NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 334

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2-AMINO-5-NITROPHENOL

(CAS NO. 121-88-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2-AMINO-5-NITROPHENOL

(CAS NO. 121-88-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

Richard D. Irwin, Ph.D., Chemical Manager

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

February 1988

NTP TR 334

NIH Publication No. 88-2590

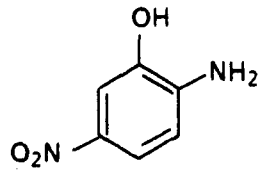
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

NOTE TO THE READER

This study was performed under the direction of the National Institute of Environmental Health Sciences as a function of the National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for public peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

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



2-AMINO-5-NITROPHENOL

CAS No. 121-88-0

$C_6H_6O_3N_2$ Molecular weight 154.1

ABSTRACT

2-Amino-5-nitrophenol is used as a colorant in semipermanent hair dyes and in the manufacture of C.I. Solvent Red 8, an azo dye for synthetic resins, lacquers, and wood stains. 2-Amino-5-nitrophenol was nominated for toxicology and carcinogenesis studies by the National Cancer Institute because of widespread human exposure associated with its use in hair dyes.

Toxicology and carcinogenesis studies were conducted by administering 2-amino-5-nitrophenol (98% pure) by gavage in corn oil 5 days per week to groups of F344/N rats and B6C3F$_1$ mice of each sex in 16-day, 13-week, and 2-year studies. In the 2-year studies, male and female rats were given doses of 0, 100, or 200 mg/kg and male and female mice were given doses of 0, 400, or 800 mg/kg.

Sixteen-Day and Thirteen-Week Studies: During the 16-day studies, F344/N rats of each sex received 0, 156, 313, 625, 1,250, or 2,500 mg/kg 2-amino-5-nitrophenol by gavage in corn oil vehicle. One of five males that received 2,500 mg/kg, 1/5 females that received 1,250 mg/kg, and 2/5 females that received 313 mg/kg died before the end of the studies. Final mean body weights of rats that received 1,250 or 2,500 mg/kg were 11% and 30% lower than that of vehicle controls for males and 9% and 13% lower for females. B6C3F$_1$ mice of each sex received doses of 0, 313, 625, 1,250, 2,500, or 5,000 mg/kg 2-amino-5-nitrophenol. Two of five males and 5/5 females that received 500 mg/kg, 3/5 males and 3/5 females that received 2,500 mg/kg, 3/5 females that received 1,250 mg/kg, 1/5 females that received 625 mg/kg, and 2/5 male vehicle controls died before the end of the studies. Final mean body weights of chemically exposed mice were not different from those of the vehicle controls. Rats that received 625, 1,250, or 2,500 mg/kg and male mice that received 5,000 mg/kg had loose stools.

In 13-week studies, F344/N rats and B6C3F$_1$ mice of both sexes received 0, 100, 200, 400, 800, or 1,600 mg/kg 2-amino-5-nitrophenol by gavage in corn oil. Five of 10 male and 2/10 female rats that received 1,600 mg/kg, 1/10 male and 3/10 female rats that received 800 mg/kg, and 1/10 male rats that received 400 mg/kg died before the end of the studies. Final mean body weights of males that received 400, 800, or 1,600 mg/kg were 10%, 25%, and 43% lower than that of vehicle controls. The final mean body weight of females that received 1,600 mg/kg was 16% lower than that of vehicle controls.

Four of 10 male and 3/10 female mice that received 1,600 mg/kg died before the end of the 13-week studies. The final mean body weight of male mice that received 1,600 mg/kg was 11% lower than that of vehicle controls; male and female mice that received 1,600 mg/kg appeared lethargic.

During the 13-week studies, acute/chronic perivasculitis of vessels of the cecum and colon was observed in rats that received 400, 800, or 1,600 mg/kg and in mice that received 1,600 mg/kg.

Body Weight and Survival in the Two-Year Studies: Mean body weights of rats receiving 200 mg/kg were 5%-10% lower than those of vehicle controls after week 33 for males and 4%-5% lower than those of vehicle controls after week 93 for females. Survival of male rats was significantly lower than that of vehicle controls after week 99 for the 100 mg/kg dose group and after week 75 for the 200 mg/kg dose group (final survival: vehicle control, 33/50; 100 mg/kg group, 16/50; 200 mg/kg group, 4/50). Survival of female rats was comparable to that of vehicle controls (30/50; 32/50; 29/50). Loose or poorly formed stools were observed for male rats and occasionally for females that received 200 mg/kg.

Mean body weights of mice that received 800 mg/kg were 8%-11% lower than those of vehicle controls between weeks 29 and 74 for males and 8%-13% lower than those of vehicle controls after week 69 for females; mean body weights of mice that received 400 mg/kg were greater than those of vehicle controls after week 69 for males and 5%-9% lower than those of vehicle controls after week 69 for females. Survival of mice that received 800 mg/kg was significantly reduced compared with that of vehicle controls after week 20 for males and week 22 for females and was not considered adequate to evaluate a carcinogenic response (final survival--male: vehicle control, 31/50; 400 mg/kg group, 36/50; 800 mg/kg group, 12/50; female: 37/50; 36/50; 10/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Pigmentation was present at increased incidences in all groups of chemically exposed animals and was characterized by varying amounts of an orange, granular pigment present in the fibrous connective tissue of the lamina propria, in the submucosa, and around vessels in the submucosa of the cecum and colon. Pigmentation of the rectum was observed at increased incidences in male rats that received 100 mg/kg, male and female rats that received 200 mg/kg, and both groups of chemically exposed mice. No pigmentation was found in the intestines of vehicle control rats or mice. Associated with pigmentation was an increased incidence of acute/chronic inflammation in the cecum and colon of all groups of chemically exposed rats and mice; this inflammation was similar to that observed in the 13-week studies but was of greater severity. Acute/chronic inflammation was also present in the rectum of male rats that received 100 mg/kg, male and female rats that received 200 mg/kg, and male mice that received 800 mg/kg.

The incidence of pancreatic acinar cell adenomas was significantly increased ($P \leq 0.002$) in male rats that received 100 mg/kg 2-amino-5-nitrophenol (vehicle control, 1/50; 100 mg/kg, 10/50; 200 mg/kg, 3/49); the increase was considered to be associated with chemical exposure. The reduced survival of male rats that received 200 mg/kg markedly reduced the sensitivity of this group for detecting the presence of neoplasms. The incidences of adenomas or carcinomas (combined) of the preputial or clitoral glands were marginally increased in male or female rats that received 200 mg/kg 2-amino-5-nitrophenol (preputial gland: 3/50; 2/50; 5/50; clitoral gland: 3/50; 3/50; 7/50). Neoplasms found in the intestinal tract of 3/50 male rats that received 100 mg/kg (one leiomyoma of the small intestine, one adenocarcinoma of the jejunum, one leiomyoma of the cecum), 2/50 male rats that received 200 mg/kg (one lipoma and one osteosarcoma of the cecum), and 1/50 female rats that received 200 mg/kg (one leiomyoma of the cecum) were not considered to be the result of chemical exposure. No compound-related neoplasms were found in mice exposed to 2-amino-5-nitrophenol in the 2-year studies.

Genetic Toxicology: 2-Amino-5-nitrophenol was mutagenic in *Salmonella typhimurium* strains TA98, TA100, and TA1537 when tested in a preincubation protocol with and without exogenous metabolic activation, and it exhibited equivocal mutagenic activity in strain TA1535 in the presence of induced liver S9. 2-Amino-5-nitrophenol induced forward mutations in mouse L5178Y lymphoma cells in the absence of metabolic activation; it was not tested with S9. An increase in chromosomal aberrations and sister chromatid exchanges was observed in cultured Chinese hamster ovary (CHO) cells following incubation with 2-amino-5-nitrophenol both in the presence and absence of exogenous metabolic activation.

Data Audit: The data, documents, and pathology materials from the 2-year studies of 2-amino-5-nitrophenol were audited at the NTP Archives. The audit findings show that the conduct of the studies is documented adequately and support the data and results given in this Technical Report.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** for male F344/N rats that received 100 mg/kg 2-amino-5-nitrophenol, as shown by the increased incidence of acinar cell adenomas of the pancreas. Reduced survival of male F344/N rats that received 200 mg/kg decreased the sensitivity of this group for detecting a carcinogenic response. There was *no evidence of carcinogenic activity* for female rats that received 100 or 200 mg/kg per day. Marginally increased incidences of preputial or clitoral gland adenomas or carcinomas (combined) occurred in male and female F344/N rats administered 200 mg/kg 2-amino-5-nitrophenol. There was *no evidence of carcinogenic activity* for $B6C3F_1$ mice that received 400 mg/kg 2-amino-5-nitrophenol; reduced survival of $B6C3F_1$ mice that received 800 mg/kg caused this group to be considered inadequate for detecting a carcinogenic response.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF 2-AMINO-5-NITROPHENOL

Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses			
0, 100, or 200 mg/kg 2-amino-5-nitrophenol in corn oil 5 d/wk	0, 100, or 200 mg/kg 2-amino-5-nitrophenol in corn oil 5 d/wk	0, 400, or 800 mg/kg 2-amino-5-nitrophenol in corn oil 5 d/wk	0, 400, or 800 mg/kg 2-amino-5-nitrophenol in corn oil 5 d/wk
Survival rates in the 2-year study			
33/50; 16/50; 4/50	30/50; 32/50; 29/50	31/50; 36/50; 12/50	37/50; 36/50; 10/50
Nonneoplastic effects			
Inflammation and pigmentation of the large intestine	Inflammation and pigmentation of the large intestine	Inflammation and pigmentation of the large intestine	Inflammation and pigmentation of the large intestine
Neoplastic effects			
Pancreatic acinar cell adenomas	None	None	None
Level of evidence of carcinogenic activity			
Some evidence	No evidence	No evidence	No evidence
Genetic toxicology			
Positive in *S. typhimurium* TA98 > TA1537 > TA100 without metabolic activation; equivocal in *S. typhimurium* TA1535 in the presence of hamster liver S9; positive in mouse lymphoma L5178Y cells without activation; positive for induction of chromosomal aberrations and sister chromatid exchanges in CHO cells with and without metabolic activation.			

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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.

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.

