	+
***N,N*-Dimethylaniline** **NTP TR 360** 	13/50, 4/50, 3/50	11/50, 7/50, 0/50	+ S	–	–	–	–
4-Hexylresorcinol **NTP TR 330** 	12/49, 7/50, 1/50	16/50, 3/50, 2/50	–	–	–	–	–
α-Methylbenzyl Alcohol **NTP TR 369** 	15/50, 2/50, 0/50	12/50, 2/50, 2/50	+ K	–	–	–	–
Monuron **NTP TR 266** 	5/50, 0/50, 0/50	10/50, 2/50, 2/50	+ K,L	–	–	–	–

TABLE 17
Results of Carcinogenicity Tests of Selected Chemicals Causing Decreased Incidences of Mononuclear Cell Leukemia in Male and Female Fisher Rats (continued)

	Incidences of Leukemia		Carcinogenicity				*Salmonella*
Chemical	Male Rats	Female Rats	♂ Rat	♀ Rat	♂ Mouse	♀ Mouse	Test Result
Nalidixic Acid **NTP 368** 	22/50, 13/50, 17/50	20/50, 9/50, 7/50	+ P	+ C	–	–	–
***p*-Nitrobenzoic Acid** **NTP TR 442** 	29/50, 35/50, 26/50, 2/50	17/50, 11/50, 3/50, 0/50	–	+ C	–	–	+
4,4′-Oxydianiline **NCI TR 205** 	27/50, 4/50, 4/50, 3/50	3/50, 1/50, 2/50, 0/50	+ L,T	+ L,T	+ L,T,H	+ L,T,H	+

[a] Incidences given in increasing order of dose level beginning with control.
[b] Levels of carcinogenic evidence: + = some or clear evidence, – = no or equivocal evidence; C = clitoral gland, H = harderian gland, He = hemangiosarcoma, K = kidney, L = liver, P = preputial gland, S = spleen, T = thyroid gland.

of tubules within the renal papilla, hyperplasia of the renal pelvis, or significant increases in the incidences of kidney neoplasms) was not observed. In addition, compared to $\alpha_{2\mu}$-globulin-associated nephrotoxicity where there is an exacerbation of spontaneous chronic progressive nephropathy, there was a decrease in the severity of nephropathy in rats exposed to *p*-nitrobenzoic acid. The lack of cytotoxicity in male rats with hyaline droplet accumulation would suggest that *p*-nitrobenzoic acid might not bind strongly to $\alpha_{2\mu}$-globulin, thus $\alpha_{2\mu}$-globulin accumulation might be below the concentration that elicits a cytotoxic response and subsequently a carcinogenic effect.

In NTP studies, oncocytic hyperplasia has not commonly been associated with the spectrum of renal proliferative lesions thought to be important in the development of renal tubule adenomas and carcinomas. Renal tubule neoplasms are thought to originate from proximal tubules, while oncocytic proliferative lesions are thought to originate from distal tubules (Bannasch *et al.*, 1986). In addition, oncocytic proliferative lesions are different from renal tubule proliferative lesions in that cells in oncocytic proliferative lesions are usually much larger and have a more densely packed granular eosinophilic cytoplasm; the characteristic granular appearance of the cytoplasm is caused by populations of atypical mitochondria. In the present studies, oncocytic hyperplastic lesions did not progress to oncocytomas. Rat renal oncocytomas appear to be benign end stage lesions that do not progress to malignant neoplasms (Bannasch *et al.*, 1986). In the NTP database, kidney proliferative lesions and neoplasms include documented oncocytic hyperplasias and oncocytomas, but no malignant oncocytic neoplasms have been observed.

The step sections revealed additional renal tubule neoplasms and hyperplasia in control and exposed male rats, but, in exposed males, incidences of renal tubule adenoma or carcinoma (combined) from both the single- and step-section evaluations were similar to that of the controls (1/50, 1/50, 3/50, 3/50). The incidences of renal tubule hyperplasia in 1,250 ppm males and of oncocytic hyperplasia in 5,000 ppm males were significantly greater than those of the controls. An increase in nonneoplastic lesions alone is not considered to be evidence of a carcinogenic effect. Further, the incidences of renal tubule adenoma (1/50, 1/50, 1/50, 3/50) from the step-section evaluation fell within the historical range for renal tubule adenoma from step-section evaluations in male control rats from other NTP studies (range 0% to 8%, 18/608, mean 3%; Table A4b). Thus, *p*-nitrobenzoic acid did not cause chemical-related increases in the incidences of kidney neoplasms either by the initial single-section evaluation or by the step-section evaluation. There were no renal tubule neoplasms in female rats.

In the 2-year rat study, the incidences of clitoral gland adenoma in 1,250, 2,500, and 5,000 ppm females, the incidence of clitoral gland carcinoma in 2,500 ppm females, and the incidences of clitoral gland adenoma or carcinoma (combined) in all exposed groups of females (0 ppm, 4/50; 1,250 ppm, 14/49; 2,500 ppm, 15/49; 5,000 ppm, 15/50) were significantly greater than those in the controls by both the life table and logistic regression tests. The incidences of clitoral gland adenoma or carcinoma (combined) in each exposed group (29% to 31%) were greater than that in historical controls (mean incidence, 11%; range, 2% to 21%). Based on these clitoral gland neoplasms, there was some evidence of a carcinogenic effect of *p*-nitrobenzoic acid in the female rat. The neoplasm incidences were not considered to represent a clear carcinogenic response because the incidences of clitoral gland neoplasms were approximately the same in each exposure group, despite a fourfold increase in dose from the lowest exposure level to the highest. In addition, there was no notable decrease in the time to occurrence of neoplasm (mean time to diagnosis: 0 ppm, 699 days; 1,250 ppm, 712 days; 2,500 ppm, 672 days; or 5,000 ppm, 683 days) nor was there an increased incidence in clitoral gland hyperplasia.

A chemical-related increase in the incidence of clitoral gland neoplasms is often accompanied by an increase in the incidence of preputial gland neoplasms (male counterparts of clitoral gland neoplasms). In this study, a slight increase in the incidence of preputial gland neoplasms was observed in animals receiving 5,000 ppm *p*-nitrobenzoic acid. However, because of improved survival in this group, some increase in neoplasm incidence would be expected to occur by chance, and the life table test indicated that the slight increase was not statistically significant. The life table test was given primary emphasis because 21 of the 25 neoplasms occurred in animals that died early, suggesting that these neoplasms may have contributed to their deaths. Moreover, the neoplasm incidence in 5,000 ppm males (18%) fell well within the historical control range (2%-30%), and there was no chemical-related increase in preputial gland hyperplasia. Thus, the slight increase in preputial gland neoplasms was not considered to be chemical related.

The mechanism for the formation of clitoral gland neoplasms following exposure to *p*-nitrobenzoic acid could not be fully explained by the results of the present studies. Clitoral gland neoplasms have usually been observed with those chemicals that are genotoxic (Ashby and Tennant, 1991). Chemicals shown to induce clitoral gland neoplasms generally are strong mutagens in a variety of *Salmonella* test strains, and also induce neoplasms of the Zymbal's gland, skin, mammary gland, or a combination of these sites (Copeland-Haines and Eustis, 1990). *p*-Nitrobenzoic acid was positive in only one of the *Salmonella* test strains used and was negative in the *in vivo* mouse micronucleus test.

The incidences of thyroid gland C-cell adenoma (9/50, 5/49, 4/50, 2/50) and adenoma or carcinoma (combined) (10/50, 5/49, 6/50, 2/50) were significantly decreased in 5,000 ppm female rats. This response could not be conclusively related to *p*-nitrobenzoic acid exposure because the incidence of C-cell adenoma or carcinoma (combined) is highly variable in historical controls. There were no chemical-related decreased incidences of thyroid gland C-cell neoplasms in male rats.

At the end of the 2-year mouse study, the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in 1,250 and 5,000 ppm females were significantly greater than that of the controls by pairwise comparison (3/50, 10/49, 4/50, 9/50). However, the occurrence of lung neoplasms was not considered to be related to chemical administration because these neoplasms were not increased by the trend statistic; the incidences of alveolar/bronchiolar adenoma or carcinoma (combined) were within the historical range for control female B6C3F$_1$ mice in recent NTP feed studies (range 2% to 26%, 106/1,371, mean 8%); and there was no increase in the incidence of alveolar epithelial hyperplasia, a preneoplastic lesion. In other NTP studies where the lung was a target site for chemical-induced neoplasms in mice, the chemical is usually genotoxic, there are preneoplastic lesions, and males and females are both affected.

Nitroaromatic compounds are an important class of chemicals and it is estimated that 10% of chemicals used in various chemical industries are nitroaromatic chemicals. In a review of 301 chemicals studied by NTP, there were 84 aromatic amino/nitro-type chemicals: 59 were carcinogenic (93% of these chemicals were positive in the *S. typhimurium* assay); 8 gave only equivocal evidence of a carcinogenic response (63% were positive in the *S. typhimurium* assay); and 17 gave no evidence of a carcinogenic response (71% were positive in the *S. typhimurium* assay) (Ashby and Tennant, 1991). *p*-Nitrobenzoic acid fell into the class of aromatic amino/nitro-type chemicals that gave only some evidence for carcinogenic activity in the rodent. The benzoic acid moiety on the aromatic ring allows for *p*-nitrobenzoic acid to be conjugated with glucuronic acid, and may allow for more rapid excretion of the chemical in the urine than the other aromatic/amino chemicals that have been shown to cause some or clear evidence of carcinogenic activity in the rodent.

The regional position of substitutions on the aromatic ring plays an important role in the eventual metabolism and carcinogenic activity of the chemical (Jakoby *et al.*, 1982; Rickert, 1987). In several series of aromatic isomers tested for carcinogenic activity, the ortho-substituted chemical was more carcinogenic than the meta- or para-substituted chemicals. For example, in a 13-week study of *o*-, *m*-, and *p*-nitrotoluene, *o*-nitrotoluene caused mesothelioma and mesothelial cell hyperplasia in male rats, but no preneoplastic lesions or neoplasms were observed with *m*- or *p*-nitrotoluene (NTP, 1992). Weisburger *et al.* (1978) reported that ortho-substituted aromatic compounds are more potent carcinogens than corresponding isomers with meta- or para-substitutions. This was observed with *o*-, *m*-, and *p*-toluidine, where *o*-toluidine was carcinogenic in rats, while carcinogenic activity was not reported in rats treated with *m*- or *p*-toluidine. Information on the carcinogenic potential of *m*- and *o*-nitrobenzoic acid is not available, and the results on the carcinogenic activity of *p*-nitrobenzoic acid reported here may not be predictive of the carcinogenic activity of the other isomers.

CONCLUSIONS

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of *p*-nitrobenzoic acid in male F344/N rats exposed to 1,250, 2,500, or 5,000 ppm. There was *some evidence of carcinogenic activity* of *p*-nitrobenzoic acid in female F344/N rats based on increases in the incidences of clitoral gland adenoma and of clitoral gland adenoma or carcinoma (combined). There was *no evidence of carcinogenic activity* of *p*-nitrobenzoic acid in male or female B6C3F$_1$ mice exposed to 1,250, 2,500, or 5,000 ppm.

There were chemical-related decreases in the incidences of mononuclear cell leukemia in exposed male and female rats. *p*-Nitrobenzoic acid caused mild hematologic toxicity in female rats.

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

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

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	32	34	34	25
Natural deaths	6	3	3	4
Survivors				
Terminal sacrifice	12	13	13	21
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Endocrine System				
Adrenal medulla	(10)	(10)	(10)	(10)
Pheochromocytoma benign			1 (10%)	
Pituitary gland	(10)	(10)	(10)	(10)
Pars distalis, adenoma	1 (10%)	2 (20%)	4 (40%)	1 (10%)
Genital System				
Preputial gland	(10)	(10)	(10)	(10)
Adenoma	1 (10%)		1 (10%)	1 (10%)
Testes	(10)	(10)	(10)	(10)
Bilateral, interstitial cell, adenoma	4 (40%)	7 (70%)	7 (70%)	
Interstitial cell, adenoma	5 (50%)	1 (10%)	2 (20%)	1 (10%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Lymph node, mandibular	(10)	(10)	(10)	(10)
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Spleen	(10)	(10)	(10)	(10)
Histiocytic sarcoma				1 (10%)
Thymus	(9)	(9)	(10)	(10)
Epithelial cell, thymoma benign			1 (10%)	
Integumentary System				
Mammary gland	(10)	(8)	(9)	(8)
Fibroadenoma	1 (10%)			
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma				1 (10%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
15-Month Interim Evaluation (continued)				
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Histiocytic sarcoma				1 (10%)
Leukemia mononuclear		1 (10%)		
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Intestine large, colon	(49)	(50)	(49)	(50)
Polyp adenomatous			1 (2%)	
Intestine large, rectum	(49)	(50)	(49)	(50)
Intestine large, cecum	(49)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)			
Intestine small, duodenum	(48)	(48)	(49)	(50)
Intestine small, jejunum	(49)	(49)	(49)	(50)
Carcinoma	2 (4%)			
Intestine small, ileum	(48)	(49)	(49)	(50)
Liver	(49)	(50)	(50)	(50)
Hepatocellular carcinoma	3 (6%)			2 (4%)
Hepatocellular adenoma	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Hepatocellular adenoma, multiple		2 (4%)		
Osteosarcoma, metastatic, bone			1 (2%)	
Mesentery	(17)	(13)	(13)	(17)
Carcinoma, metastatic, kidney			1 (8%)	
Schwannoma malignant, metastatic, peripheral nerve		1 (8%)		
Pancreas	(49)	(50)	(49)	(50)
Schwannoma malignant, metastatic, peripheral nerve		1 (2%)		
Acinar cell, adenoma	2 (4%)	3 (6%)		
Pharynx	(1)		(3)	
Palate, squamous cell papilloma	1 (100%)		2 (67%)	
Salivary glands	(49)	(49)	(50)	(50)
Schwannoma malignant	1 (2%)			1 (2%)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(49)	(49)	(50)
Leiomyoma			1 (2%)	
Tongue				(2)
Squamous cell papilloma				1 (50%)

Table A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	2 (4%)		1 (2%)	2 (4%)
Pheochromocytoma benign	8 (16%)	7 (14%)	5 (10%)	11 (22%)
Bilateral, pheochromocytoma benign	2 (4%)	4 (8%)	2 (4%)	1 (2%)
Islets, pancreatic	(49)	(50)	(49)	(50)
Adenoma	2 (4%)	1 (2%)	2 (4%)	
Carcinoma	1 (2%)			
Parathyroid gland	(48)	(49)	(47)	(49)
Pituitary gland	(49)	(50)	(49)	(49)
Pars distalis, adenoma	19 (39%)	12 (24%)	16 (33%)	12 (24%)
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(49)	(49)	(49)	(50)
C-cell, adenoma	4 (8%)	2 (4%)	2 (4%)	3 (6%)
C-cell, carcinoma		1 (2%)	3 (6%)	1 (2%)
Follicular cell, carcinoma				1 (2%)
General Body System				
Tissue NOS	(1)	(2)		(2)
Genital System				
Epididymis	(50)	(50)	(49)	(50)
Preputial gland	(50)	(50)	(49)	(50)
Adenoma	3 (6%)	2 (4%)	4 (8%)	3 (6%)
Carcinoma	1 (2%)	1 (2%)	3 (6%)	5 (10%)
Bilateral, adenoma		1 (2%)		
Bilateral, carcinoma			1 (2%)	1 (2%)
Duct, squamous cell papilloma			1 (2%)	
Prostate	(50)	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(49)	(50)
Schwannoma malignant, metastatic, peripheral nerve		1 (2%)		
Testes	(50)	(50)	(49)	(50)
Bilateral, interstitial cell, adenoma	34 (68%)	36 (72%)	35 (71%)	21 (42%)
Interstitial cell, adenoma	10 (20%)	9 (18%)	9 (18%)	15 (30%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(24)	(26)	(30)	(14)
Mediastinal, carcinoma, metastatic, kidney			1 (3%)	
Pancreatic, carcinoma, metastatic, kidney			1 (3%)	
Renal, carcinoma, metastatic, kidney			1 (3%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(49)	(49)	(49)	(50)
Lymph node, mesenteric	(49)	(50)	(49)	(50)
Carcinoma, metastatic, kidney			1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Fibrosarcoma			1 (2%)	
Histiocytic sarcoma				1 (2%)
Thymus	(48)	(50)	(48)	(46)
Epithelial cell, thymoma benign	1 (2%)	1 (2%)	1 (2%)	
Integumentary System				
Mammary gland	(49)	(49)	(49)	(46)
Fibroadenoma	2 (4%)	1 (2%)	4 (8%)	2 (4%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma			1 (2%)	1 (2%)
Keratoacanthoma	3 (6%)	3 (6%)	3 (6%)	2 (4%)
Squamous cell papilloma			2 (4%)	
Trichoepithelioma				1 (2%)
Subcutaneous tissue, fibroma	4 (8%)	6 (12%)	4 (8%)	7 (14%)
Subcutaneous tissue, fibrosarcoma	1 (2%)			4 (8%)
Subcutaneous tissue, lipoma		1 (2%)		1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma		2 (4%)	1 (2%)	1 (2%)
Skeletal muscle	(1)		(1)	(1)
Schwannoma malignant, metastatic, peripheral nerve	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Glioma malignant	1 (2%)			
Peripheral nerve	(2)	(5)	(1)	
Schwannoma malignant	1 (50%)	1 (20%)		
Spinal cord	(2)	(4)	(2)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma		1 (2%)		
Carcinoma, multiple, metastatic, kidney			1 (2%)	
Osteosarcoma, multiple, metastatic, bone		1 (2%)	1 (2%)	
Squamous cell carcinoma				1 (2%)
Nose	(50)	(50)	(50)	(50)
Nasolacrimal duct, squamous cell carcinoma	1 (2%)			
Trachea	(49)	(49)	(50)	(50)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Special Senses System				
Ear		(1)	(1)	
Pinna, fibrosarcoma		1 (100%)		
Zymbal's gland	(2)			
Adenoma	1 (50%)			
Carcinoma	1 (50%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Pelvis, transitional epithelium, papilloma	1 (2%)			
Renal tubule, adenoma			1 (2%)	
Renal tubule, carcinoma			1 (2%)	
Urinary bladder	(50)	(50)	(49)	(50)
Leiomyosarcoma	1 (2%)			
Schwannoma malignant, metastatic, peripheral nerve		1 (2%)		
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	29 (58%)	35 (70%)	26 (52%)	2 (4%)
Mesothelioma benign			1 (2%)	
Mesothelioma malignant		2 (4%)	1 (2%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	9	9	10	4
2-Year study	48	50	49	46
Total primary neoplasms				
15-Month interim evaluation	12	11	16	5
2-Year study	146	138	139	108
Total animals with benign neoplasms				
15-Month interim evaluation	9	9	10	4
2-Year study	47	48	48	41
Total benign neoplasms				
15-Month interim evaluation	12	10	16	4
2-Year study	99	94	101	85
Total animals with malignant neoplasms				
15-Month interim evaluation		1		1
2-Year study	39	38	34	19
Total malignant neoplasms				
15-Month interim evaluation		1		1
2-Year study	47	44	38	23
Total animals with metastatic neoplasms				
2-Year study	1	2	2	
Total metastatic neoplasms				
2-Year study	1	5	8	

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

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

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

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

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

	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	6	7	7	7	8	8	8	8	0	1	1	2	2	2	2	2	3	3	3	3	3	3	3	3	3	
	8	3	3	4	0	0	9	9	2	0	4	2	4	9	9	9	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	0	0	0	0	0	0	0	Total
Carcass ID Number	2	0	4	1	2	4	0	3	2	0	2	3	4	2	3	4	0	0	1	1	2	3	3	3	4	Tissues/
	1	2	7	8	0	3	5	3	3	9	8	5	2	2	2	8	1	4	1	5	7	6	7	9	0	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma								X							X											2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma								X																		3
Hepatocellular adenoma														X												2
Mesentery			+			+						+	+			+		+				+		+		17
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell, adenoma															X		X									2
Pharynx											+															1
Palate, squamous cell papilloma											X															1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																	X	X								2
Pheochromocytoma benign	X		X			X									X			X					X			8
Bilateral, pheochromocytoma benign							X																			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma											X										X					2
Carcinoma																	X									1
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X			X		X	X				X	X		X			X	X		X		X	X	X	X	19
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma		X						X												X						4
General Body System																										
Tissue NOS																										1

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

	2	2	3	3	4	4	4	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6
Number of Days on Study	4	9	8	9	1	3	5	0	0	1	3	4	4	4	5	5	6	8	8	0	1	1	3	4	4
	6	9	1	2	9	8	1	3	5	7	5	1	7	8	6	6	1	4	8	2	7	7	1	5	5
	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
Carcass ID Number	5	1	1	1	0	2	3	1	4	4	0	1	3	4	0	2	1	1	4	2	0	3	4	2	3
	6	2	9	0	8	4	1	3	4	6	3	7	8	9	7	5	6	4	1	9	6	4	5	6	0
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma														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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+				+	+	+		+	+				+		+		+		+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Epithelial cell, thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma									X																
Subcutaneous tissue, fibroma																				X					
Subcutaneous tissue, fibrosarcoma																									X
Subcutaneous tissue, sarcoma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																					
Schwannoma malignant, metastatic, peripheral nerve				X																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant						X																			
Peripheral nerve				+																					
Schwannoma malignant				X																					
Spinal cord				+																					

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

	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	6	7	7	7	8	8	8	8	0	1	1	2	2	2	2	2	3	3	3	3	3	3	3	3	3	
	8	3	3	4	0	0	9	9	2	0	4	2	4	9	9	9	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	0	0	0	0	0	0	0	Total
Carcass ID Number	2	0	4	1	2	4	0	3	2	0	2	3	4	2	3	4	0	0	1	1	2	3	3	3	4	Tissues/
	1	2	7	8	0	3	5	3	3	9	8	5	2	2	2	8	1	4	1	5	7	6	7	9	0	Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X									X	X								3
Carcinoma																										1
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	34
Interstitial cell, adenoma				X			X					X														10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+	+	+	+	+			+	+	+	+	+						+						24
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Epithelial cell, thymoma benign																			X							1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma																	X						X			2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma	X			X																						3
Subcutaneous tissue, fibroma									X	X									X							4
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Schwannoma malignant, metastatic, peripheral nerve																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
Peripheral nerve												+														2
Schwannoma malignant																										1
Spinal cord												+														2

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

Number of Days on Study	246	299	381	392	419	438	451	503	505	517	535	541	547	548	556	556	561	584	588	602	617	617	631	645	645
Carcass ID Number	056	012	019	010	008	024	031	013	044	046	003	017	038	049	007	025	016	014	041	029	006	034	045	026	030
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasolacrimal duct, squamous cell carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland			+												+										
Adenoma															X										
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, transitional epithelium, papilloma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X	X	X	X	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 *p*-Nitrobenzoic Acid: 0 ppm (continued)

	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	6	7	7	7	8	8	8	8	0	1	1	2	2	2	2	2	3	3	3	3	3	3	3	3	3	
	8	3	3	4	0	0	9	9	2	0	4	2	4	9	9	9	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	0	0	0	0	0	0	0	Total
Carcass ID Number	2	0	4	1	2	4	0	3	2	0	2	3	4	2	3	4	0	0	1	1	2	3	3	3	4	Tissues/
	1	2	7	8	0	3	5	3	3	9	8	5	2	2	2	8	1	4	1	5	7	6	7	9	0	Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasolacrimal duct, squamous cell carcinoma										X																1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Zymbal's gland																										2
Adenoma																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pelvis, transitional epithelium, papilloma																							X			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma											X															1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X	X	X	X		X		X	X	X	X			X	X		X						29

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

Number of Days on Study	310	392	415	454	493	505	527	532	532	538	539	561	584	587	588	591	602	624	631	637	647	652	665	673	673
Carcass ID Number	109	067	087	082	088	072	081	062	063	104	090	093	075	108	102	101	065	076	091	078	106	080	089	071	094
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular adenoma, multiple										X															
Mesentery	+		+					+									+					+		+	
Schwannoma malignant, metastatic, peripheral nerve	X																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, peripheral nerve	X																								
Acinar cell, adenoma																									
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																X									
Bilateral, pheochromocytoma benign																					X		X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																		X							
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X		X		X			X			X			X					X	
Pars intermedia, adenoma																									
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X															
C-cell, carcinoma																									
General Body System																									
Tissue NOS																									

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	7	7	7	0	0	0	0	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	3	4	4	0	0	2	2	0	2	2	8	8	9	9	9	9	9	9	9	9	9	9	9	9	9	
	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	Total
Carcass ID Number	9	6	6	7	7	7	9	0	8	0	7	8	6	6	6	7	8	8	9	9	9	9	0	0	1	Tissues/
	7	1	9	0	9	4	6	7	3	3	3	6	4	6	8	7	4	5	2	5	8	9	0	5	0	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma												X											X			2
Hepatocellular adenoma, multiple													X													2
Mesentery		+					+		+		+	+	+							+						13
Schwannoma malignant, metastatic, peripheral nerve																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, peripheral nerve																										1
Acinar cell, adenoma			X													X			X							3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign											X		X			X	X				X			X		7
Bilateral, pheochromocytoma benign									X													X				4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X											X				X						X	X		12
Pars intermedia, adenoma								X																		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																X										2
C-cell, carcinoma																	X									1
General Body System																										
Tissue NOS									+			+														2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Number of Days on Study	310	392	415	454	493	505	527	532	532	538	539	561	584	587	588	591	602	624	631	637	647	652	665	673	673
Carcass ID Number	109	067	087	082	088	072	081	062	063	104	090	093	075	108	102	101	065	076	091	078	106	080	089	071	094
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Carcinoma																	X								
Bilateral, adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, peripheral nerve	X																								
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma								X	X		X	X		X	X				X	X		X		X	X
Interstitial cell, adenoma		X		X	X		X			X			X			X	X				X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+	+	+		+	+	+	+			+	+		+	+	+		+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epithelial cell, thymoma benign																									
Integumentary System																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																			X	X					
Subcutaneous tissue, fibroma		X																					X		
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																X							X		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+																	+	+			+	+		
Schwannoma malignant	X																								
Spinal cord																		+	+			+	+		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, multiple, metastatic, bone																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Number of Days on Study	673	674	674	700	700	702	702	710	722	722	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	097	061	069	070	079	074	096	107	083	103	073	086	064	066	068	077	084	085	092	095	098	099	100	105	110	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X																2
Carcinoma																										1
Bilateral, adenoma								X																		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, peripheral nerve																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	36
Interstitial cell, adenoma																										9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+	+	+	+		+		+									+				26
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Epithelial cell, thymoma benign														X												1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma								X																		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma				X																						3
Subcutaneous tissue, fibroma			X									X						X						X		6
Subcutaneous tissue, lipoma																								X		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										5
Schwannoma malignant																										1
Spinal cord																										4
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																						X				1
Osteosarcoma, multiple, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Number of Days on Study	310	392	415	454	493	505	527	532	532	538	539	561	584	587	588	591	602	624	631	637	647	652	665	673	673
Carcass ID Number	109	067	087	082	088	072	081	062	063	104	090	093	075	108	102	101	065	076	091	078	106	080	089	071	094
Special Senses System																									
Ear																							+		
Pinna, fibrosarcoma																							X		
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, peripheral nerve	X																								
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
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Number of Days on Study	673	674	674	700	700	702	702	710	722	722	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	097	061	069	070	079	074	096	107	083	103	073	086	064	066	068	077	084	085	092	095	098	099	100	105	110	Total Tissues/ Tumors
Special Senses System																										
Ear																										1
Pinna, fibrosarcoma																										1
Eye																							+			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, peripheral nerve																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X		X	X	X	X	X	X		X	X	X				X			X		X	X			35
Mesothelioma malignant									X												X					2

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

Number of Days on Study	4	5	5	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6
	2	0	0	0	0	1	3	4	5	6	7	7	8	0	0	0	3	3	4	5	5	6	7	7	7
	6	5	6	6	6	7	2	1	6	8	0	3	8	4	4	9	1	2	3	1	7	8	2	3	4
Carcass ID Number	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	5	3	4	5	6	2	3	2	6	5	7	3	5	3	3	2	6	4	3	5	6	3	2	4	5
	9	1	8	6	7	8	0	2	9	3	0	8	0	7	9	3	6	7	5	7	4	3	6	9	4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Osteosarcoma, metastatic, bone											X														
Mesentery	+						+	+												+					+
Carcinoma, metastatic, kidney								X																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																+									
Palate, squamous cell papilloma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																							X		
Pheochromocytoma benign								X					X												
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X									X	X		X	X							X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, carcinoma															X										
General Body System																									
None																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	674	679	679	687	696	700	702	702	709	722	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	1555	1540	1662	1660	1551	1661	1244	1665	1444	1245	1452	1552	1221	1227	1229	1332	1334	1336	1441	1443	1445	1446	1558	1663	1668	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous																		X								1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																						X				1
Osteosarcoma, metastatic, bone																										1
Mesentery	+			+			+			+						+			+				+		+	13
Carcinoma, metastatic, kidney																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pharynx							+	+																		3
Palate, squamous cell papilloma							X	X																		2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma									X																	1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign								X							X								X			5
Bilateral, pheochromocytoma benign	X																					X				2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X				X													2
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X	X			X				X		X						X				X		X	X	16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma														X										X		2
C-cell, carcinoma		X			X																					3
General Body System																										
None																										

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	426	505	506	506	506	517	532	541	556	568	570	573	588	604	604	609	631	632	643	651	657	668	672	673	674
Carcass ID Number	159	131	148	156	167	128	130	122	169	153	170	138	150	137	139	123	166	147	135	157	164	133	126	149	154
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																	X	
Carcinoma																				X		X			
Bilateral, carcinoma																									
Duct, squamous cell papilloma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X	X	X	X	X	X			X		X	X	X			X	X		X	X
Interstitial cell, adenoma		X		X									X						X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+	+		+	+	+		+	+	+			+		+	+	+	+			+
Mediastinal, carcinoma, metastatic, kidney								X																	
Pancreatic, carcinoma, metastatic, kidney								X																	
Renal, carcinoma, metastatic, kidney								X																	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney								X																	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Epithelial cell, thymoma benign				X																					
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																X						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma											X														
Skeletal muscle																	+								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																									
Spinal cord																	+								

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	674	679	679	687	696	700	702	702	709	722	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	155	140	162	160	151	161	124	165	144	125	142	152	121	127	129	132	134	136	141	143	145	146	158	163	168	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X																	X								4
Carcinoma							X																			3
Bilateral, carcinoma						X																				1
Duct, squamous cell papilloma			X																							1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	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			X	X						9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+	+	+	+		+		+	+				+	+			+	+		+	+		+	30
Mediastinal, carcinoma, metastatic, kidney																										1
Pancreatic, carcinoma, metastatic, kidney																										1
Renal, carcinoma, metastatic, kidney																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, kidney																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma												X														1
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Epithelial cell, thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma									X	X	X								X							4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma				X																						1
Keratoacanthoma					X								X											X		3
Squamous cell papilloma																	X							X		2
Subcutaneous tissue, fibroma																	X	X								4
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve			+																							1
Spinal cord			+																							2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	426	505	506	506	506	517	532	541	556	568	570	573	588	604	604	609	631	632	643	651	657	668	672	673	674
Carcass ID Number	159	131	148	156	167	128	130	122	169	153	170	138	150	137	139	123	166	147	135	157	164	133	126	149	154
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, multiple, metastatic, kidney								X																	
Osteosarcoma, multiple, metastatic, bone											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																	+								
Eye																			+						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Renal tubule, carcinoma								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X			X	X			X	X			X	X	X	X	X	X	X		X
Mesothelioma benign																									
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	674	679	679	687	696	700	702	702	709	722	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	155	140	162	160	151	161	124	165	144	125	142	152	121	127	129	132	134	136	141	143	145	146	158	163	168	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X							1
Carcinoma, multiple, metastatic, kidney																										1
Osteosarcoma, multiple, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye														+												2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																									X	1
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X				X		X					X	X			X	X		X	X		X	26
Mesothelioma benign							X																			1
Mesothelioma malignant										X																1

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

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
	0	0	9	0	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
	1	1	2	2	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	Total
Carcass ID Number	8	9	1	2	8	8	8	8	9	9	9	9	0	0	0	0	1	1	1	1	1	2	2	2	3	Tissues/
	6	6	5	0	2	3	4	9	0	1	4	9	2	3	7	8	0	1	2	7	8	1	6	9	0	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma									X					X												2
Hepatocellular adenoma																		X								2
Mesentery			+								+			+			+	+	+							17
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																					X					1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue												+														2
Squamous cell papilloma												X														1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant		X																								2
Pheochromocytoma benign		X		X									X	X		X		X	X							11
Bilateral, pheochromocytoma benign																							X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X				X	X	X						X	X		X		X	X		X				12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X													X												3
C-cell, carcinoma																										1
Follicular cell, carcinoma																								X		1
General Body System																										
Tissue NOS															+											2

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	191	434	445	458	483	506	506	518	532	542	548	567	608	615	617	618	647	654	681	689	694	695	696	700	703
Carcass ID Number	192	222	225	193	188	198	200	181	206	185	205	216	227	187	204	195	209	223	228	214	213	201	219	224	197
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X					X					
Carcinoma									X	X						X	X	X							
Bilateral, carcinoma								X																	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X						X			X		X		X		X	X		X	X
Interstitial cell, adenoma					X				X		X			X				X		X			X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+					+	+	+				+	+	+				+	+				+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Thymus	M	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																					X				
Keratoacanthoma																					X			X	
Trichoepithelioma																						X			
Subcutaneous tissue, fibroma					X							X					X	X					X		
Subcutaneous tissue, fibrosarcoma														X								X			
Subcutaneous tissue, lipoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																X									
Skeletal muscle							+																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X	
Squamous cell carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	710	710	719	720	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	186	196	215	220	182	183	184	189	190	191	194	199	202	203	207	208	210	211	212	217	218	221	226	229	230	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		3
Carcinoma																										5
Bilateral, carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X				X		X		X				X		X		X		X	X		X	X	X	21
Interstitial cell, adenoma	X				X						X	X	X				X		X			X				15
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+															+		+			14
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	46
Fibroadenoma		X																X								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Keratoacanthoma																										2
Trichoepithelioma																										1
Subcutaneous tissue, fibroma			X																X							7
Subcutaneous tissue, fibrosarcoma	X					X																				4
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																									2
Squamous cell carcinoma																					X					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	191	434	445	458	483	506	506	518	532	542	548	567	608	615	617	618	647	654	681	689	694	695	696	700	703
Carcass ID Number	192	222	225	193	188	198	200	181	206	185	205	216	227	187	204	195	209	223	228	214	213	201	219	224	197
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Leukemia mononuclear			X													X									
Mesothelioma malignant																			X						

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	710	710	719	720	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	186	196	215	220	182	183	184	189	190	191	194	199	202	203	207	208	210	211	212	217	218	221	226	229	230	Total Tissues/ Tumors
Special Senses System																										
Eye																							+			1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear																										2
Mesothelioma malignant																										1

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	10/50 (20%)	11/50 (22%)	7/50 (14%)	12/50 (24%)
Adjusted rate[b]	44.4%	57.2%	33.4%	42.6%
Terminal rate[c]	3/12 (25%)	6/13 (46%)	3/13 (23%)	6/21 (29%)
First incidence (days)	631	591	541	608
Life table test[d]	P=0.253N	P=0.580N	P=0.228N	P=0.339N
Logistic regression test[d]	P=0.476N	P=0.587N	P=0.206N	P=0.500
Cochran-Armitage test[d]	P=0.406			
Fisher exact test[d]		P=0.500	P=0.298N	P=0.405
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	11/50 (22%)	11/50 (22%)	8/50 (16%)	13/50 (26%)
Adjusted rate	50.6%	57.2%	35.7%	44.8%
Terminal rate	4/12 (33%)	6/13 (46%)	3/13 (23%)	6/21 (29%)
First incidence (days)	631	591	541	608
Life table test	P=0.259N	P=0.483N	P=0.229N	P=0.303N
Logistic regression test	P=0.494N	P=0.475N	P=0.202N	P=0.531
Cochran-Armitage test	P=0.374			
Fisher exact test		P=0.595N	P=0.306N	P=0.408
Liver: Hepatocellular Adenoma				
Overall rate	2/49 (4%)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted rate	11.7%	23.0%	7.7%	7.9%
Terminal rate	1/12 (8%)	2/13 (15%)	1/13 (8%)	1/21 (5%)
First incidence (days)	645	538	729 (T)	694
Life table test	P=0.242N	P=0.386	P=0.465N	P=0.513N
Logistic regression test	P=0.336N	P=0.385	P=0.448N	P=0.605N
Cochran-Armitage test	P=0.424N			
Fisher exact test		P=0.349	P=0.492N	P=0.684N
Liver: Hepatocellular Carcinoma				
Overall rate	3/49 (6%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adjusted rate	11.8%	0.0%	0.0%	9.5%
Terminal rate	0/12 (0%)	0/13 (0%)	0/13 (0%)	2/21 (10%)
First incidence (days)	617	–[e]	–	729 (T)
Life table test	P=0.396N	P=0.104N	P=0.104N	P=0.324N
Logistic regression test	P=0.476N	P=0.109N	P=0.107N	P=0.422N
Cochran-Armitage test	P=0.525N			
Fisher exact test		P=0.117N	P=0.117N	P=0.490N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	4/49 (8%)	4/50 (8%)	1/50 (2%)	4/50 (8%)
Adjusted rate	19.2%	23.0%	7.7%	17.1%
Terminal rate	1/12 (8%)	2/13 (15%)	1/13 (8%)	3/21 (14%)
First incidence (days)	617	538	729 (T)	694
Life table test	P=0.277N	P=0.581N	P=0.154N	P=0.381N
Logistic regression test	P=0.402N	P=0.592N	P=0.140N	P=0.516N
Cochran-Armitage test	P=0.511N			
Fisher exact test		P=0.631N	P=0.175N	P=0.631N

Table A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Mammary Gland: Fibroadenoma				
Overall rate	2/50 (4%)	1/50 (2%)	4/50 (8%)	2/50 (4%)
Adjusted rate	16.7%	5.6%	24.0%	8.6%
Terminal rate	2/12 (17%)	0/13 (0%)	1/13 (8%)	1/21 (5%)
First incidence (days)	729 (T)	710	709	710
Life table test	P=0.470N	P=0.468N	P=0.389	P=0.492N
Logistic regression test	P=0.552N	P=0.442N	P=0.396	P=0.526N
Cochran-Armitage test	P=0.477			
Fisher exact test		P=0.500N	P=0.339	P=0.691N
Pancreas: Adenoma				
Overall rate	2/49 (4%)	3/50 (6%)	0/49 (0%)	0/50 (0%)
Adjusted rate	16.7%	18.9%	0.0%	0.0%
Terminal rate	2/12 (17%)	2/13 (15%)	0/13 (0%)	0/21 (0%)
First incidence (days)	729 (T)	674	–	–
Life table test	P=0.032N	P=0.538	P=0.217N	P=0.124N
Logistic regression test	P=0.040N	P=0.571	P=0.217N	P=0.124N
Cochran-Armitage test	P=0.072N			
Fisher exact test		P=0.510	P=0.247N	P=0.242N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	3/49 (6%)	1/50 (2%)	2/49 (4%)	0/50 (0%)
Adjusted rate	22.2%	3.0%	13.1%	0.0%
Terminal rate	2/12 (17%)	0/13 (0%)	1/13 (8%)	0/21 (0%)
First incidence (days)	714	624	709	–
Life table test	P=0.052N	P=0.268N	P=0.467N	P=0.048N
Logistic regression test	P=0.065N	P=0.259N	P=0.434N	P=0.052N
Cochran-Armitage test	P=0.102N			
Fisher exact test		P=0.301N	P=0.500N	P=0.117N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	19/49 (39%)	12/50 (24%)	16/49 (33%)	12/49 (24%)
Adjusted rate	79.7%	45.5%	57.0%	48.1%
Terminal rate	8/12 (67%)	4/13 (31%)	4/13 (31%)	9/21 (43%)
First incidence (days)	547	505	506	608
Life table test	P=0.013N	P=0.070N	P=0.224N	P=0.003N
Logistic regression test	P=0.072N	P=0.054N	P=0.188N	P=0.020N
Cochran-Armitage test	P=0.145N			
Fisher exact test		P=0.085N	P=0.337N	P=0.096N
Preputial Gland: Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	4/49 (8%)	3/50 (6%)
Adjusted rate	21.1%	13.6%	16.5%	10.4%
Terminal rate	2/12 (17%)	0/13 (0%)	1/13 (8%)	1/21 (5%)
First incidence (days)	689	588	532	617
Life table test	P=0.382N	P=0.603N	P=0.555	P=0.434N
Logistic regression test	P=0.522N	P=0.611N	P=0.560	P=0.554N
Cochran-Armitage test	P=0.556			
Fisher exact test		P=0.661N	P=0.489	P=0.661N