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. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

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

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

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

- The 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 lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The 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.

These considerations together with the definitions as written should be used as composite guidelines for selecting one of the five categories. Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the induction by chemicals of more neoplasms than are generally found, or the earlier induction by chemicals of neoplasms that are commonly observed. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

CONTENTS

CONTENTS (Continued)

APPENDIXES

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on 2-amino-5-nitrophenol on March 4, 1987, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

Robert A. Scala, Ph.D. (Chair)
Senior Scientific Advisor, Medicine and Environmental Health Department
Research and Environmental Health Division, Exxon Corporation
East Millstone, New Jersey

Michael A. Gallo, Ph.D. (Principal Reviewer)
Associate Professor, Director of Toxicology
Department of Environmental and Community Medicine, UMDNJ - Rutgers Medical School
Piscataway, New Jersey

Frederica Perera, Dr. P.H.*
Division of Environmental Sciences
School of Public Health, Columbia University, New York, New York

Ad Hoc Subcommittee Panel of Experts

Charles C. Capen, D.V.M., Ph.D.
Department of Veterinary Pathobiology
Ohio State University
Columbus, Ohio

Vernon M. Chinchilli, Ph.D.
Department of Biostatistics
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

John J. Crowley, Ph.D.*
Division of Public Health Science
The Fred Hutchinson Cancer Research Center
Seattle, Washington

Kim Hooper, Ph.D. (Principal Reviewer)
Hazard Evaluation System and Information Services
Department of Health Services
State of California
Berkeley, California

Donald H. Hughes, Ph.D. (Principal Reviewer)
Scientific Coordinator, Regulatory Services Division, The Procter and Gamble Company
Cincinnati, Ohio

Franklin E. Mirer, Ph.D.*
Director, Health and Safety Department
International Union, United Auto Workers, Detroit, Michigan

James A. Popp, D.V.M., Ph.D.
Head, Department of Experimental Pathology and Toxicology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

I.F.H. Purchase, B.V.Sc., Ph.D., F.R.C. Path.*
Director, Central Toxicology Laboratory
Imperial Chemical Industries, PLC
Alderley Park, England

Andrew Sivak, Ph.D.
Vice President, Biomedical Science
Arthur D. Little, Inc.
Cambridge, Massachusetts

*Unable to attend meeting

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2-AMINO-5-NITROPHENOL

On March 4, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of 2-amino-5-nitrophenol received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. R. Irwin, NTP, introduced the studies of 2-amino-5-nitrophenol in rats and mice by reviewing the experimental design, results, and proposed conclusions (some evidence of carcinogenic activity for male rats; no evidence of carcinogenic activity for female rats; no evidence of carcinogenic activity for male or female mice).

Dr. Gallo, a principal reviewer, agreed with the conclusions as written. He noted that the maximum tolerated dose appeared to have been exceeded in both mice and rats and suggested that the criteria for setting doses based on 13-week studies should be reexamined. Dr. Gallo said that the report should note that a structurally related chemical, 2,4-dinitrophenol, is cataractogenic in some animal species and in humans.

As a second principal reviewer, Dr. Hughes agreed with the conclusions for female rats and male and female mice but thought that the conclusions for male rats should be changed to either equivocal evidence of carcinogenic activity or no evidence of carcinogenic activity. The incidence of acinar cell adenomas in low dose male rats was not different from that seen in historical vehicle control animals. The lack of dose response and closely associated hyperplastic response were also noted. Dr. Hughes said that the lack of chemical stability to water and light made the gavage route appropriate even though the primary route of human exposure was dermal. Dr. Irwin commented that poor survival reduced the sensitivity for detecting an effect in high dose rats. However, 3/13 high dose male rats that survived until week 98 of the study, which is when most of the acinar cell tumors begin to be observed, were found to have pancreatic acinar cell tumors. Dr. J. Huff, NIEHS, emphasized that the primary comparisons should be with concurrent vehicle control animals, and Dr. Scala added that historical vehicle controls should be used only to supplement the primary analysis.

As a third principal reviewer, Dr. Hooper agreed with the conclusions for male rats and male and female mice but felt that the conclusion for female rats should be equivocal evidence of carcinogenic activity, based on the occurrence of clitoral gland adenomas in the high dose group at a rate well above the historical vehicle control range along with a positive trend. Since there was an increased incidence of carcinomas of the preputial gland in high dose male rats, he thought that some discussion would be helpful on the ontologic relationship between the glands. Dr. S. Eustis, NIEHS, said that the clitoral and preputial glands are analogous. Dr. J. Haseman, NIEHS, commented that there were two clitoral gland carcinomas in low dose females but none in the high dose group and when benign and malignant tumors were combined, the positive trend was eliminated.

Dr. Gallo moved that the Technical Report on 2-amino-5-nitrophenol be accepted with revisions as discussed and with the conclusions as written for male rats, some evidence of carcinogenic activity, and for female rats and male and female mice, no evidence of carcinogenic activity. Dr. Hooper seconded the motion, which was approved unanimously with seven votes.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2-Amino-5-nitrophenol is based on the 13-week studies that began in June 1980 and ended in September 1980 and on the 2-year studies that began in May 1981 and ended in May 1983 at Physiological Research Laboratories.

National Toxicology Program
(Evaluated Experiment, Interpreted Results, and Reported Findings)

R. Irwin, Ph.D., Chemical Manager

Jack Bishop, Ph.D.
Douglas Bristol, Ph.D.
John Bucher, Ph.D.
Scot L. Eustis, D.V.M., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
C.W. Jameson, Ph.D.
E.E. McConnell, D.V.M.
John Mennear, Ph.D.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
James K. Selkirk, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report for Rats on 6/24/86)

LeRoy Hall, D.V.M., Ph.D. (Chair) (NTP)
Michael Elwell, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Bhola Gupta, B.V.Sc., Ph.D. (NTP)
Micheal Jokinen, D.V.M. (Experimental Pathology Laboratories, Inc.)
Steven Stefanski, D.V.M., M.S. (NTP)
Billy C. Ward, D.V.M., Ph.D. (Physiological Research Laboratories)

(Evaluated Slides and Prepared Pathology Report for Mice on 6/26/86)

Steven Stefanski, D.V.M., M.S. (Chair) (NTP)
Michael Elwell, D.V.M., Ph.D. (NTP)
Scot L. Eustis, D.V.M., Ph.D. (NTP)
Bhola Gupta, B.V.Sc., Ph.D. (NTP)
LeRoy Hall, D.V.M., Ph.D. (NTP)
James MacLachlan, B.V.Sc., Ph.D.
North Carolina State University
Linda Uraih, D.V.M., M.S. (NTP)

Principal Contributors at Physiological Research Laboratories
(Conducted Studies and Evaluated Tissues)

J. Conroy, D.V.M.
M. Cowan, M.S.
D. Elsberry, Ph.D.
A. Hall, D.V.M.
R. Pieper, M.S.
B. Ward, D.V.M., Ph.D.

Principal Contributors at Experimental Pathology Laboratories, Inc.
(Provided Pathology Quality Assurance)

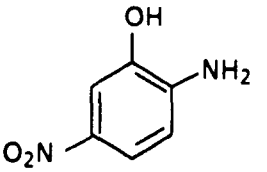
J. Gauchat
J. Hardisty, D.V.M.
Micheal Jokinen, D.V.M.

Principal Contributors at Carltech Associates, Inc.
(Contractor for Technical Report Preparation)

William D. Theriault, Ph.D.
Abigail C. Jacobs, Ph.D.
John Warner, M.S.

I. INTRODUCTION

I. INTRODUCTION



2-AMINO-5-NITROPHENOL

CAS No. 121-88-0

$C_6H_6O_3N_2$ Molecular weight 154.1

2-Amino-5-nitrophenol is an orange crystalline solid that melts at 207°-208° C and is insoluble in water but soluble in most common organic solvents. It has been used as an intermediate for the manufacture of several azo dyes of which only C.I. Solvent Red 8, used for coloring synthetic resins, lacquers, inks, and wood stains, is of commercial importance in the United States (USITC, 1982; Colour Index, 1971). In this application, 2-amino-5-nitrophenol is first converted to a diazonium salt and then coupled to other dye constituents via a diazo linkage. It is also used in semipermanent hair colorants to produce red and gold/blond shades by mixing unmodified 2-amino-5-nitrophenol with a blend of several other dyes in a shampoo base to produce the final color or tint desired. Semipermanent colorants contain dyes that penetrate into the cortex of the hair shaft upon application and slowly diffuse out with washing. In general, hair coloration is stable through five or six shampoo washings (Kirk-Othmer, 1978).

2-Amino-5-nitrophenol is not produced in commercial quantities in the United States at the present time. Between 1973 and 1979, U.S. imports averaged 13.4×10^6 g per year; recent import figures have not been reported by the U.S. Department of Commerce (USITC, 1982). 2-Amino-5-nitrophenol was reported in the Environmental Protection Agency TSCA inventory in 1980 (NIOSH, 1981).

The LD_{50} value of 2-amino-5-nitrophenol in rats was reported to be greater than 4,000 mg/kg by oral administration and greater than 800 mg/kg for administration by intraperitoneal injection (Burnett et al., 1977). No other toxicity data and no reports dealing with the disposition or metabolism of 2-amino-5-nitrophenol were found in the literature. However, the absorption of 2-amino-4-nitrophenol, a closely related structural isomer, has been examined. Percutaneous absorption of 2-amino-4-nitrophenol was determined after application to rat skin of two hair dyeing formulations containing [^{14}C]2-amino-4-nitrophenol (Hofer et al., 1982). After 1 and 5 days, 0.21% and 0.36%, respectively, of the radioactivity administered in formulation 1, and 1.12% and 1.67%, respectively, of the radioactivity administered in formulation 2, had been absorbed. Absorbed material was excreted predominantly in the urine within 24 hours after the initial application. Five days after oral administration of [^{14}C]2-amino-4-nitrophenol to rats, 68.9% of the administered radioactivity had been excreted in the urine and 25.4% in the feces. At least part of the radioactivity detected in feces originated from absorbed material, since within 3 hours following administration, approximately 4% of the administered radioactivity was eliminated in the bile.

No long-term toxicity or carcinogenicity studies of 2-amino-5-nitrophenol have been published. The long-term toxicity and carcinogenicity of a commercial hair coloring formulation containing 2-amino-5-nitrophenol as well as 17 other dyes were examined in a dermal study conducted with random-bred Swiss Webster mice (Jacobs et al., 1984). The formulation contained 5.5% dyes by weight, with water and other constituents accounting for the remaining 94.5%. The amount of 2-amino-5-nitrophenol present was 0.15% by weight of the formulation. Dosed and control groups contained 60 male or 60 female mice that were individually housed. Each animal in the dosed group received 50 µl of the neat formulation three times per week for 20 months and then was killed; a necropsy was performed on

each animal. Controls were shaved in the same manner as dosed animals but were otherwise untreated. After 9 months of exposure, 10 animals were randomly selected from dosed and control groups for hematologic analysis and urinalysis. Survival and mean body weights of dosed animals did not differ significantly from control values during the study, and no differences were found in hematologic and clinical chemistry determinations between exposed and control animals. The neoplasms observed in this study were considered characteristic of aging Swiss Webster mice and occurred with similar incidences in dosed and control animals.

4-Amino-2-nitrophenol, a structural isomer of 2-amino-5-nitrophenol, has been tested in 2-year carcinogenicity studies by the National Cancer Institute (NCI, 1978). Groups of 50 F344/N rats and 50 B6C3F$_1$ mice of each sex received diets containing 1,250 or 2,500 ppm 4-amino-2-nitrophenol for 103 weeks. Survival and mean body weights of dosed animals were not significantly different from those of controls during the studies. The incidence of transitional cell carcinomas of the urinary bladder was significantly increased in high dose male rats (11/39) compared with those in low dose (0/46) and control (0/15) male rats, and the increased incidence was attributed to chemical exposure. Transitional cell carcinomas of the urinary bladder were also observed in one low dose and two high dose female rats. No neoplasms associated with chemical exposure were observed in mice.

The mutagenicity of 2-amino-5-nitrophenol has been examined in a number of studies. *Salmonella typhimurium* strain TA1538, containing a frameshift alteration in the *his* operon, exhibited a dose-related increase in revertant colonies when treated with 0, 10, 20, 50, or 100 µg 2-amino-5-nitrophenol (purity unspecified) per plate in the presence of human or rat liver S9 (Ames et al., 1975). Chiu et al. (1978) reported mutagenic activity in *S. typhimurium* strain TA98 but not in TA100 with a plate incorporation procedure after exposure at 0.1-10 µmol of 2-amino-5-nitrophenol (purity unspecified) without exogenous metabolic activation.

In an effort to eliminate the possibility that minor contaminants might have been responsible for mutagenic activity, 2-amino-5-nitrophenol was synthesized, purified, and then tested for mutagenic activity in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 at doses up to 1,000 µg/plate with and without metabolic activation. A dose-related increase in revertant colonies was observed in TA98 and TA1538 with and without activation (Shahin et al., 1982a). In NTP Salmonella assays, mutagenic activity was observed in the frameshift mutant strains TA98 and TA1537 after exposure to 2-amino-5-nitrophenol in a preincubation protocol with and without Aroclor-1254 induced male Sprague Dawley rat or Syrian hamster liver S9; a weakly positive response was obtained with and without S9 in TA100, and questionable mutagenic activity was detected in TA1535 in trials conducted in the presence of hamster liver S9 (Zeiger et al., 1987; Appendix E, Table E1).

Exposure to 2-amino-5-nitrophenol at concentrations of 25-300 µg/ml induced forward mutations in mouse L5178Y lymphoma cells in the absence of exogenous metabolic activation; the compound was not tested with activation (Table E2). In NTP cytogenetic studies, incubation of 2-amino-5-nitrophenol in the presence or absence of Aroclor-1254 induced male Sprague Dawley rat liver S9 induced sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary (CHO) cells (Tables E3 and E4). In a dominant lethal study reported by Burnett et al. (1977), male Charles River CD rats received intraperitoneal injections of 20 mg/kg 2-amino-5-nitrophenol three times per week for 8 weeks and then were mated to untreated females. When comparisons were made of females mated to exposed males vs. those mated to control males, no differences were found in the number of live fetuses per female, the number of resorptions per pregnancy, or the percent of litters with resorptions.

Only limited data have been published on the mutagenicity of structural isomers of 2-amino-5-nitrophenol. Induction of frameshift mutations in *S. typhimurium* strains TA98 and TA1538 has been reported following exposure to 2-amino-4-nitrophenol (Ames et al., 1975; Garner and Nutman, 1977; Shahin et al., 1982a) and commercial grade 4-amino-2-nitrophenol (Garner

and Nutman, 1977; Dunkel et al., 1985; Shahin et al., 1982b). Highly purified 4-amino-2-nitrophenol caused no increase in *his*$^+$ revertant colonies in any of five strains of *S. typhimurium*, including TA98 and TA1538, leading the authors to postulate that the mutagenic activity observed in previous studies may be due to contaminants (Shahin et al., 1982b).

In NTP studies, 2-amino-4-nitrophenol (commercial grade) was mutagenic in *S. typhimurium* TA98 with and without S9 and in TA100 only in the presence of S9. In additional studies, 99.6% pure 4-amino-2-nitrophenol was a direct-acting frameshift mutagen, causing increases in *his*$^+$ revertant colonies in *S. typhimurium* strains TA97 and TA98, and was positive in the mouse lymphoma L5178Y/TK$^{+/-}$ forward mutation assay. Exposure to 2-amino-4-nitrophenol induced chromosomal aberrations and sister chromatid exchanges in CHO cells in the presence or absence of S9 (NTP, 1988a).

In contrast to the clastogenicity observed in vitro, 2-amino-4-nitrophenol did not induce formation of micronuclei in CFY rats administered 5,000 mg/kg (Hossack and Richardson, 1977), and both 2-amino-4-nitrophenol and 4-amino-2-nitrophenol were negative in the dominant lethal study conducted by Burnett et al. (1977). 4-Amino-2-nitrophenol did not induce unscheduled DNA synthesis in F344 rat primary hepatocyte cultures over a dose range of 0-10 µg/ml (Williams et al., 1982).

Study Rationale

The lack of adequate carcinogenicity studies and the report (Ames et al., 1975) that 2-amino-5-nitrophenol and several other chemicals used to color hair dyes were mutagenic in *S. typhimurium* prompted the National Cancer Institute to nominate several of these chemicals, including 2-amino-5-nitrophenol, for 2-year toxicology and carcinogenesis studies.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 2-AMINO-5-NITROPHENOL

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 2-AMINO-5-NITROPHENOL

2-Amino-5-nitrophenol was obtained in one lot (lot no. A8777) from Lowenstein Dyes, Cosmetics, Inc. (Brooklyn, New York). Purity and identity analyses were conducted at Midwest Research Institute (MRI). (MRI reports on analyses performed in support of the 2-amino-5-nitrophenol studies are on file at NIEHS.) Lot no. A8777 was obtained as brown amorphous granules. Melting point analysis indicated an endotherm at 200.5°-205° C and a broad, unresolved exotherm at 219.5°-241° C. Chemical identity was confirmed by spectroscopy. The infrared (Figure 1), ultraviolet/visible, and nuclear magnetic resonance (Figure 2) spectra were consistent with the literature spectra (Sadtler Standard Spectra) of 2-amino-5-nitrophenol.

Purity was determined by elemental analysis, water analysis, nonaqueous titration of the phenolic and amino groups, thin-layer chromatography, and high-performance liquid chromatography. Cumulative data indicated that lot no. A8777 was approximately 98% pure. Results of elemental analyses agreed with the theoretical values. The water content by Karl Fischer titration was 1.5%. Nonaqueous titration of the phenolic group with tetrabutylammonium hydroxide indicated a purity of 98.8%. Nonaqueous titration of the amino group with perchloric acid indicated a purity of 98.7%. Thin-layer chromatography on silica gel plates with a hexanes:ethyl acetate:95% ethanol (60:35:5) solvent system indicated a major spot, two trace impurities, and two slight trace impurities. Chromatography with a chloroform:methanol (90:10) solvent system indicated a major spot, two trace impurities, and one slight trace impurity. Visualization was by ultraviolet light (254 nm) and a dimethylaminobenzaldehyde-tin chloride-hydrochloric acid spray (Touchstone and Dobbins, 1978). Three impurity peaks with a combined area totaling 0.14% of the major peak area were detected by high-performance liquid chromatography on a μBondapak C_{18} column with a mobile phase of aqueous 5 mM heptane sulfonic acid containing 1% acetic acid:5 mM heptane sulfonic acid in methanol containing 1% acetic acid (84:16). The flow rate was 1 ml/minute, and ultraviolet detection was at 254 nm; three impurity peaks with a combined area 0.05% of the major peak were detected with a 60:40 solvent ratio. The results of an analysis with an intermediate (80:20) solvent ratio indicated that different impurities were detected by the two systems; taken together, the analysis indicated five impurities with a combined relative area of 0.18%.

Stability of the bulk chemical was determined by high-performance liquid chromatography with a μBondapak C_{18} column with a mobile phase of water:acetonitrile (70:30) at a flow rate of 2 ml/minute and ultraviolet detection at 254 nm. The results indicated that 2-amino-5-nitrophenol was stable as a bulk chemical when kept in the dark under nitrogen for 2 weeks at temperatures from −20° C to 60° C. Confirmation of bulk chemical stability during the toxicology and carcinogenesis studies (storage at 5° C) was obtained by nonaqueous titration with 0.1 N perchloric acid and the same high-performance liquid chromatographic system. No degradation was detected over the course of the studies. Identity of the chemical at the study laboratory was confirmed by infrared spectroscopy.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Initial dose formulation studies were carried out with 2-amino-5-nitrophenol mixed in feed at 0.6% (w/w). Homogeneous feed blends could be prepared at this concentration; however, the formulated diets were found to be unstable after 2 weeks' storage at temperatures of about −20° C. (The stability was monitored by high-performance liquid chromatography with a μBondapak C_{18} column and a mobile phase of 1% acetic acid in water:1% acetic acid in methanol (55:45) at a flow rate of 1.2 ml/minute and with detection at 254 nm.) Therefore, corn oil suspensions of the study material were prepared for gavage administration.