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Preputial Gland: Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	4/49 (8%)	6/50 (12%)
Adjusted rate	2.7%	2.9%	15.9%	15.0%
Terminal rate	0/12 (0%)	0/13 (0%)	0/13 (0%)	0/21 (0%)
First incidence (days)	548	602	651	518
Life table test	P=0.031	P=0.744N	P=0.234	P=0.094
Logistic regression test	P=0.002	P=0.743	P=0.192	P=0.009
Cochran-Armitage test	P=0.013			
Fisher exact test		P=0.753N	P=0.175	P=0.056
Preputial Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	8/49 (16%)	9/50 (18%)
Adjusted rate	23.2%	16.1%	29.8%	23.8%
Terminal rate	2/12 (17%)	0/13 (0%)	1/13 (8%)	1/21 (5%)
First incidence (days)	548	588	532	518
Life table test	P=0.176	P=0.579N	P=0.254	P=0.278
Logistic regression test	P=0.024	P=0.607N	P=0.219	P=0.055
Cochran-Armitage test	P=0.052			
Fisher exact test		P=0.643N	P=0.168	P=0.117
Skin: Keratoacanthoma				
Overall rate	3/50 (6%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted rate	10.5%	10.5%	19.4%	6.9%
Terminal rate	0/12 (0%)	0/13 (0%)	2/13 (15%)	0/21 (0%)
First incidence (days)	505	631	696	694
Life table test	P=0.242N	P=0.600N	P=0.595N	P=0.350N
Logistic regression test	P=0.345N	P=0.655N	P=0.618N	P=0.479N
Cochran-Armitage test	P=0.397N			
Fisher exact test		P=0.661N	P=0.661N	P=0.500N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted rate	10.5%	10.5%	30.1%	10.1%
Terminal rate	0/12 (0%)	0/13 (0%)	3/13 (23%)	0/21 (0%)
First incidence (days)	505	631	687	694
Life table test	P=0.386N	P=0.600N	P=0.433	P=0.482N
Logistic regression test	P=0.535N	P=0.655N	P=0.421	P=0.633N
Cochran-Armitage test	P=0.537			
Fisher exact test		P=0.661N	P=0.357	P=0.661N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	4/50 (8%)	6/50 (12%)	4/50 (8%)	7/50 (14%)
Adjusted rate	21.7%	28.5%	20.6%	21.2%
Terminal rate	1/12 (8%)	2/13 (15%)	2/13 (15%)	1/21 (5%)
First incidence (days)	602	392	609	483
Life table test	P=0.509	P=0.441	P=0.583N	P=0.496
Logistic regression test	P=0.298	P=0.414	P=0.572N	P=0.303
Cochran-Armitage test	P=0.254			
Fisher exact test		P=0.370	P=0.643N	P=0.262

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Skin (Subcutaneous Tissue): Fibrosarcoma				
Overall rate	1/50 (2%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	3.7%	0.0%	0.0%	14.1%
Terminal rate	0/12 (0%)	0/13 (0%)	0/13 (0%)	1/21 (5%)
First incidence (days)	645	–	–	615
Life table test	P=0.065	P=0.479N	P=0.472N	P=0.319
Logistic regression test	P=0.036	P=0.493N	P=0.492N	P=0.223
Cochran-Armitage test	P=0.028			
Fisher exact test		P=0.500N	P=0.500N	P=0.181
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma				
Overall rate	2/50 (4%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	5.9%	0.0%	0.0%	14.1%
Terminal rate	0/12 (0%)	0/13 (0%)	0/13 (0%)	1/21 (5%)
First incidence (days)	451	–	–	615
Life table test	P=0.181	P=0.221N	P=0.213N	P=0.501
Logistic regression test	P=0.104	P=0.270N	P=0.307N	P=0.346
Cochran-Armitage test	P=0.104			
Fisher exact test		P=0.247N	P=0.247N	P=0.339
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	6/50 (12%)	6/50 (12%)	4/50 (8%)	11/50 (22%)
Adjusted rate	26.3%	28.5%	20.6%	32.5%
Terminal rate	1/12 (8%)	2/13 (15%)	2/13 (15%)	2/21 (10%)
First incidence (days)	451	392	609	483
Life table test	P=0.294	P=0.544N	P=0.311N	P=0.399
Logistic regression test	P=0.106	P=0.595N	P=0.322N	P=0.170
Cochran-Armitage test	P=0.086			
Fisher exact test		P=0.620N	P=0.370N	P=0.143
Testes: Adenoma				
Overall rate	44/50 (88%)	45/50 (90%)	44/49 (90%)	36/50 (72%)
Adjusted rate	100.0%	100.0%	100.0%	91.9%
Terminal rate	12/12 (100%)	13/13 (100%)	13/13 (100%)	18/21 (86%)
First incidence (days)	381	392	505	483
Life table test	P<0.001N	P=0.374N	P=0.293N	P=0.001N
Logistic regression test	P<0.001N	P=0.580N	P=0.437N	P=0.007N
Cochran-Armitage test	P=0.010N			
Fisher exact test		P=0.500	P=0.514	P=0.039N
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/49 (8%)	2/49 (4%)	2/49 (4%)	3/50 (6%)
Adjusted rate	19.0%	9.9%	15.4%	11.0%
Terminal rate	1/12 (8%)	1/13 (8%)	2/13 (15%)	1/21 (5%)
First incidence (days)	547	538	729 (T)	608
Life table test	P=0.290N	P=0.303N	P=0.297N	P=0.308N
Logistic regression test	P=0.414N	P=0.315N	P=0.280N	P=0.431N
Cochran-Armitage test	P=0.469N			
Fisher exact test		P=0.339N	P=0.339N	P=0.489N

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Thyroid Gland (C-cell): Carcinoma				
Overall rate	0/49 (0%)	1/49 (2%)	3/49 (6%)	1/50 (2%)
Adjusted rate	0.0%	7.7%	11.2%	2.9%
Terminal rate	0/12 (0%)	1/13 (8%)	0/13 (0%)	0/21 (0%)
First incidence (days)	–	729 (T)	604	618
Life table test	P=0.478	P=0.516	P=0.159	P=0.545
Logistic regression test	P=0.382	P=0.516	P=0.133	P=0.497
Cochran-Armitage test	P=0.358			
Fisher exact test		P=0.500	P=0.121	P=0.505
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	4/49 (8%)	3/49 (6%)	5/49 (10%)	4/50 (8%)
Adjusted rate	19.0%	17.4%	24.9%	13.5%
Terminal rate	1/12 (8%)	2/13 (15%)	2/13 (15%)	1/21 (5%)
First incidence (days)	547	538	604	608
Life table test	P=0.396N	P=0.456N	P=0.575	P=0.442N
Logistic regression test	P=0.567N	P=0.464N	P=0.569	P=0.587N
Cochran-Armitage test	P=0.513			
Fisher exact test		P=0.500N	P=0.500	P=0.631N
All Organs: Mononuclear Cell Leukemia				
Overall rate	29/50 (58%)	35/50 (70%)	26/50 (52%)	2/50 (4%)
Adjusted rate	76.2%	79.9%	76.3%	4.9%
Terminal rate	4/12 (33%)	5/13 (38%)	7/13 (54%)	0/21 (0%)
First incidence (days)	503	415	506	445
Life table test	P<0.001N	P=0.424	P=0.215N	P<0.001N
Logistic regression test	P<0.001N	P=0.177	P=0.127N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.149	P=0.344N	P<0.001N
All Organs: Benign Neoplasms				
Overall rate	48/50 (96%)	48/50 (96%)	48/50 (96%)	42/50 (84%)
Adjusted rate	100.0%	100.0%	100.0%	97.7%
Terminal rate	12/12 (100%)	13/13 (100%)	13/13 (100%)	20/21 (95%)
First incidence (days)	246	392	505	483
Life table test	P=0.002N	P=0.322N	P=0.283N	P=0.003N
Logistic regression test	P<0.001N	P=0.457N	P=0.374N	P=0.005N
Cochran-Armitage test	P=0.010N			
Fisher exact test		P=0.691N	P=0.691N	P=0.046N
All Organs: Malignant Neoplasms				
Overall rate	39/50 (78%)	38/50 (76%)	35/50 (70%)	19/50 (38%)
Adjusted rate	84.6%	83.3%	86.0%	50.3%
Terminal rate	5/12 (42%)	6/13 (46%)	8/13 (62%)	5/21 (24%)
First incidence (days)	381	310	506	445
Life table test	P<0.001N	P=0.317N	P=0.172N	P<0.001N
Logistic regression test	P<0.001N	P=0.478N	P=0.092N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.500N	P=0.247N	P<0.001N

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	50/50 (100%)	49/50 (98%)	46/50 (92%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	12/12 (100%)	13/13 (100%)	13/13 (100%)	21/21 (100%)
First incidence (days)	246	310	505	445
Life table test	P=0.005N	P=0.366N	P=0.279N	P=0.009N
Logistic regression test	P=0.002N	P=0.773	P=0.297N	P=0.026N
Cochran-Armitage test	P=0.034N			
Fisher exact test		P=0.500	P=0.753N	P=0.181N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, pancreas, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; 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 exposure group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test 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 an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE A4a
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			
Benzyl Acetate	0/50	0/50	0/50
C.I. Pigment Red 23	0/50	0/50	0/50
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
Total	1/399 (0.3%)	3/399 (0.8%)	4/399 (1.0%)
Standard deviation	0.7%	1.0%	1.5%
Range	0%-2%	0%-2%	0%-4%
Overall Historical Incidence			
Total	9/1,251 (0.7%)	6/1,251 (0.5%)	15/1,251 (1.2%)
Standard deviation	1.5%	1.1%	1.7%
Range	0%-6%	0%-4%	0%-6%

[a] Data as of 20 August 1992

TABLE A4b
Historical Incidence of Renal Tubule Lesions from Single and Step Sections in Male F344/N Rats

Study	Incidence in Controls: Hyperplasia	Adenoma	Carcinoma	Adenoma or Carcinoma
Single Sections (Standard Evaluation)				
Nitrofurantoin[a]	2/50	0/50	0/50	0/50
Furosemide[a]	4/50	1/50	0/50	1/50
Phenylbutazone[b]	3/50	0/50	0/50	0/50
α-Methylbenzyl Alcohol[b]	0/50	0/50	0/50	0/50
Toluene[c]	4/60	0/60	0/60	0/60
2,4-Diaminophenol Dihydrochloride[b]	0/50	0/50	1/50	1/50
Mercuric Chloride[b]	1/50	0/50	0/50	0/50
Quercetin[a]	1/50	0/50	0/50	0/50
Coumarin[b]	1/49	1/49	0/49	1/49
3,4-Dihydrocoumarin[b]	0/50	0/50	0/50	0/50
o-Benzyl-*p*-Chlorophenol[b]	0/50	1/50	0/50	1/50
C.I. Pigment Red 23[a]	3/50	0/50	0/50	0/50
Overall Historical Incidence				
Total	19/609 (3.1%)	3/609 (0.5%)	1/609 (0.2%)	4/609 (0.7%)
Standard deviation	3.0%	0.9%	0.6%	1.0%
Range	0%-8%	0%-2%	0%-2%	0%-2%
Step Sections (Extended Evaluations)				
Nitrofurantoin	9/50	3/50	0/50	3/50
Furosemide	2/50	2/50	0/50	2/50
Phenylbutazone	2/50	0/50	0/50	0/50
α-Methylbenzyl Alcohol	1/49	1/49	0/49	1/49
Toluene	0/60	5/60	0/60	5/60
2,4-Diaminophenol Dihydrochloride	3/50	0/50	0/50	0/50
Mercuric Chloride	2/50	4/50	0/50	4/50
Quercetin	2/50	1/50	0/50	1/50
Coumarin	2/49	0/49	0/49	0/49
3,4-Dihydrocoumarin	0/50	1/50	0/50	1/50
o-Benzyl-*p*-Chlorophenol	3/50	0/50	0/50	0/50
C.I. Pigment Red 23	3/50	1/50	0/50	1/50
Overall Historical Incidence				
Total	29/608 (4.8%)	18/608 (3.0%)	0/608 (0%)	18/608 (3.0%)
Standard deviation	4.6%	3.0%		3.0%
Range	0%-18%	0%-8%		0%-8%

TABLE A4b
Historical Incidence of Renal Tubule Lesions from Single and Step Sections in Male F344/N Rats (continued)

Study	Incidence in Controls Hyperplasia	Adenoma	Carcinoma	Adenoma or Carcinoma
Single and Step Sections Combined				
Nitrofurantoin	10/50	3/50	0/50	3/50
Furosemide	6/50	3/50	0/50	3/50
Phenylbutazone	5/50	0/50	0/50	0/50
α-Methylbenzyle Alcohol	1/49	1/49	0/49	1/49
Toluene	4/60	5/60	0/60	5/60
2,4-Diaminophenol Dihydrochloride	3/50	0/50	1/50	1/50
Mercuric Chloride	3/50	4/50	0/50	4/50
Quercetin	3/50	1/50	0/50	1/50
Coumarin	3/49	1/49	0/49	1/49
3,4-Dihydrocoumarin	0/50	1/50	0/50	1/50
o-Benzyl-*p*-Chlorophenol	3/50	1/50	0/50	1/50
C.I. Pigment Red 23	6/50	1/50	0/50	1/50
Overall Historical Incidence				
Total	47/608 (7.7%)	21/608 (3.5%)	1/608 (0.2%)	22/608 (3.6%)
Standard deviation	5.2%	2.9%	0.8%	2.7%
Range	0%-20%	0%-8%	0%-2%	0%-8%

[a] Feed study
[b] Gavage study
[c] Inhalation study

TABLE A4c
Historical Incidence of Preputial Gland Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls: Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	2/50	0/50	2/50
C.I. Pigment Red 23	3/49	2/49	5/49
C.I. Pigment Red 3	6/49	1/49	7/49
Nitrofurantoin	6/48	6/48	12/48
o-Nitroanisole	4/50	7/50	11/50
Polysorbate 80	5/48	5/48	10/48
Rhodamine 6G	2/49	2/49	4/49
Roxarsone	7/49	0/49	7/49
Total	35/392 (8.9%)	23/392 (5.9%)	58/392 (14.8%)
Standard deviation	4.0%	5.7%	7.4%
Range	4%-14%	0%-14%	4%-25%
Overall Historical Incidence			
Total[b]	94/1,169 (8.0%)	46/1,169 (3.9%)	139/1,169 (11.9%)
Standard deviation	5.6%	4.0%	7.8%
Range	2%-24%	0%-14%	2%-30%

[a] Data as of 20 August 1992
[b] Data from Quercetin, TR 409, censored due to low denominator (adenoma, 2/13; carcinoma, 1/13; adenoma or carcinoma, 3/13)

TABLE A4d
Historical Incidence of Mononuclear Cell Leukemia in Untreated Male F344/N Rats[a]

Study	Incidence in Controls Mononuclear Cell Leukemia[b]
Historical Incidence at Southern Research Institute	
Benzyl Acetate	16/50
C.I. Pigment Red 23	28/50
C.I. Pigment Red 3	22/50
Nitrofurantoin	23/50
o-Nitroanisole	26/50
Polysorbate 80	23/50
Rhodamine 6G	27/50
Roxarsone	27/50
Total	192/400 (48.0%)
Standard deviation	7.9%
Range	32%-56%
Overall Historical Incidence	
Total	603/1,253 (48.1%)
Standard deviation	8.7%
Range	32%-62%

[a] Data as of 20 August 1992
[b] Includes incidences of lymphocytic, monocytic, or undifferentiated leukemia.

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	32	34	34	25
Natural deaths	6	3	3	4
Survivors				
Terminal sacrifice	12	13	13	21
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(9)
Parasite metazoan				2 (22%)
Intestine large, rectum	(10)	(10)	(10)	(10)
Parasite metazoan	2 (20%)	1 (10%)		
Liver	(10)	(10)	(10)	(10)
Basophilic focus	5 (50%)	1 (10%)	5 (50%)	2 (20%)
Clear cell focus	2 (20%)			
Degeneration, cystic		1 (10%)	1 (10%)	
Fatty change	10 (100%)	8 (80%)	10 (100%)	9 (90%)
Hepatodiaphragmatic nodule			5 (50%)	
Inflammation, focal	8 (80%)	6 (60%)	7 (70%)	6 (60%)
Mixed cell focus		1 (10%)		
Bile duct, hyperplasia	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Mesentery	(1)	(1)	(2)	(3)
Accessory spleen	1 (100%)		1 (50%)	
Fat, necrosis		1 (100%)	1 (50%)	3 (100%)
Pancreas	(10)	(10)	(10)	(10)
Accessory spleen				1 (10%)
Atrophy, focal	7 (70%)	4 (40%)	4 (40%)	6 (60%)
Stomach, forestomach	(10)	(10)	(10)	(10)
Mineralization, focal	1 (10%)			
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule				1 (10%)
Focal cellular change	1 (10%)		2 (20%)	1 (10%)
Pituitary gland	(10)	(10)	(10)	(10)
Angiectasis			1 (10%)	1 (10%)
Cyst		1 (10%)		1 (10%)
Pars distalis, focal cellular change	6 (60%)	4 (40%)		3 (30%)
Thyroid gland	(10)	(10)	(10)	(10)
Degeneration, cystic			1 (10%)	
Ultimobranchial cyst				1 (10%)
C-cell, hyperplasia	1 (10%)	3 (30%)		
Follicular cell, hyperplasia				1 (10%)

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

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Epididymis	(10)	(10)	(10)	(10)
Inflammation, chronic		1 (10%)		
Preputial gland	(10)	(10)	(10)	(10)
Degeneration, cystic	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Inflammation, chronic	1 (10%)		1 (10%)	
Prostate	(10)	(10)	(10)	(10)
Inflammation, suppurative	8 (80%)	6 (60%)	7 (70%)	5 (50%)
Testes	(10)	(10)	(10)	(10)
Bilateral, interstitial cell, hyperplasia	1 (10%)		1 (10%)	3 (30%)
Germinal epithelium, degeneration	1 (10%)	1 (10%)		
Interstitial cell, hyperplasia	5 (50%)	2 (20%)	2 (20%)	3 (30%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Myelofibrosis		1 (10%)		
Lymph node	(2)		(2)	(1)
Mediastinal, congestion	2 (100%)		2 (100%)	1 (100%)
Mediastinal, hyperplasia			1 (50%)	
Lymph node, mandibular	(10)	(10)	(10)	(10)
Congestion			1 (10%)	
Hyperplasia		1 (10%)	1 (10%)	
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Edema		1 (10%)		
Hyperplasia, lymphoid		1 (10%)		1 (10%)
Spleen	(10)	(10)	(10)	(10)
Pigmentation	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Thymus	(9)	(9)	(10)	(10)
Cyst				1 (10%)
Integumentary System				
Mammary gland	(10)	(8)	(9)	(8)
Dilatation	1 (10%)			
Skin	(10)	(10)	(10)	(10)
Exudate				1 (10%)
Hemorrhage, focal			1 (10%)	
Inflammation, chronic, focal				1 (10%)
Ulcer				1 (10%)
Nervous System				
Brain	(10)	(10)	(10)	(10)
Compression		1 (10%)		

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar epithelium, hyperplasia			1 (10%)	1 (10%)
Nose	(10)	(10)	(10)	(10)
Fungus		1 (10%)		1 (10%)
Inflammation, suppurative		1 (10%)	1 (10%)	1 (10%)
Respiratory epithelium, hyperplasia, focal				1 (10%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Pelvis, dilatation		1 (10%)		
Renal tubule, hyperplasia			1 (10%)	
Renal tubule, pigmentation	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Special Senses System				
2-Year Study				
Alimentary System				
Intestine large, colon	(49)	(50)	(49)	(50)
Parasite metazoan	2 (4%)		1 (2%)	
Intestine large, rectum	(49)	(50)	(49)	(50)
Parasite metazoan	1 (2%)	3 (6%)	5 (10%)	1 (2%)
Intestine large, cecum	(49)	(50)	(49)	(50)
Inflammation, chronic		1 (2%)		
Parasite metazoan		1 (2%)		
Intestine small, duodenum	(48)	(48)	(49)	(50)
Mucosa, hyperplasia	1 (2%)			
Intestine small, jejunum	(49)	(49)	(49)	(50)
Necrosis		1 (2%)		
Ulcer		1 (2%)		
Intestine small, ileum	(48)	(49)	(49)	(50)
Diverticulum		1 (2%)		
Fibrosis		1 (2%)		
Inflammation, chronic, focal		1 (2%)		
Ulcer		1 (2%)		

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(49)	(50)	(50)	(50)
Angiectasis	4 (8%)	6 (12%)	6 (12%)	1 (2%)
Atrophy, focal	1 (2%)			
Autolysis			1 (2%)	
Basophilic focus	13 (27%)	18 (36%)	25 (50%)	33 (66%)
Clear cell focus	6 (12%)	8 (16%)	9 (18%)	12 (24%)
Congestion, focal	3 (6%)	1 (2%)		
Degeneration, cystic	7 (14%)	10 (20%)	10 (20%)	12 (24%)
Developmental malformation				1 (2%)
Eosinophilic focus	5 (10%)	5 (10%)	7 (14%)	5 (10%)
Fatty change	15 (31%)	13 (26%)	11 (22%)	7 (14%)
Fibrosis, focal			1 (2%)	
Focal cellular change		1 (2%)	1 (2%)	
Hematopoietic cell proliferation			1 (2%)	2 (4%)
Hemorrhage, focal				1 (2%)
Hepatodiaphragmatic nodule	7 (14%)	2 (4%)	7 (14%)	9 (18%)
Hepatodiaphragmatic nodule, multiple	2 (4%)	1 (2%)	1 (2%)	
Hyperplasia, histiocytic	1 (2%)			
Hyperplasia, lymphoid	1 (2%)			
Hyperplasia, multifocal	13 (27%)	12 (24%)	13 (26%)	4 (8%)
Infiltration cellular, mixed cell	7 (14%)	5 (10%)	4 (8%)	3 (6%)
Inflammation, focal	10 (20%)	10 (20%)	15 (30%)	26 (52%)
Mixed cell focus	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Necrosis, focal		6 (12%)	3 (6%)	1 (2%)
Pigmentation	1 (2%)			
Thrombosis			2 (4%)	
Bile duct, hyperplasia	48 (98%)	48 (96%)	49 (98%)	48 (96%)
Centrilobular, atrophy	22 (45%)	27 (54%)	23 (46%)	5 (10%)
Centrilobular, congestion	1 (2%)			
Centrilobular, necrosis	2 (4%)		1 (2%)	1 (2%)
Mesentery	(17)	(13)	(13)	(17)
Accessory spleen		2 (15%)		1 (6%)
Angiectasis		1 (8%)		
Fibrosis	1 (6%)		1 (8%)	1 (6%)
Hemorrhage	1 (6%)			
Inflammation, chronic			1 (8%)	1 (6%)
Fat, necrosis	12 (71%)	4 (31%)	3 (23%)	13 (76%)
Pancreas	(49)	(50)	(49)	(50)
Accessory spleen	1 (2%)			
Atrophy, diffuse		1 (2%)		
Atrophy, focal	23 (47%)	28 (56%)	25 (51%)	21 (42%)
Edema	1 (2%)	1 (2%)		
Inflammation, chronic			1 (2%)	1 (2%)
Necrosis	1 (2%)			
Acinar cell, focal cellular change		1 (2%)		
Acinar cell, hyperplasia		1 (2%)	2 (4%)	
Artery, inflammation, chronic			1 (2%)	1 (2%)
Duct, dilatation			2 (4%)	
Salivary glands	(49)	(49)	(50)	(50)
Atrophy, focal				1 (2%)

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Edema	1 (2%)	1 (2%)	1 (2%)	
Erosion	1 (2%)	1 (2%)		
Inflammation, chronic	2 (4%)	2 (4%)	3 (6%)	
Ulcer	1 (2%)	2 (4%)	4 (8%)	
Mucosa, hyperplasia	4 (8%)	3 (6%)	5 (10%)	
Stomach, glandular	(50)	(49)	(49)	(50)
Erosion	4 (8%)	2 (4%)	1 (2%)	
Hyperplasia, focal, lymphoid			1 (2%)	
Pigmentation, focal	2 (4%)	1 (2%)	1 (2%)	
Mucosa, hyperplasia		1 (2%)		
Tongue				(2)
Hyperplasia, squamous				1 (50%)
Cardiovascular System				
Blood vessel	(49)	(50)	(50)	(50)
Mesenteric artery, inflammation, chronic	1 (2%)	1 (2%)		2 (4%)
Heart	(50)	(50)	(50)	(50)
Inflammation, chronic, focal	1 (2%)	1 (2%)		1 (2%)
Thrombosis			2 (4%)	1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Angiectasis			1 (2%)	1 (2%)
Atrophy			1 (2%)	
Congestion	2 (4%)			
Focal cellular change	3 (6%)	7 (14%)	9 (18%)	8 (16%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		
Hyperplasia, focal				1 (2%)
Infiltration cellular, lymphocyte	1 (2%)			
Vacuolization cytoplasmic		1 (2%)		
Adrenal medulla	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Hyperplasia	11 (22%)	8 (16%)	15 (30%)	9 (18%)
Pituitary gland	(49)	(50)	(49)	(49)
Angiectasis	1 (2%)	3 (6%)	2 (4%)	3 (6%)
Cyst	3 (6%)	3 (6%)	3 (6%)	3 (6%)
Hemorrhage	1 (2%)		1 (2%)	
Pars distalis, focal cellular change	5 (10%)	2 (4%)	6 (12%)	9 (18%)
Pars distalis, hyperplasia, focal	3 (6%)	7 (14%)	4 (8%)	1 (2%)
Pars nervosa, focal cellular change			1 (2%)	
Thyroid gland	(49)	(49)	(49)	(50)
Degeneration, cystic	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Ultimobranchial cyst			2 (4%)	1 (2%)
C-cell, hyperplasia	5 (10%)	10 (20%)	5 (10%)	9 (18%)
Follicle, dilatation	1 (2%)	1 (2%)		
Follicular cell, hyperplasia	2 (4%)	1 (2%)	1 (2%)	

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
General Body System				
Tissue NOS	(1)	(2)		(2)
Anterior, fibrosis	1 (100%)			
Anterior, inflammation, chronic	1 (100%)			
Oral, inflammation, chronic				1 (50%)
Genital System				
Epididymis	(50)	(50)	(49)	(50)
Inflammation, chronic				2 (4%)
Epithelium, degeneration		1 (2%)		
Preputial gland	(50)	(50)	(49)	(50)
Degeneration, cystic	47 (94%)	47 (94%)	48 (98%)	48 (96%)
Hyperplasia	4 (8%)		1 (2%)	3 (6%)
Inflammation, chronic	1 (2%)		2 (4%)	
Prostate	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Inflammation, suppurative	37 (74%)	31 (62%)	36 (72%)	39 (78%)
Epithelium, hyperplasia, focal	1 (2%)	7 (14%)	2 (4%)	
Seminal vesicle	(50)	(50)	(49)	(50)
Dilatation	2 (4%)	1 (2%)		
Inflammation, chronic		1 (2%)		1 (2%)
Testes	(50)	(50)	(49)	(50)
Congestion				1 (2%)
Mineralization, focal				1 (2%)
Artery, inflammation, chronic				1 (2%)
Bilateral, interstitial cell, hyperplasia	1 (2%)		2 (4%)	7 (14%)
Germinal epithelium, degeneration	6 (12%)	11 (22%)	13 (27%)	14 (28%)
Interstitial cell, hyperplasia	10 (20%)	13 (26%)	7 (14%)	14 (28%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hemorrhage				2 (4%)
Hypercellularity	5 (10%)	3 (6%)	6 (12%)	5 (10%)
Hyperplasia, focal, histiocytic	1 (2%)	1 (2%)		3 (6%)
Metaplasia, osseous		1 (2%)		
Myelofibrosis		1 (2%)	1 (2%)	1 (2%)
Lymph node	(24)	(26)	(30)	(14)
Inguinal, hyperplasia			1 (3%)	4 (29%)
Lumbar, hyperplasia				1 (7%)
Mediastinal, angiectasis		3 (12%)		1 (7%)
Mediastinal, congestion	1 (4%)	2 (8%)	4 (13%)	4 (29%)
Mediastinal, hyperplasia	1 (4%)	1 (4%)		4 (29%)
Mediastinal, pigmentation			3 (10%)	
Pancreatic, angiectasis	1 (4%)		1 (3%)	1 (7%)
Pancreatic, edema	2 (8%)		1 (3%)	1 (7%)
Pancreatic, hyperplasia	2 (8%)			1 (7%)
Pancreatic, hyperplasia, lymphoid				1 (7%)
Pancreatic, hyperplasia, macrophage				1 (7%)

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(49)	(49)	(49)	(50)
Angiectasis			1 (2%)	
Congestion	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Ectasia		1 (2%)		
Edema			1 (2%)	
Hemorrhage				1 (2%)
Hyperplasia	7 (14%)	7 (14%)	6 (12%)	16 (32%)
Lymph node, mesenteric	(49)	(50)	(49)	(50)
Congestion				1 (2%)
Edema	1 (2%)		2 (4%)	1 (2%)
Hyperplasia	5 (10%)	3 (6%)	1 (2%)	7 (14%)
Hyperplasia, lymphoid	1 (2%)			2 (4%)
Spleen	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			
Congestion	1 (2%)			
Cyst	1 (2%)			
Degeneration, fatty			1 (2%)	
Fibrosis	12 (24%)	14 (28%)	12 (24%)	7 (14%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)	7 (14%)	9 (18%)
Necrosis, focal	1 (2%)	4 (8%)	1 (2%)	
Pigmentation	50 (100%)	50 (100%)	50 (100%)	50 (100%)
Red pulp, hyperplasia, focal, histiocytic		1 (2%)		
Thymus	(48)	(50)	(48)	(46)
Congestion	1 (2%)			
Cyst				1 (2%)
Hemorrhage			1 (2%)	
Epithelial cell, hyperplasia		1 (2%)		
Integumentary System				
Mammary gland	(49)	(49)	(49)	(46)
Dilatation	18 (37%)	11 (22%)	18 (37%)	9 (20%)
Hemorrhage		2 (4%)		
Hyperplasia	6 (12%)	3 (6%)	2 (4%)	2 (4%)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Hemorrhage, focal	1 (2%)	2 (4%)		
Hyperkeratosis, focal		2 (4%)	4 (8%)	2 (4%)
Hyperplasia, focal			1 (2%)	
Inflammation, chronic, focal	1 (2%)		3 (6%)	1 (2%)
Ulcer	1 (2%)		1 (2%)	
Epidermis, hyperplasia, focal		2 (4%)	4 (8%)	2 (4%)
Subcutaneous tissue, angiectasis	1 (2%)			
Subcutaneous tissue, congestion				1 (2%)
Subcutaneous tissue, inflammation, chronic, focal				1 (2%)

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fracture	1 (2%)			2 (4%)
Hyperostosis			1 (2%)	1 (2%)
Trabecula, proliferation			1 (2%)	
Skeletal muscle	(1)		(1)	(1)
Inflammation, chronic				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	8 (16%)	4 (8%)	5 (10%)	2 (4%)
Hemorrhage	2 (4%)	4 (8%)		
Meninges, fibrosis, focal		1 (2%)		
Spinal cord	(2)	(4)	(2)	
Demyelination		1 (25%)		
Hemorrhage, focal	1 (50%)	1 (25%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	2 (4%)		2 (4%)	2 (4%)
Edema	1 (2%)			
Fibrosis, focal	1 (2%)		1 (2%)	
Hemorrhage, focal	1 (2%)	3 (6%)	3 (6%)	
Hyperplasia, diffuse, macrophage		1 (2%)		
Hyperplasia, focal, macrophage	2 (4%)	2 (4%)	2 (4%)	
Infiltration cellular, mixed cell			1 (2%)	2 (4%)
Necrosis, focal	1 (2%)			
Alveolar epithelium, hyperplasia	6 (12%)	6 (12%)	6 (12%)	3 (6%)
Nose	(50)	(50)	(50)	(50)
Fungus	6 (12%)	8 (16%)	8 (16%)	7 (14%)
Inflammation, suppurative	8 (16%)	10 (20%)	11 (22%)	8 (16%)
Respiratory epithelium, ulcer		1 (2%)		
Special Senses System				
Eye		(1)	(2)	(1)
Atrophy			1 (50%)	1 (100%)
Cataract		1 (100%)	2 (100%)	1 (100%)
Retina, degeneration		1 (100%)	2 (100%)	1 (100%)

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Autolysis			1 (2%)	
Congestion		1 (2%)		
Cyst		1 (2%)		1 (2%)
Infarct			1 (2%)	
Nephropathy	50 (100%)	50 (100%)	50 (100%)	50 (100%)
Thrombosis			1 (2%)	
Pelvis, dilatation	1 (2%)			
Pelvis, transitional epithelium, hyperplasia	1 (2%)	2 (4%)		
Renal tubule, hyperplasia		3 (6%)	1 (2%)	1 (2%)
Renal tubule, hyperplasia, oncocytic	1 (2%)		1 (2%)	5 (10%)
Renal tubule, pigmentation	50 (100%)	50 (100%)	50 (100%)	50 (100%)
Renal tubule, vacuolization cytoplasmic				1 (2%)
Urinary bladder	(50)	(50)	(49)	(50)
Dilatation	1 (2%)			
Hemorrhage	2 (4%)	1 (2%)		
Inflammation, chronic				1 (2%)
Transitional epithelium, hyperplasia	1 (2%)			

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

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	21	23	27	26
Natural deaths	2	4	2	3
Survivors				
Terminal sacrifice	27	23	21	21
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Endocrine System				
Pituitary gland	(10)	(10)	(9)	(10)
Pars distalis, adenoma	2 (20%)	2 (20%)	1 (11%)	3 (30%)
Thyroid gland	(10)	(10)	(10)	(10)
C-cell, adenoma			1 (10%)	
Genital System				
Uterus	(10)	(10)	(10)	(10)
Endometrium, polyp stromal		3 (30%)	3 (30%)	1 (10%)
Endometrium, sarcoma stromal			1 (10%)	
Hematopoietic System				
Lymph node	(1)	(4)	(2)	(2)
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Spleen	(10)	(10)	(10)	(10)
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Fibroadenoma		1 (10%)		
Systemic Lesions				
Multiple organs[b]	(10)	(10)	(10)	(10)
Leukemia mononuclear		1 (10%)		

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
15-Month Interim Evaluation (continued)				
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
General Body System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland				1 (2%)
Intestine large, colon	(50)	(48)	(50)	(50)
Leiomyosarcoma, metastatic, uterus		1 (2%)		
Intestine large, cecum	(50)	(47)	(50)	(49)
Intestine small, duodenum	(50)	(50)	(50)	(49)
Intestine small, ileum	(50)	(47)	(50)	(48)
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma	2 (4%)			
Sarcoma, metastatic, mesentery			1 (2%)	
Mesentery	(10)	(8)	(9)	(6)
Sarcoma			1 (11%)	
Schwannoma malignant, metastatic, uterus			1 (11%)	
Pancreas	(50)	(50)	(49)	(49)
Acinar cell, adenoma			1 (2%)	
Pharynx			(1)	
Palate, squamous cell papilloma			1 (100%)	
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(49)	(49)
Stomach, glandular	(50)	(50)	(49)	(49)
Tongue			(1)	(1)
Squamous cell papilloma			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Osteosarcoma, metastatic, bone		1 (2%)		
Adrenal medulla	(49)	(50)	(50)	(50)
Osteosarcoma, metastatic, bone		1 (2%)		
Pheochromocytoma benign	2 (4%)	1 (2%)	3 (6%)	
Islets, pancreatic	(50)	(50)	(49)	(49)
Adenoma	1 (2%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Pituitary gland	(50)	(50)	(50)	(49)
Osteosarcoma, metastatic, bone		1 (2%)		
Pars distalis, adenoma	18 (36%)	27 (54%)	25 (50%)	23 (47%)
Pars distalis, carcinoma	1 (2%)			
Pars nervosa, ganglioneuroma				1 (2%)
Thyroid gland	(50)	(49)	(50)	(50)
C-cell, adenoma	9 (18%)	4 (8%)	4 (8%)	2 (4%)
C-cell, adenoma, multiple		1 (2%)		
C-cell, carcinoma	1 (2%)		2 (4%)	
Follicular cell, carcinoma		1 (2%)		1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(50)	(49)	(49)	(50)
Adenoma	4 (8%)	12 (24%)	9 (18%)	11 (22%)
Carcinoma	1 (2%)	2 (4%)	4 (8%)	3 (6%)
Bilateral, adenoma			1 (2%)	1 (2%)
Bilateral, carcinoma			1 (2%)	1 (2%)
Ovary	(50)	(50)	(50)	(49)
Granulosa cell tumor benign	1 (2%)			
Neoplasm NOS		1 (2%)		
Uterus	(50)	(50)	(50)	(49)
Histiocytic sarcoma			1 (2%)	
Leiomyosarcoma		1 (2%)		
Endometrium, polyp stromal	5 (10%)	10 (20%)	11 (22%)	5 (10%)
Endometrium, polyp stromal, multiple		1 (2%)	1 (2%)	
Endometrium, sarcoma stromal		1 (2%)	1 (2%)	
Endometrium, schwannoma malignant	1 (2%)		2 (4%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(13)	(10)	(9)	(8)
Renal, sarcoma, metastatic, mesentery			1 (11%)	
Lymph node, mandibular	(50)	(50)	(50)	(50)
Lymph node, mesenteric	(49)	(50)	(50)	(49)
Spleen	(50)	(50)	(50)	(49)
Fibrosarcoma			1 (2%)	
Sarcoma, metastatic, mesentery			1 (2%)	
Thymus	(49)	(48)	(50)	(50)

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	1 (2%)			
Carcinoma	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Fibroadenoma	17 (34%)	15 (30%)	19 (38%)	19 (38%)
Fibroadenoma, multiple	5 (10%)	7 (14%)	7 (14%)	5 (10%)
Skin	(50)	(50)	(50)	(50)
Basal cell carcinoma				1 (2%)
Basosquamous tumor malignant	1 (2%)			
Squamous cell papilloma				1 (2%)
Subcutaneous tissue, fibroma	2 (4%)	1 (2%)		3 (6%)
Subcutaneous tissue, lipoma	1 (2%)			
Subcutaneous tissue, schwannoma malignant		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma	1 (2%)	1 (2%)	1 (2%)	
Skeletal muscle			(1)	(1)
Rhabdomyosarcoma			1 (100%)	
Sarcoma				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma NOS		1 (2%)		
Glioma malignant	1 (2%)			
Peripheral nerve	(2)	(4)	(2)	
Schwannoma malignant		1 (25%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)			
Carcinoma, metastatic, thyroid gland				1 (2%)
Osteosarcoma, multiple, metastatic, bone		1 (2%)		
Squamous cell carcinoma				1 (2%)
Nose	(50)	(50)	(50)	(49)
Trachea	(50)	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland				1 (2%)
Special Senses System				
Zymbal's gland			(1)	
Carcinoma			1 (100%)	

Table B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Pelvis, transitional epithelium, mesenchymal tumor			1 (2%)	
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Leukemia mononuclear	17 (34%)	11 (22%)	3 (6%)	
Mesothelioma malignant				1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	2	5	5	4
2-Year study	44	48	50	45
Total primary neoplasms				
15-Month interim evaluation	2	7	6	4
2-Year study	95	102	107	83
Total animals with benign neoplasms				
15-Month interim evaluation	2	5	4	4
2-Year study	40	41	44	41
Total benign neoplasms				
15-Month interim evaluation	2	6	5	4
2-Year study	68	79	84	72
Total animals with malignant neoplasms				
15-Month interim evaluation		1	1	
2-Year study	21	19	21	10
Total malignant neoplasms				
15-Month interim evaluation		1	1	
2-Year study	27	21	22	11
Total animals with metastatic neoplasms				
2-Year study		2	2	1
Total metastatic neoplasms				
2-Year study		5	4	3
Total animals with uncertain neoplasms benign or malignant				
2-Year study		2	1	
Total uncertain neoplasms				
2-Year study		2	1	

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

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

Number of Days on Study	490	556	566	605	631	647	653	657	664	667	679	679	680	687	694	700	700	702	702	709	714	722	724	731	731
Carcass ID Number	282	280	259	264	243	244	263	258	288	279	285	287	269	256	252	262	265	247	267	242	276	278	245	241	246
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									X
Mesentery	+								+	+							+		+	+			+	+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth														+											
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign						X														X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X	X	X	X		X	X	X	X		X					X	X	X
Pars distalis, carcinoma																						X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma		X									X														
C-cell, carcinoma																			X						
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X						X												
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign								X																	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal	X																					X			
Endometrium, schwannoma malignant										X															
Vagina										+															

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

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

Number of Days on Study	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
	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	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	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	Total
	4	4	5	5	5	5	5	5	6	6	6	6	7	7	7	7	7	7	7	8	8	8	8	8	9	Tissues/
	8	9	0	1	3	4	5	7	0	1	6	8	0	1	2	3	4	5	7	1	3	4	6	9	0	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma						X																				2
Mesentery																	+					+				10
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X											X	X	X		X									X	18
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma						X					X	X				X			X			X		X		9
C-cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X							X								4
Carcinoma											X															1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrium, polyp stromal				X	X														X							5
Endometrium, schwannoma malignant																										1
Vagina		+																							+	3