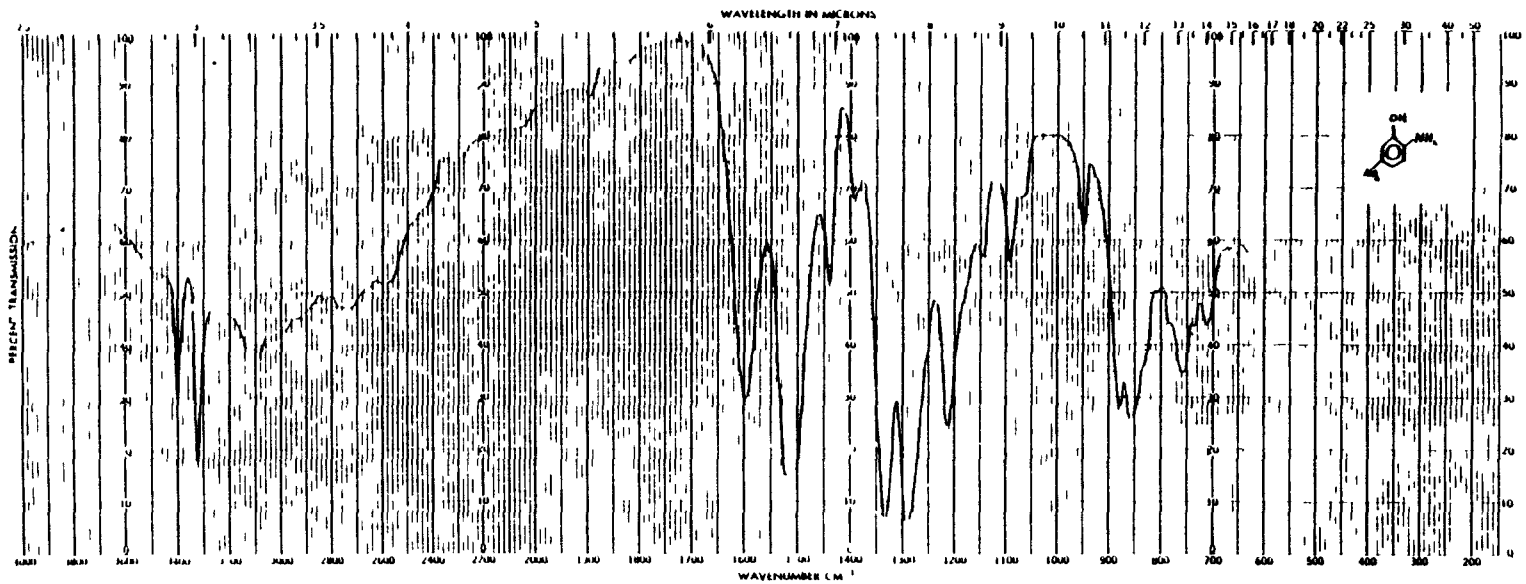


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF 2-AMINO-5-NITROPHENOL (LOT NO. A8777)

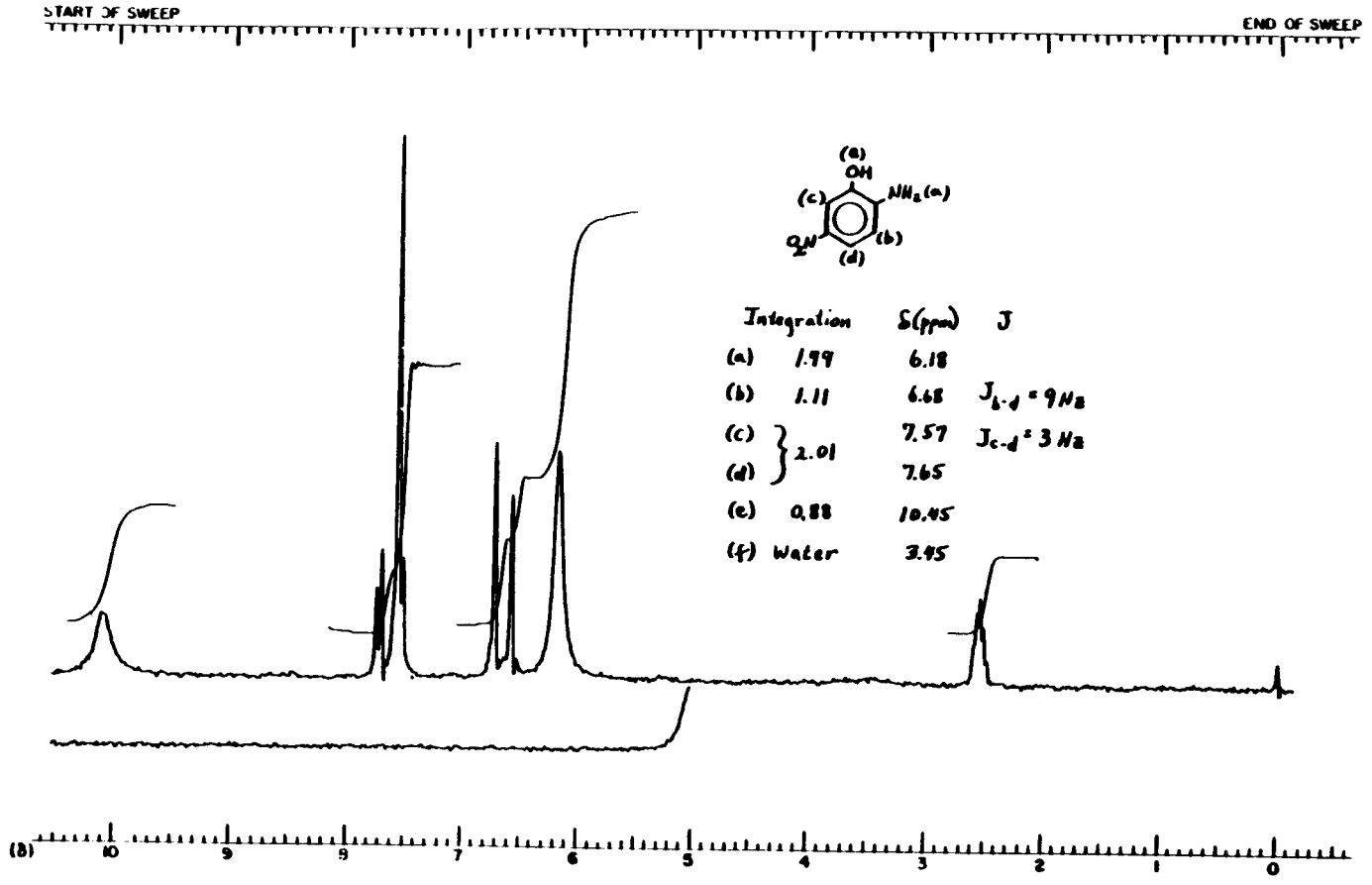


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 2-AMINO-5-NITROPHENOL (LOT NO. A8777)

2-Amino-5-nitrophenol and corn oil were mixed to give the desired concentrations (Table 1). Dose mixture stability studies were performed by extracting samples with methanol and analyzing the extract by high-performance liquid chromatography with a μBondapak C_{18} column and a mobile phase of 1% acetic acid in water:1% acetic acid in methanol (60:40) at a flow rate of 1 ml/minute and detection at 254 nm. The results showed that 2-amino-5-nitrophenol was stable in corn oil for 14 days in the dark at 5° or 25° C. Samples exposed for 3 hours to air and light at room temperature also showed no decrease in concentration. Chemical/vehicle gavage mixtures were stored under nitrogen in foil-wrapped serum bottles at 25° C or lower for no longer than 14 days.

The study and analytical chemistry laboratories periodically determined (by methanolic extraction and spectrophotometric quantitation at 263 nm) if the dose mixtures were within the specifications of the target concentrations of 2-amino-5-nitrophenol. Dose preparations were analyzed once during the 13-week studies. The results ranged from 92.3% to 101.3% of the target concentrations (Table 2). During the 2-year studies, the dose preparations were analyzed periodically with concentrations varying from 93.0% to 108.0% of the target concentrations (Table 3). Because 33/33 dose mixtures analyzed were within ±10% of the target concentrations, the dose mixtures were estimated to have been within specifications 100% of the time. Referee analyses were performed periodically by the analytical chemistry laboratory. Good agreement was generally found between the results from the two laboratories (Table 4).

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
2-Amino-5-nitrophenol and corn oil blended with a Polytron® homogenizer operated at high speed for 2 min; suspension mixed with a magnetic stirring bar for 15 min before dosing	2-Amino-5-nitrophenol mixed with corn oil in a Polytron® homogenizer for 15 sec at setting no. 1 and for 45 sec at setting no. 8; suspension degassed under vacuum	Same as 13-wk studies except mixed for 15 sec at setting no. 5 and for 5 min at setting no. 8
Maximum Storage Time		
14 d	14 d	14 d
Storage Conditions		
Stored protected from light at 4° C after headspace of the container flushed with nitrogen	Same as 16-d studies	25° C in the dark after headspace of the container flushed with nitrogen

TABLE 2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Concentration of 2-Amino-5-nitrophenol in Corn Oil (mg/ml)		Determined as a Percent of Target
Target	Determined (a)	
10	9.84	98.4
20	19.1	95.5
40	36.9	92.3
80	80.5	100.6
160	162	101.3
320	318	99.4

(a) Results of duplicate analysis; mixed on 6/6/80.

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Date Mixed	Concentration of 2-Amino-5-nitrophenol in Corn Oil for Target Concentration (mg/ml) (a)		
	20	40	80
05/05/81	19.5	40.5	80.5
05/26/81	21.0	42.9	86.4
07/21/81	20.4	40.2	81.1
11/10/81	20.0	39.3	78.3
12/17/81	19.3	41.1	86.0
05/04/82	20.1	37.5	79.7
06/02/82	20.4	40.4	79.8
09/28/82	18.6	38.0	77.9
12/28/82	19.5	39.9	83.5
02/01/83	20.9	41.0	79.8
03/08/83	18.7	38.7	74.7
Mean (mg/ml)	19.9	40.0	80.7
Standard deviation	0.81	1.53	3.48
Coefficient of variation (percent)	4.1	3.8	4.3
Range (mg/ml)	18.6-21.0	37.5-42.9	74.7-86.4
Number of samples	11	11	11

(a) Results of duplicate analysis

TABLE 4. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
05/26/81	80	86.4	80.0
07/21/81	40	40.2	39.5
09/28/82	80	77.9	79.3
02/01/83	40	41.0	35.5

(a) Results of duplicate analysis
(b) Results of triplicate analysis

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 19 days before the studies began. Rats were 7 weeks old and mice were 7-9 weeks old when placed on study. Groups of five rats of each sex were administered 2-amino-5-nitrophenol at 0, 156, 313, 625, 1,250, or 2,500 mg/kg in corn oil by gavage in 12 doses over 16 days. Groups of five mice of each sex were administered 2-amino-5-nitrophenol at 0, 313, 625, 1,250, 2,500, or 5,000 mg/kg on the same schedule. Rats and mice were observed twice per day. Body weights were recorded on day 1 and then once per week. A necropsy was performed on all animals. Selected animals in the three highest dose groups were examined histologically. Tissues and groups examined are presented in Table 5.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of 2-amino-5-nitrophenol and to determine the doses to be used in the 2-year studies.

Four- to five-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 3 weeks, distributed to weight classes, and assigned to cages according to a table of random numbers. The cages were then assigned to dosed and vehicle control groups according to a table of random numbers. Groups of 10 rats and 10 mice of each sex were administered 2-amino-5-nitrophenol at 0, 100, 200, 400, 800, or 1,600 mg/kg in corn oil by gavage, 5 days per week for 13 weeks. Further experimental details are summarized in Table 5.

Animals were checked two times per day; moribund animals were killed. Individual animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 100, or 200 mg/kg 2-amino-5-nitrophenol in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 2-amino-5-nitrophenol at 0, 400, or 800 mg/kg on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice at 5-6 weeks. The animals were quarantined at the study facility for 14 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were 46 days old and the mice were 53 days old when placed on study. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix F).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses		
Rats--0, 156, 313, 625, 1,250, or 2,500 mg/kg 2-amino-5-nitrophenol in corn oil by gavage; dose vol--10 ml/kg; mice--0, 313, 625, 1,250, 2,500, or 5,000 mg/kg; dose vol--10 ml/kg	0, 100, 200, 400, 800, or 1,600 mg/kg 2-amino-5-nitrophenol in corn oil by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--0, 100, or 200 mg/kg 2-amino-5-nitrophenol in corn oil by gavage; mice--0, 400, or 800 mg/kg; dose vol--rats: 5 ml/kg; mice: 10 ml/kg
Date of First Dose		
8/20/79	6/16/80	Rats--5/26/81; mice--5/12/81
Date of Last Dose		
9/4/79	9/12/80	Rats--5/16/83; mice--5/2/83
Duration of Dosing		
5 d/wk for 12 doses over 16 d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and 1 × wk thereafter	Same as 16-d studies	Observed 2 × d; weighed initially, 1 × wk for 12 wk, and monthly thereafter
Necropsy and Histologic Examination		
Necropsy performed on all animals; histologic exam performed on 0-2 animals of the three highest dose groups	Necropsy performed on all animals; histologic exam performed on vehicle controls, highest dose groups, animals dying before the end of the studies, liver of all mice, and cecum and colon of rats in the 400 and 800 mg/kg groups	Necropsy performed on all animals; complete histologic exam performed on all mice, all male rats, and vehicle control and high dose female rats; the following tissues examined histologically for low dose female rats: adrenal glands, bone marrow, cecum, colon, kidneys, mesenteric lymph nodes, and rectum
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory		
Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories
Method of Animal Identification		
Rats--tail mark; mice--ear punch	Toe clip	Toe and ear clip
Time Held Before Study		
19 d	20 d	14 d
Age When Placed on Study		
Rats--7 wk; mice--7-9 wk	Rats--7-8 wk; mice--8-9 wk	Rats--6-7 wk; mice--7-8 wk
Age When Killed		
Rats--10 wk; mice--10-11 wk	Rats--21-22 wk; mice--22-23 wk	Rats--111 wk; mice--112 wk
Necropsy Dates		
Rats--9/6/79-9/7/79; mice--9/5/79	Rats--9/15/80-9/16/80; mice--9/16/80-9/17/80	Rats--5/23/83-5/25/83; mice--5/9/83-5/11/83

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL (Continued)

Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMAL MAINTENANCE (Continued)		
Method of Animal Distribution		
Animals distributed to weight classes and assigned to cages according to a table of random numbers	Same as 16-d studies	Animals assigned to groups according to a table of random numbers
Feed		
Rodent Laboratory Chow 5001® meal (Ralston Purina Co., St. Louis, MO)	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding		
Heat-treated aspen wood shavings (Minnesota Sawdust and Shavings Co., Anoka, MN)	Same as 16-d studies	Same as 16-d studies
Water		
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies	Same as 16-d studies; softened with sodium zeolite to <1 grain/gal
Cages		
Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as 16-d studies	Same as 16-d studies
Cage Filters		
Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 16-d studies	Same as 16-d studies
Animals per Cage		
5	5	5
Other Chemicals on Study in the Same Room		
None	None	None
Animal Room Environment		
Temp--68°-72° F; hum--52%-68%; light 12 h/d	Temp--68°-80° F; hum--37%-74%; light 12 h/d	Temp--71°-76° F; hum--30%-74%; fluorescent light 12 h/d; >15 room air changes/h

The C57BL/6N mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 5. Cages were not rotated during the studies.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week.

Body weights by cage were recorded once per week for the first 12 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 5) were performed on all high dose and vehicle control animals and on low dose animals dying through month 21 of the study. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose group were examined histopathologically. If mortality in the highest dose group exceeded that in the vehicle control group by 15%, complete histopathologic examinations were performed on all animals in the second highest dose group in addition to those in the high dose group.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be missing or dead from other than natural

causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance include pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are used in the analysis of tumor incidence, and reported P values are one-sided.

Life Table Analysis--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analysis--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendixes containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SIXTEEN-DAY STUDIES

One of five males that received 2,500 mg/kg 2-amino-5-nitrophenol, 1/5 females that received 1,250 mg/kg, and 2/5 females that received 313 mg/kg died before the end of the studies (Table 6). The final mean body weights of rats that received 1,250 or 2,500 mg/kg were 11% and 30% lower than that of the vehicle controls for males and 9% and 13% lower for females. Rats in the three highest dose groups had loose stools throughout the studies. Gross lesions observed at necropsy in chemically exposed rats were of the same type as those found in the vehicle controls.

THIRTEEN-WEEK STUDIES

Five of 10 males and 2/10 females that received 1,600 mg/kg, 1/10 males and 3/10 females that received 800 mg/kg, and 1/10 males that received 400 mg/kg died before the end of the studies (Table 7). Final mean body weights of males that received 400, 800, or 1,600 mg/kg were 10%, 25%, and 43% lower than that of vehicle controls. The final mean body weight of females that received 1,600 mg/kg was 16% lower than that of vehicle controls. Loose stools and occasional mucoid feces were observed throughout the studies for rats that received 800 or 1,600 mg/kg and during the last 4 weeks for rats that received 400 mg/kg.

Vasculitis of the cecum or colon was found in the 800 and 1,600 mg/kg groups of male and female rats but was minimal in males and absent in females in the 400 mg/kg group and in vehicle controls (Table 8). The lesion was characterized by an acute and chronic perivasculitis and vasculitis of blood vessels in the submucosa of the cecum and colon. An inflammatory component consisting of infiltration of polymorphonuclear and mononuclear cells with varying degrees of fibroblast proliferation in the vessel adventitia was also present; the inflammatory component extended a considerable distance from the vessel in the more severe instances. Degeneration and hyalinization of the vessel occurred in severe

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	137 ± 5	195 ± 5	+58 ± 2	--
156	5/5	134 ± 6	190 ± 5	+56 ± 3	97
313	5/5	136 ± 4	198 ± 6	+62 ± 6	102
625	5/5	136 ± 8	180 ± 5	+44 ± 3	92
1,250	5/5	137 ± 3	174 ± 3	+37 ± 2	89
2,500	(d) 4/5	139 ± 2	137 ± 6	-2 ± 4	70
FEMALE					
0	5/5	112 ± 2	141 ± 3	+29 ± 3	--
156	5/5	107 ± 2	141 ± 3	+34 ± 1	100
313	(e) 3/5	109 ± 2	144 ± 1	+32 ± 2	102
625	5/5	104 ± 3	132 ± 2	+28 ± 2	94
1,250	(f) 4/5	107 ± 3	128 ± 2	+23 ± 2	91
2,500	5/5	109 ± 2	123 ± 5	+14 ± 3	87

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 11
(e) Day of death: 9,11
(f) Day of death: 10

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	174 ± 4	362 ± 7	+188 ± 5	--
100	10/10	176 ± 4	349 ± 6	+173 ± 4	96
200	(d) 9/10	174 ± 4	346 ± 4	+171 ± 3	96
400	(e) 9/10	181 ± 4	327 ± 8	+147 ± 6	90
800	(f) 9/10	175 ± 4	272 ± 6	+96 ± 6	75
1,600	(g) 5/10	175 ± 4	207 ± 8	+34 ± 5	57
FEMALE					
0	10/10	125 ± 1	193 ± 2	+68 ± 2	--
100	(d) 9/10	133 ± 2	198 ± 5	+65 ± 4	103
200	(d) 9/10	135 ± 2	199 ± 2	+62 ± 2	103
400	10/10	131 ± 2	192 ± 3	+61 ± 4	99
800	(h) 7/10	130 ± 2	191 ± 5	+62 ± 3	99
1,600	(i) 8/10	129 ± 2	162 ± 5	+34 ± 4	84

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Gavage-related death during week 13
(e) Week of death: 8
(f) Week of death: 6
(g) Week of death: 2,2,10,10; one gavage-related death during week 1.
(h) Week of death: 2,5; one gavage-related death during week 13.
(i) Week of death: 10; one gavage-related death during week 2.