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

Number of Days on Study	490	556	566	605	631	647	653	657	664	667	679	679	680	687	694	700	700	702	702	709	714	722	724	731	731
Carcass ID Number	282	280	259	264	243	244	263	258	288	279	285	287	269	256	252	262	265	247	267	272	276	278	245	241	246
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+				+	+	+		+	+		+	+				+			+		+	+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Carcinoma																						X			
Fibroadenoma			X				X		X				X					X			X				
Fibroadenoma, multiple												X							X	X				X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant																									
Subcutaneous tissue, fibroma																			X						
Subcutaneous tissue, lipoma															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant														X											
Peripheral nerve								+												+					
Spinal cord								+																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																							X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X	X	X	X		X	X		X	X	X			X			X		X	X		

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

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	248	249	250	251	253	254	255	257	260	261	266	268	270	271	272	273	274	275	277	281	283	284	286	289	290	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node			+																							13
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma												X														2
Fibroadenoma						X	X	X			X				X	X		X				X	X	X	X	17
Fibroadenoma, multiple																										5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor malignant																							X			1
Subcutaneous tissue, fibroma								X																		2
Subcutaneous tissue, lipoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant																										1
Peripheral nerve																										2
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye							+																			2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X					X															X			17

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

Number of Days on Study	1 5 0	4 4 1	4 8 3	4 9 6	5 1 0	5 2 1	5 4 8	5 6 6	5 7 0	6 3 2	6 5 1	6 6 5	6 7 4	6 7 4	6 7 4	6 7 6	6 9 4	6 9 5	6 9 6	6 9 6	6 9 6	6 9 6	7 0 0	7 0 2	7 0 2
Carcass ID Number	3 3 5	3 0 3	3 2 4	3 2 7	3 0 2	3 3 3	3 1 9	3 2 6	3 1 7	3 4 1	3 4 4	3 2 0	3 0 1	3 2 1	3 3 8	3 1 0	3 5 0	3 2 3	3 3 1	3 4 5	3 4 7	3 4 8	3 3 2	3 1 2	3 2 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, uterus																						X			
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery				+									+				+								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone		X																							
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone		X																							
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone		X																							
Pars distalis, adenoma					X	X		X	X	X	X	X			X	X		X	X					X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X					X										
C-cell, adenoma, multiple																									
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X						X					X	X	X
Carcinoma																	X			X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																						X			
Endometrium, polyp stromal						X		X																	
Endometrium, polyp stromal, multiple																									
Endometrium, sarcoma stromal																	X								
Vagina																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Number of Days on Study	708	728	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	311	313	304	305	306	307	308	309	314	315	316	318	325	328	329	330	334	336	337	339	340	342	343	346	349	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyosarcoma, metastatic, uterus																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+							+			+							+		+						8
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Pheochromocytoma benign																					X					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Pars distalis, adenoma					X	X		X	X	X	X	X	X	X			X	X		X			X	X	X	27
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma										X											X					4
C-cell, adenoma, multiple														X												1
Follicular cell, carcinoma			X																							1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Adenoma								X			X		X	X		X		X					X			12
Carcinoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplasm NOS																								X		1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Endometrium, polyp stromal		X				X	X		X							X	X		X		X					10
Endometrium, polyp stromal, multiple	X																									1
Endometrium, sarcoma stromal																										1
Vagina																						+				1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Number of Days on Study	150	441	483	496	510	521	548	566	570	632	651	675	674	674	674	676	694	695	696	696	696	696	700	702	702
Carcass ID Number	335	303	324	327	302	333	319	326	317	341	344	320	301	321	338	310	350	323	331	345	347	348	332	312	322
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+				+	+	+			+				+		+						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X																
Fibroadenoma			X			X		X					X		X			X				X			X
Fibroadenoma, multiple												X		X		X					X			X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																			X						
Subcutaneous tissue, schwannoma malignant							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma NOS																									
Peripheral nerve	+									+		+													
Schwannoma malignant	X																								
Spinal cord										+		+													
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, multiple, metastatic, bone		X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye		+																							
Lacrimal gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X		X	X		X				X		X						

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	0	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	8	8	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	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	Total
Carcass ID Number	1	1	0	0	0	0	0	0	1	1	1	1	2	2	2	3	3	3	3	3	4	4	4	4	4	Tissues/
	1	3	4	5	6	7	8	9	4	5	6	8	5	8	9	0	4	6	7	9	0	2	3	6	9	Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+								+						+											10
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma														X												2
Fibroadenoma		X		X				X		X			X							X			X			15
Fibroadenoma, multiple																	X							X		7
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma NOS																		X								1
Peripheral nerve																							+			4
Schwannoma malignant																										1
Spinal cord																										2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, multiple, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+																								2
Lacrimal gland				+																						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X								X						X					X	X					11

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

Number of Days on Study	241	379	379	434	461	492	496	499	518	538	553	588	604	643	647	647	650	653	664	668	685	694	695	695	702
Carcass ID Number	369	365	396	404	397	394	379	387	403	407	389	370	362	385	388	401	405	380	410	368	390	382	367	386	364
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery									X																
Mesentery		+				+		+	+	+	+					+									
Sarcoma									X																
Schwannoma malignant, metastatic, uterus										X															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Acinar cell, adenoma																									
Pharynx																									
Palate, squamous cell papilloma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X																
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X	X			X	X		X	X	X		X	X			X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X							X						X
C-cell, carcinoma																									
General Body System																									
None																									

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	0	0	0	1	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	
	2	8	9	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
	3	3	4	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4	4	4	4	Total
Carcass ID Number	9	6	0	7	6	6	7	7	7	7	7	7	7	8	8	8	9	9	9	9	9	0	0	0	0	Tissues/
	3	3	0	5	1	6	1	2	3	4	6	7	8	1	3	4	1	2	5	8	9	2	6	8	9	Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Mesentery					+		+																			9
Sarcoma																										1
Schwannoma malignant, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell, adenoma																		X								1
Pharynx		+																								1
Palate, squamous cell papilloma		X																								1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue					+																					1
Squamous cell papilloma					X																					1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign							X				X															3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X		X		X	X		X	X	X	X	X		X		X	X	X			X	25
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																									X	4
C-cell, carcinoma													X						X							2
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

	2	3	3	4	4	4	4	4	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	6	7
Number of Days on Study	4	7	7	3	6	9	9	9	1	3	5	8	0	4	4	4	5	5	6	6	8	9	9	9	0
	1	9	9	4	1	2	6	9	8	8	3	8	4	3	7	7	0	3	4	8	5	4	5	5	2
	3	3	3	4	3	3	3	3	4	4	3	3	3	3	3	4	4	3	4	3	3	3	3	3	3
Carcass ID Number	6	6	9	0	9	9	7	8	0	0	8	7	6	8	8	0	0	8	1	6	9	8	6	8	6
	9	5	6	4	7	4	9	7	3	7	9	0	2	5	8	1	5	0	0	8	0	2	7	6	4
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X						X						X	X			X	X	
Carcinoma								X								X									
Bilateral, adenoma																									
Bilateral, carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Endometrium, polyp stromal				X					X		X					X			X						
Endometrium, polyp stromal, multiple																									
Endometrium, sarcoma stromal												X													
Endometrium, schwannoma malignant										X		X													
Vagina											+														+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+			+			+							+	+	+				
Renal, sarcoma, metastatic, mesentery									X																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Sarcoma, metastatic, mesentery									X																
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
Fibroadenoma		X		X	X		X				X			X		X						X	X		
Fibroadenoma, multiple																			X	X					X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Skeletal muscle			+																						
Rhabdomyosarcoma			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve						+												+							
Spinal cord						+												+							

Table B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	702	708	709	714	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	393	363	400	375	361	366	371	372	373	374	376	377	378	381	383	384	391	392	395	398	399	402	406	408	409	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X							X									X					9
Carcinoma									X											X						4
Bilateral, adenoma													X													1
Bilateral, carcinoma																	X									1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma								X																		1
Endometrium, polyp stromal		X		X	X			X										X					X			11
Endometrium, polyp stromal, multiple			X																							1
Endometrium, sarcoma stromal																										1
Endometrium, schwannoma malignant																										2
Vagina		+																								3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+						+																	9
Renal, sarcoma, metastatic, mesentery																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																						X				1
Sarcoma, metastatic, mesentery																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma												X												X		3
Fibroadenoma			X			X	X					X				X		X	X		X	X			X	19
Fibroadenoma, multiple	X			X									X		X											7
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma			X																							1
Skeletal muscle																										1
Rhabdomyosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										2
Spinal cord																										2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	241	379	379	434	461	492	496	499	518	538	553	588	604	643	647	647	650	653	664	668	685	694	695	695	702
Carcass ID Number	369	365	396	404	397	394	379	387	403	407	389	370	362	385	388	401	405	380	410	368	390	382	367	386	364
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye									+															+	
Harderian gland																									
Zymbal's gland															+										
Carcinoma															X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pelvis, transitional epithelium, mesenchymal tumor																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear						X														X	X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	702	708	709	714	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	393	363	400	375	361	366	371	372	373	374	376	377	378	381	383	384	391	392	395	398	399	402	406	408	409	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										2
Harderian gland																				+						1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pelvis, transitional epithelium, mesenchymal tumor																						X				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma								X																		1
Leukemia mononuclear																										3

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

	4	4	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7
Number of Days on Study	4	8	9	1	2	3	4	5	6	7	0	1	1	2	7	8	8	9	9	0	0	0	0	0	0
	1	3	3	8	8	2	1	6	5	4	2	1	8	2	4	7	9	5	5	0	2	2	7	8	8
	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
Carcass ID Number	3	4	5	2	5	6	2	3	4	2	5	4	5	5	2	6	6	5	6	4	2	6	6	2	3
	9	6	6	9	1	6	8	0	8	4	0	1	8	3	5	7	9	4	2	7	6	3	8	1	3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland										X															
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+		+																			+	
Pancreas	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X	X	X	X				X		X		X	X		X	X	X		X	X	
Pars nervosa, ganglioneuroma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma		X																							
Follicular cell, carcinoma										X															
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X			X											X				X			X		
Carcinoma					X														X						
Bilateral, adenoma																									
Bilateral, carcinoma													X												
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal									X				X	X		X					X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	709	709	714	714	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	443	455	459	460	422	423	427	431	432	434	435	436	437	438	440	442	444	445	449	452	457	461	464	465	470	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery														+			+				+					6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																	+									1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X				X		X	X				X					X			X	X				23
Pars nervosa, ganglioneuroma																X										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																						X				2
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X	X			X						X	X			X		11
Carcinoma				X																						3
Bilateral, adenoma									X																	1
Bilateral, carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrium, polyp stromal																										5

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	441	483	493	518	528	532	541	556	565	574	602	611	618	622	674	687	689	695	695	700	702	702	707	708	708
Carcass ID Number	439	446	456	429	451	466	428	430	448	424	450	441	458	453	425	467	469	454	462	447	426	463	468	421	433
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+		+			+		+			+	+					+						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X																	
Fibroadenoma		X		X			X				X				X	X	X	X	X		X			X	X
Fibroadenoma, multiple																				X		X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma	X																								
Squamous cell papilloma																									
Subcutaneous tissue, fibroma												X					X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+																	
Sarcoma								X																	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, thyroid gland										X															
Squamous cell carcinoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland										X															
Special Senses System																									
Eye										+															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	709	709	714	714	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	443	455	459	460	422	423	427	431	432	434	435	436	437	438	440	442	444	445	449	452	457	461	464	465	470	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node												+														8
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma										X																2
Fibroadenoma	X					X		X							X	X				X					X	19
Fibroadenoma, multiple		X	X																				X			5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Squamous cell papilloma																							X			1
Subcutaneous tissue, fibroma											X															3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																		X								1
Carcinoma, metastatic, thyroid gland																										1
Squamous cell carcinoma																			X							1
Nose	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Special Senses System																										
Eye																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant			X																							1

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	2/49 (4%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate[b]	5.4%	4.3%	11.7%	0.0%
Terminal rate[c]	0/26 (0%)	1/23 (4%)	2/21 (10%)	0/21 (0%)
First incidence (days)	647	730 (T)	518	_[e]
Life table test[d]	P=0.298N	P=0.557N	P=0.402	P=0.289N
Logistic regression test[d]	P=0.242N	P=0.510N	P=0.526	P=0.220N
Cochran-Armitage test[d]	P=0.237N			
Fisher exact test[d]		P=0.492N	P=0.510	P=0.242N
Clitoral Gland: Adenoma				
Overall rate	4/50 (8%)	12/49 (24%)	10/49 (20%)	12/50 (24%)
Adjusted rate	11.9%	42.5%	33.7%	42.1%
Terminal rate	2/27 (7%)	7/22 (32%)	4/20 (20%)	7/21 (33%)
First incidence (days)	653	665	496	483
Life table test	P=0.034	P=0.013	P=0.030	P=0.013
Logistic regression test	P=0.046	P=0.013	P=0.050	P=0.023
Cochran-Armitage test	P=0.066			
Fisher exact test		P=0.024	P=0.068	P=0.027
Clitoral Gland: Carcinoma				
Overall rate	1/50 (2%)	2/49 (4%)	5/49 (10%)	4/50 (8%)
Adjusted rate	3.7%	6.0%	19.3%	11.7%
Terminal rate	1/27 (4%)	0/22 (0%)	3/20 (15%)	0/21 (0%)
First incidence (days)	730 (T)	694	499	528
Life table test	P=0.085	P=0.460	P=0.056	P=0.139
Logistic regression test	P=0.117	P=0.459	P=0.084	P=0.224
Cochran-Armitage test	P=0.116			
Fisher exact test		P=0.492	P=0.098	P=0.181
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	14/49 (29%)	15/49 (31%)	15/50 (30%)
Adjusted rate	11.9%	45.9%	48.9%	47.7%
Terminal rate	2/27 (7%)	7/22 (32%)	7/20 (35%)	7/21 (33%)
First incidence (days)	653	665	496	483
Life table test	P=0.008	P=0.005	P=0.001	P=0.002
Logistic regression test	P=0.011	P=0.004	P=0.003	P=0.004
Cochran-Armitage test	P=0.018			
Fisher exact test		P=0.008	P=0.004	P=0.005
Mammary Gland: Fibroadenoma				
Overall rate	22/50 (44%)	22/50 (44%)	26/50 (52%)	24/50 (48%)
Adjusted rate	59.6%	57.1%	70.4%	61.4%
Terminal rate	13/27 (48%)	8/23 (35%)	11/21 (52%)	7/21 (33%)
First incidence (days)	566	483	379	483
Life table test	P=0.161	P=0.363	P=0.073	P=0.198
Logistic regression test	P=0.280	P=0.502	P=0.187	P=0.327
Cochran-Armitage test	P=0.333			
Fisher exact test		P=0.580N	P=0.274	P=0.421

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Mammary Gland: Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	7.0%	6.6%	11.3%	7.0%
Terminal rate	1/27 (4%)	1/23 (4%)	2/21 (10%)	1/21 (5%)
First incidence (days)	722	570	241	556
Life table test	P=0.481	P=0.636	P=0.404	P=0.605
Logistic regression test	P=0.583N	P=0.691	P=0.623	P=0.699N
Cochran-Armitage test	P=0.569			
Fisher exact test		P=0.691N	P=0.500	P=0.691N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	9.3%	6.6%	11.3%	7.0%
Terminal rate	1/27 (4%)	1/23 (4%)	2/21 (10%)	1/21 (5%)
First incidence (days)	667	570	241	556
Life table test	P=0.546N	P=0.562N	P=0.554	P=0.596N
Logistic regression test	P=0.422N	P=0.500N	P=0.564N	P=0.490N
Cochran-Armitage test	P=0.456N			
Fisher exact test		P=0.500N	P=0.661N	P=0.500N
Mammary Gland: Adenoma or Fibroadenoma				
Overall rate	23/50 (46%)	22/50 (44%)	26/50 (52%)	24/50 (48%)
Adjusted rate	60.6%	57.1%	70.4%	61.4%
Terminal rate	13/27 (48%)	8/23 (35%)	11/21 (52%)	7/21 (33%)
First incidence (days)	566	483	379	483
Life table test	P=0.196	P=0.427	P=0.098	P=0.247
Logistic regression test	P=0.340	P=0.576N	P=0.249	P=0.408
Cochran-Armitage test	P=0.396			
Fisher exact test		P=0.500N	P=0.345	P=0.500
Mammary Gland: Adenoma, Fibroadenoma, or Carcinoma				
Overall rate	25/50 (50%)	24/50 (48%)	28/50 (56%)	26/50 (52%)
Adjusted rate	64.7%	60.9%	73.9%	65.0%
Terminal rate	14/27 (52%)	9/23 (39%)	12/21 (57%)	8/21 (38%)
First incidence (days)	566	483	241	483
Life table test	P=0.186	P=0.409	P=0.093	P=0.229
Logistic regression test	P=0.362	P=0.579N	P=0.304	P=0.408
Cochran-Armitage test	P=0.396			
Fisher exact test		P=0.500N	P=0.344	P=0.500
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	18/50 (36%)	27/50 (54%)	25/50 (50%)	23/49 (47%)
Adjusted rate	46.6%	74.8%	76.4%	59.8%
Terminal rate	8/27 (30%)	15/23 (65%)	14/21 (67%)	7/20 (35%)
First incidence (days)	657	510	538	518
Life table test	P=0.112	P=0.030	P=0.023	P=0.096
Logistic regression test	P=0.200	P=0.034	P=0.025	P=0.184
Cochran-Armitage test	P=0.272			
Fisher exact test		P=0.054	P=0.113	P=0.184

Table B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	19/50 (38%)	27/50 (54%)	25/50 (50%)	23/49 (47%)
Adjusted rate	48.4%	74.8%	76.4%	59.8%
Terminal rate	8/27 (30%)	15/23 (65%)	14/21 (67%)	7/20 (35%)
First incidence (days)	657	510	538	518
Life table test	P=0.139	P=0.045	P=0.035	P=0.125
Logistic regression test	P=0.248	P=0.051	P=0.038	P=0.237
Cochran-Armitage test	P=0.330			
Fisher exact test		P=0.080	P=0.157	P=0.243
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/50 (4%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	6.6%	3.1%	0.0%	9.9%
Terminal rate	1/27 (4%)	0/23 (0%)	0/21 (0%)	1/21 (5%)
First incidence (days)	702	696	–	611
Life table test	P=0.294	P=0.552N	P=0.295N	P=0.427
Logistic regression test	P=0.315	P=0.535N	P=0.290N	P=0.480
Cochran-Armitage test	P=0.337			
Fisher exact test		P=0.500N	P=0.247N	P=0.500
Thyroid Gland (C-cell): Adenoma				
Overall rate	9/50 (18%)	5/49 (10%)	4/50 (8%)	2/50 (4%)
Adjusted rate	29.3%	17.4%	13.6%	6.7%
Terminal rate	7/27 (26%)	3/23 (13%)	1/21 (5%)	1/21 (5%)
First incidence (days)	556	632	588	483
Life table test	P=0.045N	P=0.284N	P=0.241N	P=0.059N
Logistic regression test	P=0.023N	P=0.249N	P=0.165N	P=0.027N
Cochran-Armitage test	P=0.019N			
Fisher exact test		P=0.205N	P=0.117N	P=0.026N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	10/50 (20%)	5/49 (10%)	6/50 (12%)	2/50 (4%)
Adjusted rate	31.4%	17.4%	22.2%	6.7%
Terminal rate	7/27 (26%)	3/23 (13%)	3/21 (14%)	1/21 (5%)
First incidence (days)	556	632	588	483
Life table test	P=0.041N	P=0.213N	P=0.391N	P=0.038N
Logistic regression test	P=0.021N	P=0.176N	P=0.308N	P=0.016N
Cochran-Armitage test	P=0.016N			
Fisher exact test		P=0.140N	P=0.207N	P=0.014N
Uterus: Stromal Polyp				
Overall rate	5/50 (10%)	11/50 (22%)	12/50 (24%)	5/50 (10%)
Adjusted rate	15.9%	38.9%	37.9%	13.2%
Terminal rate	3/27 (11%)	7/23 (30%)	4/21 (19%)	0/21 (0%)
First incidence (days)	490	521	434	565
Life table test	P=0.523	P=0.050	P=0.023	P=0.513
Logistic regression test	P=0.406N	P=0.075	P=0.063	P=0.534N
Cochran-Armitage test	P=0.411N			
Fisher exact test		P=0.086	P=0.054	P=0.630N

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	5/50 (10%)	12/50 (24%)	13/50 (26%)	5/50 (10%)
Adjusted rate	15.9%	40.7%	39.4%	13.2%
Terminal rate	3/27 (11%)	7/23 (30%)	4/21 (19%)	0/21 (0%)
First incidence (days)	490	521	434	565
Life table test	P=0.540	P=0.032	P=0.014	P=0.513
Logistic regression test	P=0.379N	P=0.047	P=0.044	P=0.534N
Cochran-Armitage test	P=0.389N			
Fisher exact test		P=0.054	P=0.033	P=0.630N
All Organs: Mononuclear Cell Leukemia				
Overall rate	17/50 (34%)	11/50 (22%)	3/50 (6%)	0/50 (0%)
Adjusted rate	38.6%	32.5%	8.5%	0.0%
Terminal rate	3/27 (11%)	4/23 (17%)	0/21 (0%)	0/21 (0%)
First incidence (days)	490	566	492	–
Life table test	P<0.001N	P=0.272N	P=0.008N	P<0.001N
Logistic regression test	P<0.001N	P=0.159N	P<0.001N	P<0.001N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.133N	P<0.001N	P<0.001N
All Organs: Benign Neoplasms				
Overall rate	40/50 (80%)	41/50 (82%)	44/50 (88%)	41/50 (82%)
Adjusted rate	84.9%	93.0%	95.6%	88.8%
Terminal rate	20/27 (74%)	20/23 (87%)	19/21 (90%)	16/21 (76%)
First incidence (days)	490	483	379	483
Life table test	P=0.128	P=0.206	P=0.035	P=0.150
Logistic regression test	P=0.311	P=0.339	P=0.072	P=0.473
Cochran-Armitage test	P=0.424			
Fisher exact test		P=0.500	P=0.207	P=0.500
All Organs: Malignant Neoplasms				
Overall rate	22/50 (44%)	19/50 (38%)	22/50 (44%)	11/50 (22%)
Adjusted rate	49.0%	48.3%	62.3%	31.4%
Terminal rate	6/27 (22%)	6/23 (26%)	10/21 (48%)	2/21 (10%)
First incidence (days)	490	150	241	441
Life table test	P=0.113N	P=0.541N	P=0.259	P=0.104N
Logistic regression test	P=0.007N	P=0.188N	P=0.383N	P=0.004N
Cochran-Armitage test	P=0.017N			
Fisher exact test		P=0.342N	P=0.580N	P=0.016N
All Organs: Benign or Malignant Neoplasms				
Overall rate	44/50 (88%)	48/50 (96%)	50/50 (100%)	45/50 (90%)
Adjusted rate	88.0%	98.0%	100.0%	91.8%
Terminal rate	21/27 (78%)	22/23 (96%)	21/21 (100%)	17/21 (81%)
First incidence (days)	490	150	241	441
Life table test	P=0.143	P=0.103	P=0.017	P=0.138
Logistic regression test	P=0.559	P=0.156	P=0.032	P=0.564
Cochran-Armitage test	P=0.519			
Fisher exact test		P=0.134	P=0.013	P=0.500

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

(T)Terminal sacrifice

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.

[b] 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 exposure group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test 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 an exposure group is indicated by N.

[e] Not applicable; no neoplasms in animal group

TABLE B4a
Historical Incidence of Clitoral Gland Neoplasms in Untreated Female F344/N Rats[a]

Study	Incidence in Controls: Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	0/50	1/50	1/50
C.I. Pigment Red 23	5/47	3/47	7/47
C.I. Pigment Red 3	9/47	0/47	9/47
Nitrofurantoin	1/44	4/44	5/44
o-Nitroanisole	3/45	4/45	7/45
Polysorbate 80	3/48	7/48	10/48
Rhodamine 6G	5/42	1/42	6/42
Roxarsone	1/44	1/44	2/44
Total	27/367 (7.4%)	21/367 (5.7%)	47/367 (12.8%)
Standard deviation	6.4%	5.1%	6.6%
Range	0%-19%	0%-15%	2%-21%
Overall Historical Incidence			
Total[b]	90/1,096 (8.2%)	31/1,096 (2.8%)	120/1,096 (10.9%)
Standard deviation	4.6%	4.0%	5.3%
Range	0%-19%	0%-15%	2%-21%

[a] Data as of 20 August 1992
[b] Data from Quercetin, TR 409, censored due to low denominator (adenoma, 4/14; carcinoma, 1/14; adenoma or carcinoma, 5/14)

TABLE B4b
Historical Incidence of Mononuclear Cell Leukemia in Untreated Female F344/N Rats[a]

Study	Incidence in Controls Mononuclear Cell Leukemia[b]
Historical Incidence at Southern Research Institute	
Benzyl Acetate	9/50
C.I. Pigment Red 23	14/50
C.I. Pigment Red 3	10/50
Nitrofurantoin	13/50
o-Nitroanisole	14/50
Polysorbate 80	26/50
Rhodamine 6G	11/50
Roxarsone	14/50
Total	111/400 (27.8%)
Standard deviation	10.6%
Range	18%-52%
Overall Historical Incidence	
Total	324/1,251 (25.9%)
Standard deviation	8.6%
Range	14%-52%

[a] Data as of 20 August 1992
[b] Includes incidences of lymphocytic, monocytic, or undifferentiated leukemia.

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	21	23	27	26
Natural deaths	2	4	2	3
Survivors				
Terminal sacrifice	27	23	21	21
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(10)	(10)
Parasite metazoan	1 (10%)		1 (10%)	
Intestine large, rectum	(10)	(10)	(10)	(9)
Parasite metazoan		1 (10%)		1 (11%)
Liver	(10)	(10)	(10)	(10)
Basophilic focus	8 (80%)	5 (50%)	6 (60%)	8 (80%)
Clear cell focus		1 (10%)		
Fatty change		1 (10%)		
Hepatodiaphragmatic nodule	3 (30%)	1 (10%)	1 (10%)	4 (40%)
Inflammation, focal	7 (70%)	9 (90%)	4 (40%)	4 (40%)
Mixed cell focus	1 (10%)		1 (10%)	
Bile duct, hyperplasia	4 (40%)	6 (60%)	6 (60%)	6 (60%)
Mesentery	(1)	(1)	(1)	
Fat, necrosis	1 (100%)	1 (100%)	1 (100%)	
Pancreas	(10)	(10)	(10)	(10)
Accessory spleen	1 (10%)	1 (10%)		
Atrophy, focal	5 (50%)	4 (40%)	2 (20%)	2 (20%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Accessory adrenal cortical nodule	1 (10%)			
Focal cellular change			2 (20%)	
Pituitary gland	(10)	(10)	(9)	(10)
Angiectasis	7 (70%)	2 (20%)	5 (56%)	3 (30%)
Cyst	1 (10%)	2 (20%)		2 (20%)
Pars distalis, focal cellular change				1 (10%)
Pars distalis, hyperplasia, focal	5 (50%)	2 (20%)	5 (56%)	1 (10%)
Thyroid gland	(10)	(10)	(10)	(10)
Ultimobranchial cyst		2 (20%)	1 (10%)	
C-cell, hyperplasia				3 (30%)

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

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Clitoral gland	(10)	(10)	(10)	(10)
Degeneration, cystic	8 (80%)	5 (50%)	8 (80%)	4 (40%)
Ovary	(10)	(10)	(10)	(10)
Cyst		4 (40%)	4 (40%)	1 (10%)
Uterus	(10)	(10)	(10)	(10)
Hydrometra		2 (20%)	2 (20%)	1 (10%)
Endometrium, hyperplasia, cystic		1 (10%)		2 (20%)
Endometrium, infarct	1 (10%)			
Vagina		(1)		
Cyst		1 (100%)		
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Hyperplasia, focal, histiocytic	1 (10%)	2 (20%)		
Lymph node	(1)	(4)	(2)	(2)
Mediastinal, congestion	1 (100%)	2 (50%)	2 (100%)	
Mediastinal, pigmentation				1 (50%)
Pancreatic, congestion		1 (25%)		
Pancreatic, pigmentation				1 (50%)
Lymph node, mandibular	(10)	(10)	(10)	(10)
Congestion		1 (10%)		
Hyperplasia, lymphoid		2 (20%)		
Spleen	(10)	(10)	(10)	(10)
Cyst				1 (10%)
Pigmentation	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Integumentary System				
Mammary gland	(10)	(10)	(10)	(10)
Dilatation	1 (10%)	2 (20%)	3 (30%)	2 (20%)
Hyperplasia		1 (10%)	3 (30%)	1 (10%)
Musculoskeletal System				
Bone	(10)	(10)	(10)	(10)
Hyperostosis	1 (10%)	2 (20%)		
Nervous System				
Brain	(10)	(10)	(10)	(10)
Compression			1 (10%)	
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar epithelium, hyperplasia				1 (10%)

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
15-Month Interim Evaluation (continued)				
Special Senses System				
Eye	(2)			
Cataract	1 (50%)			
Fibrosis	1 (50%)			
Retina, degeneration	1 (50%)			
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Nephropathy	10 (100%)	10 (100%)	9 (90%)	9 (90%)
Renal tubule, pigmentation	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Systems Examined With No Lesions Observed				
Cardiovascular System				
General Body System				
2-Year Study				
Alimentary System				
Intestine large, rectum	(50)	(48)	(50)	(49)
Parasite metazoan		6 (13%)	2 (4%)	3 (6%)
Intestine large, cecum	(50)	(47)	(50)	(49)
Parasite metazoan		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	2 (4%)		2 (4%)
Basophilic focus	32 (64%)	38 (76%)	44 (88%)	47 (94%)
Clear cell focus	4 (8%)	6 (12%)	7 (14%)	12 (24%)
Eosinophilic focus	4 (8%)	4 (8%)		1 (2%)
Fatty change	14 (28%)	13 (26%)	7 (14%)	7 (14%)
Fibrosis, focal	1 (2%)		2 (4%)	
Focal cellular change	1 (2%)	1 (2%)	2 (4%)	
Hematopoietic cell proliferation		2 (4%)	2 (4%)	1 (2%)
Hepatodiaphragmatic nodule	5 (10%)	5 (10%)	11 (22%)	12 (24%)
Hepatodiaphragmatic nodule, multiple		2 (4%)	2 (4%)	3 (6%)
Hyperplasia, histiocytic				1 (2%)
Hyperplasia, lymphoid				1 (2%)
Hyperplasia, multifocal	9 (18%)	10 (20%)	3 (6%)	2 (4%)
Infiltration cellular, mixed cell	1 (2%)	4 (8%)	3 (6%)	1 (2%)
Inflammation, focal	26 (52%)	24 (48%)	37 (74%)	41 (82%)
Mixed cell focus	4 (8%)	8 (16%)	3 (6%)	7 (14%)
Necrosis, focal	2 (4%)	1 (2%)		1 (2%)
Pigmentation	1 (2%)			
Thrombosis	1 (2%)			
Bile duct, dilatation		1 (2%)		
Bile duct, hyperplasia	23 (46%)	19 (38%)	18 (36%)	27 (54%)
Centrilobular, atrophy	14 (28%)	11 (22%)	4 (8%)	2 (4%)
Centrilobular, congestion			1 (2%)	
Centrilobular, hemorrhage	1 (2%)			
Centrilobular, necrosis	1 (2%)		1 (2%)	

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(10)	(8)	(9)	(6)
Accessory spleen		1 (13%)		1 (17%)
Cyst			1 (11%)	
Inflammation, chronic		1 (13%)	1 (11%)	1 (17%)
Fat, necrosis	6 (60%)	3 (38%)	6 (67%)	4 (67%)
Pancreas	(50)	(50)	(49)	(49)
Atrophy, diffuse	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Atrophy, focal	16 (32%)	14 (28%)	19 (39%)	11 (22%)
Cyst				1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)	
Acinar cell, depletion secretory			1 (2%)	
Duct, dilatation		1 (2%)		
Stomach, forestomach	(50)	(50)	(49)	(49)
Edema		1 (2%)		
Hemorrhage, focal	1 (2%)			
Inflammation, chronic	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Ulcer	1 (2%)		2 (4%)	
Mucosa, hyperplasia	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Stomach, glandular	(50)	(50)	(49)	(49)
Bacterium	1 (2%)			
Erosion	2 (4%)	1 (2%)		
Inflammation, chronic	1 (2%)			
Ulcer	1 (2%)			
Tongue			(1)	(1)
Hypertrophy, squamous				1 (100%)
Tooth	(1)			
Gingiva, hyperplasia	1 (100%)			
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Mesenteric artery, inflammation, chronic	1 (2%)			2 (4%)
Mesenteric artery, thrombosis	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Bacterium	1 (2%)			
Embolus	1 (2%)			
Inflammation, chronic, focal	2 (4%)			1 (2%)
Artery, inflammation, chronic			2 (4%)	
Endocrine System				
Adrenal cortex	(49)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)		1 (2%)	3 (6%)
Angiectasis	1 (2%)	2 (4%)		
Congestion	4 (8%)	1 (2%)		2 (4%)
Degeneration, cystic			2 (4%)	
Depletion cellular	1 (2%)			
Focal cellular change	13 (27%)	9 (18%)	8 (16%)	13 (26%)
Hyperplasia, focal	1 (2%)			
Infiltration cellular, lymphocyte	1 (2%)			
Vacuolization cytoplasmic		1 (2%)		
Capsule, extra adrenal tissue, fibrosis				1 (2%)

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal medulla	(49)	(50)	(50)	(50)
Hyperplasia	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Pituitary gland	(50)	(50)	(50)	(49)
Angiectasis	12 (24%)	11 (22%)	7 (14%)	8 (16%)
Cyst	3 (6%)	4 (8%)	2 (4%)	2 (4%)
Granuloma	1 (2%)			
Hemorrhage	1 (2%)			
Pars distalis, cyst		1 (2%)		1 (2%)
Pars distalis, focal cellular change	6 (12%)	4 (8%)	2 (4%)	2 (4%)
Pars distalis, hyperplasia, focal	11 (22%)	9 (18%)	9 (18%)	8 (16%)
Rathke's cleft, hyperplasia, cystic		1 (2%)		
Thyroid gland	(50)	(49)	(50)	(50)
Degeneration, cystic	1 (2%)			
Inflammation, focal		1 (2%)		
Ultimobranchial cyst			2 (4%)	
C-cell, hyperplasia	10 (20%)	8 (16%)	11 (22%)	11 (22%)
Follicle, dilatation		1 (2%)		
Follicular cell, hyperplasia		2 (4%)		
General Body System				
None				
Genital System				
Clitoral gland	(50)	(49)	(49)	(50)
Atrophy		1 (2%)		
Cyst	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Degeneration, cystic	34 (68%)	38 (78%)	39 (80%)	35 (70%)
Hyperplasia	10 (20%)	6 (12%)	6 (12%)	7 (14%)
Inflammation, chronic		1 (2%)	1 (2%)	
Duct, hyperplasia, squamous		1 (2%)		
Ovary	(50)	(50)	(50)	(49)
Angiectasis			1 (2%)	1 (2%)
Atrophy			1 (2%)	
Cyst	5 (10%)	6 (12%)	6 (12%)	8 (16%)
Hemorrhage	1 (2%)			
Bilateral, cyst			1 (2%)	
Corpus luteum, hyperplasia, lymphoid	2 (4%)	1 (2%)		
Corpus luteum, thecal cell, hyperplasia	2 (4%)	1 (2%)		
Uterus	(50)	(50)	(50)	(49)
Hydrometra	1 (2%)	4 (8%)	3 (6%)	2 (4%)
Endometrium, cyst		1 (2%)	1 (2%)	1 (2%)
Endometrium, hyperplasia, cystic	3 (6%)	9 (18%)	4 (8%)	4 (8%)
Endometrium, infarct	1 (2%)			
Vagina	(3)	(1)	(3)	
Cyst	2 (67%)	1 (100%)	1 (33%)	
Cyst, multiple			1 (33%)	
Inflammation, chronic			1 (33%)	
Mucosa, hyperplasia	1 (33%)			

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hypercellularity	2 (4%)	4 (8%)	2 (4%)	3 (6%)
Hyperplasia, focal, histiocytic	2 (4%)	2 (4%)	4 (8%)	4 (8%)
Metaplasia, osseous	1 (2%)			
Myelofibrosis	1 (2%)			
Lymph node	(13)	(10)	(9)	(8)
Deep cervical, angiectasis			1 (11%)	
Inguinal, depletion lymphoid		1 (10%)		
Inguinal, hyperplasia				2 (25%)
Mediastinal, angiectasis			1 (11%)	
Mediastinal, congestion		1 (10%)	5 (56%)	1 (13%)
Mediastinal, depletion lymphoid		1 (10%)		
Mediastinal, hyperplasia				3 (38%)
Mediastinal, hyperplasia, lymphoid		1 (10%)		
Mediastinal, hyperplasia, macrophage			1 (11%)	
Mediastinal, pigmentation			2 (22%)	1 (13%)
Pancreatic, congestion		1 (10%)		
Pancreatic, depletion lymphoid		1 (10%)		
Pancreatic, edema				1 (13%)
Pancreatic, hyperplasia, lymphoid				1 (13%)
Pancreatic, inflammation, chronic				1 (13%)
Renal, hyperplasia, macrophage				1 (13%)
Renal, pigmentation				1 (13%)
Lymph node, mandibular	(50)	(50)	(50)	(50)
Congestion	1 (2%)		2 (4%)	4 (8%)
Depletion lymphoid		1 (2%)		
Hyperplasia		2 (4%)	2 (4%)	1 (2%)
Pigmentation				2 (4%)
Lymph node, mesenteric	(49)	(50)	(50)	(49)
Congestion		1 (2%)		
Depletion lymphoid		1 (2%)		
Hyperplasia	1 (2%)			
Hyperplasia, lymphoid		1 (2%)	1 (2%)	
Spleen	(50)	(50)	(50)	(49)
Fibrosis	1 (2%)	6 (12%)		1 (2%)
Hematopoietic cell proliferation	2 (4%)	14 (28%)	9 (18%)	8 (16%)
Necrosis, focal	2 (4%)		1 (2%)	
Pigmentation	50 (100%)	50 (100%)	50 (100%)	49 (100%)
Thymus	(49)	(48)	(50)	(50)
Congestion				1 (2%)
Cyst	1 (2%)		1 (2%)	
Fibrosis	1 (2%)			
Hyperplasia, lymphoid		1 (2%)		

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Dilatation	43 (86%)	38 (76%)	39 (78%)	35 (70%)
Hyperplasia	9 (18%)	14 (28%)	10 (20%)	15 (30%)
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion			1 (2%)	
Hemorrhage, focal			1 (2%)	
Inflammation, chronic, focal		1 (2%)		
Ulcer		1 (2%)		
Subcutaneous tissue, inflammation, chronic, focal			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fracture healed			1 (2%)	
Hyperostosis	17 (34%)	9 (18%)	9 (18%)	9 (18%)
Inflammation, chronic, focal	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	8 (16%)	16 (32%)	10 (20%)	14 (28%)
Demyelination, focal			1 (2%)	
Hemorrhage	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Spinal cord	(1)	(2)	(2)	
Hemorrhage, focal			1 (50%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Bacterium	1 (2%)			
Congestion		1 (2%)	2 (4%)	
Fibrosis, focal	1 (2%)			1 (2%)
Hemorrhage, focal			2 (4%)	
Hyperplasia, focal, macrophage			1 (2%)	2 (4%)
Infiltration cellular, mixed cell	1 (2%)	1 (2%)	1 (2%)	
Metaplasia, focal, osseous	1 (2%)			
Thrombosis	1 (2%)			
Alveolar epithelium, hyperplasia	3 (6%)	3 (6%)	4 (8%)	3 (6%)
Mediastinum, infiltration cellular, lymphocyte		1 (2%)		
Nose	(50)	(50)	(50)	(49)
Fungus				1 (2%)
Inflammation, suppurative	2 (4%)	4 (8%)	5 (10%)	2 (4%)
Nasolacrimal duct, cyst		1 (2%)		

Table B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Special Senses System				
Eye	(2)	(2)	(2)	(1)
Atrophy			1 (50%)	
Cataract	2 (100%)	1 (50%)	2 (100%)	1 (100%)
Hemorrhage	1 (50%)	1 (50%)	1 (50%)	
Inflammation, chronic	1 (50%)	1 (50%)	1 (50%)	
Necrosis, focal		1 (50%)		
Retina, degeneration	2 (100%)	1 (50%)	2 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Atrophy, focal			1 (2%)	
Bacterium	1 (2%)			
Congestion		1 (2%)		
Cyst			1 (2%)	1 (2%)
Fibrosis, focal			1 (2%)	
Nephropathy	50 (100%)	49 (98%)	49 (98%)	49 (98%)
Cortex, renal tubule, autolysis	1 (2%)			
Glomerulus, autolysis	1 (2%)			
Interstitium, infarct				1 (2%)
Papilla, epithelium, hyperplasia, focal				1 (2%)
Renal tubule, hyperplasia			1 (2%)	
Renal tubule, hyperplasia, oncocytic		1 (2%)		5 (10%)
Renal tubule, pigmentation	50 (100%)	50 (100%)	50 (100%)	50 (100%)
Urinary bladder	(50)	(50)	(50)	(50)
Transitional epithelium, hyperplasia			1 (2%)	

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

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths		1		2
Moribund	9	4	10	2
Natural deaths	2	9	1	2
Survivors				
Terminal sacrifice	39	36	39	44
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma		2 (20%)		
Hepatocellular adenoma	1 (10%)	1 (10%)	1 (10%)	
Hepatocellular adenoma, multiple	1 (10%)	1 (10%)	1 (10%)	
Endocrine System				
Thyroid gland	(10)	(10)	(10)	(10)
Follicular cell, adenoma	1 (10%)			
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Subcutaneous tissue, lipoma			1 (10%)	
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar adenoma		1 (10%)	2 (20%)	1 (10%)
Special Senses System				
Ear			(1)	
Schwannoma benign			1 (100%)	

Systems Examined With No Neoplasms Observed
Cardiovascular System
General Body System
Genital System
Hematopoietic System
Musculoskeletal System
Nervous System
Urinary System

Table C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study				
Alimentary System				
Gallbladder	(48)	(45)	(50)	(48)
Intestine small, jejunum	(50)	(43)	(49)	(46)
Adenocarcinoma	3 (6%)	1 (2%)		
Intestine small, ileum	(50)	(42)	(49)	(46)
Liver	(50)	(50)	(50)	(48)
Hemangiosarcoma		1 (2%)		
Hepatocellular carcinoma	6 (12%)	9 (18%)	12 (24%)	4 (8%)
Hepatocellular carcinoma, multiple	2 (4%)	4 (8%)	4 (8%)	4 (8%)
Hepatocellular adenoma	14 (28%)	10 (20%)	5 (10%)	11 (23%)
Hepatocellular adenoma, multiple	3 (6%)	7 (14%)	7 (14%)	3 (6%)
Hepatocholangiocarcinoma			1 (2%)	
Mesentery	(2)	(1)	(2)	(2)
Sarcoma	1 (50%)			
Pancreas	(50)	(48)	(50)	(47)
Sarcoma, metastatic, mesentery	1 (2%)			
Stomach, forestomach	(50)	(47)	(50)	(47)
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(50)	(47)	(50)	(47)
Carcinoid tumor NOS		1 (2%)		
Sarcoma, metastatic, mesentery	1 (2%)			
Cardiovascular System				
None				
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(49)
Sarcoma, metastatic, mesentery	1 (2%)			
Adrenal medulla	(50)	(49)	(50)	(49)
Pheochromocytoma benign			1 (2%)	
Islets, pancreatic	(50)	(49)	(50)	(48)
Adenoma		1 (2%)		
Pituitary gland	(46)	(46)	(50)	(46)
Pars distalis, adenoma				1 (2%)
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(50)	(49)	(50)	(49)
C-cell, carcinoma	1 (2%)			
Follicular cell, adenoma	1 (2%)	1 (2%)		
General Body System				
None				
Genital System				
Epididymis	(50)	(49)	(50)	(50)
Prostate	(50)	(49)	(50)	(50)
Seminal vesicle	(50)	(49)	(50)	(50)
Testes	(50)	(49)	(50)	(50)
Interstitial cell, adenoma	1 (2%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Hemangioma		1 (2%)		
Lymph node	(4)	(1)	(4)	(4)
Lymph node, mandibular	(49)	(47)	(50)	(50)
Mast cell tumor NOS			1 (2%)	
Lymph node, mesenteric	(50)	(49)	(50)	(47)
Spleen	(50)	(49)	(50)	(49)
Hemangiosarcoma	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Integumentary System				
Skin	(50)	(49)	(50)	(50)
Hemangioma		1 (2%)		
Hemangiosarcoma	1 (2%)			
Subcutaneous tissue, mast cell tumor NOS			1 (2%)	
Musculoskeletal System				
Skeletal muscle	(1)		(1)	
Hemangiosarcoma	1 (100%)		1 (100%)	
Nervous System				
None				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	10 (20%)	6 (12%)	6 (12%)
Alveolar/bronchiolar adenoma, multiple	3 (6%)	2 (4%)	2 (4%)	3 (6%)
Alveolar/bronchiolar carcinoma	1 (2%)	3 (6%)	2 (4%)	5 (10%)
Hepatocellular carcinoma, metastatic, liver	4 (8%)	2 (4%)	6 (12%)	4 (8%)
Nose	(50)	(49)	(49)	(50)
Nasolacrimal duct, mast cell tumor NOS			1 (2%)	
Special Senses System				
Harderian gland	(1)	(3)	(3)	(1)
Adenoma	1 (100%)	3 (100%)	2 (67%)	1 (100%)
Adenoma, multiple			1 (33%)	
Urinary System				
Kidney	(50)	(49)	(50)	(48)
Transitional epithelium, carcinoma		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Lymphoma malignant mixed			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	2	5	6	1
2-Year study	33	36	35	30
Total primary neoplasms				
15-Month interim evaluation	3	5	6	1
2-Year study	48	59	52	41
Total animals with benign neoplasms				
15-Month interim evaluation	2	3	6	1
2-Year study	20	29	20	22
Total benign neoplasms				
15-Month interim evaluation	3	3	6	1
2-Year study	26	37	25	25
Total animals with malignant neoplasms				
15-Month interim evaluation		2		
2-Year study	18	19	21	14
Total malignant neoplasms				
15-Month interim evaluation		2		
2-Year study	22	21	24	16
Total animals with metastatic neoplasms				
2-Year study	5	2	6	4
Total metastatic neoplasms				
2-Year study	7	2	6	4
Total animals with uncertain neoplasms benign or malignant				
2-Year study		1	1	
Total uncertain neoplasms				
2-Year study		1	3	

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

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

	4	5	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	1	3	3	9	6	6	7	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	9	2	7	7	0	6	5	0	0	8	8	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	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	2	1	3	5	0	1	4	0	0	2	4	0	0	0	0	0	0	1	1	1	1	1	1	1	1
	6	8	3	0	7	9	8	6	9	7	4	1	2	3	4	5	8	0	1	2	3	4	5	6	7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma										X															
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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																
Mesentery				+		+																			
Sarcoma				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery				X																					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery				X																					
Tooth																					+				
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery				X																					
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, carcinoma	X																								
Follicular cell, adenoma																								X	
General Body System																									
None																									
Genital System																									
Coagulating gland									+																
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

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

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	020	021	022	023	024	025	028	029	030	031	032	034	035	036	037	038	039	040	041	042	043	045	046	047	049	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma	X																X									3
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																			X							6
Hepatocellular carcinoma, multiple																						X	X			2
Hepatocellular adenoma							X		X			X			X	X					X					14
Hepatocellular adenoma, multiple																									X	3
Mesentery																										2
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Tooth																						+				2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, carcinoma																										1
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Coagulating gland																										1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	4 1 9	5 3 2	5 3 7	5 9 7	6 6 0	6 6 6	6 7 5	7 2 0	7 2 0	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
Carcass ID Number	0 2 6	0 1 8	0 3 3	0 5 0	0 0 7	0 1 9	0 4 8	0 0 6	0 0 9	0 2 7	0 4 4	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 8	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7
Genital System (continued)																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																								X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+										+
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									+
Hemangiosarcoma																									X
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple																X									
Alveolar/bronchiolar carcinoma																					X				
Hepatocellular carcinoma, metastatic, liver							X					X													X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye									+																
Harderian gland									+																
Adenoma									X																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 0 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 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	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 5	0 4 6	0 4 7	0 4 9	Total Tissues/ Tumors
Genital System (continued)																										
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																			+		+					4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X										X	X						4
Thymus	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Hemangiosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X										X						X					3
Alveolar/bronchiolar adenoma, multiple												X		X												3
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver																						X				4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye												+														2
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic								X											X							2

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

	0	4	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	0	4	3	7	0	6	7	8	9	0	0	2	2	2	2	2	2	3	3	3	3	3	3	3	3
	7	2	7	5	1	5	5	1	5	0	1	0	5	8	9	9	9	0	0	0	0	0	0	0	0
	1	1	1	1	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	1	1	0	0	6	0	0	8	7	0	8	9	6	6	6	6	6	6	6	6	7	7	7	7	7
	0	8	4	6	8	0	1	8	6	8	9	0	3	1	2	4	5	6	7	9	0	1	2	3	4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	M	+	A	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	A	A	A	A	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	A	A	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	A	A	A	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	A	A	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	A	A	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, ileum	A	A	A	A	A	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma									X		X	X		X	X							X		X	
Hepatocellular carcinoma, multiple				X	X	X																			
Hepatocellular adenoma		X	X		X										X				X			X			
Hepatocellular adenoma, multiple							X																		X
Mesentery																									
Pancreas	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor NOS											X														
Cardiovascular System																									
Heart	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X															
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	I	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pars intermedia, adenoma																									
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma											X														
General Body System																									
Tissue NOS																									
Genital System																									
Coagulating gland																				+				+	
Epididymis	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Carcass ID Number	075	077	078	079	080	081	082	083	084	085	086	087	091	092	093	094	095	096	097	098	099	102	103	105	107	Total Tissues/ Tumors
Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adenocarcinoma								X																		1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X														1
Hepatocellular carcinoma								X														X				9
Hepatocellular carcinoma, multiple			X																							4
Hepatocellular adenoma			X						X									X		X						10
Hepatocellular adenoma, multiple				X								X	X	X											X	7
Mesentery																									+	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoid tumor NOS																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	I	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars intermedia, adenoma																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										1
General Body System																										
Tissue NOS															+											1
Genital System																										
Coagulating gland																										2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

	0	4	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	0	4	3	7	0	6	7	8	9	0	0	2	2	2	2	2	2	3	3	3	3	3	3	3	3
	7	2	7	5	1	5	5	1	5	0	1	0	5	8	9	9	9	0	0	0	0	0	0	0	0
	1	1	1	1	0	1	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcass ID Number	1	1	0	0	6	0	0	8	7	0	8	9	6	6	6	6	6	6	6	7	7	7	7	7	7
	0	8	4	6	8	0	1	8	6	8	9	0	3	1	2	4	5	6	7	9	0	1	2	3	4
Hematopoietic System																									
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma									X																
Lymph node																									
Lymph node, mandibular	+	A	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Thymus	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma									X																
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X		X				X				X		X						X			X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma													X					X		X					
Hepatocellular carcinoma, metastatic, liver											X														
Nose	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland								+						+											
Adenoma								X						X											
Urinary System																									
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																									
Urethra									+																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 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 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	0 7 5	0 7 7	0 7 8	0 7 9	0 8 0	0 8 1	0 8 2	0 8 3	0 8 4	0 8 5	0 8 6	0 8 7	0 9 1	0 9 2	0 9 3	0 9 4	0 9 5	0 9 6	0 9 7	0 9 8	0 9 9	1 0 2	1 0 3	1 0 5	1 0 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Lymph node													+													1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X													X						X						10
Alveolar/bronchiolar adenoma, multiple						X									X											2
Alveolar/bronchiolar carcinoma																										3
Hepatocellular carcinoma, metastatic, liver								X																		2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland						+																				3
Adenoma						X																				3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, carcinoma													X													1
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic					X																					1

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

Number of Days on Study	451	496	522	588	638	675	681	681	693	695	703	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	176	139	128	159	163	138	123	167	168	166	122	121	124	125	126	127	129	130	131	132	133	134	135	136	137
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma		X	X	X						X							X						X		
Hepatocellular carcinoma, multiple						X								X											
Hepatocellular adenoma																							X		X
Hepatocellular adenoma, multiple								X		X						X									
Hepatocholangiocarcinoma																					X				
Mesentery							+																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																X									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	160	161	162	164	165	169	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X	X						X		X	X									X				12
Hepatocellular carcinoma, multiple						X			X																	4
Hepatocellular adenoma			X	X								X														5
Hepatocellular adenoma, multiple														X	X				X						X	7
Hepatocholangiocarcinoma																										1
Mesentery															+											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth										+												+				2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign								X																		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	451	496	522	588	638	675	681	681	693	695	703	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	176	139	128	159	163	138	123	167	168	166	122	121	124	125	126	127	129	130	131	132	133	134	135	136	137
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+								+																
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor NOS																			X						
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, mast cell tumor NOS																			X						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Hemangiosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X		X					X	X		
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																					X				
Hepatocellular carcinoma, metastatic, liver						X				X				X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasolacrimal duct, mast cell tumor NOS																			X						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland					+		+	+																	
Adenoma							X	X																	
Adenoma, multiple					X																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																								X	
Lymphoma malignant mixed	X																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154	155	156	157	158	160	161	162	164	165	169	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node														+							+					4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor NOS																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, mast cell tumor NOS																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle												+														1
Hemangiosarcoma												X														1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X						X											6
Alveolar/bronchiolar adenoma, multiple		X												X												2
Alveolar/bronchiolar carcinoma																								X		2
Hepatocellular carcinoma, metastatic, liver			X	X								X														6
Nose	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasolacrimal duct, mast cell tumor NOS																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										3
Adenoma																										2
Adenoma, multiple																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																					X					2
Lymphoma malignant mixed																										1

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

Number of Days on Study	007	007	188	378	582	667	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	188	210	239	204	217	186	181	182	183	184	185	187	189	190	191	192	193	194	195	196	197	198	199	200	201
Alimentary System																									
Esophagus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma					X					X															
Hepatocellular carcinoma, multiple						X																			
Hepatocellular adenoma						X	X				X						X	X				X			
Hepatocellular adenoma, multiple															X										
Mesentery											+														
Pancreas	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																								+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Pituitary gland	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																					X				
Thyroid gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	202	203	205	206	207	208	209	211	212	213	214	215	216	218	219	220	221	222	223	224	225	226	227	228	229	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma									X								X									4
Hepatocellular carcinoma, multiple			X								X	X														4
Hepatocellular adenoma			X			X				X				X									X			11
Hepatocellular adenoma, multiple												X									X					3
Mesentery															+											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Tooth																+										2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	007	007	188	378	582	667	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	188	210	239	204	217	186	181	182	183	184	185	187	189	190	191	192	193	194	195	196	197	198	199	200	201
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+											+										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X							
Alveolar/bronchiolar adenoma, multiple								X							X										
Alveolar/bronchiolar carcinoma																							X	X	
Hepatocellular carcinoma, metastatic, liver						X				X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland										+															
Adenoma										X															
Urinary System																									
Kidney	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									

Table C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	202	203	205	206	207	208	209	211	212	213	214	215	216	218	219	220	221	222	223	224	225	226	227	228	229	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+										+										4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma															X											1
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X	X	X				X							X											6
Alveolar/bronchiolar adenoma, multiple											X															3
Alveolar/bronchiolar carcinoma	X								X						X											5
Hepatocellular carcinoma, metastatic, liver									X		X															4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary Bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																X			X							2

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Harderian Gland: Adenoma				
Overall rate[a]	1/50 (2%)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted rate[b]	2.3%	7.6%	6.6%	2.3%
Terminal rate[c]	0/39 (0%)	1/36 (3%)	0/39 (0%)	1/44 (2%)
First incidence (days)	720	681	638	729 (T)
Life table test[d]	P=0.473N	P=0.284	P=0.303	P=0.744N
Logistic regression test[d]	P=0.538	P=0.298	P=0.394	P=0.761
Cochran-Armitage test[d]	P=0.500N			
Fisher exact test[d]		P=0.309	P=0.309	P=0.753N
Liver: Hepatocellular Adenoma				
Overall rate	17/50 (34%)	17/50 (34%)	12/50 (24%)	14/48 (29%)
Adjusted rate	36.4%	41.4%	29.1%	31.1%
Terminal rate	10/39 (26%)	13/36 (36%)	10/39 (26%)	13/44 (30%)
First incidence (days)	532	442	681	667
Life table test	P=0.145N	P=0.496	P=0.215N	P=0.250N
Logistic regression test	P=0.277N	P=0.557N	P=0.187N	P=0.384N
Cochran-Armitage test	P=0.276N			
Fisher exact test		P=0.583N	P=0.189N	P=0.384N
Liver: Hepatocellular Carcinoma				
Overall rate	8/50 (16%)	13/50 (26%)	16/50 (32%)	8/48 (17%)
Adjusted rate	19.1%	29.6%	35.7%	17.4%
Terminal rate	6/39 (15%)	6/36 (17%)	11/39 (28%)	6/44 (14%)
First incidence (days)	597	575	496	582
Life table test	P=0.366N	P=0.145	P=0.060	P=0.531N
Logistic regression test	P=0.388	P=0.203	P=0.052	P=0.421
Cochran-Armitage test	P=0.513N			
Fisher exact test		P=0.163	P=0.050	P=0.572
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	22/50 (44%)	26/50 (52%)	23/50 (46%)	19/48 (40%)
Adjusted rate	47.4%	56.0%	50.6%	41.3%
Terminal rate	15/39 (38%)	16/36 (44%)	17/39 (44%)	17/44 (39%)
First incidence (days)	532	442	496	582
Life table test	P=0.121N	P=0.223	P=0.491	P=0.234N
Logistic regression test	P=0.453N	P=0.295	P=0.566	P=0.548
Cochran-Armitage test	P=0.265N			
Fisher exact test		P=0.274	P=0.500	P=0.406N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	6/50 (12%)	12/50 (24%)	8/50 (16%)	9/50 (18%)
Adjusted rate	15.4%	29.2%	20.5%	20.5%
Terminal rate	6/39 (15%)	8/36 (22%)	8/39 (21%)	9/44 (20%)
First incidence (days)	729 (T)	537	729 (T)	729 (T)
Life table test	P=0.545	P=0.077	P=0.385	P=0.378
Logistic regression test	P=0.393	P=0.091	P=0.385	P=0.378
Cochran-Armitage test	P=0.413			
Fisher exact test		P=0.096	P=0.387	P=0.288

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	5/50 (10%)
Adjusted rate	2.6%	8.0%	5.1%	11.4%
Terminal rate	1/39 (3%)	2/36 (6%)	2/39 (5%)	5/44 (11%)
First incidence (days)	729 (T)	725	729 (T)	729 (T)
Life table test	P=0.116	P=0.279	P=0.500	P=0.133
Logistic regression test	P=0.095	P=0.279	P=0.500	P=0.133
Cochran-Armitage test	P=0.078			
Fisher exact test		P=0.309	P=0.500	P=0.102
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	7/50 (14%)	14/50 (28%)	10/50 (20%)	13/50 (26%)
Adjusted rate	17.9%	34.2%	25.6%	29.5%
Terminal rate	7/39 (18%)	10/36 (28%)	10/39 (26%)	13/44 (30%)
First incidence (days)	729 (T)	537	729 (T)	729 (T)
Life table test	P=0.303	P=0.053	P=0.293	P=0.166
Logistic regression test	P=0.165	P=0.064	P=0.293	P=0.166
Cochran-Armitage test	P=0.178			
Fisher exact test		P=0.070	P=0.298	P=0.105
Small Intestine (Jejunum): Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate	7.4%	2.8%	0.0%	0.0%
Terminal rate	2/39 (5%)	1/36 (3%)	0/39 (0%)	0/44 (0%)
First incidence (days)	728	729 (T)	–[e]	–
Life table test	P=0.039N	P=0.338N	P=0.126N	P=0.105N
Logistic regression test	P=0.042N	P=0.336N	P=0.131N	P=0.113N
Cochran-Armitage test	P=0.044N			
Fisher exact test		P=0.309N	P=0.121N	P=0.121N
Spleen: Hemangiosarcoma				
Overall rate	4/50 (8%)	1/49 (2%)	1/50 (2%)	1/49 (2%)
Adjusted rate	10.3%	2.8%	2.4%	2.3%
Terminal rate	4/39 (10%)	1/36 (3%)	0/39 (0%)	1/44 (2%)
First incidence (days)	729 (T)	729 (T)	695	729 (T)
Life table test	P=0.113N	P=0.204N	P=0.185N	P=0.145N
Logistic regression test	P=0.134N	P=0.204N	P=0.185N	P=0.145N
Cochran-Armitage test	P=0.137N			
Fisher exact test		P=0.187N	P=0.181N	P=0.187N
All Organs: Hemangiosarcoma				
Overall rate	6/50 (12%)	2/50 (4%)	2/50 (4%)	1/50 (2%)
Adjusted rate	14.9%	5.6%	4.9%	2.3%
Terminal rate	5/39 (13%)	2/36 (6%)	1/39 (3%)	1/44 (2%)
First incidence (days)	728	729 (T)	695	729 (T)
Life table test	P=0.032N	P=0.164N	P=0.142N	P=0.044N
Logistic regression test	P=0.040N	P=0.162N	P=0.143N	P=0.049N
Cochran-Armitage test	P=0.042N			
Fisher exact test		P=0.134N	P=0.134N	P=0.056N

Table C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	6/50 (12%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	14.9%	7.8%	4.9%	2.3%
Terminal rate	5/39 (13%)	2/36 (6%)	1/39 (3%)	1/44 (2%)
First incidence (days)	728	695	695	729 (T)
Life table test	P=0.028N	P=0.284N	P=0.142N	P=0.044N
Logistic regression test	P=0.035N	P=0.261N	P=0.143N	P=0.049N
Cochran-Armitage test	P=0.035N			
Fisher exact test		P=0.243N	P=0.134N	P=0.056N
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rate	5.1%	2.8%	7.0%	4.5%
Terminal rate	2/39 (5%)	1/36 (3%)	2/39 (5%)	2/44 (5%)
First incidence (days)	729 (T)	729 (T)	451	729 (T)
Life table test	P=0.554	P=0.528N	P=0.502	P=0.651N
Logistic regression test	P=0.502	P=0.528N	P=0.508	P=0.651N
Cochran-Armitage test	P=0.500			
Fisher exact test		P=0.500N	P=0.500	P=0.691N
All Organs: Benign Neoplasms				
Overall rate	20/50 (40%)	29/50 (58%)	22/50 (44%)	23/50 (46%)
Adjusted rate	43.0%	62.8%	49.6%	50.0%
Terminal rate	13/39 (33%)	19/36 (53%)	17/39 (44%)	21/44 (48%)
First incidence (days)	532	442	451	188
Life table test	P=0.351N	P=0.054	P=0.421	P=0.500
Logistic regression test	P=0.496	P=0.056	P=0.427	P=0.322
Cochran-Armitage test	P=0.519			
Fisher exact test		P=0.055	P=0.420	P=0.343
All Organs: Malignant Neoplasms				
Overall rate	18/50 (36%)	20/50 (40%)	22/50 (44%)	14/50 (28%)
Adjusted rate	40.6%	44.0%	48.2%	30.4%
Terminal rate	13/39 (33%)	11/36 (31%)	16/39 (41%)	12/44 (27%)
First incidence (days)	419	442	451	582
Life table test	P=0.126N	P=0.340	P=0.286	P=0.181N
Logistic regression test	P=0.201N	P=0.429	P=0.284	P=0.286N
Cochran-Armitage test	P=0.200N			
Fisher exact test		P=0.418	P=0.270	P=0.260N
All Organs: Benign or Malignant Neoplasms				
Overall rate	33/50 (66%)	36/50 (72%)	36/50 (72%)	31/50 (62%)
Adjusted rate	68.6%	73.5%	74.8%	65.9%
Terminal rate	24/39 (62%)	23/36 (64%)	27/39 (69%)	28/44 (64%)
First incidence (days)	419	442	451	188
Life table test	P=0.137N	P=0.248	P=0.361	P=0.235N
Logistic regression test	P=0.496N	P=0.337	P=0.364	P=0.464N
Cochran-Armitage test	P=0.304N			
Fisher exact test		P=0.333	P=0.333	P=0.418N

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

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and spleen; 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 exposure group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test 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 an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

TABLE C4
Historical Incidence of Lung Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Alveolar/bronchiolar Adenoma	Alveolar/bronchiolar Carcinoma	Alveolar/bronchiolar Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	9/50	5/50	14/50
C.I. Pigment Red 23	4/49	2/49	5/49
C.I. Pigment Red 3	2/50	0/50	2/50
Ethylene Glycol	7/54	1/54	7/54
Nitrofurantoin	5/50	1/50	6/50
o-Nitroanisole	5/50	1/50	6/50
Polysorbate 80	5/49	1/49	6/49
Rhodamine 6G	6/50	3/50	9/50
Roxarsone	5/50	6/50	11/50
Total	48/452 (10.6%)	20/452 (4.4%)	66/452 (14.6%)
Standard deviation	3.8%	4.1%	7.1%
Range	4%-18%	2%-12%	4%-28%
Overall Historical Incidence			
Total	181/1,369 (13.2%)	68/1,369 (5.0%)	242/1,369 (17.7%)
Standard deviation	5.8%	4.0%	7.3%
Range	4%-26%	0%-14%	4%-30%

[a] Data as of 20 August 1992

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths		1		2
Moribund	9	4	10	2
Natural deaths	2	9	1	2
Survivors				
Terminal sacrifice	39	36	39	44
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Basophilic focus		1 (10%)		1 (10%)
Inflammation, subacute			1 (10%)	
Karyomegaly				1 (10%)
Mixed cell focus	1 (10%)			1 (10%)
Necrosis		1 (10%)		
Vacuolization cytoplasmic	2 (20%)	2 (20%)	2 (20%)	1 (10%)
Mesentery	(1)			(2)
Fat, necrosis	1 (100%)			2 (100%)
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy		1 (10%)	1 (10%)	
Stomach, glandular	(10)	(10)	(10)	(10)
Mineralization			1 (10%)	
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hypertrophy	1 (10%)	1 (10%)	1 (10%)	2 (20%)
Pituitary gland	(10)	(9)	(10)	(10)
Pars distalis, hyperplasia		1 (11%)		
Thyroid gland	(10)	(10)	(10)	(10)
Follicle, degeneration				1 (10%)
Genital System				
Preputial gland	(10)	(10)	(10)	(10)
Atrophy		1 (10%)		
Inflammation, subacute				1 (10%)
Duct, cyst	2 (20%)	1 (10%)	3 (30%)	3 (30%)

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

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
15-Month Interim Evaluation (continued)				
Hematopoietic System				
Lymph node, mesenteric	(10)	(10)	(10)	(10)
Angiectasis	1 (10%)	1 (10%)		
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation	1 (10%)	1 (10%)	1 (10%)	
Hyperplasia, lymphoid		2 (20%)		
Thymus	(10)	(9)	(10)	(10)
Cyst				1 (10%)
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Pinna, inflammation, subacute			1 (10%)	
Subcutaneous tissue, hemorrhage				1 (10%)
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar epithelium, hyperplasia		1 (10%)	1 (10%)	
Nose	(10)	(10)	(10)	(10)
Lumen, hemorrhage				1 (10%)
Special Senses System				
Eye	(1)		(2)	(1)
Retrobulbar, hemorrhage	1 (100%)		2 (100%)	1 (100%)
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Fibrosis			1 (10%)	
Hydronephrosis			1 (10%)	
Inflammation, subacute			1 (10%)	
Mineralization	9 (90%)	4 (40%)	5 (50%)	4 (40%)
Renal tubule, casts		1 (10%)		
Renal tubule, pigmentation		1 (10%)		
Renal tubule, regeneration	7 (70%)	6 (60%)	7 (70%)	3 (30%)

Systems Examined With No Lesions Observed
Cardiovascular System
General Body System
Musculoskeletal System
Nervous System

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study				
Alimentary System				
Gallbladder	(48)	(45)	(50)	(48)
Epithelium, hyperplasia				1 (2%)
Intestine small, jejunum	(50)	(43)	(49)	(46)
Peyer's patch, hyperplasia, lymphoid		1 (2%)		
Liver	(50)	(50)	(50)	(48)
Basophilic focus	1 (2%)	3 (6%)		4 (8%)
Clear cell focus	4 (8%)	6 (12%)	5 (10%)	2 (4%)
Cytologic alterations			1 (2%)	
Eosinophilic focus	4 (8%)	17 (34%)	5 (10%)	4 (8%)
Hematopoietic cell proliferation	2 (4%)			
Inflammation, subacute	1 (2%)		1 (2%)	
Mixed cell focus	6 (12%)	5 (10%)	5 (10%)	2 (4%)
Necrosis	4 (8%)		1 (2%)	
Regeneration	1 (2%)			
Vacuolization cytoplasmic	2 (4%)	1 (2%)	4 (8%)	3 (6%)
Hepatocyte, hypertrophy, focal				1 (2%)
Mesentery	(2)	(1)	(2)	(2)
Fat, inflammation, granulomatous			1 (50%)	
Fat, necrosis	1 (50%)	1 (100%)	1 (50%)	2 (100%)
Pancreas	(50)	(48)	(50)	(47)
Edema			1 (2%)	
Inflammation, chronic	1 (2%)			
Acinus, atrophy	1 (2%)		1 (2%)	
Acinus, depletion secretory		1 (2%)	1 (2%)	
Duct, cyst	1 (2%)	1 (2%)	1 (2%)	
Salivary glands	(50)	(49)	(50)	(50)
Acinus, atrophy		1 (2%)		
Duct, cyst		1 (2%)		
Stomach, forestomach	(50)	(47)	(50)	(47)
Cyst				1 (2%)
Hyperplasia	6 (12%)	4 (9%)		
Inflammation, subacute	1 (2%)	3 (6%)		
Ulcer	1 (2%)			
Stomach, glandular	(50)	(47)	(50)	(47)
Cyst		1 (2%)	2 (4%)	1 (2%)
Ulcer	2 (4%)			
Tooth	(2)		(2)	(2)
Dysplasia			1 (50%)	1 (50%)
Inflammation, chronic			1 (50%)	1 (50%)
Inflammation, subacute	2 (100%)			1 (50%)
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Cardiomyopathy		1 (2%)		
Fibrosis			1 (2%)	1 (2%)
Inflammation, chronic			1 (2%)	
Mineralization				1 (2%)
Artery, inflammation, subacute		1 (2%)		

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of p-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(49)
Accessory adrenal cortical nodule	1 (2%)	2 (4%)	1 (2%)	
Hyperplasia		1 (2%)		1 (2%)
Hypertrophy	14 (28%)	17 (35%)	16 (32%)	15 (31%)
Spindle cell, hyperplasia			1 (2%)	1 (2%)
Islets, pancreatic	(50)	(49)	(50)	(48)
Hyperplasia	1 (2%)	3 (6%)		
Pituitary gland	(46)	(46)	(50)	(46)
Pars distalis, cyst	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Thyroid gland	(50)	(49)	(50)	(49)
Follicle, cyst	2 (4%)	1 (2%)		3 (6%)
Follicular cell, hyperplasia	15 (30%)	12 (24%)	8 (16%)	9 (18%)
General Body System				
None				
Genital System				
Coagulating gland	(1)	(2)		
Dilatation	1 (100%)	1 (50%)		
Epididymis	(50)	(49)	(50)	(50)
Cyst, multiple			1 (2%)	
Inflammation, granulomatous			1 (2%)	1 (2%)
Preputial gland	(50)	(49)	(50)	(50)
Abscess		2 (4%)	1 (2%)	2 (4%)
Atrophy			1 (2%)	
Cyst			1 (2%)	1 (2%)
Infiltration cellular, subacute				1 (2%)
Inflammation, chronic			1 (2%)	
Inflammation, subacute	11 (22%)	2 (4%)	10 (20%)	4 (8%)
Duct, cyst	31 (62%)	36 (73%)	36 (72%)	27 (54%)
Prostate	(50)	(49)	(50)	(50)
Atrophy	1 (2%)			
Inflammation, subacute			1 (2%)	
Polyarteritis				1 (2%)
Seminal vesicle	(50)	(49)	(50)	(50)
Atrophy	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Dilatation	1 (2%)	6 (12%)	1 (2%)	
Inflammation, chronic			1 (2%)	
Inflammation, subacute			1 (2%)	

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Congestion				1 (2%)
Hypercellularity	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Lymph node	(4)	(1)	(4)	(4)
Axillary, hyperplasia, lymphoid			1 (25%)	1 (25%)
Bronchial, hyperplasia, lymphoid				2 (50%)
Inguinal, angiectasis	1 (25%)			
Inguinal, hyperplasia, lymphoid	1 (25%)		1 (25%)	1 (25%)
Mediastinal, hyperplasia, lymphoid			1 (25%)	
Pancreatic, mineralization	1 (25%)			
Renal, hyperplasia, lymphoid		1 (100%)		
Lymph node, mandibular	(49)	(47)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		1 (2%)	3 (6%)
Infiltration cellular, mast cell				1 (2%)
Lymph node, mesenteric	(50)	(49)	(50)	(47)
Angiectasis	17 (34%)	20 (41%)	20 (40%)	17 (36%)
Atrophy	1 (2%)			
Hematopoietic cell proliferation		1 (2%)	2 (4%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)	2 (4%)	2 (4%)	
Spleen	(50)	(49)	(50)	(49)
Atrophy	1 (2%)	2 (4%)	3 (6%)	5 (10%)
Hematopoietic cell proliferation	11 (22%)	8 (16%)	10 (20%)	6 (12%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		2 (4%)
Necrosis			1 (2%)	
Thymus	(45)	(47)	(47)	(47)
Atrophy	4 (9%)	1 (2%)	2 (4%)	1 (2%)
Cyst	1 (2%)	4 (9%)	1 (2%)	
Necrosis			1 (2%)	
Integumentary System				
Skin	(50)	(49)	(50)	(50)
Ulcer		1 (2%)		1 (2%)
Dermis, inflammation, chronic		1 (2%)		
Dermis, inflammation, subacute		1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, abscess	1 (2%)			
Subcutaneous tissue, inflammation, chronic			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, hyperostosis		1 (2%)		
Femur, fibrous osteodystrophy				1 (2%)
Nervous System				
None				

Table C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion				1 (2%)
Hemorrhage			1 (2%)	
Infiltration cellular, histiocyte		1 (2%)	1 (2%)	3 (6%)
Inflammation, granulomatous	1 (2%)			
Inflammation, subacute				3 (6%)
Thrombosis			1 (2%)	
Alveolar epithelium, hyperplasia	2 (4%)	7 (14%)	7 (14%)	8 (16%)
Bronchiole, hyperplasia			1 (2%)	
Nose	(50)	(49)	(49)	(50)
Congestion		1 (2%)		
Glands, inflammation, subacute				1 (2%)
Nasolacrimal duct, ectasia			1 (2%)	
Nasolacrimal duct, inflammation, subacute			1 (2%)	
Special Senses System				
Eye	(2)			
Cataract	1 (50%)			
Urinary System				
Kidney	(50)	(49)	(50)	(48)
Fibrosis	4 (8%)	2 (4%)	2 (4%)	2 (4%)
Glomerulosclerosis	2 (4%)	5 (10%)	6 (12%)	2 (4%)
Hemorrhage				1 (2%)
Infarct	7 (14%)	4 (8%)	5 (10%)	3 (6%)
Infiltration cellular, lymphocyte	1 (2%)			
Inflammation, subacute			1 (2%)	
Metaplasia, osseous	1 (2%)	1 (2%)	1 (2%)	
Mineralization	41 (82%)	33 (67%)	23 (46%)	31 (65%)
Cortex, cyst	11 (22%)	6 (12%)	5 (10%)	3 (6%)
Renal tubule, casts	7 (14%)	7 (14%)	7 (14%)	3 (6%)
Renal tubule, regeneration	43 (86%)	37 (76%)	35 (70%)	32 (67%)
Urethra		(1)		
Bulbourethral gland, hemorrhage		1 (100%)		
Urinary bladder	(50)	(50)	(50)	(48)
Dilatation			1 (2%)	

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

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths			1	2
Moribund	9	8	12	10
Natural deaths	3	5	4	8
Survivors				
Terminal sacrifice	38	36	33	30
Missing		1		
Animals examined microscopically	60	59	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma	1 (10%)			
Hepatocellular adenoma		2 (20%)	4 (40%)	1 (10%)
Hematopoietic System				
Bone marrow	(10)	(10)	(10)	(10)
Hemangiosarcoma			1 (10%)	
Lymph node			(2)	
Renal, hemangiosarcoma			1 (50%)	
Systems Examined With No Neoplasms Observed				
Cardiovascular System				
Endocrine System				
General Body System				
Genital System				
Integumentary System				
Musculoskeletal System				
Nervous System				
Respiratory System				
Special Senses System				
Urinary System				
2-Year Study				
Alimentary System				
Gallbladder	(50)	(48)	(47)	(48)
Histiocytic sarcoma		1 (2%)		
Intestine small, duodenum	(49)	(46)	(47)	(46)
Polyp adenomatous				1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)
Intestine small, jejunum	(49)	(46)	(47)	(46)
Adenocarcinoma			1 (2%)	
Intestine small, ileum	(49)	(46)	(47)	(45)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(49)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Hepatocellular carcinoma	4 (8%)	5 (10%)	4 (8%)	6 (12%)
Hepatocellular carcinoma, multiple			1 (2%)	1 (2%)
Hepatocellular adenoma	8 (16%)	9 (18%)	11 (22%)	4 (8%)
Hepatocellular adenoma, multiple	3 (6%)	4 (8%)	2 (4%)	1 (2%)
Histiocytic sarcoma	1 (2%)	2 (4%)	3 (6%)	
Mesentery	(4)	(8)	(5)	(6)
Histiocytic sarcoma		1 (13%)		
Osteosarcoma, metastatic, bone				1 (17%)
Sarcoma				1 (17%)
Pancreas	(50)	(47)	(49)	(49)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Sarcoma, metastatic, mesentery				1 (2%)
Salivary glands	(50)	(49)	(50)	(50)
Stomach, forestomach	(50)	(49)	(49)	(49)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Squamous cell papilloma	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Stomach, glandular	(49)	(49)	(49)	(49)
Histiocytic sarcoma		1 (2%)		
Tooth			(1)	
Histiocytic sarcoma			1 (100%)	
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Endocrine System				
Adrenal cortex	(49)	(48)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Sarcoma, metastatic, mesentery				1 (2%)
Adrenal medulla	(49)	(48)	(50)	(50)
Pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(50)	(49)	(49)	(50)
Carcinoma			1 (2%)	
Pituitary gland	(48)	(48)	(49)	(48)
Pars distalis, adenoma	7 (15%)	6 (13%)	9 (18%)	5 (10%)
Pars distalis, carcinoma	1 (2%)			
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(50)	(49)	(50)	(50)
Follicular cell, adenoma		1 (2%)	2 (4%)	
Follicular cell, carcinoma	1 (2%)			1 (2%)
General Body System				
None				

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Genital System				
Ovary	(50)	(48)	(49)	(48)
Cystadenoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Histiocytic sarcoma		2 (4%)	1 (2%)	
Luteoma		1 (2%)		
Sarcoma, metastatic, mesentery				1 (2%)
Uterus	(50)	(49)	(50)	(50)
Hemangiosarcoma			1 (2%)	
Histiocytic sarcoma	1 (2%)	2 (4%)	1 (2%)	
Leiomyoma				1 (2%)
Leiomyosarcoma	1 (2%)			
Polyp stromal		1 (2%)	2 (4%)	
Sarcoma, metastatic, mesentery				1 (2%)
Sarcoma stromal	1 (2%)			
Vagina	(1)		(1)	
Squamous cell papilloma	1 (100%)			
Hematopoietic System				
Bone marrow	(50)	(49)	(48)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	
Histiocytic sarcoma		1 (2%)	1 (2%)	
Lymph node	(8)	(10)	(13)	(15)
Axillary, fibrosarcoma, metastatic, skin			1 (8%)	
Iliac, histiocytic sarcoma		1 (10%)	1 (8%)	
Inguinal, histiocytic sarcoma		1 (10%)	1 (8%)	
Mediastinal, histiocytic sarcoma		1 (10%)		
Pancreatic, histiocytic sarcoma			1 (8%)	
Pancreatic, sarcoma, metastatic, mesentery				1 (7%)
Renal, histiocytic sarcoma		1 (10%)	1 (8%)	
Lymph node, mandibular	(50)	(49)	(50)	(49)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Lymph node, mesenteric	(50)	(49)	(48)	(48)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Spleen	(50)	(49)	(49)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	
Histiocytic sarcoma		1 (2%)	1 (2%)	
Sarcoma, metastatic, mesentery				1 (2%)
Thymus	(50)	(48)	(48)	(46)
Fibrosarcoma, metastatic, skin			1 (2%)	
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma		1 (2%)		

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Integumentary System				
Mammary gland	(50)	(49)	(50)	(49)
Adenoma	1 (2%)			1 (2%)
Skin	(50)	(49)	(50)	(50)
Schwannoma NOS			1 (2%)	
Subcutaneous tissue, basal cell carcinoma		1 (2%)		
Subcutaneous tissue, fibrosarcoma		1 (2%)	1 (2%)	
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, histiocytic sarcoma			1 (2%)	
Subcutaneous tissue, sarcoma	1 (2%)		1 (2%)	1 (2%)
Subcutaneous tissue, schwannoma malignant	1 (2%)			
Subcutaneous tissue, thymoma malignant, metastatic, thymus		1 (2%)		
Musculoskeletal System				
Bone	(50)	(49)	(49)	(50)
Femur, osteosarcoma				1 (2%)
Skeletal muscle	(1)	(1)	(2)	(2)
Fibrosarcoma			2 (100%)	
Hemangiosarcoma	1 (100%)			
Hepatocellular carcinoma, metastatic, liver		1 (100%)		
Sarcoma, metastatic, mesentery				1 (50%)
Nervous System				
Brain	(49)	(49)	(50)	(50)
Carcinoma, metastatic, pituitary gland	1 (2%)			
Glioma NOS		1 (2%)		
Meninges, histiocytic sarcoma		1 (2%)	1 (2%)	
Olfactory lobe, histiocytic sarcoma		1 (2%)		
Respiratory System				
Lung	(50)	(49)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	5 (10%)	3 (6%)	8 (16%)
Alveolar/bronchiolar carcinoma		4 (8%)	1 (2%)	
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		1 (2%)
Fibrosarcoma, metastatic, skin			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)	4 (8%)	1 (2%)	
Osteosarcoma, metastatic, bone				1 (2%)
Sarcoma, metastatic, mesentery				1 (2%)
Mediastinum, hemangiosarcoma, metastatic, spleen	1 (2%)			
Nose	(50)	(49)	(48)	(50)
Glands, histiocytic sarcoma		1 (2%)		
Special Senses System				
Harderian gland	(3)	(2)		
Adenoma	3 (100%)	1 (50%)		