TABLE 8. INCIDENCE AND SEVERITY OF VASCULITIS OF THE CECUM OR COLON IN RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Dose (mg/kg)	Incidence	Severity (a) Minimal	Mild	Moderate	Marked
MALE					
0	0/10	--	--	--	--
400	3/10	3	--	--	--
800	5/9	4	--	1	--
1,600	8/10	4	2	2	--
FEMALE					
0	0/10	--	--	--	--
400	0/10	--	--	--	--
800	3/8	3	--	--	--
1,600	8/10	2	3	3	--

(a) Number of animals with indicated severity

instances; however, occlusion was not observed in any animal. Liver weight to body weight ratios of all dosed groups of male rats except the 100 mg/kg group and of all dosed groups of female rats were significantly greater than those of the vehicle controls (Table 9).

Dose Selection Rationale: 2-Amino-5-nitrophenol doses selected for rats for the 2-year studies were 100 and 200 mg/kg, administered in corn oil by gavage 5 days per week. Because of histologic lesions observed in the cecum and colon of rats of each sex and the reduction in mean body weight and survival, doses of 400 mg/kg or more were considered to be potentially life threatening over a period of 2 years.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 5%-10% lower than those of the vehicle controls after week 33 (Table 10 and Figure 3). Mean body weights of high dose female rats were 4%-5% lower than those of the vehicle controls after week 93. Loose or poorly formed stools were observed periodically during the study for high dose male rats but with increasing frequency beginning at month 15. Loose stools were observed only occasionally for high dose females and were not observed for low dose or vehicle control animals.

TABLE 9. ABSOLUTE AND RELATIVE LIVER WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL (a)

Dose (mg/kg)	Number Examined	Final Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Final Body Weight (mg/g)
MALE				
0	10	362 ± 22.4	13,288 ± 2,920	36.4 ± 6.17
100	10	349 ± 17.7	14,356 ± 1,320	41.2 ± 3.48
200	9	346 ± 12.2	(b) 16,361 ± 1,054	(b) 47.2 ± 2.42
400	9	(b) 327 ± 23.6	15,227 ± 1,856	(b) 46.5 ± 3.42
800	9	(b) 272 ± 17.5	14,974 ± 1,031	(b) 55.3 ± 4.84
1,600	5	(b) 207 ± 18.1	12,304 ± 1,170	(b) 59.6 ± 3.08
FEMALE				
0	10	193 ± 7.2	6,216 ± 778	32.3 ± 4.11
100	9	198 ± 15.0	(b) 7,362 ± 768	(b) 37.3 ± 3.34
200	9	199 ± 5.1	(b) 7,786 ± 676	(b) 39.2 ± 2.78
400	10	192 ± 8.9	(b) 7,736 ± 788	(b) 40.3 ± 3.49
800	7	191 ± 13.0	(b) 8,357 ± 508	(b) 43.9 ± 2.65
1,600	8	(b) 162 ± 14.9	(b) 8,969 ± 783	(b) 55.3 ± 2.33

(a) Mean ± standard deviation
(b) $P<0.01$ vs. vehicle controls by Dunnett's test (Dunnett, 1955)

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	100 mg/kg Av. Wt. (grams)	100 mg/kg Wt. (percent of veh. controls)	100 mg/kg No. of Survivors	200 mg/kg Av. Wt. (grams)	200 mg/kg Wt. (percent of veh. controls)	200 mg/kg No. of Survivors
MALE								
0	130	50	131	101	50	127	98	50
1	172	50	167	97	50	165	96	49
2	204	50	200	98	50	197	97	49
3	234	50	231	99	50	226	97	49
4	250	50	249	100	49	245	98	49
5	264	50	262	99	49	255	97	48
6	283	50	281	99	49	273	96	48
7	297	50	296	100	49	286	96	48
8	313	50	313	100	47	300	96	46
9	325	50	326	100	45	312	96	46
10	339	50	340	100	45	324	96	46
11	349	50	349	100	45	331	95	46
12	360	50	359	100	45	342	95	46
16	392	50	396	101	45	383	98	45
20	415	50	415	100	45	396	95	45
24	440	50	439	100	45	420	95	45
28	449	50	452	101	45	429	96	44
33	470	50	465	99	45	442	94	44
37	484	50	481	99	45	450	93	44
41	495	50	491	99	45	466	94	44
45	503	50	501	100	45	470	93	44
50	509	50	511	100	45	475	93	43
54	508	50	513	101	45	472	93	43
59	518	50	518	100	45	475	92	42
63	514	50	511	99	45	470	91	42
67	528	50	522	99	45	478	91	42
72	528	49	521	99	43	484	92	40
76	525	49	521	99	42	484	92	36
80	522	49	523	100	41	479	92	34
85	521	47	515	99	36	479	92	29
89	519	45	508	98	35	478	92	23
93	506	41	500	99	30	483	95	17
98	489	39	486	99	26	443	91	13
101	486	36	475	98	22	439	90	8
FEMALE								
0	107	50	106	99	50	105	98	50
1	128	50	126	98	50	124	97	49
2	141	50	142	101	50	139	99	49
3	154	50	156	101	50	154	100	47
4	161	50	163	101	50	162	101	47
5	169	50	170	101	50	170	101	47
6	176	50	177	101	50	177	101	47
7	179	50	181	101	50	180	101	47
8	185	50	184	99	50	185	100	46
9	190	50	189	99	50	188	99	45
10	196	50	196	100	50	195	99	44
11	198	50	198	100	50	196	99	44
12	202	50	203	100	50	200	99	44
16	215	50	215	100	50	211	98	44
20	218	50	218	100	50	215	99	44
24	227	50	229	101	50	224	99	44
28	231	50	231	100	50	227	98	44
33	237	50	236	100	50	233	98	44
37	245	50	243	99	50	241	98	44
41	252	48	250	99	50	246	98	44
45	256	48	255	100	49	251	98	44
50	262	48	261	100	49	255	97	43
54	267	47	268	100	49	259	97	43
59	278	47	277	100	49	267	96	43
63	284	47	283	100	46	272	96	42
67	294	47	292	99	46	282	96	42
72	302	47	303	100	45	289	96	41
76	307	46	309	101	45	295	96	40
80	313	45	320	102	42	306	98	39
85	315	43	324	103	41	308	98	39
89	324	40	331	102	40	314	97	39
93	329	38	343	104	37	314	95	35
98	330	37	337	102	35	316	96	32
101	332	35	342	103	33	320	96	30

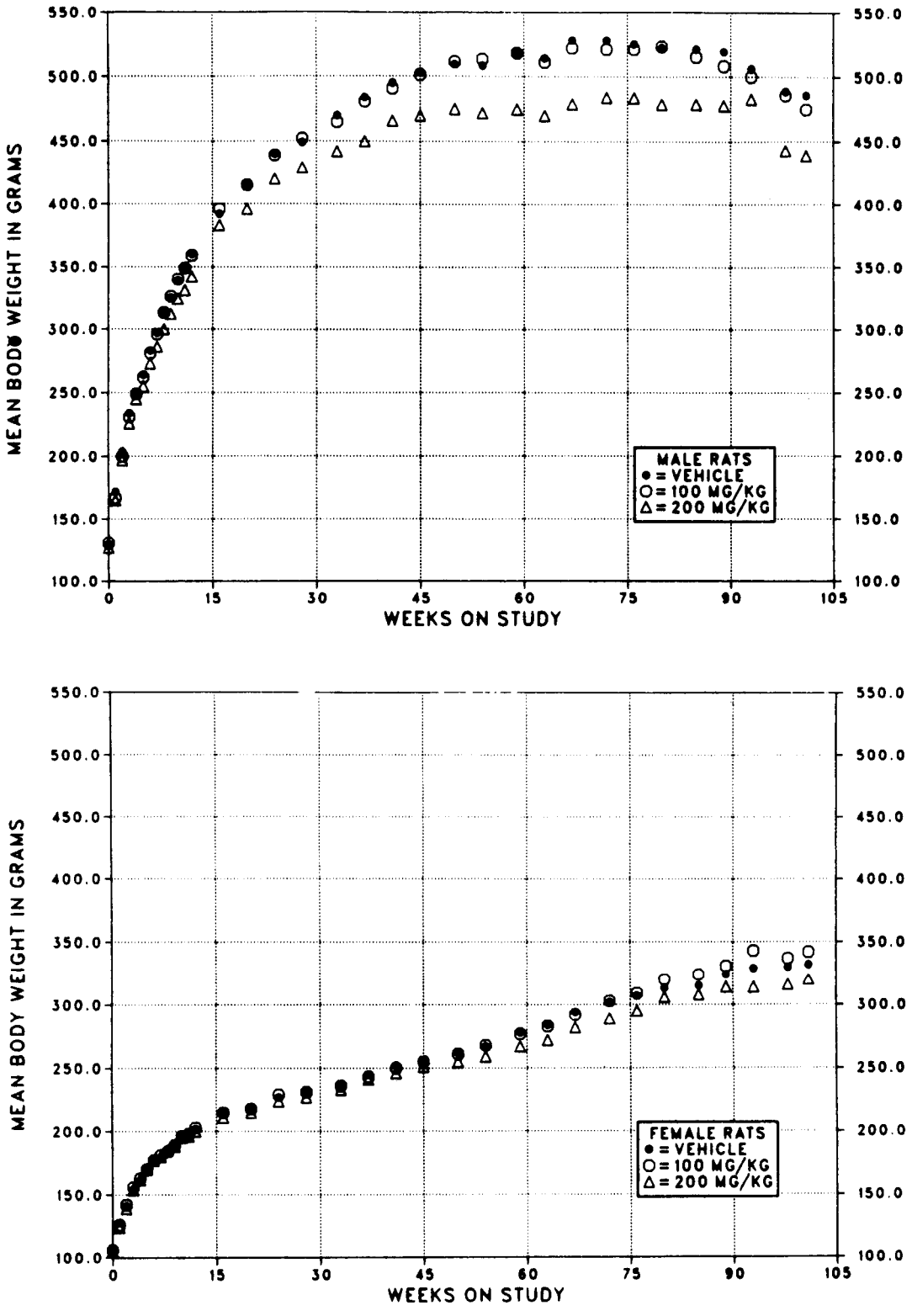


FIGURE 3. GROWTH CURVES FOR RATS ADMINISTERED 2-AMINO-5-NITROPHENOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered 2-amino-5-nitrophenol at the doses used in these studies and for vehicle controls are shown in Table 11 and in the Kaplan and Meier curves in Figure 4. The survival of both the low (after week 99) and high (after week 75) dose groups of male rats was significantly lower than that of the vehicle controls. No significant differences in survival were observed between any groups of female rats.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the pancreas, cecum, colon, rectum, jejunum, small intestine, preputial gland, clitoral gland, bone marrow, lymph nodes, and eye. Because of markedly reduced survival in high dose male rats, the statistical sensitivity of this group for detecting the presence of carcinogenic responses was reduced. The response of the low dose group, therefore, served as the primary basis for evaluating carcinogenic activity in male rats.

Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes). Historical incidences of tumors in corn oil vehicle control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table B3 (footnotes). Historical incidences of tumors in corn oil vehicle control female rats are listed in Table B4. Findings on nonneoplastic lesions are summarized in Table B5.

TABLE 11. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	100 mg/kg	200 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	17	30	42
Accidentally killed	0	4	4
Killed at termination	33	16	3
Died during termination period	0	0	1
Survival P values (c)	<0.001	0.004	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	16	17
Accidentally killed	0	2	4
Killed at termination	30	32	29
Survival P values (c)	0.897	0.674	0.973

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

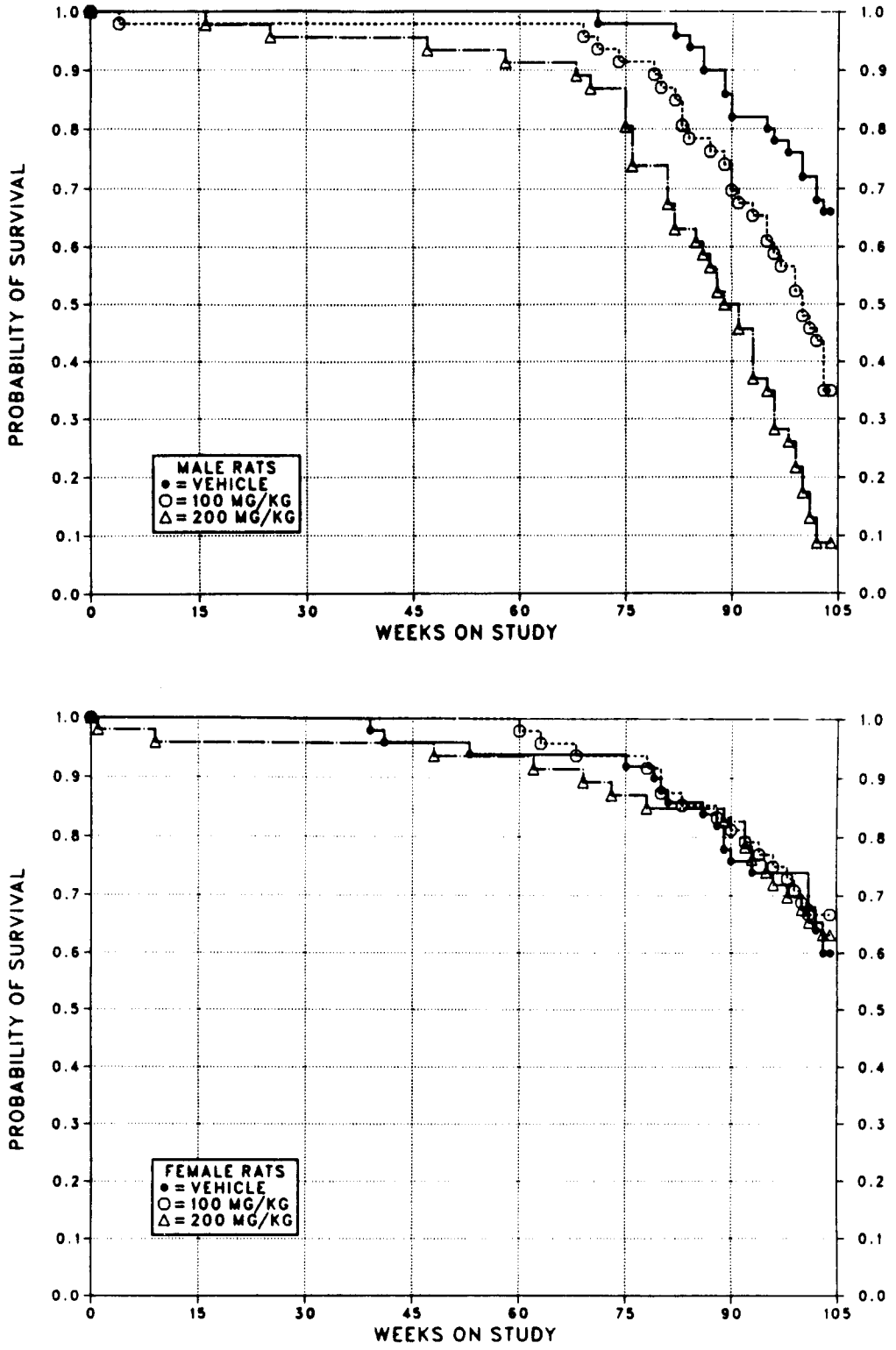


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED 2-AMINO-5-NITROPHENOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Pancreas: Acinar cell adenomas and adenomas or carcinomas (combined) in male rats occurred with significant positive trends, and the incidences in the low dose group were significantly greater than those in the vehicle controls (Table 12). Pancreatic tumors were not observed in female rats.

Cecum, Colon, Rectum, Jejunum, or Small Intestine: Acute/chronic inflammation, ulcers, and pigmentation of the cecum, colon, and rectum were observed at increased incidences in all groups of dosed rats with the exception of low dose females, in which no rectal lesions were observed (Table 13). The changes were characterized by focal ulceration of the intestinal mucosa with infiltration of neutrophils, mononuclear cells, and occasionally a few giant cells within the submucosa which were usually adjacent to vessels. In some animals, inflammatory changes without any apparent ulcerative or necrotizing lesions in the mucosa were noted. More severe lesions were characterized by segmental to diffuse necrosis and loss of mucosa with a marked inflammatory response and proliferation of granulation tissue. Varying amounts of an orange, granular pigment were present in the fibrous connective tissue of the lamina propria, in the submucosa, and around vessels in the submucosa of the cecum, colon, and rectum. In several animals, pigmentation also was seen in the adventitia of vessels in the adjacent mesentery.

Neoplasms were found in the intestinal tract of 3/50 low dose males (one leiomyoma of the small intestine, one adenocarcinoma of the jejunum, one leiomyoma of the cecum), 2/50 high dose males (one lipoma of the cecum, one osteosarcoma of the cecum), and 1/50 high dose female (one leiomyoma of the cecum) (Table 13).

TABLE 12. ANALYSIS OF PANCREATIC ACINAR CELL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (a)

	Vehicle Control	100 mg/kg	200 mg/kg
Hyperplasia			
Overall Rates	3/50 (6%)	3/50 (6%)	6/49 (12%)
Adenoma			
Overall Rates	1/50 (2%)	10/50 (20%)	3/49 (6%)
Adjusted Rates	3.0%	44.2%	42.3%
Terminal Rates	1/33 (3%)	5/16 (31%)	1/4 (25%)
Week of First Observation	104	80	98
Life Table Tests	P<0.001	P<0.001	P=0.004
Incidental Tumor Tests	P=0.061	P=0.002	P=0.117
Carcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adenoma or Carcinoma (b)			
Overall Rates	1/50 (2%)	11/50 (22%)	3/49 (6%)
Adjusted Rates	3.0%	46.2%	42.3%
Terminal Rates	1/33 (3%)	5/16 (31%)	1/4 (25%)
Week of First Observation	104	80	98
Life Table Tests	P<0.001	P<0.001	P=0.004
Incidental Tumor Tests	P=0.079	P=0.001	P=0.117

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Historical incidence in NTP studies (mean ± SD): 80/1,381 (6% ± 8%)

TABLE 13. NUMBER OF RATS WITH SELECTED LESIONS OF THE CECUM, COLON, RECTUM, JEJUNUM, OR SMALL INTESTINE IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Site/Lesion	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
No. examined (a)	50	50	50
Cecum			
Acute/chronic inflammation	0	12	17
Ulcer	0	3	5
Pigmentation	0	44	42
Lipoma	0	0	1
Leiomyoma	0	1	0
Osteosarcoma	0	0	1
Colon			
Acute/chronic inflammation	0	10	24
Ulcer	0	4	10
Pigmentation	0	43	39
Rectum			
Acute/chronic inflammation	0	15	11
Ulcer	0	9	21
Pigmentation	0	42	37
Jejunum			
Adenocarcinoma	0	1	0
Small intestine			
Leiomyoma	0	1	0
FEMALE			
No. examined (a)	50	50	50
Cecum			
Acute/chronic inflammation	0	25	6
Ulcer	0	1	3
Pigmentation	0	43	42
Leiomyoma	0	0	1
Colon			
Acute/chronic inflammation	0	17	16
Ulcer	0	2	4
Pigmentation	0	39	38
Rectum			
Acute/chronic inflammation	0	0	14
Ulcer	0	0	24
Pigmentation	0	0	41

(a) Number examined microscopically for cecum, colon, jejunum, and small intestine and grossly for rectum

Preputial Gland or Clitoral Gland: Preputial gland carcinomas and adenomas or carcinomas (combined) in male rats occurred with significant positive trends by the life table test; the incidences of preputial gland carcinomas and adenomas or carcinomas (combined) in high dose male rats were significantly greater than those in the vehicle controls by the life table test (Table 14). Clitoral gland adenomas in female rats occurred with a significant positive trend; the incidences of clitoral gland adenomas or carcinomas (combined) in dosed female rats were not significantly greater than that in the vehicle controls.