Table D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(49)	(50)	(50)
Histiocytic sarcoma		2 (4%)	1 (2%)	
Osteosarcoma, metastatic, bone				1 (2%)
Urinary bladder	(50)	(49)	(49)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(49)	(50)	(50)
Histiocytic sarcoma	1 (2%)	2 (4%)	3 (6%)	
Lymphoma malignant lymphocytic	6 (12%)	8 (16%)	7 (14%)	5 (10%)
Lymphoma malignant mixed	3 (6%)	3 (6%)	2 (4%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	1	2	4	1
2-Year study	36	38	35	32
Total primary neoplasms				
15-Month interim evaluation	1	2	6	1
2-Year study	53	61	61	42
Total animals with benign neoplasms				
15-Month interim evaluation		2	4	1
2-Year study	22	22	23	20
Total benign neoplasms				
15-Month interim evaluation		2	4	1
2-Year study	29	33	32	23
Total animals with malignant neoplasms				
15-Month interim evaluation	1		1	
2-Year study	23	23	23	17
Total malignant neoplasms				
15-Month interim evaluation	1		2	
2-Year study	24	27	28	19
Total animals with metastatic neoplasms				
2-Year study	3	4	2	2
Total metastatic neoplasms				
2-Year study	3	9	4	12
Total animals with uncertain neoplasms benign or malignant				
2-Year study		1	1	
Total uncertain neoplasms				
2-Year study		1	1	

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

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

Number of Days on Study	364	423	533	533	589	616	639	689	693	723	728	728	735	735	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	255	286	251	290	253	249	278	250	269	287	241	273	242	243	244	245	246	247	248	252	254	256	257	258	259
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma			X													X									
Hepatocellular adenoma												X								X			X	X	
Hepatocellular adenoma, multiple					X																	X			
Histiocytic sarcoma																									
Mesentery					+			+																+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign						X																			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	M	M
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X							X				X		X	
Pars distalis, carcinoma								X																	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma																									
General Body System																									
None																									

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 0 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	2 6 0	2 6 1	2 6 2	2 6 3	2 6 4	2 6 5	2 6 6	2 6 7	2 6 8	2 7 0	2 7 1	2 7 2	2 7 4	2 7 5	2 7 6	2 7 7	2 7 9	2 8 0	2 8 1	2 8 2	2 8 3	2 8 4	2 8 5	2 8 8	2 8 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		1
Hepatocellular carcinoma						X											X									4
Hepatocellular adenoma	X	X			X																				X	8
Hepatocellular adenoma, multiple										X																3
Histiocytic sarcoma																							X			1
Mesentery																					+					4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma															X											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma						X						X												X		7
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, carcinoma	X																									1
General Body System																										
None																										

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

Number of Days on Study	364	423	533	539	589	616	639	689	693	723	728	728	735	735	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	255	286	251	290	253	249	278	250	269	287	241	273	242	243	244	245	246	247	248	252	254	256	257	258	259
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leiomyosarcoma																									
Sarcoma stromal																									
Vagina					+																				
Squamous cell papilloma					X																				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph node	+			+	+				+	+	+										+				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma																									X
Subcutaneous tissue, schwannoma malignant																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																					+				
Hemangiosarcoma																					X				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Carcinoma, metastatic, pituitary gland								X																	
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																	
Hepatocellular carcinoma, metastatic, liver																									
Mediastinum, hemangiosarcoma, metastatic, spleen									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 0 ppm (continued)

Number of Days on Study	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	260	261	262	263	264	265	266	267	268	270	271	272	274	275	276	277	279	280	281	282	283	284	285	288	289	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																							X			1
Leiomyosarcoma		X																								1
Sarcoma stromal									X																	1
Vagina																										1
Squamous cell papilloma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																	X									1
Lymph node														+												8
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Hemangiosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, pituitary gland																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X									X							3
Hepatocellular carcinoma, metastatic, liver						X																				1
Mediastinum, hemangiosarcoma, metastatic, spleen																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

Number of Days on Study	364	423	533	533	589	616	639	689	693	723	728	728	735	735	735	735	735	735	735	735	735	735	735	735	735
Carcass ID Number	255	286	251	290	253	249	278	250	269	287	241	273	242	243	244	245	246	247	248	252	254	256	257	258	259
Special Senses System																									
Eye							+					+													
Harderian gland							+				+	+													
Adenoma							X				X	X													
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymphoma malignant lymphocytic		X								X	X												X		
Lymphoma malignant mixed																	X					X			

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 0 ppm (continued)

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

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

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	735	735	735	735	735	735	735	735	735	
Carcass ID Number	316	318	319	321	322	324	329	330	331	334	336	338	339	340	341	342	326	327	328	344	345	346	347	348	349	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma		X	X						X																	5
Hepatocellular adenoma			X		X	X				X					X											9
Hepatocellular adenoma, multiple												X										X				4
Histiocytic sarcoma																										2
Mesentery							+			+					+						+					8
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver		X																								1
Squamous cell papilloma																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver		X																								1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X				X										X							X		X		6
Pars intermedia, adenoma					X																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma	X																									1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Number of Days on Study	4	5	5	5	5	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
	0	2	5	9	9	2	5	7	8	8	8	0	0	3	3	3	3	3	3	3	3	3	3	3
	0	6	0	4	8	0	7	8	1	5	5	1	1	1	1	1	1	1	1	1	1	1	1	1
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
	2	0	1	0	3	0	5	3	3	2	3	2	4	0	0	0	0	0	1	1	1	1	1	1
	0	6	7	8	7	2	0	2	3	5	5	3	3	1	3	4	5	9	0	1	2	3	4	5
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Cystadenoma														X										
Histiocytic sarcoma		X	X																					
Luteoma																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X	X																					
Polyp stromal																								
Hematopoietic System																								
Blood																								+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X													
Histiocytic sarcoma		X																						
Lymph node	+	+			+			+			+	+												
Iliac, histiocytic sarcoma		X																						
Inguinal, histiocytic sarcoma		X																						
Mediastinal, histiocytic sarcoma		X																						
Renal, histiocytic sarcoma		X																						
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X													
Histiocytic sarcoma		X																						
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																								
Histiocytic sarcoma		X																						
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, basal cell carcinoma					X																			
Subcutaneous tissue, fibrosarcoma																								
Subcutaneous tissue, thymoma malignant, metastatic, thymus																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																								
Hepatocellular carcinoma, metastatic, liver																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	735	735	735	735	735	735	735	735	735	
Carcass ID Number	316	318	319	321	322	324	329	330	331	334	336	338	339	340	341	342	326	327	328	344	345	346	347	348	349	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma		X																								2
Histiocytic sarcoma																										2
Luteoma																		X								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Polyp stromal																		X								1
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Lymph node										+			+							+	+					10
Iliac, histiocytic sarcoma																										1
Inguinal, histiocytic sarcoma																										1
Mediastinal, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic, liver		X																								1
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, basal cell carcinoma																										1
Subcutaneous tissue, fibrosarcoma	X																									1
Subcutaneous tissue, thymoma malignant, metastatic, thymus		X																								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle		+																								1
Hepatocellular carcinoma, metastatic, liver		X																								1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Number of Days on Study	4 0 0	5 2 6	5 5 0	5 9 4	5 9 8	6 2 0	6 5 7	6 7 8	6 8 1	6 8 5	6 8 5	7 0 1	7 0 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	3 2 0	3 0 6	3 1 7	3 0 8	3 3 7	3 0 2	3 5 0	3 3 2	3 3 3	3 2 5	3 3 5	3 2 3	3 4 3	3 0 1	3 0 3	3 0 4	3 0 5	3 0 9	3 1 0	3 1 1	3 1 2	3 1 3	3 1 4	3 1 5
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma NOS				X																				
Meninges, histiocytic sarcoma		X																						
Olfactory lobe, histiocytic sarcoma		X																						
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X	X				X									
Alveolar/bronchiolar carcinoma																X						X		
Alveolar/bronchiolar carcinoma, multiple																							X	
Hepatocellular carcinoma, metastatic, liver													X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glands, histiocytic sarcoma		X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																								
Eye									+															
Harderian gland									+															
Adenoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X	X																					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X	X																					
Lymphoma malignant lymphocytic																X					X	X		
Lymphoma malignant mixed																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 1,250 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	735	735	735	735	735	735	735	735	735	
Carcass ID Number	316	318	319	321	322	324	329	330	331	334	336	338	339	340	341	342	326	327	328	344	345	346	347	348	349	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Glioma NOS																										1
Meninges, histiocytic sarcoma																										1
Olfactory lobe, histiocytic sarcoma																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma		X													X											5
Alveolar/bronchiolar carcinoma											X													X		4
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver		X	X						X																	4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Glands, histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Ear													+													1
Eye																										1
Harderian gland																	+									2
Adenoma																	X									1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Lymphoma malignant lymphocytic							X						X								X		X	X		8
Lymphoma malignant mixed								X		X										X						3

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

Number of Days on Study	007	480	490	569	589	624	629	638	651	678	680	689	707	707	715	720	720	731	731	731	731	731	731	731	731
Carcass ID Number	404	362	407	370	365	392	378	382	372	394	395	402	364	393	384	375	398	361	363	366	367	368	369	371	373
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, ileum	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma		X					X			X					X				X						
Hepatocellular adenoma, multiple																						X			
Histiocytic sarcoma						X				X															
Mesentery								+					+												
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+																			
Histiocytic sarcoma						X																			
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma															X										
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X							X	X					X				X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma												X											X		
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	374	376	377	379	380	381	383	385	386	387	388	389	390	391	396	397	399	400	401	403	405	406	408	409	410	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma			X																							1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X	X							X											X				4
Hepatocellular carcinoma, multiple																		X								1
Hepatocellular adenoma			X								X	X		X				X					X			11
Hepatocellular adenoma, multiple																					X					2
Histiocytic sarcoma										X																3
Mesentery						+						+		+												5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma											X	X														2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										1
Histiocytic sarcoma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma				X		X												X			X					9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										2
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	007	480	490	569	589	624	629	638	651	678	680	689	707	707	715	720	720	731	731	731	731	731	731	731	731
Carcass ID Number	404	362	407	370	365	392	378	382	372	394	395	402	364	393	384	375	398	361	363	366	367	368	369	371	373
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																				X					
Histiocytic sarcoma						X																			
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Histiocytic sarcoma																									
Polyp stromal																									
Vagina																									
Hematopoietic System																									
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																				X					
Histiocytic sarcoma						X																			
Lymph node				+	+	+	+	+	+				+			+									
Axillary, fibrosarcoma, metastatic, skin							X																		
Iliac, histiocytic sarcoma						X																			
Inguinal, histiocytic sarcoma						X																			
Pancreatic, histiocytic sarcoma						X																			
Renal, histiocytic sarcoma						X																			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Histiocytic sarcoma						X																			
Thymus	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin							X																		
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma NOS			X																						
Subcutaneous tissue, fibrosarcoma							X																		
Subcutaneous tissue, hemangiosarcoma														X											
Subcutaneous tissue, histiocytic sarcoma										X															
Subcutaneous tissue, sarcoma									X																

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	374	376	377	379	380	381	383	385	386	387	388	389	390	391	396	397	399	400	401	403	405	406	408	409	410	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																										1
Histiocytic sarcoma																										1
Oviduct															+											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma										X																1
Polyp stromal													X				X									2
Vagina				+																						1
Hematopoietic System																										
Blood														+												1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Lymph node					+				+	+		+					+									13
Axillary, fibrosarcoma, metastatic, skin																										1
Iliac, histiocytic sarcoma																										1
Inguinal, histiocytic sarcoma																										1
Pancreatic, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, skin																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma NOS																										1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, sarcoma																										1

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

	0	4	4	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7
Number of Days on Study	0	8	9	6	8	2	2	3	5	7	8	8	0	0	1	2	2	3	3	3	3	3	3	3	3
	7	0	0	9	9	4	9	8	1	8	0	9	7	7	5	0	0	1	1	1	1	1	1	1	1
	4	3	4	3	3	3	3	3	3	3	3	4	3	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	0	6	0	7	6	9	7	8	7	9	9	0	6	9	8	7	9	6	6	6	6	6	6	7	7
	4	2	7	0	5	2	8	2	2	4	5	2	4	3	4	5	8	1	3	6	7	8	9	1	3
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+				+								
Fibrosarcoma													X				X								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meninges, histiocytic sarcoma						X																			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X					X					
Alveolar/bronchiolar carcinoma																	X								
Fibrosarcoma, metastatic, skin							X																		
Hepatocellular carcinoma, metastatic, liver																									
Nose	A	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X				X															
Lymphoma malignant lymphocytic								X																	
Lymphoma malignant mixed				X												X									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 2,500 ppm (continued)

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	374	376	377	379	380	381	383	385	386	387	388	389	390	391	396	397	399	400	401	403	405	406	408	409	410	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skeletal muscle																										2
Fibrosarcoma																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meninges, histiocytic sarcoma																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			3
Alveolar/bronchiolar carcinoma																										1
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																		X								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear															+											1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma										X																3
Lymphoma malignant lymphocytic					X	X			X	X		X					X									7
Lymphoma malignant mixed																										2

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

	0	0	4	4	4	5	5	5	5	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7
Number of Days on Study	0	0	5	7	9	1	6	7	8	1	3	3	3	4	6	7	0	0	1	1	3	3	3	3	3
	7	7	7	1	0	9	5	0	4	6	0	6	7	6	5	8	0	9	2	5	0	0	0	0	0
	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
Carcass ID Number	3	4	4	6	4	2	4	5	3	6	6	3	3	3	6	6	5	2	6	2	2	2	2	2	2
	0	6	8	5	4	6	2	3	8	1	2	9	6	7	8	7	1	5	3	8	1	2	3	4	7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Polyp adenomatous																	X								
Sarcoma, metastatic, mesentery												X													
Intestine small, jejunum	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	A	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma										X															
Hepatocellular carcinoma, multiple															X										
Hepatocellular adenoma													X												
Hepatocellular adenoma, multiple																									
Mesentery				+		+			+			+					+								
Osteosarcoma, metastatic, bone				X																					
Sarcoma												X													
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery												X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery												X													
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma														X											
General Body System																									
None																									
Genital System																									
Clitoral gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Cystadenoma																X									
Sarcoma, metastatic, mesentery												X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Sarcoma, metastatic, mesentery												X													

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	429	431	432	433	434	435	440	441	443	445	447	449	450	452	454	455	456	457	458	459	460	464	466	469	470	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Polyp adenomatous																										1
Sarcoma, metastatic, mesentery																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma					X									X		X	X		X							6
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma		X																	X					X		4
Hepatocellular adenoma, multiple															X											1
Mesentery			+																							6
Osteosarcoma, metastatic, bone																										1
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, mesentery																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																					X					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma				X	X				X				X									X				5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Cystadenoma																										1
Sarcoma, metastatic, mesentery																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																		X								1
Sarcoma, metastatic, mesentery																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	007	007	457	471	490	519	565	578	584	616	630	636	637	646	665	678	700	709	712	715	730	730	730	730	730
Carcass ID Number	430	446	448	465	444	426	442	453	438	461	462	439	436	437	468	467	451	425	463	428	421	422	423	424	427
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node								+	+			+	+	+	+		+	+	+	+					
Pancreatic, sarcoma, metastatic, mesentery												X													
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery												X													
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma				X																					
Skeletal muscle												+						+							
Sarcoma, metastatic, mesentery												X													
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X											X			X			
Alveolar/bronchiolar carcinoma, multiple																									
Osteosarcoma, metastatic, bone				X																					
Sarcoma, metastatic, mesentery												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, bone				X																					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																	X		X						
Lymphoma malignant mixed																		X		X					

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid: 5,000 ppm (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	429	431	432	433	434	435	440	441	443	445	447	449	450	452	454	455	456	457	458	459	460	464	466	469	470	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+	+				+	+					+									15
Pancreatic, sarcoma, metastatic, mesentery																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																										1
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	M	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X																	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femur, osteosarcoma																										1
Skeletal muscle																										2
Sarcoma, metastatic, mesentery																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X										X						X	X					X	8
Alveolar/bronchiolar carcinoma, multiple																		X								1
Osteosarcoma, metastatic, bone																										1
Sarcoma, metastatic, mesentery																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, bone																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic						X					X						X									5
Lymphoma malignant mixed																										2

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Harderian Gland: Adenoma				
Overall rate[a]	3/50 (6%)	1/49 (2%)	0/50 (0%)	0/50 (0%)
Adjusted rate[b]	7.2%	2.8%	0.0%	0.0%
Terminal rate[c]	0/38 (0%)	1/36 (3%)	0/33 (0%)	0/30 (0%)
First incidence (days)	639	730 (T)	–[e]	–
Life table test[d]	P=0.061N	P=0.334N	P=0.149N	P=0.171N
Logistic regression test[d]	P=0.047N	P=0.312N	P=0.121N	P=0.128N
Cochran-Armitage test[d]	P=0.044N			
Fisher exact test[d]		P=0.316N	P=0.121N	P=0.121N
Liver: Hepatocellular Adenoma				
Overall rate	11/50 (22%)	13/49 (27%)	13/50 (26%)	5/50 (10%)
Adjusted rate	27.2%	31.9%	34.0%	15.6%
Terminal rate	9/38 (24%)	9/36 (25%)	9/33 (27%)	4/30 (13%)
First incidence (days)	589	620	480	637
Life table test	P=0.162N	P=0.359	P=0.290	P=0.192N
Logistic regression test	P=0.080N	P=0.382	P=0.390	P=0.131N
Cochran-Armitage test	P=0.055N			
Fisher exact test		P=0.385	P=0.408	P=0.086N
Liver: Hepatocellular Carcinoma				
Overall rate	4/50 (8%)	5/49 (10%)	5/50 (10%)	7/50 (14%)
Adjusted rate	9.8%	13.0%	15.2%	21.0%
Terminal rate	3/38 (8%)	3/36 (8%)	5/33 (15%)	5/30 (17%)
First incidence (days)	533	685	730 (T)	616
Life table test	P=0.112	P=0.466	P=0.420	P=0.163
Logistic regression test	P=0.164	P=0.487	P=0.489	P=0.232
Cochran-Armitage test	P=0.210			
Fisher exact test		P=0.487	P=0.500	P=0.262
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	15/50 (30%)	16/49 (33%)	15/50 (30%)	11/50 (22%)
Adjusted rate	36.1%	38.6%	39.5%	32.3%
Terminal rate	12/38 (32%)	11/36 (31%)	11/33 (33%)	8/30 (27%)
First incidence (days)	533	620	480	616
Life table test	P=0.418N	P=0.436	P=0.433	P=0.483N
Logistic regression test	P=0.240N	P=0.473	P=0.570	P=0.326N
Cochran-Armitage test	P=0.171N			
Fisher exact test		P=0.473	P=0.586N	P=0.247N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	3/50 (6%)	5/49 (10%)	3/50 (6%)	8/50 (16%)
Adjusted rate	7.5%	12.9%	8.7%	24.3%
Terminal rate	2/38 (5%)	3/36 (8%)	2/33 (6%)	6/30 (20%)
First incidence (days)	689	685	715	570
Life table test	P=0.035	P=0.324	P=0.599	P=0.050
Logistic regression test	P=0.052	P=0.343	P=0.643	P=0.071
Cochran-Armitage test	P=0.079			
Fisher exact test		P=0.346	P=0.661N	P=0.100

Table D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	0/50 (0%)	5/49 (10%)	1/50 (2%)	1/50 (2%)
Adjusted rate	0.0%	13.9%	2.9%	3.3%
Terminal rate	0/38 (0%)	5/36 (14%)	0/33 (0%)	1/30 (3%)
First incidence (days)	–	730 (T)	720	730 (T)
Life table test	P=0.572N	P=0.029	P=0.468	P=0.453
Logistic regression test	P=0.568N	P=0.029	P=0.491	P=0.453
Cochran-Armitage test	P=0.471N			
Fisher exact test		P=0.027	P=0.500	P=0.500
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/50 (6%)	10/49 (20%)	4/50 (8%)	9/50 (18%)
Adjusted rate	7.5%	26.1%	11.3%	27.5%
Terminal rate	2/38 (5%)	8/36 (22%)	2/33 (6%)	7/30 (23%)
First incidence (days)	689	685	715	570
Life table test	P=0.063	P=0.031	P=0.428	P=0.027
Logistic regression test	P=0.088	P=0.031	P=0.475	P=0.039
Cochran-Armitage test	P=0.147			
Fisher exact test		P=0.033	P=0.500	P=0.061
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	7/48 (15%)	6/48 (13%)	9/49 (18%)	5/48 (10%)
Adjusted rate	18.3%	16.7%	24.1%	17.9%
Terminal rate	6/37 (16%)	6/36 (17%)	6/33 (18%)	5/28 (18%)
First incidence (days)	728	730 (T)	589	730 (T)
Life table test	P=0.517	P=0.526N	P=0.309	P=0.583N
Logistic regression test	P=0.533N	P=0.564N	P=0.388	P=0.615N
Cochran-Armitage test	P=0.374N			
Fisher exact test		P=0.500N	P=0.410	P=0.379N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	8/48 (17%)	6/48 (13%)	9/49 (18%)	5/48 (10%)
Adjusted rate	20.2%	16.7%	24.1%	17.9%
Terminal rate	6/37 (16%)	6/36 (17%)	6/33 (18%)	5/28 (18%)
First incidence (days)	689	730 (T)	589	730 (T)
Life table test	P=0.504N	P=0.418N	P=0.406	P=0.474N
Logistic regression test	P=0.429N	P=0.427N	P=0.501	P=0.452N
Cochran-Armitage test	P=0.288N			
Fisher exact test		P=0.387N	P=0.519	P=0.276N
All Organs: Hemangiosarcoma				
Overall rate	4/50 (8%)	1/49 (2%)	2/50 (4%)	0/50 (0%)
Adjusted rate	10.1%	2.5%	5.6%	0.0%
Terminal rate	3/38 (8%)	0/36 (0%)	1/33 (3%)	0/30 (0%)
First incidence (days)	693	685	707	–
Life table test	P=0.078N	P=0.204N	P=0.397N	P=0.098N
Logistic regression test	P=0.062N	P=0.186N	P=0.356N	P=0.082N
Cochran-Armitage test	P=0.052N			
Fisher exact test		P=0.187N	P=0.339N	P=0.059N

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
All Organs: Histiocytic Sarcoma				
Overall rate	1/50 (2%)	2/49 (4%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.6%	4.2%	7.5%	0.0%
Terminal rate	1/38 (3%)	0/36 (0%)	1/33 (3%)	0/30 (0%)
First incidence (days)	730 (T)	526	624	–
Life table test	P=0.388N	P=0.496	P=0.281	P=0.547N
Logistic regression test	P=0.275N	P=0.444	P=0.306	P=0.547N
Cochran-Armitage test	P=0.335N			
Fisher exact test		P=0.492	P=0.309	P=0.500N
All Organs: Malignant Lymphoma (Lymphocytic or Mixed)				
Overall rate	9/50 (18%)	11/49 (22%)	9/50 (18%)	7/50 (14%)
Adjusted rate	21.5%	30.6%	24.0%	20.6%
Terminal rate	6/38 (16%)	11/36 (31%)	6/33 (18%)	3/30 (10%)
First incidence (days)	423	730 (T)	569	700
Life table test	P=0.473N	P=0.347	P=0.487	P=0.586N
Logistic regression test	P=0.344N	P=0.378	P=0.598	P=0.458N
Cochran-Armitage test	P=0.262N			
Fisher exact test		P=0.382	P=0.602N	P=0.393N
All Organs: Malignant Lymphoma or Histiocytic Sarcoma				
Overall rate	10/50 (20%)	13/49 (27%)	11/50 (22%)	7/50 (14%)
Adjusted rate	24.0%	33.4%	27.5%	20.6%
Terminal rate	7/38 (18%)	11/36 (31%)	6/33 (18%)	3/30 (10%)
First incidence (days)	423	526	569	700
Life table test	P=0.367N	P=0.274	P=0.390	P=0.495N
Logistic regression test	P=0.210N	P=0.297	P=0.499	P=0.363N
Cochran-Armitage test	P=0.175N			
Fisher exact test		P=0.298	P=0.500	P=0.298N
All Organs: Benign Neoplasms				
Overall rate	22/50 (44%)	22/49 (45%)	23/50 (46%)	21/50 (42%)
Adjusted rate	49.8%	53.3%	56.6%	59.5%
Terminal rate	16/38 (42%)	17/36 (47%)	16/33 (48%)	16/30 (53%)
First incidence (days)	589	620	480	570
Life table test	P=0.244	P=0.486	P=0.314	P=0.299
Logistic regression test	P=0.452	P=0.543	P=0.471	P=0.481
Cochran-Armitage test	P=0.449N			
Fisher exact test		P=0.545	P=0.500	P=0.500N
All Organs: Malignant Neoplasms				
Overall rate	23/50 (46%)	24/49 (49%)	23/50 (46%)	18/50 (36%)
Adjusted rate	51.9%	56.7%	51.9%	45.6%
Terminal rate	17/38 (45%)	18/36 (50%)	12/33 (36%)	9/30 (30%)
First incidence (days)	423	526	569	471
Life table test	P=0.472N	P=0.407	P=0.387	P=0.527N
Logistic regression test	P=0.193N	P=0.463	P=0.560	P=0.275N
Cochran-Armitage test	P=0.138N			
Fisher exact test		P=0.462	P=0.579N	P=0.208N

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	36/50 (72%)	38/49 (78%)	35/50 (70%)	33/50 (66%)
Adjusted rate	75.0%	82.5%	72.8%	78.5%
Terminal rate	26/38 (68%)	28/36 (78%)	20/33 (61%)	21/30 (70%)
First incidence (days)	423	526	480	471
Life table test	P=0.294	P=0.311	P=0.376	P=0.287
Logistic regression test	P=0.211N	P=0.347	P=0.390N	P=0.507N
Cochran-Armitage test	P=0.198N			
Fisher exact test		P=0.343	P=0.500N	P=0.333N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and pituitary gland; 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 exposure group incidence are the P values corresponding to pairwise comparisons between the controls and that exposure group. The life table test 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 an exposure group is indicated by N.
[e] Not applicable; no neoplasms in animal group

Table D4
Historical Incidence of Lung Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Alveolar/bronchiolar Adenoma	Alveolar/bronchiolar Carcinoma	Alveolar/bronchiolar Adenoma or Carcinoma
Historical Incidence at Southern Research Institute			
Benzyl Acetate	1/50	0/50	1/50
C.I. Pigment Red 23	1/50	0/50	1/50
C.I. Pigment Red 3	3/50	1/50	4/50
Ethylene Glycol	0/50	1/50	1/50
Nitrofurantoin	2/50	1/50	3/50
o-Nitroanisole	4/50	2/50	6/50
Polysorbate 80	3/50	0/50	3/50
Rhodamine 6G	3/50	1/50	4/50
Roxarsone	1/50	2/50	3/50
Total	18/450 (4.0%)	8/450 (1.8%)	26/450 (5.8%)
Standard deviation	2.7%	1.6%	3.4%
Range	0%-8%	0%-4%	2%-12%
Overall Historical Incidence			
Total	78/1,371 (5.7%)	30/1,371 (2.2%)	106/1,371 (7.7%)
Standard deviation	4.9%	2.3%	5.0%
Range	0%-24%	0%-8%	2%-26%

[a] Data as of 20 August 1992

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Accidental deaths			1	2
Moribund	9	8	12	10
Natural deaths	3	5	4	8
Survivors				
Terminal sacrifice	38	36	33	30
Missing		1		
Animals examined microscopically	60	59	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Angiectasis				1 (10%)
Basophilic focus				1 (10%)
Eosinophilic focus		1 (10%)		
Inflammation, subacute	1 (10%)			2 (20%)
Karyomegaly			1 (10%)	
Necrosis	1 (10%)			
Vacuolization cytoplasmic	1 (10%)			
Bile duct, cyst			1 (10%)	
Mesentery	(1)		(1)	(1)
Cyst	1 (100%)			
Fat, hemorrhage	1 (100%)			
Fat, inflammation, suppurative			1 (100%)	
Fat, necrosis			1 (100%)	1 (100%)
Pancreas	(10)	(10)	(10)	(10)
Acinus, atrophy	1 (10%)			
Stomach, forestomach	(10)	(10)	(10)	(10)
Hyperplasia		1 (10%)		
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(10)
Hyperplasia			1 (10%)	
X-zone, vacuolization cytoplasmic		4 (40%)	1 (10%)	1 (10%)
Pituitary gland	(10)	(10)	(9)	(10)
Pars distalis, hyperplasia	1 (10%)			2 (20%)
Thyroid gland	(10)	(10)	(10)	(10)
Follicle, cyst	1 (10%)			

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

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
15-Month Interim Evaluation (continued)				
Genital System				
Ovary	(10)	(10)	(10)	(10)
Angiectasis	2 (20%)			
Cyst		4 (40%)	3 (30%)	1 (10%)
Follicle, hemorrhage			1 (10%)	
Uterus	(10)	(10)	(10)	(10)
Dilatation		1 (10%)	2 (20%)	2 (20%)
Hyperplasia, cystic	8 (80%)	10 (100%)	9 (90%)	9 (90%)
Hematopoietic System				
Lymph node			(2)	
Iliac, hyperplasia, lymphoid			1 (50%)	
Lymph node, mesenteric	(9)	(10)	(10)	(10)
Necrosis				1 (10%)
Spleen	(10)	(10)	(10)	(10)
Hematopoietic cell proliferation			1 (10%)	
Hemorrhage			1 (10%)	
Hyperplasia, lymphoid	1 (10%)			
Integumentary System				
Skin	(10)	(10)	(10)	(10)
Inflammation, suppurative			1 (10%)	
Dermis, inflammation, subacute	1 (10%)			
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Infiltration cellular, lymphocyte			1 (10%)	1 (10%)
Mineralization	2 (20%)	1 (10%)	1 (10%)	
Renal tubule, casts		1 (10%)	1 (10%)	
Renal tubule, regeneration	4 (40%)		3 (30%)	1 (10%)

Systems Examined With No Lesions Observed
Cardiovascular System
General Body System
Musculoskeletal System
Nervous System
Respiratory System
Special Senses System

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study				
Alimentary System				
Gallbladder	(50)	(48)	(47)	(48)
Dilatation				1 (2%)
Inflammation, subacute		1 (2%)		
Intestine small, jejunum	(49)	(46)	(47)	(46)
Peyer's patch, hyperplasia, lymphoid			1 (2%)	
Peyer's patch, necrosis				1 (2%)
Liver	(50)	(49)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)		
Basophilic focus	1 (2%)	5 (10%)	1 (2%)	1 (2%)
Clear cell focus				1 (2%)
Developmental malformation		1 (2%)		
Eosinophilic focus	4 (8%)	5 (10%)	6 (12%)	2 (4%)
Fatty change, focal		1 (2%)		
Fibrosis			1 (2%)	
Hematopoietic cell proliferation	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Infiltration cellular, lymphocyte		1 (2%)		
Inflammation, subacute	2 (4%)			2 (4%)
Mineralization		1 (2%)	1 (2%)	
Mixed cell focus	3 (6%)	3 (6%)	1 (2%)	
Necrosis	1 (2%)	3 (6%)	2 (4%)	2 (4%)
Thrombosis		1 (2%)		
Vacuolization cytoplasmic	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Bile duct, hyperplasia				1 (2%)
Hepatocyte, hypertrophy, diffuse			1 (2%)	
Mesentery	(4)	(8)	(5)	(6)
Inflammation, subacute		2 (25%)	1 (20%)	1 (17%)
Pigmentation, hemosiderin	1 (25%)			
Polyarteritis		1 (13%)		
Fat, hemorrhage				1 (17%)
Fat, inflammation, granulomatous	1 (25%)			
Fat, inflammation, subacute				1 (17%)
Fat, necrosis	3 (75%)	4 (50%)	3 (60%)	1 (17%)
Pancreas	(50)	(47)	(49)	(49)
Basophilic focus				1 (2%)
Congestion		1 (2%)		
Edema	1 (2%)		1 (2%)	2 (4%)
Inflammation, suppurative		1 (2%)		
Acinus, atrophy			1 (2%)	3 (6%)
Acinus, depletion secretory	1 (2%)	2 (4%)	3 (6%)	3 (6%)
Duct, cyst	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Duct, degeneration		1 (2%)		
Duct, inflammation, chronic		1 (2%)		
Salivary glands	(50)	(49)	(50)	(50)
Cytoplasmic alteration				1 (2%)
Stomach, forestomach	(50)	(49)	(49)	(49)
Diverticulum	1 (2%)			
Hyperplasia	7 (14%)	4 (8%)	4 (8%)	1 (2%)
Inflammation, subacute	2 (4%)		3 (6%)	1 (2%)
Polyarteritis		1 (2%)		
Ulcer		1 (2%)		

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, glandular	(49)	(49)	(49)	(49)
Cyst	1 (2%)	3 (6%)	4 (8%)	1 (2%)
Erosion		2 (4%)	1 (2%)	1 (2%)
Hyperplasia		1 (2%)		
Inflammation, chronic			1 (2%)	
Polyarteritis		1 (2%)		
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Hemorrhage				1 (2%)
Infiltration cellular, histiocyte	1 (2%)			1 (2%)
Inflammation, subacute	1 (2%)			
Coronary artery, amyloid deposition				1 (2%)
Endocrine System				
Adrenal cortex	(49)	(48)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia				1 (2%)
Hypertrophy	3 (6%)	2 (4%)	1 (2%)	
Vacuolization cytoplasmic			1 (2%)	
Spindle cell, hyperplasia		1 (2%)		
X-zone, vacuolization cytoplasmic	2 (4%)	1 (2%)		1 (2%)
Adrenal medulla	(49)	(48)	(50)	(50)
Hyperplasia	2 (4%)			1 (2%)
Islets, pancreatic	(50)	(49)	(49)	(50)
Hyperplasia		1 (2%)		
Pituitary gland	(48)	(48)	(49)	(48)
Pars distalis, angiectasis		1 (2%)	1 (2%)	1 (2%)
Pars distalis, cyst		1 (2%)	1 (2%)	
Pars distalis, hyperplasia	10 (21%)	10 (21%)	14 (29%)	9 (19%)
Pars intermedia, hyperplasia	1 (2%)			
Thyroid gland	(50)	(49)	(50)	(50)
C-cell, hyperplasia			1 (2%)	
Follicle, cyst		1 (2%)	3 (6%)	2 (4%)
Follicle, degeneration				1 (2%)
Follicular cell, hyperplasia	17 (34%)	14 (29%)	24 (48%)	8 (16%)
General Body System				
None				

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Genital System				
Clitoral gland	(50)	(49)	(50)	(49)
Inflammation, subacute				1 (2%)
Duct, cyst	3 (6%)	9 (18%)	11 (22%)	11 (22%)
Ovary	(50)	(48)	(49)	(48)
Abscess	2 (4%)	2 (4%)		6 (13%)
Atrophy			1 (2%)	
Cyst	17 (34%)	9 (19%)	15 (31%)	14 (29%)
Hemorrhage				5 (10%)
Inflammation, subacute				1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)		
Pigmentation, hemosiderin	1 (2%)			
Oviduct			(1)	
Cyst			1 (100%)	
Uterus	(50)	(49)	(50)	(50)
Angiectasis		1 (2%)		1 (2%)
Atrophy			1 (2%)	2 (4%)
Cyst		1 (2%)	2 (4%)	
Dilatation	7 (14%)	10 (20%)	6 (12%)	4 (8%)
Hemorrhage	3 (6%)	1 (2%)		
Hyperplasia, cystic	43 (86%)	45 (92%)	48 (96%)	37 (74%)
Inflammation, subacute				1 (2%)
Thrombosis		1 (2%)		
Vagina	(1)		(1)	
Inflammation, granulomatous			1 (100%)	
Hematopoietic System				
Bone marrow	(50)	(49)	(48)	(50)
Atrophy			1 (2%)	
Hypercellularity	5 (10%)	1 (2%)	1 (2%)	4 (8%)
Myeloid cell, depletion cellular				1 (2%)
Lymph node	(8)	(10)	(13)	(15)
Axillary, hyperplasia, lymphoid		1 (10%)		
Iliac, hyperplasia, lymphoid	2 (25%)		2 (15%)	3 (20%)
Inguinal, hyperplasia, lymphoid	1 (13%)			3 (20%)
Mediastinal, edema				1 (7%)
Mediastinal, hyperplasia, lymphoid	3 (38%)	2 (20%)	1 (8%)	1 (7%)
Mediastinal, inflammation, subacute				2 (13%)
Pancreatic, hyperplasia, lymphoid			1 (8%)	
Renal, hyperplasia	1 (13%)			
Renal, hyperplasia, lymphoid	4 (50%)	2 (20%)		3 (20%)
Renal, inflammation, subacute				1 (7%)
Lymph node, mandibular	(50)	(49)	(50)	(49)
Angiectasis		2 (4%)		
Cyst		1 (2%)		
Hyperplasia, lymphoid	1 (2%)	1 (2%)		2 (4%)
Infiltration cellular, mast cell	1 (2%)		1 (2%)	

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

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mesenteric	(50)	(49)	(48)	(48)
Angiectasis	3 (6%)	4 (8%)	5 (10%)	5 (10%)
Cyst	1 (2%)			
Hematopoietic cell proliferation	1 (2%)			
Hyperplasia, lymphoid	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Spleen	(50)	(49)	(49)	(50)
Atrophy				2 (4%)
Congestion	1 (2%)			
Hematopoietic cell proliferation	12 (24%)	18 (37%)	14 (29%)	16 (32%)
Hyperplasia, lymphoid	12 (24%)	12 (24%)	9 (18%)	13 (26%)
Necrosis		1 (2%)		
Pigmentation, hemosiderin	1 (2%)		1 (2%)	1 (2%)
Thymus	(50)	(48)	(48)	(46)
Atrophy	1 (2%)		1 (2%)	4 (9%)
Integumentary System				
Mammary gland	(50)	(49)	(50)	(49)
Hyperplasia, lobular	1 (2%)			
Duct, cyst			1 (2%)	2 (4%)
Skin	(50)	(49)	(50)	(50)
Parakeratosis		1 (2%)		
Dermis, inflammation, subacute	1 (2%)	3 (6%)	2 (4%)	3 (6%)
Dermis, subcutaneous tissue, inflammation, subacute		1 (2%)		
Epidermis, necrosis		1 (2%)		
Subcutaneous tissue, edema		1 (2%)		
Subcutaneous tissue, hemorrhage			1 (2%)	
Subcutaneous tissue, inflammation, subacute		1 (2%)		
Musculoskeletal System				
Bone	(50)	(49)	(49)	(50)
Osteopetrosis			1 (2%)	
Cranium, fibrous osteodystrophy		3 (6%)		1 (2%)
Femur, fibrous osteodystrophy	2 (4%)	2 (4%)	3 (6%)	5 (10%)
Nervous System				
Brain	(49)	(49)	(50)	(50)
Compression	1 (2%)		4 (8%)	
Cyst	1 (2%)			
Vacuolization cytoplasmic		1 (2%)		
Meninges, infiltration cellular			1 (2%)	

Table D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
2-Year Study (continued)				
Respiratory System				
Lung	(50)	(49)	(50)	(50)
Congestion			1 (2%)	
Edema				1 (2%)
Hemorrhage		1 (2%)		1 (2%)
Infiltration cellular, lymphocyte		1 (2%)		
Infiltration cellular, histiocyte	2 (4%)	2 (4%)		
Inflammation, subacute				1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	3 (6%)		1 (2%)
Mediastinum, inflammation, subacute		1 (2%)		
Nose	(50)	(49)	(48)	(50)
Glands, cyst	1 (2%)			1 (2%)
Lumen, fungus		1 (2%)		
Special Senses System				
Eye	(2)	(1)		
Atrophy		1 (100%)		
Cataract	1 (50%)			
Inflammation, subacute	1 (50%)			
Cornea, inflammation, subacute	1 (50%)			
Harderian gland	(3)	(2)		
Inflammation, chronic		1 (50%)		
Urinary System				
Kidney	(50)	(49)	(50)	(50)
Fibrosis		1 (2%)		
Glomerulosclerosis	4 (8%)	3 (6%)		1 (2%)
Infarct	2 (4%)		1 (2%)	
Infiltration cellular, lymphocyte	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Inflammation, subacute	1 (2%)			1 (2%)
Metaplasia, osseous			2 (4%)	2 (4%)
Mineralization	15 (30%)	7 (14%)	7 (14%)	5 (10%)
Polyarteritis		1 (2%)		
Capsule, fibrosis				1 (2%)
Glomerulus, amyloid deposition				2 (4%)
Renal tubule, casts	4 (8%)	2 (4%)	1 (2%)	4 (8%)
Renal tubule, degeneration	1 (2%)			
Renal tubule, dilatation	1 (2%)		1 (2%)	4 (8%)
Renal tubule, hyperplasia	1 (2%)			
Renal tubule, pigmentation				1 (2%)
Renal tubule, regeneration	18 (36%)	14 (29%)	12 (24%)	9 (18%)
Urinary bladder	(50)	(49)	(49)	(50)
Dilatation		1 (2%)	1 (2%)	

APPENDIX E
GENETIC TOXICOLOGY

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GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1987). *p*-Nitrobenzoic acid was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of *p*-nitrobenzoic acid. The high dose was limited to 3,333 μg/plate. All positive trials were repeated under the conditions that elicited the positive response.

In this test, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose related, not reproducible, or is 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. There was no minimum percentage or fold increase required for a chemical to the judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1985) and Zeiger *et al.* (1987). *p*-Nitrobenzoic acid was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of *p*-nitrobenzoic acid; the high dose was limited by toxicity. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with *p*-nitrobenzoic acid in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing *p*-nitrobenzoic acid was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for approximately 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with *p*-nitrobenzoic acid, serum-free medium, and S9 for approximately 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no *p*-nitrobenzoic acid, and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen in the absence of S9 at doses of 498 μg/mL and above, incubation time was lengthened for these cultures to ensure a sufficient number of scorable (second-division metaphase) cells.

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

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with *p*-nitrobenzoic acid for 18.5 to 19.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with *p*-nitrobenzoic acid and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test: because cell cycle delay was anticipated in the absence of S9, the incubation period was extended.

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. Generally, 200 first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

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

Mouse Peripheral Blood Micronucleus Test Protocol

A detailed discussion of this assay can be found in MacGregor *et al.* (1990). Peripheral blood samples were obtained from male and female $B6C3F_1$ mice at the end of the 13-week study. Smears were immediately prepared and fixed in absolute methanol, stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor *et al.*, 1983), and coded. Slides were scanned to determine the frequency of micronuclei in 10,000 normochromatic erythrocytes (NCEs) in each of 10 animals per dose group. The criteria of Schmid (1976) were used to define micronuclei, with the additional requirement that the micronuclei exhibit the characteristic fluorescent emissions of DNA (blue with 360 nm and orange with 540 nm ultraviolet illumination); the minimum size limit was approximately one-twentieth the diameter of the NCE cell.

The frequency of micronucleated cells among NCEs was analyzed by a statistical software package (ILS, 1990) which employed a one-tailed trend test across dose groups and a *t*-test for pairwise comparisons of each dose group to the concurrent control.

RESULTS

p-Nitrobenzoic acid, tested in a preincubation protocol at concentrations of 1 to 3,333 μg/plate, with and without induced rat or hamster S9, was mutagenic in strain TA100 (Table E1; Zeiger *et al.*, 1987). No mutagenicity was detected in strains TA1535, TA1537, or TA98, with or without S9.

In cytogenetic tests with cultured CHO cells, *p*-nitrobenzoic acid induced significant increases in SCEs (Table E2; Zeiger *et al.*, 1987) and Abs (Table E3; Zeiger *et al.*, 1987) at dose levels which induced cell cycle delay in the absence of S9; no increases in either endpoint were observed in the presence of S9. In the SCE test without S9, doses ranging from 498 to 1,000 μg/mL produced positive responses, induced cell cycle delay, and required use of an extended harvest protocol to allow accumulation of sufficient cells for metaphase analysis. Doses producing positive responses in the Abs assay without S9 ranged from 875 to 1,750 μg/mL *p*-nitrobenzoic acid. As with the SCE test, cell harvest was delayed to permit a sufficient number of cells to progress to metaphase for analysis.

Despite the positive results obtained in the *in vitro* studies, results of a single NTP *in vivo* genotoxicity study were negative. In this study, the frequencies of micronucleated normochromatic erythrocytes in the peripheral blood of male and female mice were found to be unaffected by administration of *p*-nitrobenzoic acid in feed for 13 weeks (Table E4).

TABLE E1
Mutagenicity of *p*-Nitrobenzoic Acid 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% hamster S9 Trial 3
TA100	0.0	98 ± 5.8	106 ± 13.9	144 ± 11.5	140 ± 7.8	146 ± 14.4
	1.0					
	3.3		95 ± 15.6			
	10.0	83 ± 4.4	121 ± 9.6		159 ± 11.0	86 ± 5.8
	33.0	126 ± 6.1	118 ± 6.7	214 ± 17.2	173 ± 7.6	109 ± 12.0
	100.0	169 ± 12.8	146 ± 7.8	241 ± 13.8	228 ± 5.9	151 ± 16.2
	333.0	Toxic	283 ± 19.3	329 ± 7.4	321 ± 17.0	244 ± 5.6
	1,000.0	Toxic		Toxic	542 ± 29.7	373 ± 65.2
	3,333.0		5 ± 2.9			
Trial summary		Weakly Positive	Positive	Positive	Positive	Positive
Positive control[c]		1,417 ± 47.1	765 ± 76.9	1,987 ± 60.5	1,688 ± 111.4	1,314 ± 35.7

Strain	Dose (µg/plate)	Revertants/plate +10% rat S9 Trial 1	+10% rat S9 Trial 2	+10% rat S9 Trial 3
TA100 (continued)	0.0	130 ± 10.5	163 ± 5.2	133 ± 10.2
	1.0			
	3.3			
	10.0		168 ± 3.7	116 ± 8.2
	33.0	164 ± 12.1	182 ± 9.2	126 ± 1.2
	100.0	232 ± 17.1	224 ± 9.0	169 ± 5.8
	333.0	274 ± 9.5	351 ± 15.6	227 ± 2.7
	1,000.0	Toxic	501 ± 19.4	401 ± 26.5
	3,333.0	17 ± 7.2		
Trial summary		Positive	Positive	Positive
Positive control		1,675 ± 99.1	2,329 ± 49.4	2,086 ± 106.3

TABLE E1
Mutagenicity of *p*-Nitrobenzoic Acid 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
TA1535	0.0	11 ± 1.2		16 ± 0.9	8 ± 0.7	11 ± 0.7	
	1.0						
	3.3				6 ± 1.3		
	10.0	5 ± 1.3			5 ± 1.5		
	33.0	7 ± 0.7		14 ± 1.2	7 ± 0.9	16 ± 1.2	
	100.0	9 ± 0.7		17 ± 1.5	8 ± 1.2	15 ± 0.9	
	333.0	7 ± 1.8		3 ± 0.7	7 ± 1.2	4 ± 0.9	
	1,000.0	5 ± 1.5		1 ± 1.0		2 ± 1.5	
	3,333.0			0 ± 0.0		0 ± 0.0	
Trial summary		Negative		Negative	Negative	Negative	
Positive control		319 ± 66.5		145 ± 9.7	148 ± 12.8	115 ± 13.2	
TA1537	0.0	8 ± 1.2	6 ± 0.9	18 ± 0.9		14 ± 0.7	
	1.0		4 ± 1.5				
	3.3		5 ± 0.9				
	10.0	10 ± 0.7	5 ± 2.7				
	33.0	5 ± 1.7	5 ± 0.6	14 ± 0.6		14 ± 3.0	
	100.0	8 ± 0.3	6 ± 0.9	17 ± 2.3		16 ± 1.5	
	333.0	0 ± 0.3		15 ± 0.3		10 ± 3.9	
	1,000.0	1 ± 0.6		10 ± 0.9		3 ± 1.7	
	3,333.0			4 ± 0.7		1 ± 0.3	
Trial summary		Negative	Negative	Negative		Negative	
Positive control		228 ± 35.3	166 ± 75.8	335 ± 42.9		323 ± 44.3	
TA98	0.0	21 ± 1.2		28 ± 1.2	17 ± 4.7	16 ± 2.0	14 ± 0.3
	1.0						
	3.3				22 ± 0.9		18 ± 2.6
	10.0	25 ± 4.0			18 ± 2.0		25 ± 5.2
	33.0	22 ± 2.9		30 ± 1.5	20 ± 2.2	24 ± 2.9	24 ± 3.1
	100.0	22 ± 0.3		25 ± 5.8	20 ± 4.0	20 ± 6.5	14 ± 0.3
	333.0	21 ± 0.9		20 ± 3.3	18 ± 3.6	8 ± 2.0	19 ± 3.5
	1,000.0	16 ± 0.3		19 ± 3.8		10 ± 2.9	
	3,333.0			18 ± 1.8		17 ± 3.0	
Trial summary		Negative		Negative	Negative	Negative	Equivocal
Positive control		535 ± 50.4		1,484 ± 80.3	1,323 ± 73.5	1,837 ± 135.5	1,793 ± 49.9

[a] Study performed at Case Western Reserve University. The detailed protocol and these data are presented in Zeiger *et al.* (1987).
[b] Revertants are presented as mean ± standard error from three plates.
[c] 2-Aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *p*-Nitrobenzoic Acid[a]

Compound	Dose (µg/mL)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9								
Trial 1								
Summary: Weak positive								
Dimethylsulfoxide								
		50	1,045	398	0.38	8.0	25.7	
Mitomycin-C								
	0.001	50	1,050	584	0.55	11.7	25.7	46.04
	0.010	5	105	245	2.33	49.0	25.7	512.65
p-Nitrobenzoic acid								
	58.3	50	1,031	382	0.37	7.6	25.7	-2.72
	175.0	50	1,041	429	0.41	8.6	25.7	8.20
	583.0	50	1,033	570	0.55	11.4	31.3[c]	44.88*
	1,750.0	0					31.3	
					P<0.001[d]			
Trial 2								
Summary: Positive								
Dimethylsulfoxide								
		50	1,044	380	0.36	7.6	25.5	
Mitomycin-C								
	0.001	50	1,042	580	0.55	11.6	25.5	52.93
	0.010	5	105	251	2.39	50.2	25.5	556.76
p-Nitrobenzoic acid								
	498	50	1,034	505	0.48	10.1	32.4[c]	34.18*
	753	50	1,045	604	0.57	12.1	32.4[c]	58.80*
	1,000	50	1,049	629	0.59	12.6	32.4[c]	64.74*
	1,510	0						
					P<0.001			

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by *p*-Nitrobenzoic Acid (continued)

Compound	Dose (µg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)
+S9								
Summary: Negative								
Dimethylsulfoxide								
		50	1,041	346	0.33	6.9	25.5	
Cyclophosphamide								
	0.4	25	519	312	0.60	12.5	25.5	80.87
	2.0	5	105	157	1.49	31.4	25.5	349.87
p-Nitrobenzoic acid								
	175	50	1,044	393	0.37	7.9	25.5	13.26
	583	50	1,037	328	0.31	6.6	25.5	-4.84
	1,750	50	1,027	364	0.35	7.3	25.5	6.64
					P=0.485			

* Positive (P≤0.01)
[a] Study performed at Litton Bionetics, Inc. The protocol is presented in detail by Galloway *et al.* (1985); data published in Zeiger *et al.* (1987). SCE = sister chromatid exchange; BrdU = bromodeoxyuridine.
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells.
[c] Because of chemical-induced cell cycle delay, incubation time was lengthened to ensure sufficient metaphase cells at harvest.
[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose.

Table E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by *p*-Nitrobenzoic Acid[a]

-S9					+S9				
Dose (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (µg/mL)	Total Cells	No. of Abs	Abs/ Cell	Cells with Abs (%)
Trial 1 - Harvest time: 20.5 hours[b]					**Trial 1** - Harvest time: 12.5 hours				
Summary: Positive					Summary: Equivocal				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	8	0.04	3.0		200	10	0.05	3.5
Mitomycin-C					Cyclophosphamide				
0.05	50	22	0.44	30.0	7.5	200	30	0.15	12.0
0.08	25	37	1.48	56.0	37.5	25	38	1.52	84.0
p-Nitrobenzoic acid					*p*-Nitrobenzoic acid				
875	200	21	0.11	8.5*	875	200	13	0.07	5.5
1,313	200	30	0.15	12.5*	1,313	200	14	0.07	5.5
1,750	50	20	0.40	26.0*	1,750	200	24	0.12	9.0*
				P<0.001[c]					P=0.015
Trial 2 - Harvest time: 21.5 hours[b]					**Trial 2** - Harvest time: 12.5 hours				
Summary: Positive					Summary: Negative				
Dimethylsulfoxide					Dimethylsulfoxide				
	200	1	0.01	0.5		200	1	0.01	0.5
Mitomycin-C					Cyclophosphamide				
0.05	200	48	0.24	15.0	7.5	200	16	0.08	7.0
0.08	25	28	1.12	48.0	37.5	25	12	0.48	36.0
p-Nitrobenzoic acid					*p*-Nitrobenzoic acid				
439.5	200	3	0.02	1.5	1,249	200	2	0.01	1.0
879.0	200	7	0.04	3.5*	1,505	200	10	0.05	4.5*
1,313.0	200	17	0.09	7.5*	1,750	200	3	0.02	1.5
				P<0.001					P=0.052

* Positive (P≤0.05)

[a] Study performed at Litton Bionetics, Inc. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway *et al.* (1985); data published in Zeiger *et al.* (1987). Abs = aberrations.

[b] Because of chemical-induced cell cycle delay, incubation time prior to addition of Colcemid was lengthened to ensure sufficient metaphase cells at harvest.

[c] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose.

TABLE E4
Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Administration of *p*-Nitrobenzoic Acid in Feed for 13 Weeks[a]

Dose (ppm)	Micronucleated Normochromatic Erythrocytes (%)[b]	Pairwise Significance
Male		
0	0.1412 ± 0.0132	
1,250	0.1466 ± 0.0119	0.365
2,500	0.1313 ± 0.0096	0.750
5,000	0.1600 ± 0.0111	0.114
10,000	0.1250 ± 0.0119	0.869
20,000	0.1492 ± 0.0092	0.300
		P=0.424
Female		
0	0.1031 ± 0.0127	
1,250	0.0992 ± 0.0062	0.590
2,500	0.0997 ± 0.0086	0.583
5,000	0.1146 ± 0.0078	0.242
10,000	0.1453 ± 0.0238	0.009
20,000	0.1032 ± 0.0058	0.497
		P=0.215

[a] Ten thousand normochromatic erythrocytes scored per animal. A detailed description of the protocol is found in MacGregor *et al.* (1990).

[b] Data presented as mean ± standard error. Pairwise comparison of treated group to concurrent control by Student's *t*-test. One-tailed trend test performed across all doses (ILS, 1990).

APPENDIX F ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Day Feed Study of *p*-Nitrobenzoic Acid 252

TABLE F2 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of *p*-Nitrobenzoic Acid 254

TABLE F3 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of *p*-Nitrobenzoic Acid 256

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TABLE F5 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of *p*-Nitrobenzoic Acid 259

TABLE F6 Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of *p*-Nitrobenzoic Acid 261

Table F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Day Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Male						
n	5	5	5	5	5	5
Necropsy body wt	210 ± 4	205 ± 6	198 ± 3	173 ± 4**	127 ± 5**	110 ± 6**
Brain						
Absolute	1.866 ± 0.013	1.840 ± 0.041	1.847 ± 0.015	1.785 ± 0.017*	1.727 ± 0.013**	1.674 ± 0.032**
Relative	8.89 ± 0.14	8.99 ± 0.12	9.34 ± 0.12	10.32 ± 0.16**	13.68 ± 0.47**	15.33 ± 0.58**
Heart						
Absolute	0.856 ± 0.019	0.859 ± 0.061	0.843 ± 0.024	0.777 ± 0.030	0.649 ± 0.022**	0.550 ± 0.041**
Relative	4.08 ± 0.09	4.18 ± 0.22	4.26 ± 0.11	4.49 ± 0.15	5.13 ± 0.20**	4.99 ± 0.25**
R. Kidney						
Absolute	1.005 ± 0.031	1.073 ± 0.068	1.093 ± 0.043	0.992 ± 0.045	0.722 ± 0.029**	0.631 ± 0.032**
Relative	4.79 ± 0.11	5.22 ± 0.19	5.52 ± 0.19**	5.72 ± 0.13**	5.69 ± 0.12**	5.75 ± 0.17**
Liver						
Absolute	12.380 ± 0.156	12.272 ± 0.420	12.555 ± 0.502	11.831 ± 0.452	7.733 ± 0.313**	6.145 ± 0.268**
Relative	58.97 ± 0.62	59.86 ± 0.51	63.39 ± 1.93	68.25 ± 1.31**	60.96 ± 1.09	56.11 ± 2.14
Lungs						
Absolute	1.204 ± 0.041	1.321 ± 0.092	1.350 ± 0.059	1.325 ± 0.081	0.908 ± 0.033**	0.881 ± 0.022**
Relative	5.73 ± 0.15	6.43 ± 0.30	6.82 ± 0.30*	7.65 ± 0.42**	7.16 ± 0.07**	8.08 ± 0.40**
Spleen						
Absolute	0.533 ± 0.017	0.556 ± 0.020	0.553 ± 0.018	0.640 ± 0.038*	0.856 ± 0.051**	0.779 ± 0.018**
Relative	2.54 ± 0.10	2.71 ± 0.06	2.80 ± 0.09	3.69 ± 0.19**	6.73 ± 0.25**	7.14 ± 0.30**
R. Testis						
Absolute	1.208 ± 0.039	1.156 ± 0.050	1.147 ± 0.016	1.100 ± 0.027	0.866 ± 0.062**	0.775 ± 0.063**
Relative	5.76 ± 0.19	5.64 ± 0.17	5.80 ± 0.12	6.35 ± 0.08	6.79 ± 0.24**	7.00 ± 0.30**
Thymus						
Absolute	0.450 ± 0.029	0.382 ± 0.022	0.402 ± 0.018	0.306 ± 0.016**	0.158 ± 0.023**	0.076 ± 0.008**
Relative	2.15 ± 0.18	1.88 ± 0.16	2.03 ± 0.07	1.77 ± 0.09	1.26 ± 0.18**	0.69 ± 0.07**

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Day Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Female						
n	5	5	5	5	5	5
Necropsy body wt	140 ± 3	139 ± 4	134 ± 3	123 ± 3**	95 ± 4**	91 ± 4**
Brain						
Absolute	1.750 ± 0.018	1.719 ± 0.016	1.878 ± 0.105	1.680 ± 0.012	1.633 ± 0.007	1.638 ± 0.026
Relative	12.48 ± 0.20	12.38 ± 0.42	14.07 ± 1.09	13.73 ± 0.33	17.29 ± 0.65**	18.07 ± 0.62**
Heart						
Absolute	0.653 ± 0.019	0.623 ± 0.022	0.635 ± 0.017	0.625 ± 0.022	0.473 ± 0.027**	0.477 ± 0.034**
Relative	4.65 ± 0.12	4.48 ± 0.12	4.74 ± 0.10	5.10 ± 0.11	4.97 ± 0.15	5.21 ± 0.17**
R. Kidney						
Absolute	0.734 ± 0.010	0.704 ± 0.015	0.694 ± 0.026	0.654 ± 0.022*	0.507 ± 0.022**	0.510 ± 0.020**
Relative	5.23 ± 0.08	5.06 ± 0.07	5.17 ± 0.18	5.33 ± 0.09	5.33 ± 0.10	5.60 ± 0.05*
Liver						
Absolute	7.497 ± 0.312	7.018 ± 0.308	7.256 ± 0.158	7.100 ± 0.415	5.221 ± 0.365**	5.228 ± 0.231**
Relative	53.34 ± 1.52	50.34 ± 1.47	54.16 ± 1.55	57.75 ± 2.12	54.81 ± 2.39	57.41 ± 1.45
Lungs						
Absolute	0.968 ± 0.026	0.988 ± 0.043	1.021 ± 0.023	0.911 ± 0.033	0.778 ± 0.031**	0.737 ± 0.027**
Relative	6.89 ± 0.09	7.12 ± 0.35	7.61 ± 0.15	7.42 ± 0.16	8.21 ± 0.29**	8.14 ± 0.43**
Spleen						
Absolute	0.404 ± 0.008	0.395 ± 0.014	0.406 ± 0.011	0.522 ± 0.023**	0.516 ± 0.032**	0.485 ± 0.038**
Relative	2.88 ± 0.10	2.84 ± 0.13	3.03 ± 0.07	4.26 ± 0.17**	5.44 ± 0.33**	5.32 ± 0.35**
Thymus						
Absolute	0.346 ± 0.010	0.361 ± 0.020	0.331 ± 0.007	0.295 ± 0.012*	0.146 ± 0.011**	0.110 ± 0.028**
Relative	2.47 ± 0.09	2.60 ± 0.17	2.47 ± 0.09	2.42 ± 0.13	1.54 ± 0.10**	1.17 ± 0.26**

* 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 F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	630 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	362 ± 5	367 ± 5	348 ± 6	347 ± 4	330 ± 7**	271 ± 3**
Brain						
Absolute	1.943 ± 0.018	1.923 ± 0.021	1.925 ± 0.019	1.941 ± 0.022	1.882 ± 0.026	1.863 ± 0.018*
Relative	5.38 ± 0.07	5.24 ± 0.05	5.55 ± 0.11	5.59 ± 0.06	5.73 ± 0.15*	6.88 ± 0.11**
Heart						
Absolute	1.156 ± 0.027	1.114 ± 0.020	1.107 ± 0.038	1.110 ± 0.015	1.039 ± 0.019**	0.918 ± 0.021**
Relative	3.20 ± 0.07	3.04 ± 0.05	3.18 ± 0.09	3.20 ± 0.04	3.15 ± 0.07	3.39 ± 0.07
R. Kidney						
Absolute	1.284 ± 0.032	1.331 ± 0.029	1.297 ± 0.031	1.341 ± 0.024	1.318 ± 0.027	1.118 ± 0.013**
Relative	3.55 ± 0.05	3.62 ± 0.05	3.73 ± 0.06*	3.86 ± 0.06**	4.00 ± 0.05**	4.13 ± 0.05**
Liver						
Absolute	12.899 ± 0.312	13.802 ± 0.241	12.765 ± 0.256	13.263 ± 0.218	12.713 ± 0.252	12.131 ± 0.185*
Relative	35.63 ± 0.40	37.61 ± 0.40*	36.72 ± 0.37*	38.18 ± 0.42**	38.54 ± 0.44**	44.80 ± 0.67**
Lungs						
Absolute	1.693 ± 0.077	2.003 ± 0.136	1.741 ± 0.111	1.734 ± 0.067	1.792 ± 0.112	1.522 ± 0.075
Relative	4.68 ± 0.19	5.45 ± 0.36	5.01 ± 0.31	4.99 ± 0.17	5.46 ± 0.39	5.63 ± 0.29*
Spleen						
Absolute	0.785 ± 0.027	0.822 ± 0.023	0.776 ± 0.015	0.800 ± 0.011	0.806 ± 0.016	1.073 ± 0.023**
Relative	2.17 ± 0.06	2.24 ± 0.05	2.23 ± 0.03	2.30 ± 0.02	2.45 ± 0.07**	3.96 ± 0.09**
R. Testis						
Absolute	1.488 ± 0.024	1.478 ± 0.032	1.455 ± 0.027	1.435 ± 0.026	1.373 ± 0.020**	0.408 ± 0.024**
Relative	4.12 ± 0.04	4.03 ± 0.08	4.18 ± 0.03	4.13 ± 0.06	4.17 ± 0.06	1.50 ± 0.08**
Thymus						
Absolute	0.333 ± 0.020	0.355 ± 0.022	0.312 ± 0.015	0.314 ± 0.014	0.304 ± 0.018	0.233 ± 0.011**
Relative	0.92 ± 0.04	0.97 ± 0.06	0.90 ± 0.04	0.90 ± 0.03	0.92 ± 0.05	0.86 ± 0.04

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	630 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm
Female						
n	10	10	10	10	10	10
Necropsy body wt	205 ± 3	206 ± 3	202 ± 3	201 ± 3	185 ± 3**	171 ± 2**
Brain						
Absolute	1.789 ± 0.025	1.822 ± 0.015	1.805 ± 0.013	1.797 ± 0.026	1.805 ± 0.011	·1.780 ± 0.027
Relative	8.72 ± 0.13	8.86 ± 0.14	8.95 ± 0.16	8.94 ± 0.11	9.79 ± 0.12**	10.41 ± 0.20**
Heart						
Absolute	0.705 ± 0.011	0.714 ± 0.017	0.703 ± 0.018	0.711 ± 0.017	0.691 ± 0.010	0.656 ± 0.012*
Relative	3.44 ± 0.05	3.48 ± 0.10	3.48 ± 0.07	3.54 ± 0.08	3.74 ± 0.05**	3.83 ± 0.06**
R. Kidney						
Absolute	0.763 ± 0.015	0.747 ± 0.016	0.736 ± 0.015	0.717 ± 0.017*	0.683 ± 0.014**	0.681 ± 0.007**
Relative	3.72 ± 0.08	3.63 ± 0.06	3.64 ± 0.06	3.56 ± 0.05	3.70 ± 0.05	3.98 ± 0.04**
Liver						
Absolute	6.582 ± 0.104	7.030 ± 0.138	6.626 ± 0.125	6.675 ± 0.114	6.257 ± 0.101	6.187 ± 0.104*
Relative	32.10 ± 0.56	34.14 ± 0.48	32.79 ± 0.54	33.20 ± 0.42	33.89 ± 0.34*	36.16 ± 0.69**
Lungs						
Absolute	1.157 ± 0.052	1.124 ± 0.042	1.139 ± 0.050	1.255 ± 0.105	1.098 ± 0.031	1.007 ± 0.034
Relative	5.62 ± 0.18	5.46 ± 0.20	5.65 ± 0.27	6.22 ± 0.49	5.94 ± 0.13	5.88 ± 0.17
Spleen						
Absolute	0.524 ± 0.020	0.522 ± 0.007	0.498 ± 0.016	0.545 ± 0.017	0.549 ± 0.006	0.676 ± 0.011**
Relative	2.55 ± 0.10	2.54 ± 0.04	2.46 ± 0.07	2.71 ± 0.05	2.98 ± 0.05**	3.95 ± 0.05**
Thymus						
Absolute	0.277 ± 0.011	0.287 ± 0.009	0.280 ± 0.009	0.295 ± 0.016	0.266 ± 0.012	0.242 ± 0.008*
Relative	1.35 ± 0.05	1.40 ± 0.06	1.38 ± 0.05	1.46 ± 0.07	1.44 ± 0.06	1.41 ± 0.04

* 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).

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male				
n	10	9	10	10
Necropsy body wt	483 ± 7	488 ± 9	490 ± 8	475 ± 5
R. Kidney				
Absolute	1.697 ± 0.045	1.720 ± 0.042	1.700 ± 0.037	1.744 ± 0.042
Relative	3.51 ± 0.07	3.52 ± 0.07	3.47 ± 0.07	3.67 ± 0.08
Liver				
Absolute	17.192 ± 0.398	16.933 ± 0.554	16.238 ± 0.393	17.289 ± 0.353
Relative	35.58 ± 0.44	34.64 ± 0.76	33.14 ± 0.69*	36.37 ± 0.67
Spleen				
Absolute	1.115 ± 0.058	1.112 ± 0.069	1.065 ± 0.031	1.046 ± 0.020
Relative	2.31 ± 0.12	2.28 ± 0.13	2.18 ± 0.07	2.20 ± 0.04
Female				
n	10	10	10	10
Necropsy body wt	297 ± 7	297 ± 7	280 ± 5	260 ± 4**
R. Kidney				
Absolute	1.000 ± 0.026	0.984 ± 0.016	0.920 ± 0.019**	0.897 ± 0.017**
Relative	3.37 ± 0.07	3.32 ± 0.05	3.29 ± 0.05	3.46 ± 0.06
Liver				
Absolute	9.103 ± 0.257	9.575 ± 0.280	8.842 ± 0.174	9.480 ± 0.279
Relative	30.69 ± 0.63	32.17 ± 0.30	31.60 ± 0.56	36.49 ± 0.81**
Spleen				
Absolute	0.512 ± 0.021	0.585 ± 0.024*	0.583 ± 0.018*	0.671 ± 0.022**
Relative	1.73 ± 0.07	1.97 ± 0.07*	2.08 ± 0.05**	2.59 ± 0.08**

* 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 F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Day Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Male						
n	5	5	5	5	5	2
Necropsy body wt	19.5 ± 0.9	19.1 ± 0.7	18.4 ± 0.5	19.0 ± 0.4	17.9 ± 0.5	18.0 ± 0.4
Brain						
Absolute	0.469 ± 0.008	0.455 ± 0.006	0.447 ± 0.008	0.457 ± 0.007	0.455 ± 0.003	0.469 ± 0.020
Relative	24.30 ± 1.00	23.92 ± 0.98	24.42 ± 0.66	24.02 ± 0.35	25.51 ± 0.81	26.12 ± 0.60
Heart						
Absolute	0.159 ± 0.011	0.149 ± 0.006	0.154 ± 0.007	0.151 ± 0.005	0.153 ± 0.008	0.142 ± 0.006
Relative	8.17 ± 0.44	7.77 ± 0.14	8.37 ± 0.24	7.96 ± 0.39	8.56 ± 0.31	7.89 ± 0.46
R. Kidney						
Absolute	0.246 ± 0.012	0.210 ± 0.016	0.185 ± 0.007**	0.205 ± 0.010	0.196 ± 0.009*	0.226 ± 0.013
Relative	12.74 ± 0.78	10.94 ± 0.63	10.06 ± 0.31*	10.76 ± 0.60	11.03 ± 0.74	12.58 ± 0.48
Liver						
Absolute	1.334 ± 0.046	1.111 ± 0.054	1.084 ± 0.025	1.265 ± 0.027	1.337 ± 0.031	1.518 ± 0.069*
Relative	68.77 ± 1.78	58.08 ± 1.51	59.07 ± 0.93	66.46 ± 1.35	75.00 ± 2.54*	84.53 ± 2.20**
Lungs						
Absolute	0.216 ± 0.009	0.192 ± 0.011	0.192 ± 0.007	0.203 ± 0.011	0.226 ± 0.007	0.227 ± 0.051
Relative	11.22 ± 0.67	10.00 ± 0.26	10.48 ± 0.41	10.70 ± 0.61	12.70 ± 0.76	12.57 ± 2.57
Spleen						
Absolute	0.058 ± 0.002	0.060 ± 0.002	0.055 ± 0.002	0.062 ± 0.003	0.060 ± 0.006	0.048 ± 0.005
Relative	2.99 ± 0.10	3.12 ± 0.09	3.02 ± 0.02	3.26 ± 0.13	3.35 ± 0.28	2.64 ± 0.20
R. Testis						
Absolute	0.100 ± 0.004	0.103 ± 0.004	0.100 ± 0.005	0.100 ± 0.003	0.097 ± 0.005	0.093 ± 0.005
Relative	5.18 ± 0.17	5.42 ± 0.29	5.47 ± 0.23	5.27 ± 0.08	5.41 ± 0.17	5.15 ± 0.15
Thymus						
Absolute	0.065 ± 0.004	0.051 ± 0.006	0.057 ± 0.005	0.067 ± 0.010	0.039 ± 0.006*	0.037 ± 0.012*
Relative	3.36 ± 0.30	2.70 ± 0.31	3.14 ± 0.32	3.57 ± 0.56	2.16 ± 0.31*	2.05 ± 0.68

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Day Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Female						
n	5	5	5	5	5	3
Necropsy body wt	16.8 ± 0.7	16.5 ± 0.4	15.9 ± 0.4	15.3 ± 0.2*	14.6 ± 0.3**	15.3 ± 0.7*
Brain						
Absolute	0.468 ± 0.007	0.444 ± 0.008	0.453 ± 0.007	0.441 ± 0.003*	0.443 ± 0.008*	0.446 ± 0.011*
Relative	28.00 ± 0.85	27.00 ± 0.69	28.48 ± 0.44	28.86 ± 0.22	30.32 ± 0.60	29.36 ± 1.90
Heart						
Absolute	0.140 ± 0.005	0.126 ± 0.005	0.120 ± 0.003**	0.115 ± 0.005**	0.111 ± 0.004**	0.117 ± 0.012**
Relative	8.39 ± 0.27	7.65 ± 0.21	7.56 ± 0.30*	7.50 ± 0.31	7.59 ± 0.14	7.66 ± 0.49
R. Kidney						
Absolute	0.197 ± 0.013	0.143 ± 0.006**	0.144 ± 0.005**	0.143 ± 0.009**	0.151 ± 0.012**	0.164 ± 0.010
Relative	11.76 ± 0.76	8.70 ± 0.28**	9.06 ± 0.19**	9.33 ± 0.53*	10.27 ± 0.72	10.76 ± 0.29
Liver						
Absolute	1.128 ± 0.059	0.967 ± 0.025	1.001 ± 0.026	1.130 ± 0.008	1.180 ± 0.040	1.243 ± 0.070
Relative	67.10 ± 1.42	58.71 ± 0.89	63.05 ± 2.45	73.92 ± 1.11*	80.58 ± 2.11**	81.68 ± 4.96**
Lungs						
Absolute	0.214 ± 0.014	0.182 ± 0.012	0.165 ± 0.005*	0.177 ± 0.010	0.184 ± 0.012	0.197 ± 0.006
Relative	12.67 ± 0.29	11.01 ± 0.63	10.40 ± 0.29*	11.56 ± 0.56	12.59 ± 0.74	13.02 ± 1.01
Spleen						
Absolute	0.065 ± 0.005	0.063 ± 0.005	0.061 ± 0.003	0.058 ± 0.004	0.051 ± 0.006*	0.050 ± 0.005
Relative	3.86 ± 0.19	3.81 ± 0.26	3.80 ± 0.13	3.79 ± 0.26	3.43 ± 0.37	3.26 ± 0.20
Thymus						
Absolute	0.082 ± 0.006	0.071 ± 0.008	0.069 ± 0.009	0.046 ± 0.004**	0.035 ± 0.005**	0.038 ± 0.002**
Relative	4.88 ± 0.36	4.29 ± 0.42	4.38 ± 0.65	2.98 ± 0.29**	2.35 ± 0.34**	2.49 ± 0.22**

* 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 F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	34.0 ± 0.7	31.7 ± 0.6*	31.8 ± 1.2	30.8 ± 0.8**	27.6 ± 0.4**	24.1 ± 0.6**
Brain						
Absolute	0.466 ± 0.007	0.481 ± 0.012	0.487 ± 0.009	0.494 ± 0.008	0.482 ± 0.012	0.465 ± 0.005
Relative	13.78 ± 0.36	15.20 ± 0.43*	15.51 ± 0.57**	16.11 ± 0.44**	17.50 ± 0.44**	19.35 ± 0.44**
Heart						
Absolute	0.160 ± 0.007	0.157 ± 0.003	0.156 ± 0.005	0.155 ± 0.004	0.137 ± 0.004**	0.126 ± 0.006**
Relative	4.71 ± 0.16	4.96 ± 0.05	4.94 ± 0.18	5.03 ± 0.10	4.98 ± 0.11	5.23 ± 0.27
R. Kidney						
Absolute	0.295 ± 0.007	0.310 ± 0.008	0.316 ± 0.010	0.302 ± 0.012	0.264 ± 0.011*	0.211 ± 0.005**
Relative	8.74 ± 0.33	9.76 ± 0.17*	10.01 ± 0.25**	9.78 ± 0.25*	9.57 ± 0.35	8.77 ± 0.16
Liver						
Absolute	1.431 ± 0.050	1.416 ± 0.048	1.470 ± 0.071	1.524 ± 0.050	1.346 ± 0.032	1.130 ± 0.047**
Relative	42.09 ± 1.02	44.58 ± 1.05	46.22 ± 1.21**	49.47 ± 1.11**	48.81 ± 1.08**	46.68 ± 0.92**
Lungs						
Absolute	0.203 ± 0.006	0.227 ± 0.010	0.221 ± 0.013	0.217 ± 0.012	0.222 ± 0.018	0.216 ± 0.012
Relative	6.00 ± 0.23	7.21 ± 0.38	7.05 ± 0.51	7.07 ± 0.39	8.02 ± 0.61**	9.04 ± 0.66**
Spleen						
Absolute	0.071 ± 0.002	0.071 ± 0.003	0.072 ± 0.004	0.077 ± 0.005	0.075 ± 0.005	0.052 ± 0.004**
Relative	2.08 ± 0.05	2.23 ± 0.09	2.26 ± 0.08	2.50 ± 0.14*	2.73 ± 0.17*	2.11 ± 0.13
R. Testis						
Absolute	0.124 ± 0.001	0.123 ± 0.002	0.139 ± 0.003	0.120 ± 0.003[b]	0.127 ± 0.006	0.097 ± 0.002**
Relative	3.65 ± 0.09	3.88 ± 0.08	4.41 ± 0.19*	3.89 ± 0.10*[b]	4.60 ± 0.19**	4.05 ± 0.11**
Thymus						
Absolute	0.055 ± 0.003	0.048 ± 0.003	0.051 ± 0.006	0.051 ± 0.005	0.041 ± 0.003	0.044 ± 0.004
Relative	1.60 ± 0.07	1.51 ± 0.09	1.58 ± 0.17	1.63 ± 0.14	1.48 ± 0.13	1.78 ± 0.12

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm
Female						
n	10	9	10	10	10	10
Necropsy body wt	26.4 ± 0.6	26.2 ± 0.4	26.8 ± 0.6	25.2 ± 0.3	22.8 ± 0.3**	20.6 ± 0.4**
Brain						
Absolute	0.520 ± 0.012	0.495 ± 0.011	0.511 ± 0.010	0.500 ± 0.010	0.499 ± 0.011	0.473 ± 0.011**
Relative	19.77 ± 0.45	18.95 ± 0.60	19.16 ± 0.50	19.85 ± 0.51	21.96 ± 0.44**	23.05 ± 0.71**
Heart						
Absolute	0.143 ± 0.004	0.128 ± 0.004	0.139 ± 0.005	0.131 ± 0.004[b]	0.125 ± 0.003*	0.123 ± 0.008**
Relative	5.45 ± 0.19	4.89 ± 0.12	5.18 ± 0.15	5.19 ± 0.16[b]	5.51 ± 0.16	5.98 ± 0.40
R. Kidney						
Absolute	0.212 ± 0.009	0.212 ± 0.007	0.226 ± 0.008	0.208 ± 0.005	0.188 ± 0.005*	0.171 ± 0.005**
Relative	8.06 ± 0.31	8.10 ± 0.28	8.45 ± 0.23	8.25 ± 0.20	8.25 ± 0.20	8.29 ± 0.19
Liver						
Absolute	1.345 ± 0.057	1.167 ± 0.098	1.401 ± 0.049	1.272 ± 0.037	1.230 ± 0.041	1.095 ± 0.024**
Relative	50.95 ± 1.45	44.82 ± 3.86	52.30 ± 1.17	50.40 ± 1.16	54.05 ± 1.59	53.23 ± 0.69
Lungs						
Absolute	0.198 ± 0.012	0.200 ± 0.007	0.207 ± 0.011	0.241 ± 0.025	0.223 ± 0.013	0.239 ± 0.012
Relative	7.49 ± 0.40	7.65 ± 0.34	7.76 ± 0.36	9.50 ± 0.88**	9.81 ± 0.53**	11.56 ± 0.42**
Spleen						
Absolute	0.090 ± 0.005	0.090 ± 0.004	0.103 ± 0.005	0.095 ± 0.004	0.084 ± 0.007	0.061 ± 0.005**
Relative	3.41 ± 0.16	3.45 ± 0.14	3.85 ± 0.14	3.75 ± 0.14	3.68 ± 0.26	2.95 ± 0.21
Thymus						
Absolute	0.065 ± 0.005	0.054 ± 0.003	0.064 ± 0.004	0.049 ± 0.002*	0.056 ± 0.005*	0.043 ± 0.003**
Relative	2.46 ± 0.16	2.07 ± 0.13	2.40 ± 0.14	1.94 ± 0.10	2.47 ± 0.25	2.06 ± 0.14

* 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 F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male				
n	10	10	10	10
Necropsy body wt	47.8 ± 1.5	44.3 ± 1.7	47.9 ± 1.6	46.2 ± 1.5
R. Kidney				
Absolute	0.397 ± 0.015	0.356 ± 0.007	0.379 ± 0.013	0.363 ± 0.014
Relative	8.32 ± 0.24	8.11 ± 0.26	7.94 ± 0.24	7.86 ± 0.23
Liver				
Absolute	2.083 ± 0.157	2.427 ± 0.377	2.001 ± 0.129	1.906 ± 0.098
Relative	43.40 ± 2.57	57.08 ± 11.55	41.64 ± 1.88	41.05 ± 0.93
Spleen				
Absolute	0.085 ± 0.013	0.081 ± 0.009	0.082 ± 0.006	0.072 ± 0.005
Relative	1.78 ± 0.24	1.90 ± 0.31	1.73 ± 0.15	1.55 ± 0.09
Female				
n	10	10	9	10
Necropsy body wt	48.9 ± 1.2	46.3 ± 2.3	43.1 ± 1.5*	38.9 ± 1.0**
R. Kidney				
Absolute	0.272 ± 0.005	0.275 ± 0.005	0.268 ± 0.008	0.279 ± 0.021
Relative	5.59 ± 0.16	6.06 ± 0.28	6.29 ± 0.32	7.32 ± 0.78*
Liver				
Absolute	1.734 ± 0.111	1.714 ± 0.038	1.662 ± 0.045	1.649 ± 0.049
Relative	35.54 ± 2.22	37.66 ± 1.60	38.95 ± 1.55	42.58 ± 1.56**
Spleen				
Absolute	0.108 ± 0.007	0.093 ± 0.003	0.116 ± 0.012	0.103 ± 0.004
Relative	2.21 ± 0.14	2.08 ± 0.17	2.80 ± 0.44	2.67 ± 0.13

* Significantly different ($P \le 0.05$) from the control group by Williams' or Dunnett's test
** $P \le 0.01$
[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 G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

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TABLE G1
Hematology Data for Rats in the 14-Day Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Male						
n	5	5	5	5	5	5
Hematocrit (%)	43.7 ± 0.8	44.2 ± 0.5	44.1 ± 0.6	42.3 ± 1.0	36.9 ± 0.6**	37.4 ± 0.9**
Hemoglobin (g/dL)	15.5 ± 0.2	15.5 ± 0.1	15.3 ± 0.2	14.8 ± 0.3	13.5 ± 0.3**	13.5 ± 0.3**
Erythrocytes ($10^6/\mu L$)	8.13 ± 0.16	8.09 ± 0.10	8.22 ± 0.10	7.77 ± 0.15	6.51 ± 0.18**	6.22 ± 0.31**
Mean cell volume (fL)	53.8 ± 0.5	54.8 ± 1.0	53.6 ± 0.4	54.6 ± 0.8	56.6 ± 0.8*	60.6 ± 2.0**
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.4 ± 0.1	0.4 ± 0.0*	0.5 ± 0.1**	0.9 ± 0.1**	1.3 ± 0.2**
Leukocytes ($10^3/\mu L$)	9.84 ± 0.57	9.42 ± 0.51	9.38 ± 1.14	10.84 ± 0.73	19.44 ± 1.38**	15.78 ± 1.62**
Segmented neutrophils ($10^3/\mu L$)	1.16 ± 0.20	1.24 ± 0.25	1.31 ± 0.16	1.73 ± 0.16	3.48 ± 0.92**	2.58 ± 0.39**
Lymphocytes ($10^3/\mu L$)	8.36 ± 0.57	7.95 ± 0.58	7.90 ± 1.08	8.95 ± 0.69	15.66 ± 0.78**	12.86 ± 1.22*
Monocytes ($10^3/\mu L$)	0.25 ± 0.03	0.19 ± 0.05	0.16 ± 0.03	0.17 ± 0.04	0.25 ± 0.09	0.34 ± 0.13
Eosinophils ($10^3/\mu L$)	0.06 ± 0.03	0.04 ± 0.02	0.02 ± 0.02	0.00 ± 0.00*	0.05 ± 0.05	0.00 ± 0.00*
Nucleated erythrocytes ($10^3/\mu L$)	0.12 ± 0.05	0.06 ± 0.04	0.17 ± 0.08	2.88 ± 0.84**	37.14 ± 4.60**	47.76 ± 6.91**
Methemoglobin (% hemoglobin)	0.14 ± 0.05	0.11 ± 0.01	0.27 ± 0.01	0.38 ± 0.13	3.06 ± 0.20**	2.48 ± 0.18**

TABLE G1
Hematology Data for Rats in the 14-Day Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	2,500 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Female						
n	5	5	5	5	5	5
Hematocrit (%)	44.7 ± 0.5	45.0 ± 0.3	44.8 ± 0.4	40.6 ± 0.7*	37.8 ± 0.6**	38.5 ± 1.2**
Hemoglobin (g/dL)	15.8 ± 0.2	16.0 ± 0.1	15.8 ± 0.2	14.4 ± 0.2*	13.4 ± 0.2**	13.7 ± 0.4**
Erythrocytes ($10^6/\mu L$)	8.27 ± 0.12	8.36 ± 0.08	8.45 ± 0.10	7.47 ± 0.11*	7.12 ± 0.10**	7.24 ± 0.32*
Mean cell volume (fL)	54.0 ± 0.3	53.8 ± 0.4	53.2 ± 0.2	54.4 ± 0.5	53.2 ± 0.8	53.2 ± 0.7
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.3 ± 0.0*	0.2 ± 0.0	0.8 ± 0.1**	0.7 ± 0.1**	0.3 ± 0.1*
Leukocytes ($10^3/\mu L$)	10.38 ± 0.64	10.42 ± 0.64	10.50 ± 1.07	10.28 ± 0.70	13.50 ± 1.25	10.92 ± 0.79
Segmented neutrophils ($10^3/\mu L$)	1.35 ± 0.12	1.48 ± 0.28	1.46 ± 0.14	1.47 ± 0.07	2.14 ± 0.25*	1.81 ± 0.33
Lymphocytes ($10^3/\mu L$)	8.69 ± 0.82	8.64 ± 0.48	8.66 ± 0.96	8.50 ± 0.69	11.04 ± 1.18	8.89 ± 0.80
Monocytes ($10^3/\mu L$)	0.29 ± 0.07	0.26 ± 0.10	0.33 ± 0.08	0.26 ± 0.07	0.31 ± 0.10	0.22 ± 0.10
Eosinophils ($10^3/\mu L$)	0.05 ± 0.04	0.04 ± 0.02	0.04 ± 0.03	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Nucleated erythrocytes ($10^3/\mu L$)	0.10 ± 0.04	0.14 ± 0.08	0.06 ± 0.02	2.42 ± 0.45*	9.03 ± 2.38**	12.26 ± 5.35**
Methemoglobin (% hemoglobin)	0.09 ± 0.02	0.16 ± 0.02*	0.35 ± 0.02**	0.53 ± 0.03**	1.63 ± 0.13**	1.27 ± 0.15**

* 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 G2
Hematology and Clinical Chemistry Data for Special Study Rats in the 13-Week Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	630 ppm	2,500 ppm	10,000 ppm
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)				
Day 7	42.8 ± 0.9	42.0 ± 0.5	43.9 ± 0.6	43.7 ± 0.5[b]
Day 30	48.0 ± 0.7	46.6 ± 0.8	46.6 ± 0.9	44.5 ± 0.7**
Day 60	45.6 ± 0.3[c]	45.1 ± 0.6[c]	44.8 ± 0.7[c]	43.6 ± 0.5*
Day 90	45.0 ± 0.7	44.3 ± 0.5	43.7 ± 0.6	42.9 ± 0.6
Hemoglobin (g/dL)				
Day 7	15.1 ± 0.1	15.1 ± 0.2	15.5 ± 0.2	15.4 ± 0.2[b]
Day 30	16.9 ± 0.2	16.6 ± 0.2	16.5 ± 0.2	15.5 ± 0.1**
Day 60	16.8 ± 0.2[c]	16.8 ± 0.3[c]	16.8 ± 0.3[c]	15.5 ± 0.2**
Day 90	16.5 ± 0.2	16.6 ± 0.2	16.4 ± 0.2	15.5 ± 0.2**
Erythrocytes ($10^6/\mu L$)				
Day 7	7.00 ± 0.15	6.92 ± 0.11	7.11 ± 0.12	7.18 ± 0.08[b]
Day 30	9.12 ± 0.13	8.84 ± 0.12	8.89 ± 0.15	7.83 ± 0.13**
Day 60	9.62 ± 0.09[c]	9.28 ± 0.12*[c]	9.46 ± 0.13[c]	8.32 ± 0.17**
Day 90	9.37 ± 0.13	9.09 ± 0.14	9.08 ± 0.13	8.18 ± 0.12**
Mean cell volume (fL)				
Day 7	61.2 ± 1.1	60.9 ± 1.3	61.9 ± 1.0	60.9 ± 0.6[b]
Day 30	52.5 ± 0.4	52.6 ± 0.3	52.5 ± 0.4	56.8 ± 0.4**
Day 60	47.4 ± 0.2[c]	48.6 ± 0.3*[c]	47.4 ± 0.2[c]	52.5 ± 0.7**
Day 90	48.0 ± 0.2	48.7 ± 0.3*	48.2 ± 0.3	52.4 ± 0.3**
Mean cell hemoglobin (pg)				
Day 7	21.7 ± 0.5	21.9 ± 0.4	21.9 ± 0.4	21.4 ± 0.3[b]
Day 30	18.6 ± 0.2	18.8 ± 0.1	18.7 ± 0.3	19.9 ± 0.2**
Day 60	17.5 ± 0.2[c]	18.1 ± 0.1*[c]	17.7 ± 0.2[c]	18.6 ± 0.2**
Day 90	17.6 ± 0.1	18.2 ± 0.2*	18.1 ± 0.2*	18.9 ± 0.2**
Mean cell hemoglobin concentration (g/dL)				
Day 7	35.5 ± 0.8	36.0 ± 0.2	35.4 ± 0.2	35.2 ± 0.3[b]
Day 30	35.3 ± 0.4	35.7 ± 0.4	35.6 ± 0.6	35.0 ± 0.4
Day 60	36.9 ± 0.4[c]	37.2 ± 0.4[c]	37.4 ± 0.4[c]	35.6 ± 0.3*
Day 90	36.7 ± 0.4	37.4 ± 0.4	37.7 ± 0.5	36.1 ± 0.3
Reticulocytes ($10^6/\mu L$)				
Day 7	0.16 ± 0.02	0.15 ± 0.02	0.17 ± 0.02	0.23 ± 0.03*[b]
Day 30	0.07 ± 0.01	0.11 ± 0.01**	0.09 ± 0.01	0.26 ± 0.03**
Day 60	0.09 ± 0.02[c]	0.08 ± 0.01[c]	0.11 ± 0.01[c]	0.20 ± 0.03**
Day 90	0.08 ± 0.01	0.06 ± 0.01	0.09 ± 0.01	0.15 ± 0.02*
Leukocytes ($10^3/\mu L$)				
Day 7	5.48 ± 0.39	5.60 ± 0.14	5.81 ± 0.41	5.30 ± 0.33[b]
Day 30	7.98 ± 0.29	7.55 ± 0.24	7.59 ± 0.28	9.35 ± 0.45
Day 60	7.06 ± 0.49[c]	7.41 ± 0.51[c]	7.17 ± 0.22[c]	7.34 ± 0.39
Day 90	7.46 ± 0.55	7.34 ± 0.54	8.14 ± 0.46	8.00 ± 0.69
Segmented neutrophils ($10^3/\mu L$)				
Day 7	0.49 ± 0.06	0.56 ± 0.07	0.60 ± 0.05	0.76 ± 0.07**[b]
Day 30	0.90 ± 0.09	0.92 ± 0.08	1.09 ± 0.12	2.01 ± 0.12**
Day 60	1.44 ± 0.20[c]	1.31 ± 0.11[c]	1.24 ± 0.16[c]	1.82 ± 0.12
Day 90	1.54 ± 0.07	1.61 ± 0.13	1.83 ± 0.15	2.31 ± 0.20**

TABLE G2
Hematology and Clinical Chemistry Data for Special Study Rats in the 13-Week Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	630 ppm	2,500 ppm	10,000 ppm
Male (continued)				
n	10	10	10	10
Hematology (continued)				
Lymphocytes ($10^3/\mu L$)				
Day 7	4.91 ± 0.39	4.96 ± 0.13	5.11 ± 0.40	4.46 ± 0.27[b]
Day 30	6.95 ± 0.27	6.40 ± 0.23	6.37 ± 0.30	7.22 ± 0.37
Day 60	5.40 ± 0.43[c]	5.98 ± 0.47[c]	5.76 ± 0.20[c]	5.47 ± 0.35
Day 90	5.86 ± 0.52	5.61 ± 0.47	6.22 ± 0.45	5.64 ± 0.65
Monocytes ($10^3/\mu L$)				
Day 7	0.06 ± 0.02	0.04 ± 0.02	0.06 ± 0.02	0.03 ± 0.02[b]
Day 30	0.13 ± 0.03	0.12 ± 0.03	0.08 ± 0.03	0.10 ± 0.03
Day 60	0.10 ± 0.03[c]	0.06 ± 0.02[c]	0.08 ± 0.03[c]	0.03 ± 0.02*
Day 90	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)				
Day 7	0.01 ± 0.01	0.05 ± 0.02	0.05 ± 0.02	0.04 ± 0.02[b]
Day 30	0.05 ± 0.02	0.10 ± 0.02	0.05 ± 0.03	0.02 ± 0.01
Day 60	0.11 ± 0.04[c]	0.09 ± 0.02[c]	0.09 ± 0.02[c]	0.03 ± 0.02*
Day 90	0.07 ± 0.02	0.12 ± 0.04	0.09 ± 0.02	0.06 ± 0.02
Heinz bodies (% RBC)				
Day 7	0.22 ± 0.03	0.26 ± 0.03	0.23 ± 0.03	0.40 ± 0.05**[b]
Day 30	0.10 ± 0.02	0.19 ± 0.04	0.08 ± 0.03	0.37 ± 0.06**
Day 60	0.09 ± 0.04[c]	0.17 ± 0.09[c]	0.26 ± 0.07*[c]	0.48 ± 0.06**
Day 90	0.10 ± 0.02	0.05 ± 0.02	0.15 ± 0.03	0.47 ± 0.12**
Methemoglobin (% hemoglobin)				
Day 7	0.39 ± 0.06	0.43 ± 0.08	0.39 ± 0.12	1.04 ± 0.22*
Day 30	0.49 ± 0.21	1.21 ± 0.24*	1.92 ± 0.40**	4.03 ± 0.18**
Day 60	0.72 ± 0.09[c]	0.59 ± 0.06[c]	0.69 ± 0.10	3.20 ± 0.25**
Day 90	0.79 ± 0.09	0.66 ± 0.09	0.89 ± 0.13	3.33 ± 0.25**
Clinical Chemistry				
Alkaline phosphatase (IU/L)				
Day 7	326 ± 7	313 ± 5	328 ± 6	283 ± 4**
Day 30	252 ± 11	259 ± 8	247 ± 5	191 ± 6**
Day 60	146 ± 6	170 ± 15	137 ± 4	116 ± 4**
Day 90	129 ± 9	117 ± 4	111 ± 3	101 ± 4**
Alanine aminotransferase (IU/L)				
Day 7	26 ± 1	28 ± 1	30 ± 1	33 ± 2**
Day 30	40 ± 2	35 ± 1	34 ± 1*	40 ± 1
Day 60	42 ± 2	43 ± 2	40 ± 2	49 ± 6
Day 90	42 ± 2	41 ± 1	42 ± 1	39 ± 2
Sorbitol dehydrogenase (IU/L)				
Day 7	63 ± 6	64 ± 7	63 ± 7	61 ± 7
Day 30	83 ± 9	70 ± 6	70 ± 5	67 ± 5
Day 60	81 ± 6	68 ± 4	70 ± 5	73 ± 6
Day 90	65 ± 6	56 ± 7	57 ± 6	49 ± 6*

TABLE G2
Hematology and Clinical Chemistry Data for Special Study Rats in the 13-Week Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	630 ppm	2,500 ppm	10,000 ppm
Female				
n	10	10	10	10
Hematology				
Hematocrit (%)				
Day 7	42.3 ± 0.5	43.2 ± 0.9	44.7 ± 1.1	43.8 ± 0.7
Day 30	46.8 ± 0.4	46.4 ± 0.7	45.5 ± 0.3*	44.0 ± 0.7**
Day 60	45.2 ± 0.4	45.7 ± 0.4	45.6 ± 0.5	42.5 ± 0.5**
Day 90	44.3 ± 0.6	43.4 ± 0.6	44.0 ± 0.5	43.0 ± 0.6
Hemoglobin (g/dL)				
Day 7	15.5 ± 0.2	15.6 ± 0.2	15.9 ± 0.2	15.6 ± 0.2
Day 30	16.8 ± 0.1	16.9 ± 0.2	16.7 ± 0.1	15.7 ± 0.2**
Day 60	16.9 ± 0.2	16.9 ± 0.1	16.7 ± 0.1	15.5 ± 0.1**
Day 90	16.6 ± 0.1	16.3 ± 0.2	16.5 ± 0.1	15.9 ± 0.1**
Erythrocytes ($10^6/\mu L$)				
Day 7	7.33 ± 0.13	7.56 ± 0.18	7.72 ± 0.21	7.74 ± 0.20
Day 30	8.77 ± 0.08	8.73 ± 0.17	8.62 ± 0.06	8.01 ± 0.14**
Day 60	9.03 ± 0.12	9.08 ± 0.11	9.05 ± 0.09	8.15 ± 0.08**
Day 90	8.65 ± 0.11	8.39 ± 0.12	8.67 ± 0.09	8.27 ± 0.10
Mean cell volume (fL)				
Day 7	57.9 ± 0.7	57.3 ± 0.6	58.0 ± 0.7	56.8 ± 0.7
Day 30	53.5 ± 0.3	53.4 ± 0.3	52.9 ± 0.4	55.0 ± 0.4*
Day 60	50.0 ± 0.5	50.3 ± 0.3	50.5 ± 0.2	52.2 ± 0.3**
Day 90	51.3 ± 0.4	51.8 ± 0.3	50.6 ± 0.4	51.9 ± 0.3
Mean cell hemoglobin (pg)				
Day 7	21.2 ± 0.3	20.7 ± 0.3	20.6 ± 0.4	20.3 ± 0.3
Day 30	19.2 ± 0.1	19.3 ± 0.2	19.4 ± 0.1	19.6 ± 0.2
Day 60	18.7 ± 0.1	18.6 ± 0.1	18.5 ± 0.2	19.0 ± 0.2
Day 90	19.2 ± 0.1	19.5 ± 0.2	19.0 ± 0.2	19.3 ± 0.2
Mean cell hemoglobin concentration (g/dL)				
Day 7	36.7 ± 0.2	36.2 ± 0.4	35.6 ± 0.5*	35.7 ± 0.3*
Day 30	36.0 ± 0.2	36.3 ± 0.4	36.8 ± 0.1	35.7 ± 0.3
Day 60	37.3 ± 0.2	36.9 ± 0.2	36.7 ± 0.3	36.4 ± 0.3*
Day 90	37.5 ± 0.3	37.6 ± 0.3	37.5 ± 0.4	37.1 ± 0.4
Reticulocytes ($10^6/\mu L$)				
Day 7	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.0**
Day 30	0.1 ± 0.0	0.0 ± 0.0	0.1 ± 0.0	0.2 ± 0.0**
Day 60	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0	0.2 ± 0.0**
Day 90	0.1 ± 0.0	0.1 ± 0.0	0.0 ± 0.0*	0.1 ± 0.0
Leukocytes ($10^3/\mu L$)				
Day 7	5.36 ± 0.42	6.04 ± 0.40	5.65 ± 0.24	6.63 ± 0.38*
Day 30	6.95 ± 0.30	6.53 ± 0.31	6.19 ± 0.42	8.82 ± 0.31**
Day 60	5.43 ± 0.26	5.60 ± 0.30	5.58 ± 0.35	6.09 ± 0.54
Day 90	6.64 ± 0.35	6.44 ± 0.44	5.58 ± 0.37	7.14 ± 0.90
Segmented neutrophils ($10^3/\mu L$)				
Day 7	0.62 ± 0.07	0.72 ± 0.11	0.63 ± 0.06	0.78 ± 0.14
Day 30	0.72 ± 0.15	0.77 ± 0.09	0.86 ± 0.13	1.45 ± 0.13**
Day 60	0.99 ± 0.08	0.93 ± 0.13	1.08 ± 0.16	1.22 ± 0.11
Day 90	1.46 ± 0.14	1.65 ± 0.19	1.28 ± 0.12	1.40 ± 0.17

TABLE G2
Hematology and Clinical Chemistry Data for Special Study Rats in the 13-Week Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	630 ppm	2,500 ppm	10,000 ppm
Female (continued)				
n	10	10	10	10
Hematology (continued)				
Lymphocytes ($10^3/\mu L$)				
Day 7	4.65 ± 0.35	5.24 ± 0.41	4.87 ± 0.19	5.66 ± 0.34*
Day 30	5.95 ± 0.27	5.68 ± 0.27	5.20 ± 0.32	7.23 ± 0.29
Day 60	4.35 ± 0.26	4.51 ± 0.21	4.36 ± 0.24	4.74 ± 0.48
Day 90	5.07 ± 0.33	4.69 ± 0.33	4.18 ± 0.32	5.64 ± 0.77
Monocytes ($10^3/\mu L$)				
Day 7	0.04 ± 0.02	0.03 ± 0.02	0.07 ± 0.02	0.04 ± 0.02
Day 30	0.10 ± 0.04	0.06 ± 0.02	0.06 ± 0.03	0.10 ± 0.03
Day 60	0.03 ± 0.02	0.07 ± 0.03	0.07 ± 0.03	0.07 ± 0.03
Day 90	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)				
Day 7	0.06 ± 0.02	0.05 ± 0.02	0.10 ± 0.02	0.04 ± 0.02
Day 30	0.07 ± 0.03	0.05 ± 0.02	0.08 ± 0.03	0.06 ± 0.02
Day 60	0.05 ± 0.02	0.11 ± 0.02	0.08 ± 0.03	0.05 ± 0.02
Day 90	0.09 ± 0.02	0.12 ± 0.02	0.09 ± 0.02	0.03 ± 0.02[c]
Heinz bodies (% RBC)				
Day 7	0.18 ± 0.04	0.19 ± 0.04	0.13 ± 0.05	0.37 ± 0.03**
Day 30	0.10 ± 0.03	0.09 ± 0.03	0.11 ± 0.03	0.24 ± 0.03**
Day 60	0.11 ± 0.02	0.12 ± 0.04	0.16 ± 0.03	0.37 ± 0.15**
Day 90	0.08 ± 0.03	0.11 ± 0.04	0.08 ± 0.02	0.25 ± 0.16**
Methemoglobin (% hemoglobin)				
Day 7	0.48 ± 0.10	0.56 ± 0.12	0.36 ± 0.10	1.29 ± 0.19**
Day 30	1.24 ± 0.23	2.34 ± 0.66	0.62 ± 0.24	3.10 ± 0.21**
Day 60	0.64 ± 0.11[c]	0.85 ± 0.08	0.73 ± 0.09[c]	1.92 ± 0.21**
Day 90	0.78 ± 0.10[c]	0.86 ± 0.06	0.95 ± 0.14	2.08 ± 0.15**
Clinical Chemistry				
Alkaline phosphatase (IU/L)				
Day 7	240 ± 7	235 ± 6	238 ± 5	208 ± 5**
Day 30	183 ± 7	169 ± 6	191 ± 6	164 ± 5
Day 60	105 ± 5	109 ± 5	107 ± 3	102 ± 4
Day 90	75 ± 2	77 ± 4	88 ± 3**	101 ± 5**
Alanine aminotransferase (IU/L)				
Day 7	26 ± 1	26 ± 1	30 ± 2	37 ± 2**
Day 30	32 ± 2	31 ± 1	33 ± 2	47 ± 2**
Day 60	45 ± 3	37 ± 2	47 ± 7	63 ± 10
Day 90	33 ± 1	34 ± 1	34 ± 1	43 ± 2**
Sorbitol dehydrogenase (IU/L)				
Day 7	70 ± 4	55 ± 6	58 ± 4	60 ± 8
Day 30	58 ± 5	59 ± 4	74 ± 7	69 ± 7
Day 60	72 ± 2	69 ± 5	73 ± 6	76 ± 5
Day 90	52 ± 6	61 ± 8	54 ± 6	52 ± 4

* 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=8 [c] n=9

TABLE G3
Hematology Data for Rats at the 15-Month Interim Evaluation in the 2-Year Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male				
n	10	8	10	10
Hematocrit (%)	47.1 ± 0.7	48.1 ± 0.6	48.6 ± 0.6	47.1 ± 0.8
Hemoglobin (g/dL)	15.5 ± 0.2	15.9 ± 0.2	16.0 ± 0.2	15.4 ± 0.2
Erythrocytes ($10^6/\mu L$)	8.81 ± 0.10	9.04 ± 0.15	9.18 ± 0.12*	9.21 ± 0.12*
Mean cell volume (fL)	53.5 ± 0.2	53.3 ± 0.5	53.0 ± 0.5	51.2 ± 0.3**
Mean cell hemoglobin (pg)	17.6 ± 0.2	17.7 ± 0.2	17.5 ± 0.2	16.7 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	32.9 ± 0.3	33.1 ± 0.3	32.9 ± 0.2	32.6 ± 0.2
Platelets ($10^3/\mu L$)	602.1 ± 14.6	579.6 ± 18.2	593.7 ± 13.2	647.3 ± 15.1
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.2 ± 0.0	0.1 ± 0.0	0.1 ± 0.0[b]
Leukocytes ($10^3/\mu L$)	8.55 ± 0.57	8.65 ± 0.41	8.58 ± 0.45	10.55 ± 0.85*
Segmented neutrophils ($10^3/\mu L$)	2.24 ± 0.36	2.20 ± 0.24	2.73 ± 0.36	2.67 ± 0.23[b]
Lymphocytes ($10^3/\mu L$)	5.93 ± 0.34	5.99 ± 0.35	5.50 ± 0.40	6.88 ± 0.32
Atypical lymphocytes ($10^3/\mu L$)	0.02 ± 0.01	0.06 ± 0.03	0.02 ± 0.01	0.02 ± 0.02
Monocytes ($10^3/\mu L$)	0.21 ± 0.06	0.28 ± 0.09	0.18 ± 0.05	0.15 ± 0.03
Eosinophils ($10^3/\mu L$)	0.14 ± 0.03	0.14 ± 0.04	0.16 ± 0.03	0.08 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)	0.09 ± 0.02	0.14 ± 0.03	0.18 ± 0.04	0.20 ± 0.03*
Methemoglobin (% hemoglobin)	0.22 ± 0.02	0.24 ± 0.02[b]	0.26 ± 0.02	0.28 ± 0.02*
Female				
n	10	10	9	10
Hematocrit (%)	46.3 ± 0.3	44.9 ± 0.4*	45.8 ± 0.4	44.1 ± 0.4**
Hemoglobin (g/dL)	16.0 ± 0.2	15.5 ± 0.2	15.7 ± 0.1	14.9 ± 0.2**
Erythrocytes ($10^6/\mu L$)	8.24 ± 0.06	8.00 ± 0.12	8.20 ± 0.07	7.84 ± 0.07**
Mean cell volume (fL)	56.3 ± 0.3	56.1 ± 0.6	55.8 ± 0.3	56.3 ± 0.3
Mean cell hemoglobin (pg)	19.4 ± 0.1	19.4 ± 0.1	19.2 ± 0.1*	19.0 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	34.5 ± 0.2	34.6 ± 0.3	34.4 ± 0.2	33.8 ± 0.1*
Platelets ($10^3/\mu L$)	560.3 ± 16.8	510.1 ± 29.2	576.7 ± 12.7	652.3 ± 21.8**
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0	0.3 ± 0.1	0.3 ± 0.0	0.3 ± 0.0
Leukocytes ($10^3/\mu L$)	4.09 ± 0.16	4.58 ± 0.40	4.52 ± 0.22	6.05 ± 0.49**
Segmented neutrophils ($10^3/\mu L$)	1.11 ± 0.08	1.42 ± 0.12*	1.10 ± 0.08	1.87 ± 0.26*
Lymphocytes ($10^3/\mu L$)	2.86 ± 0.12	3.02 ± 0.34	3.32 ± 0.21	4.06 ± 0.28**
Atypical lymphocytes ($10^3/\mu L$)	0.02 ± 0.02	0.03 ± 0.02	0.01 ± 0.01	0.02 ± 0.01
Monocytes ($10^3/\mu L$)	0.02 ± 0.02	0.01 ± 0.01	0.00 ± 0.00	0.03 ± 0.02
Eosinophils ($10^3/\mu L$)	0.05 ± 0.02	0.09 ± 0.02	0.07 ± 0.02	0.09 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.09 ± 0.04	0.19 ± 0.04[b]	0.18 ± 0.05	0.42 ± 0.08**
Methemoglobin (% hemoglobin)	0.26 ± 0.03	0.26 ± 0.02	0.28 ± 0.03[c]	0.31 ± 0.03

* 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=9 [c] n=10

TABLE G4
Hematology Data for Mice in the 14-Day Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	1,250 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Male						
n	5	4	5	4	5	2
Hematocrit (%)	47.1 ± 1.4	48.8 ± 1.6	50.5 ± 0.8	48.3 ± 0.5	50.3 ± 1.5	49.8 ± 1.0
Hemoglobin (g/dL)	15.8 ± 0.4	16.3 ± 0.1	16.7 ± 0.1	16.3 ± 0.1	15.8 ± 0.3	16.1 ± 0.2
Erythrocytes ($10^6/\mu L$)	9.89 ± 0.41	10.18 ± 0.32	10.29 ± 0.14	10.21 ± 0.13	10.31 ± 0.30	10.24 ± 0.10
Mean cell volume (fL)	47.8 ± 0.6	48.0 ± 0.0	49.2 ± 0.6	46.8 ± 0.5	48.8 ± 0.4	48.5 ± 0.5
Reticulocytes ($10^6/\mu L$)	0.3 ± 0.0	0.2 ± 0.0	0.2 ± 0.1	0.3 ± 0.1	0.5 ± 0.1	0.3 ± 0.0
Leukocytes ($10^3/\mu L$)	4.60 ± 0.68	5.13 ± 0.48	5.38 ± 0.38	4.40 ± 0.84	3.10 ± 0.38	3.70 ± 1.00
Segmented neutrophils ($10^3/\mu L$)	0.55 ± 0.07	0.44 ± 0.08	0.60 ± 0.12	0.37 ± 0.07	0.62 ± 0.03	0.53 ± 0.23
Lymphocytes ($10^3/\mu L$)	3.87 ± 0.59	4.51 ± 0.48	4.62 ± 0.28	3.92 ± 0.75	2.43 ± 0.37	3.02 ± 0.70
Monocytes ($10^3/\mu L$)	0.13 ± 0.08	0.09 ± 0.03	0.08 ± 0.02	0.06 ± 0.03	0.04 ± 0.02	0.05 ± 0.00
Eosinophils ($10^3/\mu L$)	0.05 ± 0.05	0.09 ± 0.04	0.08 ± 0.04	0.05 ± 0.03	0.02 ± 0.01	0.11 ± 0.08
Methemoglobin (% hemoglobin)	0.06 ± 0.04	0.00 ± 0.00	0.02 ± 0.01[b]	0.00 ± 0.00[c]	0.05 ± 0.03	–[d]

TABLE G4
Hematology Data for Mice in the 14-Day Feed Study of *p*-Nitrobenzoic Acid (continued)

	0 ppm	1,250 ppm	5,000 ppm	10,000 ppm	20,000 ppm	40,000 ppm
Female						
n	5	5	5	5	5	3
Hematocrit (%)	48.5 ± 1.0	48.3 ± 1.2	48.6 ± 0.9	49.2 ± 1.5	46.7 ± 0.9	46.6 ± 1.2
Hemoglobin (g/dL)	16.3 ± 0.3	16.0 ± 0.2	16.4 ± 0.1	16.1 ± 0.4	15.4 ± 0.1*	15.3 ± 0.3
Erythrocytes ($10^6/\mu L$)	9.99 ± 0.26	10.06 ± 0.27	10.17 ± 0.21	10.34 ± 0.47	9.71 ± 0.21	9.61 ± 0.28
Mean cell volume (fL)	48.4 ± 0.4	48.0 ± 0.0	47.8 ± 0.6	47.6 ± 0.9	48.2 ± 0.4	48.3 ± 0.3
Reticulocytes ($10^6/\mu L$)	0.3 ± 0.0	0.2 ± 0.0	0.2 ± 0.0	0.3 ± 0.1[b]	0.3 ± 0.1	0.3 ± 0.0
Leukocytes ($10^3/\mu L$)	3.80 ± 0.67	6.70 ± 0.50	6.58 ± 0.31	5.16 ± 0.92	3.40 ± 0.27	5.30 ± 1.40
Segmented neutrophils ($10^3/\mu L$)	0.37 ± 0.14	0.59 ± 0.11	0.85 ± 0.15*	0.69 ± 0.12[b]	0.81 ± 0.18*	0.61 ± 0.40
Lymphocytes ($10^3/\mu L$)	3.37 ± 0.61	5.80 ± 0.54	5.43 ± 0.34	4.41 ± 1.01[b]	2.56 ± 0.20	3.30 ± 1.76
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.05 ± 0.01	0.17 ± 0.05	0.13 ± 0.05[b]	0.01 ± 0.01	0.11 ± 0.07
Eosinophils ($10^3/\mu L$)	0.05 ± 0.02	0.26 ± 0.10	0.02 ± 0.02	0.10 ± 0.03[b]	0.02 ± 0.01	0.18 ± 0.12
Methemoglobin (% hemoglobin)	0.01 ± 0.01	0.07 ± 0.04	0.16 ± 0.04	0.00 ± 0.00[c]	0.27 ± 0.16	0.15 ± 0.02

* Significantly different (P≤0.05) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error
[b] n=4
[c] n=3
[d] n=0; no data reported

TABLE G5
Hematology Data for Mice at the 15-Month Interim Evaluation in the 2-Year Feed Study of *p*-Nitrobenzoic Acid[a]

	0 ppm	1,250 ppm	2,500 ppm	5,000 ppm
Male				
n	9	10	10	9
Hematocrit (%)	47.1 ± 0.5	48.2 ± 0.9	47.6 ± 0.5	48.3 ± 0.5
Hemoglobin (g/dL)	16.0 ± 0.1	16.2 ± 0.4	16.2 ± 0.1	16.3 ± 0.1*
Erythrocytes ($10^6/\mu L$)	9.94 ± 0.16	10.12 ± 0.30	10.04 ± 0.16	10.16 ± 0.14
Mean cell volume (fL)	47.3 ± 0.4	47.8 ± 0.5	47.5 ± 0.7	47.6 ± 0.5
Mean cell hemoglobin (pg)	16.1 ± 0.3	16.1 ± 0.3	16.2 ± 0.2	16.1 ± 0.2
Mean cell hemoglobin concentration (g/dL)	34.0 ± 0.4	33.7 ± 0.4	34.1 ± 0.3	33.9 ± 0.3
Platelets ($10^3/\mu L$)	1,279 ± 53	1,405 ± 68	1,310 ± 57	1,309 ± 30
Reticulocytes ($10^6/\mu L$)	0.1 ± 0.0[b]	0.2 ± 0.0[c]	0.2 ± 0.0[c]	0.2 ± 0.0
Leukocytes ($10^3/\mu L$)	4.35 ± 0.29[d]	4.54 ± 0.21	3.79 ± 0.17[d]	4.26 ± 0.34
Segmented neutrophils ($10^3/\mu L$)	1.13 ± 0.15[d]	1.40 ± 0.11	0.96 ± 0.08[d]	1.21 ± 0.15
Lymphocytes ($10^3/\mu L$)	3.14 ± 0.21[d]	3.06 ± 0.24	2.89 ± 0.22[c]	2.90 ± 0.25
Atypical lymphocytes ($10^3/\mu L$)	0.00 ± 0.00[d]	0.00 ± 0.00	0.00 ± 0.00[c]	0.00 ± 0.00
Monocytes ($10^3/\mu L$)	0.00 ± 0.00[d]	0.01 ± 0.01	0.00 ± 0.00[c]	0.01 ± 0.01
Eosinophils ($10^3/\mu L$)	0.08 ± 0.04[d]	0.09 ± 0.02	0.13 ± 0.03[c]	0.13 ± 0.04
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00[d]	0.00 ± 0.00[c]	0.00 ± 0.00[c]	0.00 ± 0.00
Methemoglobin (% hemoglobin)	0.16 ± 0.03[d]	0.17 ± 0.02	0.16 ± 0.02[c]	0.14 ± 0.02
Female				
n	10	9	9	10
Hematocrit (%)	46.3 ± 0.7	46.6 ± 0.5	47.1 ± 0.7	45.2 ± 0.5
Hemoglobin (g/dL)	16.0 ± 0.2	16.0 ± 0.1	16.2 ± 0.2	15.7 ± 0.1
Erythrocytes ($10^6/\mu L$)	9.83 ± 0.22	9.81 ± 0.11	10.11 ± 0.10	9.59 ± 0.12
Mean cell volume (fL)	47.2 ± 0.5	47.6 ± 0.3	46.8 ± 0.3	47.3 ± 0.3
Mean cell hemoglobin (pg)	16.3 ± 0.2	16.3 ± 0.1	16.0 ± 0.2	16.4 ± 0.2
Mean cell hemoglobin concentration (g/dL)	34.5 ± 0.2	34.4 ± 0.3	34.4 ± 0.4	34.8 ± 0.2
Platelets ($10^3/\mu L$)	947.4 ± 42.9	1,060.8 ± 37.1	1,074.2 ± 61.7	1,032.6 ± 44.9
Reticulocytes ($10^6/\mu L$)	0.2 ± 0.0[c]	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0[c]
Leukocytes ($10^3/\mu L$)	3.30 ± 0.33	3.62 ± 0.31	4.19 ± 0.54	3.81 ± 0.30
Segmented neutrophils ($10^3/\mu L$)	0.92 ± 0.15	1.08 ± 0.18	1.32 ± 0.40	1.00 ± 0.13
Lymphocytes ($10^3/\mu L$)	2.29 ± 0.23	2.43 ± 0.14	2.74 ± 0.21	2.73 ± 0.22
Atypical lymphocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Monocytes ($10^3/\mu L$)	0.01 ± 0.01	0.00 ± 0.00	0.02 ± 0.02	0.00 ± 0.00
Eosinophils ($10^3/\mu L$)	0.10 ± 0.02	0.11 ± 0.04	0.12 ± 0.04	0.07 ± 0.02
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Methemoglobin (% hemoglobin)	0.16 ± 0.03	0.13 ± 0.02	0.12 ± 0.02	0.11 ± 0.02

* Significantly different ($P \leq 0.05$) from the control group by Shirley's test
[a] Mean ± standard error
[b] n=7
[c] n=9
[d] n=8

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

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CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF *p*-NITROBENZOIC ACID

p-Nitrobenzoic acid was obtained from E.I. du Pont de Nemours and Company, Inc. (Wilmington, DE), in one lot (40) which was used throughout the studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of *p*-nitrobenzoic acid studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a light yellow, crystalline solid, was identified as *p*-nitrobenzoic acid by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra (*Sadtler Standard Spectra*) of *p*-nitrobenzoic acid (Figures H1 and H2). The observed melting point of 239.7° to 241.2° C was consistent with the literature reference (*Merck Index*, 1983).

The purity of *p*-nitrobenzoic acid was determined by elemental analyses, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and high-performance liquid chromatography. Functional group titration was performed by dissolving a sample of *p*-nitrobenzoic acid in methanol and titrating with 0.1 N aqueous sodium hydroxide. The titration was monitored potentiometrically using a combination pH/mV electrode filled with 4 M potassium chloride. Thin-layer chromatography was performed on Silica Gel 60 F-254 plates using two solvent systems: A) toluene:ethyl acetate:glacial acetic acid (70:25:5) and B) diethylamine:methanol:*N,N*-dimethylformamide (48:40:12). The reference standard used was 10 μg of 1-nitronaphthalene (1 μL of a 10 μg/μL solution in methanol). Visualization was accomplished with ultraviolet light (254 and 366 nm) and a spray of 5% titanous chloride in 1 N hydrochloric acid. High-performance liquid chromatography was performed using a Fisher Scientific Resolvex C_{18} column (250 × 4.6 mm ID) and a solvent system of water with 1% (v/v) phosphoric acid:methanol with 1% phosphoric acid (61:39). The flow rate was 1.0 mL/minute. Detection was with ultraviolet light at 254 nm.

Elemental analysis for carbon, hydrogen, and nitrogen were in agreement with the theoretical values for *p*-nitrobenzoic acid. Karl Fischer analysis indicated 0.08% ± 0.01% water. Functional group titration indicated a purity of 100.1% ± 0.4%. Thin-layer chromatography using system A detected one major spot and one slight trace impurity; using system B, one major spot and one trace impurity were detected. High-performance liquid chromatography indicated no impurities with areas greater than 0.1% relative to the major peak area. The overall purity was determined to be greater than 99%.

Stability studies were performed by the analytical chemistry laboratory. High-performance liquid chromatography was performed using the system described above except with a solvent ratio of 52:48. These studies indicated that *p*-nitrobenzoic acid was stable as a bulk chemical when stored in the dark for 2 weeks at temperatures up to 60° C. The study laboratory stored the bulk chemical in sealed containers, protected from light, at room temperature. Purity and stability were monitored during the 2-year study by high-performance liquid chromatography and functional group titration. No degradation of the bulk chemical was observed.

Preparation and Analysis of Dose Formulations

The dose formulations were prepared weekly by mixing *p*-nitrobenzoic acid and feed to give the required concentrations (Table H1). Mixtures were made by preparing a *p*-nitrobenzoic acid/feed premix with a spatula, which was then blended with feed in a twin shell blender for 15 minutes using an intensifier bar for the initial 5 minutes. Formulations were stored in doubled sealed plastic bags at −22° C or less for up to 3 weeks.

Homogeneity and stability studies of the dose formulations were performed by the analytical chemistry laboratory. For the homogeneity studies at the 400 ppm concentration, aliquots were extracted with methanol containing 0.5% phosphoric acid and centrifuged. Aliquots of the extracts were mixed with an internal standard solution (propiophenone diluted with mobile phase). High-performance liquid chromatography was then performed using a Brownlee RP-18 column and a mobile phase of methanol:water:phosphoric acid (42:57.5:0.5) at a flow rate of 1.0 mL/minute. Homogeneity was confirmed and the stability of the dose formulations was confirmed for at least 3 weeks when stored in the dark at room temperature. Dose formulations open to air and light were stable for 1 week.

Periodic analyses of the dose formulations of *p*-nitrobenzoic acid were conducted at the study laboratory and analytical chemistry laboratory using high-performance liquid chromatography. Dose formulations were analyzed once during the 14-day studies and were within 10% of the target concentrations (Table H2). Dose formulations for the 13-week studies were analyzed prestudy, during week 1, at study mid-point, and at the final mix (Table H3). During the 2-year studies, the dose formulations were analyzed approximately every 2 months (Table H4). All dose formulations were within 10% of the target concentrations during the 13-week studies; 95% (160/168) of the formulations were within 10% of the target concentration during the 2-year studies. 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 H5).

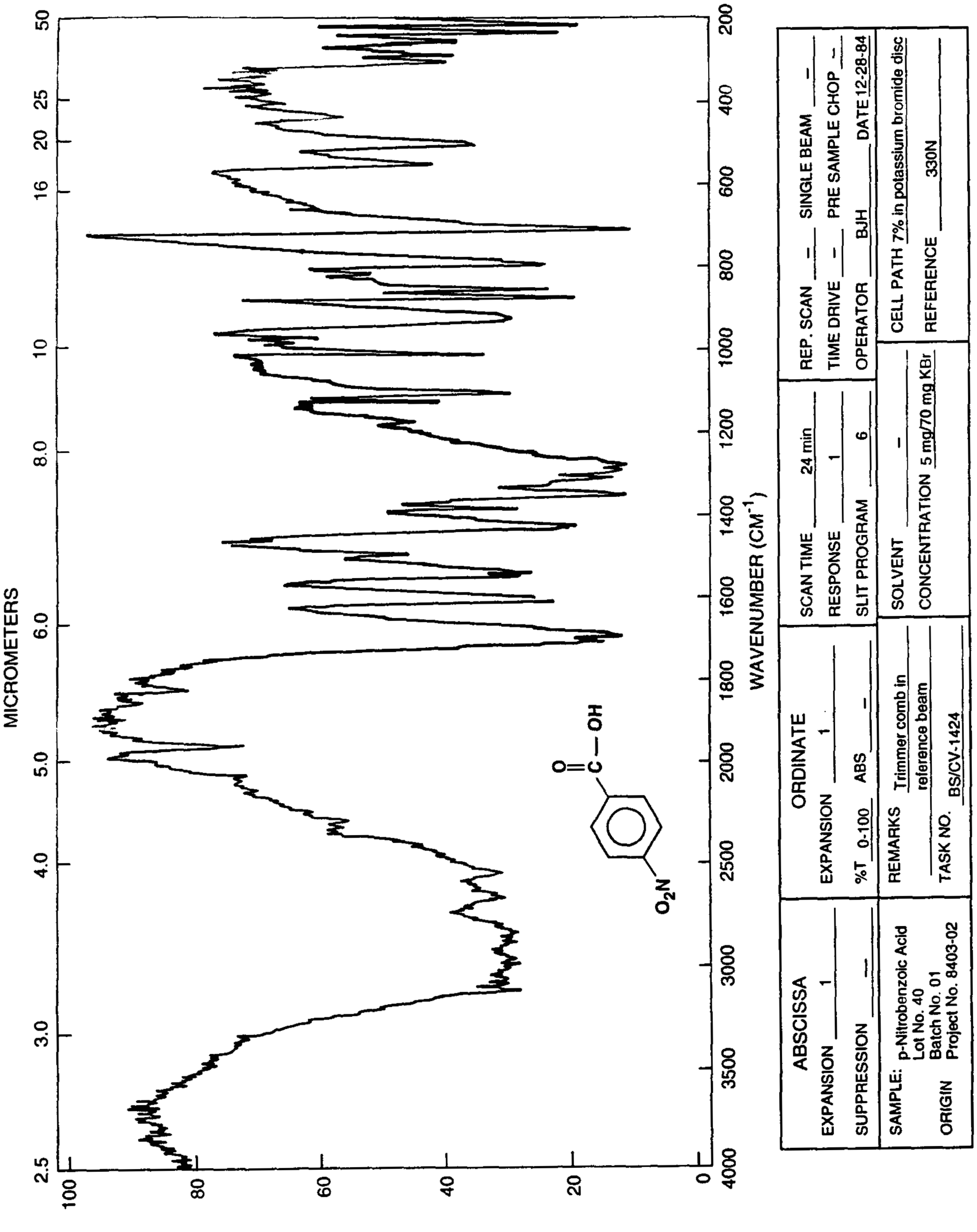
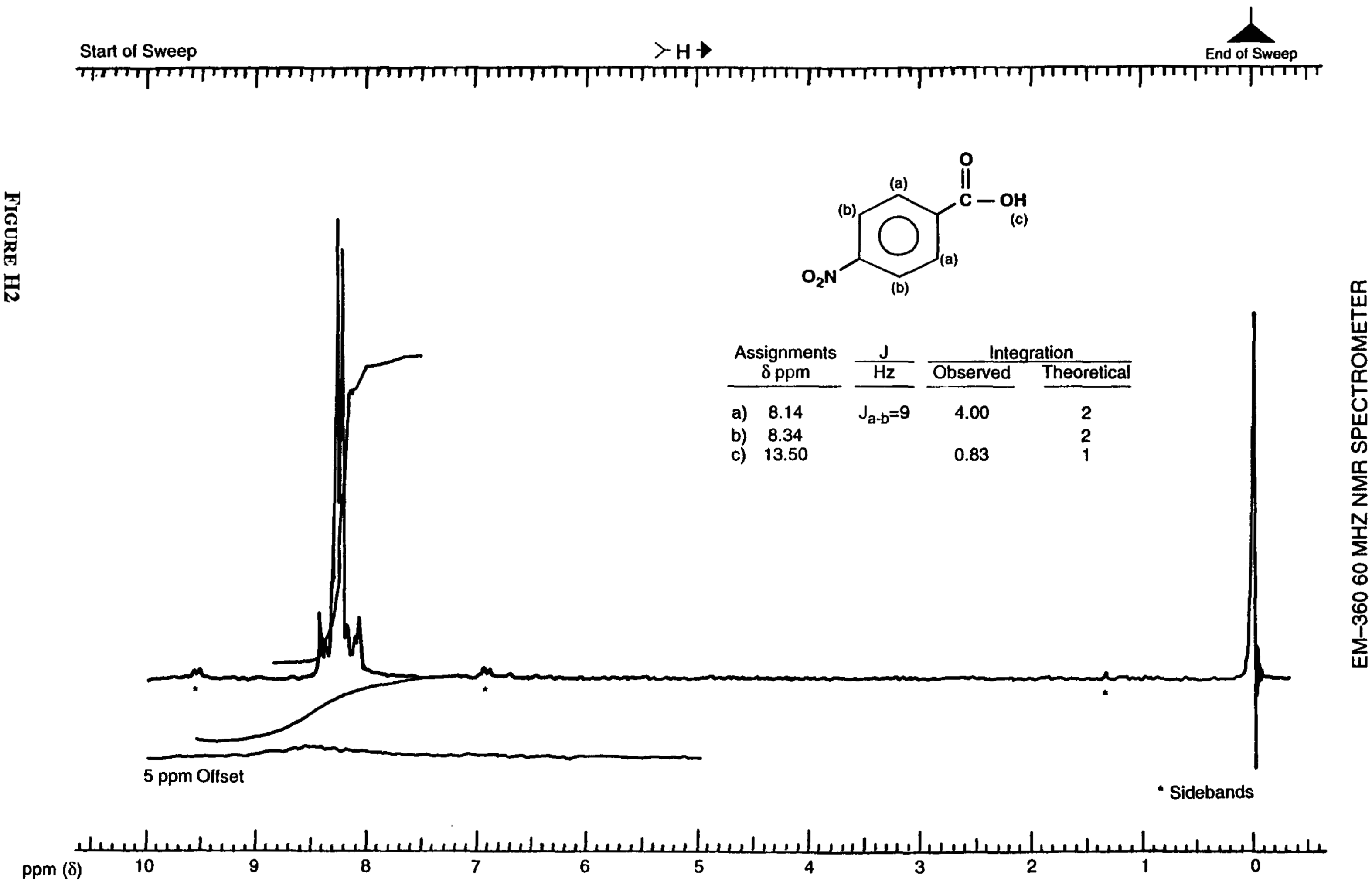


FIGURE H1
Infrared Absorption Spectrum of *p*-Nitrobenzoic Acid



Assignments δ ppm	J Hz	Integration Observed	Integration Theoretical
a) 8.14	$J_{a\text{-}b}=9$	4.00	2
b) 8.34			2
c) 13.50		0.83	1

Lock Pos. — ppm
Lock Power — mG
Decouple Pos. — ppm
Decoupling Power — mG

Spectrum Ampl 3 x 100
Filter 0.1 sec
RF Power 0.05 mG

Sweep Time 5 min
Sweep Width 10 ppm
End of Sweep 0 ppm

Nucleus proton
Zero Ref. TMS
Sample Temp. Amb °C

Sample 8403-02
p-Nitrobenzoic Acid
Lot No.: 40
Batch No.: 01
Task No.: BS/CV-1424
Solvent DMSO-d_6

Operator BJH
Date 12-19-84
Spectrum No. 330N

FIGURE H2
Nuclear Magnetic Resonance Spectrum of *p*-Nitrobenzoic Acid

TABLE H1
Preparation and Storage of Dose Formulations in the Feed Studies of *p*-Nitrobenzoic Acid

14-Day Studies	13-Week Studies	2-Year Studies
Preparation		
Premix was prepared by mixing *p*-nitrobenzoic acid and feed with a spatula; premix and feed were then layered in a twin shell blender and mixed for 15 minutes with the intensifier bar on for the first 5 minutes. Doses were prepared at study initiation.	Same as 14-day studies. Doses were prepared every 2 weeks.	Same as 14-day studies. Doses were prepared weekly.
Lot Number		
40	40	40
Maximum Storage Time		
3 weeks	3 weeks	2 weeks
Storage		
In double, sealed plastic bags at −22° C or less for 2 weeks	Same as 14-day studies	Same as 14-day studies
Study Laboratory		
Microbiological Associates, Incorporated, Bethesda, MD	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 H2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 14-Day Feed Studies of *p*-Nitrobenzoic Acid

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
6 December 1985	9-10 December 1985	2,500	2,580	+3
		5,000	4,990	0
		10,000	9,520	−5
		20,000	20,700	+4
		40,000	37,000	−7

[a] Results of duplicate analyses

TABLE H3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Feed Studies of *p*-Nitrobenzoic Acid

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
Rats				
5 May 1986	6-8 May 1986	630	703[b]	+10
		630	702[c]	+10
		630	660[d]	+5
12 May 1986	12-14 May 1986	630	677	+7
		1,250	1,330	+6
		2,500	2,470	–1
		5,000	4,930	–1
		10,000	9,710	–3
25 June 1986	26-30 June 1986	630	582	–8
		1,250	1,270	+2
		2,500	2,470	–1
		5,000	5,290	+6
		10,000	10,300	+3
6 August 1986	7-9 August 1986	630	578	–8
		1,250	1,180	–6
		2,500	2,440	–2
		5,000	5,200	+4
		10,000	9,980	0
Mice				
5 May 1986	6-8 May 1986	20,000	19,500[b]	–3
		20,000	19,900[c]	–1
		20,000	20,700[d]	+3
12 May 1986	12-14 May 1986	1,250	1,330	+6
		2,500	2,470	–1
		5,000	4,930	–1
		10,000	9,710	–3
		20,000	19,600	–2
25 June 1986	26-30 June 1986	1,250	1,270	+2
		2,500	2,470	–1
		5,000	5,290	+6
		10,000	10,300	+3
		20,000	20,000	0
6 August 1986	7-9 August 1986	1,250	1,180	–6
		2,500	2,440	–2
		5,000	5,200	+4
		10,000	9,980	0
		20,000	20,800	+4

[a] Results of duplicate analyses
[b] Sample taken from top right of blender
[c] Sample taken from top left of blender
[d] Sample taken from bottom of blender

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrobenzoic Acid

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
27 April 1988[b]	27-29 April 1988	1,250	1,270[c]	+2
		1,250	1,220[d]	−2
		1,250	1,130[e]	−10
		5,000	5,150[c]	+3
		5,000	5,080[d]	+2
		5,000	5,000[e]	0
4 May 1988[b]	4-6 May 1988	1,250	1,240[c]	−1
		1,250	1,300[d]	+4
		1,250	1,320[e]	+6
		1,250	1,380[c]	+10
		1,250	1,290[d]	+3
		1,250	1,230[e]	−2
4 May 1988[f]	4-6 May 1988	1,250	1,270	+1
		1,250	1,300	+4
		2,500	2,630	+5
		2,500	2,540	+2
		5,000	5,420	+8
		5,000	5,260	+5
18 May 1988	18-20 May 1988	1,250	1,190	−5
		1,250	1,250	0
		1,250	1,240	−1
		1,250	1,280	+2
		2,500	2,500	0
		2,500	2,580	+3
		2,500	2,540	+2
		2,500	2,600	+4
		5,000	5,180	+4
		5,000	5,320	+6
		5,000	5,210	+4
		5,000	5,150	+3
6 July 1988	7-11 July 1988	1,250	1,310	+5
		1,250	1,260	+1
		1,250	1,260	+1
		1,250	1,310	+5
		2,500	2,530	+1
		2,500	2,540	+2
		2,500	2,620	+5
		2,500	2,580	+3
		5,000	5,070	+1
		5,000	5,140	+3
		5,000	5,020	0
		5,000	5,270	+5

Table H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrobenzoic Acid (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
7 September 1988	8-12 September 1988	1,250	1,270	+2
		1,250	1,310	+5
		1,250	1,240	−1
		1,250	1,300	+4
		2,500	2,680	+7
		2,500	2,520	+1
		2,500	2,550	+2
		2,500	2,610	+4
		5,000	4,920	−2
		5,000	5,020	0
		5,000	4,980	0
		5,000	5,200	+4
9 November 1988	10-11 November 1988	1,250	1,200	−4
		1,250	1,300	+4
		1,250	1,340	+7
		1,250	1,240	−1
		2,500	2,640	+6
		2,500	2,480	−1
		2,500	2,570	+3
		2,500	2,600	+4
		5,000	5,160	+3
		5,000	5,140	+3
		5,000	4,990	0
		5,000	4,990	0
18 January 1989	19-20 January 1989	1,250	1,340	+7
		1,250	1,360	+9
		1,250	1,350	+8
		1,250	1,370	+10
		2,500	2,590	+4
		2,500	2,700	+8
		2,500	2,540	+2
		2,500	2,860[g]	+14
		5,000	5,190	+4
		5,000	5,360	+7
		5,000	5,120	+2
		5,000	5,580[g]	+12
23 January 1989	23-24 January 1989	2,500	2,590[h]	+4
		5,000	5,120[h]	+2

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrobenzoic Acid (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
22 March 1989	23-24 March 1989	1,250	1,250	0
		1,250	1,250	0
		1,250	1,260	+1
		1,250	1,350	+8
		2,500	2,630	+5
		2,500	2,720	+9
		2,500	2,580	+3
		2,500	2,530	+1
		5,000	5,190	+4
		5,000	5,080	+2
		5,000	5,260	+5
		5,000	5,370	+7
10 May 1989	11-12 May 1989	1,250	1,330	+6
		1,250	1,340	+7
		1,250	1,360	+9
		2,500	2,550	+2
		2,500	2,640	+6
		2,500	2,830[g]	+13
		5,000	5,450	+9
		5,000	5,410	+8
		5,000	5,320	+6
17 May 1989	18 May 1989	2,500	2,820[h]	+13
5 July 1989	7 July 1989	1,250	1,260	+1
		1,250	1,220	−2
		1,250	1,290	+3
		2,500	2,470	−1
		2,500	2,480	−1
		2,500	2,480	−1
		5,000	5,050	+1
		5,000	5,010	0
		5,000	5,070	+1
16 August 1989	16-22 August 1989	1,250	1,230	−2
		1,250	1,240	−1
		1,250	1,240	−1
		2,500	2,520	+1
		2,500	2,500	0
		2,500	2,540	+2
		5,000	5,350	+7
		5,000	4,920	−2
		5,000	5,210	+4

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrobenzoic Acid (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
27 October 1989	30-31 October 1989	1,250	1,320	+6
		1,250	1,240	−1
		1,250	1,310	+5
		2,500	2,630	+5
		2,500	2,510	0
		2,500	2,580	+3
		5,000	5,170	+3
		5,000	4,900	−2
		5,000	5,160	+3
8 December 1989	9, 11-12 December 1989	1,250	1,270	+2
		1,250	1,160	−7
		1,250	1,230	−2
		2,500	2,560	+2
		2,500	2,500	0
		2,500	2,530	+1
		5,000	4,860	−3
		5,000	5,000	0
		5,000	4,980	0
2 February 1990	5-6 February 1990	1,250	1,240	−1
		1,250	1,240	−1
		1,250	1,390	+11
		2,500	2,520	+1
		2,500	2,660	+6
		2,500	2,470	−1
		5,000	5,320	+6
		5,000	5,220	+4
		5,000	5,020	0
30 March 1990	2-3 April 1990	1,250	1,100[g]	−12
		1,250	1,480[g,i]	+18
		1,250	1,390[g]	+11
		2,500	2,740	+10
		2,500	2,470	−1
		2,500	2,590[i]	+4
		5,000	4,600	−8
		5,000	5,230	+5
		5,000	4,680[i]	−6
3 April 1990	4 April 1990	1,250	1,280[h]	+2
		1,250	1,280[h]	+2
		1,250	1,360[h]	+9

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Feed Studies of *p*-Nitrobenzoic Acid (continued)

Date Prepared	Date Analyzed	Target Concentration (ppm)	Determined Concentration[a] (ppm)	Difference from Target (%)
27 April 1990[j]	30 April 1990	1,250	1,190	–5
		1,250	1,240	–1
		1,250	1,290[i]	+3
		2,500	2,530	+1
		2,500	2,470	–1
		2,500	2,340	–6
		5,000	4,870[i]	–3
		5,000	5,070	+1
		5,000	4,950[i]	–1

[a] Results of duplicate analyses except where indicated
[b] Samples not used for dosing
[c] Sample taken from top right of blender
[d] Sample taken from top left of blender
[e] Sample taken from bottom of blender
[f] Used only for rats
[g] Sample remixed
[h] Results of remix
[i] Results of triplicate analyses
[j] Used only for mice

TABLE H5
Results of Referee Analysis of Dose Formulations in the 13-Week and 2-Year Feed Studies of *p*-Nitrobenzoic Acid

Date Prepared	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies			
12 May 1986	630	677	633 ± 29
6 August 1986	2,500	2,440	2,410 ± 40
2-Year Studies			
4 May 1988	1,250	1,260	1,135 ± 36
9 November 1988	5,000	5,140	4,900 ± 200
10 May 1989	2,500	2,550	2,590 ± 30
27 October 1989	1,250	1,240	1,210 ± 4

[a] Results of duplicate analyses
[b] Results of triplicate analyses (mean ± standard deviation)

APPENDIX I
FEED AND COMPOUND CONSUMPTION IN THE 2-YEAR FEED STUDIES

TABLE I1 Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid 288
TABLE I2 Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid 289
TABLE I3 Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid 290
TABLE I4 Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid 291

TABLE I1
Feed and Compound Consumption by Male Rats in the 2-Year Feed Study of p-Nitrobenzoic Acid

	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ 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)
3	17.4	207	17.6	206	107	17.7	200	222	17.4	198	437
6	20.7	283	19.5	281	87	19.3	280	172	18.7	262	356
10	18.8	338	19.0	337	70	19.2	337	142	17.5	315	278
13	17.2	362	17.2	360	60	16.6	359	116	17.4	338	258
17	20.2	387	18.6	381	61	17.5	391	112	16.4	366	224
21	18.3	409	18.9	409	58	18.6	412	113	17.8	389	229
25	17.3	426	19.0	421	56	18.9	427	110	18.5	400	232
28	18.3	435	18.0	431	52	18.4	435	106	16.6	410	202
33	19.1	450	17.4	450	48	18.0	447	101	18.6	426	218
37	17.3	460	18.4	461	50	18.4	464	99	17.8	442	201
41	16.2	469	16.2	470	43	17.7	466	95	16.7	446	187
45	17.2	475	16.9	475	44	17.6	480	91	17.3	459	188
49	19.0	478	17.1	485	44	18.8	484	97	17.9	464	194
53	16.2	480	17.4	488	45	17.7	485	91	17.3	463	186
57	17.8	482	17.5	491	45	16.6	486	86	18.0	464	194
61	16.0	484	18.4	484	48	17.2	480	89	16.4	461	178
65	15.8	483	16.4	487	42	17.1	486	88	17.7	466	191
69	15.7	482	16.6	490	42	15.7	485	81	16.2	466	174
73	15.2	474	14.3	478	37	14.2	472	75	16.5	458	180
77	15.7	475	16.1	480	42	16.3	474	86	16.9	465	182
80	17.0	472	17.1	471	45	16.2	469	87	17.7	458	193
85	17.0	463	17.6	463	48	16.7	469	89	17.9	459	195
89	16.6	462	14.6	468	39	15.8	473	84	16.8	462	182
93	16.7	455	15.6	458	43	14.9	470	79	15.9	457	174
97	15.2	442	15.6	447	44	14.3	451	79	14.8	447	165
101	15.8	449	16.3	441	46	16.6	460	90	16.3	444	184
Mean for weeks											
1-13	18.5	297	18.3	296	81	18.2	294	163	17.7	278	332
14-52	18.1	443	17.8	443	51	18.2	445	103	17.5	422	208
53-101	16.2	470	16.4	473	43	16.1	474	85	16.8	459	183

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

TABLE I2
Feed and Compound Consumption by Female Rats in the 2-Year Feed Study of *p*-Nitrobenzoic Acid

Week	0 ppm Feed (g/day)[a]	0 ppm Body Weight (g)	1,250 ppm Feed (g/day)	1,250 ppm Body Weight (g)	1,250 ppm Dose/Day[b] (mg/kg/day)	2,500 ppm Feed (g/day)	2,500 ppm Body Weight (g)	2,500 ppm Dose/Day (mg/kg/day)	5,000 ppm Feed (g/day)	5,000 ppm Body Weight (g)	5,000 ppm Dose/Day (mg/kg/day)
3	12.1	137	11.7	137	107	11.7	134	219	11.8	131	449
6	12.3	166	12.9	168	96	12.5	164	190	12.1	160	378
10	11.8	184	11.8	185	80	11.7	183	160	11.3	179	316
13	10.8	192	11.2	192	73	11.0	188	147	11.2	184	303
17	10.9	203	10.6	205	64	11.9	193	153	10.1	199	253
21	11.2	211	11.3	211	67	11.2	207	136	10.8	203	266
25	11.1	218	10.7	218	61	10.5	212	124	10.5	206	254
29	11.0	217	11.0	220	62	10.8	216	125	10.5	208	251
33	10.9	228	10.5	226	58	10.9	221	123	10.7	212	252
37	11.8	236	11.6	235	62	11.2	227	123	11.1	219	253
41	10.8	242	10.6	243	55	10.9	234	116	10.6	224	237
45	11.6	249	11.6	249	58	11.7	242	121	11.4	230	249
50	11.8	262	12.4	261	59	11.8	254	117	11.7	237	246
53	12.4	271	12.2	269	57	11.8	262	113	11.6	243	239
57	12.9	280	12.7	276	58	12.3	267	115	12.1	245	247
61	12.7	290	12.2	282	54	12.0	273	110	11.8	253	234
65	11.6	298	12.4	289	53	12.2	280	109	11.8	257	229
69	12.1	306	12.2	297	51	11.5	286	101	11.3	267	211
73	11.7	308	10.9	299	46	11.8	290	102	10.7	264	203
77	12.9	316	13.3	304	55	12.5	292	107	11.8	270	219
81	13.2	321	13.7	308	55	13.1	298	110	12.6	274	229
85	13.7	324	13.6	313	54	13.2	296	112	13.3	270	245
89	12.8	334	12.8	323	49	12.7	306	104	12.6	282	224
93	12.0	332	12.5	324	48	12.5	305	103	12.5	283	220
97	12.9	337	12.6	327	48	13.0	316	103	12.6	289	218
101	12.4	341	13.9	331	52	13.5	314	107	12.8	288	223
Mean for weeks											
1-13	11.8	170	11.9	170	89	11.7	167	179	11.6	164	362
14-52	11.2	230	11.1	230	61	11.2	223	126	10.8	215	251
53-101	12.6	312	12.7	303	52	12.5	291	107	12.1	268	226

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

TABLE I3
Feed and Compound Consumption by Male Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid

Week	0 ppm Feed (g/day)[a]	0 ppm Body Weight (g)	1,250 ppm Feed (g/day)	1,250 ppm Body Weight (g)	1,250 ppm Dose/Day[b] (mg/kg/day)	2,500 ppm Feed (g/day)	2,500 ppm Body Weight (g)	2,500 ppm Dose/Day (mg/kg/day)	5,000 ppm Feed (g/day)	5,000 ppm Body Weight (g)	5,000 ppm Dose/Day (mg/kg/day)
2	5.1	24.8	4.7	24.3	244	4.8	24.4	491	4.8	23.9	1,001
6	5.3	28.1	5.2	27.9	231	5.2	27.9	462	6.0	27.3	1,091
10	5.2	31.1	5.3	30.1	219	4.9	30.8	398	5.3	29.5	893
13	5.8	33.1	6.0	32.8	228	5.5	33.1	416	6.0	31.7	949
17	5.0	35.3	5.1	34.9	183	5.2	34.9	375	5.6	33.2	836
21	4.5	37.2	4.6	36.5	156	4.4	36.4	303	4.8	34.5	698
25	4.3	38.4	4.6	38.0	151	4.5	37.8	299	4.7	35.3	672
29	4.0	40.8	4.3	40.2	133	4.3	39.8	272	4.6	37.5	620
33	4.6	41.9	4.6	41.9	138	4.8	41.6	286	4.8	38.7	620
37	5.1	43.4	5.1	43.5	145	4.8	43.3	279	5.3	40.8	654
41	4.4	45.5	4.7	45.1	130	4.5	44.8	254	5.0	41.8	601
45	4.9	46.1	4.8	45.4	133	4.9	45.4	270	5.0	41.9	599
49	5.1	47.5	5.0	46.9	135	5.0	46.7	265	5.3	43.3	610
53	4.6	47.4	4.7	47.3	123	4.6	46.7	247	4.8	43.7	553
57	5.0	47.6	5.0	46.8	134	4.9	46.3	267	5.5	42.9	640
61	4.9	47.3	5.0	46.5	135	5.1	46.0	277	5.2	42.8	607
65	5.0	47.9	5.2	47.5	138	5.3	46.2	285	5.7	43.5	650
69	4.8	47.8	5.0	48.0	130	5.0	46.3	269	5.1	42.8	592
73	4.6	49.5	5.1	48.9	131	5.2	48.2	268	5.0	44.4	560
77	4.8	49.2	5.0	48.8	128	5.1	48.2	265	5.1	44.7	571
81	5.0	49.2	4.8	48.1	125	4.9	47.1	260	5.0	43.5	570
85	4.7	48.0	4.6	48.4	120	4.7	47.3	247	4.7	43.6	543
89	4.8	48.9	4.9	48.8	125	4.8	47.4	256	5.2	43.3	597
93	5.0	48.0	5.3	49.0	135	5.2	47.5	272	5.3	43.1	619
97	4.9	46.5	5.1	47.5	134	5.1	46.6	275	5.6	41.8	671
101	5.0	45.9	5.3	47.7	139	5.4	46.4	289	6.0	41.4	722
Mean for weeks											
1-13	5.4	29.3	5.3	28.8	230	5.1	29.1	442	5.5	28.1	983
14-52	4.7	41.8	4.8	41.4	145	4.7	41.2	289	5.0	38.6	657
53-101	4.9	47.9	5.0	47.9	131	5.0	46.9	268	5.2	43.2	607

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

Table I4
Feed and Compound Consumption by Female Mice in the 2-Year Feed Study of *p*-Nitrobenzoic Acid

	0 ppm		1,250 ppm			2,500 ppm			5,000 ppm		
Week	Feed (g/day)[a]	Body Weight (g)	Feed (g/day)	Body Weight (g)	Dose/ 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)
2	5.2	20.4	4.8	20.2	299	4.6	20.1	571	4.7	19.8	1,198
6	5.6	24.3	5.9	24.5	301	6.2	24.2	637	6.8	23.3	1,457
10	5.6	27.1	5.5	27.0	253	5.4	26.1	518	6.2	25.3	1,217
12	6.7	28.8	6.8	28.5	298	6.6	27.6	595	7.5	26.4	1,417
16	5.4	31.2	5.7	30.2	234	5.9	29.7	495	7.2	27.4	1,315
20	4.8	33.4	4.8	32.3	186	4.9	31.5	390	6.0	28.9	1,037
24	4.3	34.3	5.0	33.7	185	5.1	32.1	400	5.3	29.7	896
28	4.8	36.8	4.7	35.7	166	5.4	34.8	385	5.7	31.1	922
32	4.9	39.2	5.4	38.1	178	5.3	37.2	359	5.7	32.9	864
36	5.9	40.4	5.9	39.7	187	6.0	38.6	390	6.2	34.1	916
40	5.0	42.6	5.4	42.6	157	5.3	41.0	321	6.0	35.6	843
44	5.2	44.6	5.4	44.1	154	5.6	42.5	330	5.6	36.4	769
48	5.6	46.0	5.6	45.7	153	5.6	44.0	316	5.8	38.1	764
52	5.1	47.0	5.2	46.3	142	5.2	45.0	287	5.5	38.5	708
56	5.6	46.3	5.6	45.8	153	5.7	43.8	328	7.1	37.0	957
60	5.3	47.0	5.1	46.9	136	5.4	44.5	305	5.6	37.2	750
64	5.5	48.8	5.6	48.0	146	5.7	44.7	321	6.5	37.6	859
68	5.2	48.5	5.5	48.7	140	5.2	45.9	283	5.8	38.0	766
72	5.2	49.7	5.4	49.5	137	5.6	47.2	299	5.7	39.0	728
76	5.4	51.2	5.5	51.4	135	5.6	49.0	287	6.0	40.0	748
80	5.6	52.1	5.3	51.0	130	5.6	48.2	289	6.1	39.9	758
84	5.1	51.2	5.2	51.0	128	5.4	48.2	278	5.4	40.5	669
88	5.3	52.0	5.4	50.6	133	5.3	48.1	277	6.2	39.6	789
93	5.5	50.6	5.8	49.5	147	5.6	47.4	295	6.5	38.5	838
96	5.4	49.9	5.5	48.5	142	6.0	46.5	322	6.5	39.3	828
100	5.4	49.8	5.9	48.6	152	6.2	46.2	335	6.9	38.8	887
104	5.4	48.2	5.9	47.7	155	6.2	45.2	343	6.9	38.8	887
Mean for weeks											
1-13	5.8	25.2	5.8	25.1	288	5.7	24.5	580	6.3	23.7	1,322
14-52	5.1	39.6	5.3	38.8	174	5.4	37.6	367	5.9	33.3	903
53-104	5.4	49.6	5.5	49.0	141	5.7	46.5	305	6.2	38.8	805

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

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

TABLE J1 Ingredients of NIH-07 Rat and Mouse Ration 294
TABLE J2 Vitamins and Minerals in NIH-07 Rat and Mouse Ration 294
TABLE J3 Nutrient Composition of NIH-07 Rat and Mouse Ration 295
TABLE J4 Contaminant Levels in NIH-07 Rat and Mouse Ration 296

TABLE J1
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 J2
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 J3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.90 ± 1.03	21.30 – 24.60	26
Crude fat (% by weight)	5.31 ± 0.26	4.80 – 5.90	26
Crude fiber (% by weight)	3.64 ± 0.55	2.80 – 4.80	26
Ash (% by weight)	6.73 ± 0.31	6.12 – 7.27	26
Amino Acids (% of total diet)			
Arginine	1.287 ± 0.084	1.100 – 1.390	10
Cystine	0.306 ± 0.075	0.181 – 0.400	10
Glycine	1.160 ± 0.050	1.060 – 1.220	10
Histidine	0.580 ± 0.024	0.531 – 0.608	10
Isoleucine	0.917 ± 0.034	0.867 – 0.965	10
Leucine	1.972 ± 0.052	1.850 – 2.040	10
Lysine	1.273 ± 0.051	1.200 – 1.370	10
Methionine	0.437 ± 0.115	0.306 – 0.699	10
Phenylalanine	0.994 ± 0.125	0.665 – 1.110	10
Threonine	0.896 ± 0.055	0.824 – 0.985	10
Tryptophan	0.223 ± 0.160	0.107 – 0.671	10
Tyrosine	0.677 ± 0.105	0.564 – 0.794	10
Valine	1.089 ± 0.057	0.962 – 1.170	10
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.233	1.830 – 2.570	9
Linolenic	0.277 ± 0.036	0.210 – 0.320	9
Vitamins			
Vitamin A (IU/kg)	6,554 ± 1,288	4,100 – 9,190	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	36.92 ± 9.32	22.5 – 48.9	9
Thiamine (ppm)	19.96 ± 2.88	15.0 – 28.0	26
Riboflavin (ppm)	7.92 ± 0.93	6.10 – 9.00	10
Niacin (ppm)	100.95 ± 25.92	65.0 – 150.0	9
Pantothenic acid (ppm)	30.30 ± 3.60	23.0 – 34.6	10
Pyridoxine (ppm)	9.25 ± 2.62	5.60 – 14.0	10
Folic acid (ppm)	2.51 ± 0.64	1.80 – 3.70	10
Biotin (ppm)	0.267 ± 0.049	0.19 – 0.35	10
Vitamin B_{12} (ppb)	40.14 ± 20.04	10.6 – 65.0	10
Choline (ppm)	3,068 ± 314	2,400 – 3,430	9
Minerals			
Calcium (%)	1.26 ± 0.13	0.90 – 1.55	26
Phosphorus (%)	0.96 ± 0.05	0.88 – 1.10	26
Potassium (%)	0.887 ± 0.067	0.772 – 0.971	8
Chloride (%)	0.526 ± 0.092	0.380 – 0.635	8
Sodium (%)	0.315 ± 0.344	0.258 – 0.370	10
Magnesium (%)	0.168 ± 0.008	0.151 – 0.180	10
Sulfur (%)	0.274 ± 0.063	0.208 – 0.420	10
Iron (ppm)	356.2 ± 90.0	255.0 – 523.0	10
Manganese (ppm)	92.24 ± 5.35	81.70 – 99.40	10
Zinc (ppm)	58.14 ± 9.91	46.10 – 81.60	10
Copper (ppm)	11.50 ± 2.40	8.090 – 15.39	10
Iodine (ppm)	3.70 ± 1.14	1.52 – 5.83	10
Chromium (ppm)	1.71 ± 0.45	0.85 – 2.09	9
Cobalt (ppm)	0.797 ± 0.23	0.490 – 1.150	6

Table J4
Contaminant Levels in NIH-07 Rat and Mouse Ration

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.25 ± 0.17	0.05 – 0.60	26
Cadmium (ppm)	<0.10		26
Lead (ppm)	0.26 ± 0.18	0.10 – 0.90	26
Mercury (ppm)[b]	0.04 ± 0.01	0.02 – 0.08	26
Selenium (ppm)	0.34 ± 0.10	0.15 – 0.55	26
Aflatoxins (ppb)	<5.0		26
Nitrate nitrogen (ppm)[c]	15.21 ± 5.00	0.30 – 22.0	26
Nitrite nitrogen (ppm)[c]	0.19 ± 0.14	<0.10 – 0.60	26
BHA (ppm)[d]	1.49 ± 0.70	<2.00 – 3.00	26
BHT (ppm)[d]	1.25 ± 0.64	<1.00 – 3.00	26
Aerobic plate count (CFU/g)[e]	115,769 ± 92,211	25,000 – 380,000	26
Coliform (MPN/g)[f]	31.96 ± 29.95	<3.00 – 93	26
E. coli (MPN/g)	3.35 ± 1.20	<3.00 – 9.00	26
Total nitrosoamines (ppb)[g]	7.63 ± 2.90	2.00 – 13.70	26
N-Nitrosodimethylamine (ppb)[g]	5.33 ± 2.38	1.00 – 11.00	26
N-Nitrosopyrrolidine (ppb)[g]	2.30 ± 1.23	1.00 – 4.70	26
Pesticides (ppm)			
α-BHC[h]	<0.01		26
β-BHC	<0.02		26
γ-BHC	<0.01		26
δ-BHC	<0.01		26
Heptachlor	<0.01		26
Aldrin	<0.01		26
Heptachlor epoxide	<0.01		26
DDE	<0.01		26
DDD	<0.01		26
DDT	<0.01		26
HCB	<0.01		26
Mirex	<0.01		26
Methoxychlor	<0.05		26
Dieldrin	<0.01		26
Endrin	<0.01		26
Telodrin	<0.01		26
Chlordane	<0.05		26
Toxaphene	<0.1		26
Estimated PCBs	<0.2		26
Ronnel	<0.01		26
Ethion	<0.02		26
Trithion	<0.05		26
Diazinon	<0.1		26
Methyl parathion	<0.02		26
Ethyl parathion	<0.02		26
Malathion	0.22 ± 0.28	0.05 – 1.29	26
Endosulfan I	<0.01		26
Endosulfan II	<0.01		26
Endosulfan sulfate	<0.03		26

TABLE J4
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] The lot milled 03 September 1986 contained 0.08 ppm; all other lots were less than or equal to the detection limit.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] CFU = colony forming units
[f] MPN = most probable number
[g] All values were corrected for percent recovery.
[h] BHC is hexachlorocyclohexane or benzene hexachloride

APPENDIX K
SENTINEL ANIMAL PROGRAM

Methods 300

SENTINEL ANIMAL PROGRAM

METHODS

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

Rats

For the 2-year study, 15 male and 15 female rats were selected at the time of randomization and allocation of the animals to the various study groups. Sera were obtained from five male and five female sentinel rats at 6, 12, and 18 months into the study. Serum for the 24-month screening was obtained from five high-dose males and five mid-dose females. Blood from each collection was processed appropriately, shipped to Microbiological Associates (Bethesda, MD), and screened for the following:

Method of Analysis	Time of Analysis
ELISA	
PVM (pneumonia virus of mice)	6, 12, 18, and 24 months
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	6, 12, 18, and 24 months
KRV (Kilham rat virus)	6, 12, 18, and 24 months

Mice

For the 13-week study, samples were obtained from five male and five female controls at the end of the study. These samples were processed appropriately and were submitted to Microbiological Associates for viral titer screening. The following tests were performed:

Method of Analysis	Time of Analysis
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study termination
ELISA	
CARB (cilia-associated respiratory bacillus)	Study termination
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
MHV (mouse hepatitis virus)	Study termination
Mouse adenoma virus	Study termination
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination

Mice (continued)

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
K (papovavirus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	Study termination

For the 2-year study, 15 male and 15 female mice were selected at the time of randomization and allocation of the animals to the various study groups. Sera were obtained from as many as five male and five female sentinel mice at 6, 12, and 18 months into the study. Serum for the 24-month screening was obtained from five high-dose males and five high-dose females. Blood from each collection was processed appropriately, shipped to Microbiological Associates, and screened for the following:

Method of Analysis	Time of Analysis
ELISA	
Ectromelia virus	6, 12, 18, and 24 months
GDVII	6, 12, 18, and 24 months
LCM	18 and 24 months
MHV	6, 12, 18, and 24 months
MVM	6 and 12 months
Mouse adenoma virus	6, 12, 18, and 24 months
PVM	6, 12, 18, and 24 months
Reovirus 3	6, 12, 18, and 24 months
Sendai	6, 12, 18, and 24 months
Hemagglutination Inhibition	
K	6, 12, 18, and 24 months
Polyoma virus	6, 12, 18, and 24 months
Immunofluorescence Assay	
EDIM	6, 12, 18, and 24 months
LCM	6 and 12 months
MVM	18 and 24 months

All test results were negative.

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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)phosphonium 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 Paraffins (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

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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	α-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
384	1,2,3-Trichloropropane
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
398	Polybrominated Biphenyls
399	Titanocene Dichloride
400	2,3-Dibromo-1-propanol
401	2,4-Diaminophenol Dihydrochloride
402	Furan
403	Resorcinol
404	5,5-Diphenylhydantoin
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
414	Pentachloroanisole
415	Polysorbate 80
416	*o*-Nitroanisole
417	*p*-Nitrophenol
418	*p*-Nitroaniline
419	HC Yellow 4
420	Triamterene
421	Talc
422	Coumarin
423	Dihydrocoumarin
424	*o*-Benzyl-*p*-chlorophenol
425	Promethazine Hydrochloride
426	Corn Oil, Safflower Oil, and Tricaprylin
427	Turmeric Oleoresin
428	Manganese (II) Sulfate Monohydrate
430	C.I. Direct Blue 218
431	Benzyl Acetate
432	Barium Chloride Dihydrate
433	Tricresyl Phosphate
434	1,3-Butadiene
437	Hexachlorocyclopentadiene
440	Ozone and Ozone/NNK
443	Oxazepam

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