TABLE 14. ANALYSIS OF PREPUTIAL GLAND AND CLITORAL GLAND TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Adenoma			
Overall Rates	3/50 (6%)	2/50 (4%)	1/50 (2%)
Carcinoma			
Overall Rates	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates	0.0%	0.0%	36.0%
Terminal Rates	0/33 (0%)	0/16 (0%)	1/4 (25%)
Week of First Observation			75
Life Table Tests	P<0.001	(a)	P=0.003
Incidental Tumor Tests	P=0.015	(a)	P=0.073
Adenoma or Carcinoma (b)			
Overall Rates	3/50 (6%)	2/50 (4%)	5/50 (10%)
Adjusted Rates	8.0%	8.5%	42.4%
Terminal Rates	2/33 (6%)	0/16 (0%)	1/4 (25%)
Week of First Observation	84	100	75
Life Table Tests	P=0.011	P=0.630	P=0.013
Incidental Tumor Tests	P=0.284	P=0.486N	P=0.287
FEMALE			
Adenoma			
Overall Rates	2/50 (4%)	1/50 (2%)	7/50 (14%)
Adjusted Rates	6.7%	3.1%	21.9%
Terminal Rates	2/30 (7%)	1/32 (3%)	5/29 (17%)
Week of First Observation	104	104	73
Life Table Tests	P=0.029	P=0.477N	P=0.068
Incidental Tumor Tests	P=0.035	P=0.477N	P=0.089
Carcinoma			
Overall Rates	1/50 (2%)	2/50 (4%)	0/50 (0%)
Adenoma or Carcinoma (c)			
Overall Rates	3/50 (6%)	3/50 (6%)	7/50 (14%)
Adjusted Rates	9.6%	9.4%	21.9%
Terminal Rates	2/30 (7%)	3/32 (9%)	5/29 (17%)
Week of First Observation	103	104	73
Life Table Tests	P=0.091	P=0.638N	P=0.139
Incidental Tumor Tests	P=0.102	P=0.660N	P=0.165

(a) No P value is reported because no tumors were observed in the 100 mg/kg and vehicle control groups.
(b) Historical incidence in NTP studies (mean ± SD): 65/1,450 (4% ± 4%)
(c) Historical incidence in NTP studies (mean ± SD): 43/1,450 (3% ± 2%)

Bone Marrow: Hyperplasia was observed at increased incidences in dosed male rats (vehicle control, 5/50; low dose, 21/50; high dose, 37/50).

Lymph Nodes: Lymphangiectasis was observed at increased incidences in dosed male and female rats (male: vehicle control, 1/49; low dose, 15/47; high dose, 22/48; female: 0/50; 16/49; 24/49).

Eye: Retinal degeneration and cataracts of the crystalline lens were seen at increased incidences in low dose male and low dose female rats (retinal degeneration--male: vehicle control, 6/50; low dose, 35/50; high dose, 11/50; female: 13/50; 41/50; 25/50; cataracts--male: 7/50; 34/50; 10/50; female: 6/50; 40/50; 19/50). The incidence of eye lesions is associated with the relative location of dose groups in the cage racks; low dose animals were placed in the top two rows of the rack and were therefore closest to room lights. High dose animals were placed in the third and fourth rows, and vehicle controls, in the fifth and sixth rows.

SIXTEEN-DAY STUDIES

Two of five males and 5/5 females that received 5,000 mg/kg, 3/5 males and 3/5 females that received 2,500 mg/kg, 3/5 females that received 1,250 mg/kg, 1/5 females that received 625 mg/kg, and 2/5 male vehicle controls died before the end of the studies (Table 15). Final mean body weights of chemically exposed mice did not differ markedly from those of the vehicle control animals. During the first week of the studies, two males that received 2,500 mg/kg were observed to be prostrate and tremulous, and males that received 5,000 mg/kg had loose stools. By day 14, these animals had recovered and appeared healthy.

TABLE 15. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(d) 3/5	25.0 ± 0.9	26.3 ± 2.1	+1.5 ± 1.1	--
313	5/5	25.5 ± 1.2	27.3 ± 1.3	+1.8 ± 0.3	103.8
625	5/5	24.5 ± 1.1	27.6 ± 0.7	+3.1 ± 0.5	104.9
1,250	5/5	23.8 ± 0.6	25.2 ± 0.7	+1.4 ± 0.5	95.8
2,500	(e) 2/5	24.1 ± 0.5	27.3 ± 2.4	+2.2 ± 2.3	103.8
5,000	(f) 3/5	23.1 ± 0.9	25.0 ± 0.6	+2.3 ± 1.1	95.1
FEMALE					
0	5/5	18.6 ± 0.3	20.5 ± 0.3	+1.9 ± 0.3	--
313	5/5	20.2 ± 0.5	(g) 21.8 ± 0.5	+1.7 ± 0.4	106.3
625	(h) 4/5	20.7 ± 0.7	23.3 ± 1.1	+2.5 ± 0.3	113.7
1,250	(i) 2/5	19.9 ± 0.4	20.9 ± 0.4	+1.7 ± 0.4	102.0
2,500	(j) 2/5	20.2 ± 0.5	23.4 ± 0.0	+2.6 ± 0.3	114.1
5,000	(k) 0/5	20.5 ± 0.7	(l)	(l)	(l)

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 5,8
(e) Day of death: 2,2,6
(f) Day of death: 1,6
(g) One final weight not reported; weight change based on four reported values.
(h) Day of death: 3
(i) Day of death: 3,5,6
(j) Day of death: 3,4,6
(k) Day of death: 1,1,1,4,6
(l) No data are reported due to 100% mortality in this group.

THIRTEEN-WEEK STUDIES

Four of 10 males and 3/10 females that received 1,600 mg/kg died before the end of the studies (Table 16). The final mean body weight of male mice that received 1,600 mg/kg was 11% lower than that of the vehicle controls. Males and females that received 1,600 mg/kg appeared lethargic. Liver weight to body weight ratios of dosed mice were not significantly different from those of the vehicle controls (Table 17). Acute/chronic perivasculitis of vessels of the cecum or colon was present in four male and seven female mice that received 1,600 mg/kg but was absent from the vehicle controls and other chemically exposed groups.

Dose Selection Rationale: 2-Amino-5-nitrophenol doses selected for mice for the 2-year studies were 400 and 800 mg/kg, administered in corn oil by gavage 5 days per week. Higher doses were considered to be potentially life threatening over a period of 2 years because of reduced mean body weights and reduced survival at 1,600 mg/kg in the 13-week studies.

TABLE 16. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	24.1 ± 0.6	37.0 ± 1.2	+12.9 ± 0.8	--
100	10/10	24.2 ± 0.5	36.9 ± 0.4	+12.7 ± 0.5	99.7
200	10/10	23.4 ± 0.3	36.2 ± 0.8	+12.8 ± 0.7	97.8
400	10/10	24.1 ± 0.4	35.7 ± 0.7	+11.6 ± 0.4	96.5
800	(d) 9/10	23.9 ± 0.4	35.7 ± 0.3	+11.9 ± 0.4	96.5
1,600	(e) 6/10	24.1 ± 0.3	32.9 ± 0.7	+8.7 ± 0.6	88.9
FEMALE					
0	10/10	20.6 ± 0.6	25.5 ± 0.7	+4.9 ± 0.5	--
100	10/10	20.1 ± 0.2	26.4 ± 0.6	+6.3 ± 0.6	103.5
200	10/10	21.0 ± 0.6	26.5 ± 0.9	+5.5 ± 0.6	103.9
400	10/10	20.1 ± 0.4	26.9 ± 1.3	+6.8 ± 0.9	105.5
800	(d) 9/10	20.0 ± 0.3	25.4 ± 0.6	+5.2 ± 0.3	99.6
1,600	(f) 7/10	19.1 ± 0.5	24.8 ± 0.8	+5.8 ± 0.5	97.3

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean; subsequent calculations based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Death gavage related
(e) Week of death: 1,9,9,10
(f) Week of death: 2,7,8

TABLE 17. ABSOLUTE AND RELATIVE LIVER WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL (a)

Dose (mg/kg)	Number Examined	Final Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Final Body Weight (mg/g)
MALE				
0	10	37.0 ± 3.83	1,663 ± 360	45.3 ± 9.95
100	10	36.9 ± 1.17	1,667 ± 241	45.1 ± 5.74
200	10	36.2 ± 2.67	1,627 ± 195	44.9 ± 3.22
400	10	35.7 ± 2.09	1,491 ± 187	41.8 ± 5.16
800	9	35.7 ± 1.01	1,721 ± 178	48.2 ± 4.58
1,600	6	(b) 32.9 ± 1.75	1,598 ± 151	48.7 ± 5.55
FEMALE				
0	10	25.5 ± 2.30	1,163 ± 165	45.6 ± 4.93
100	10	26.4 ± 1.78	1,132 ± 107	43.0 ± 4.53
200	10	26.5 ± 2.69	1,294 ± 76	49.2 ± 3.87
400	10	26.9 ± 3.96	1,204 ± 129	45.3 ± 5.94
800	9	25.4 ± 1.79	1,148 ± 181	45.1 ± 5.94
1,600	7	24.8 ± 2.00	1,237 ± 174	50.2 ± 8.34

(a) Mean ± standard deviation
(b) $P<0.01$ vs. vehicle controls by Dunnett's test (Dunnett, 1955)

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The mean body weights of high dose male mice were 8%-11% lower than those of the vehicle controls from week 29 to week 74 (Table 18 and Figure 5). The mean body weights of low dose male mice were greater than those of the vehicle controls throughout most of the study. The mean body weights of high dose female mice were 8%-13% lower than those of the vehicle controls from week 69 to the end of the study. The mean body weights of low dose female mice were 5%-9% lower than those of the vehicle controls from week 69 to the end of the study. Compound-related effects observed up to 2 hours after gavage administration of 2-amino-5-nitrophenol included lethargy, prostration, cyanosis, and tremors. These effects were observed more frequently in high dose than in low dose animals and were not observed in vehicle controls.

TABLE 18. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Weeks on Study	Vehicle Controls Av. Wt. (grams)	Vehicle Controls No. of Survivors	400 mg/kg Av. Wt. (grams)	400 mg/kg Wt. (percent of veh. controls)	400 mg/kg No. of Survivors	800 mg/kg Av. Wt. (grams)	800 mg/kg Wt. (percent of veh. controls)	800 mg/kg No. of Survivors
MALE								
0	24.3	50	24.4	100	50	23.7	98	50
1	25.2	50	25.3	100	49	25.5	101	50
2	27.0	49	27.2	101	49	26.8	99	50
3	28.4	49	27.8	98	49	27.5	97	50
4	28.4	49	28.5	100	49	27.8	98	50
5	30.4	49	30.4	100	49	30.0	99	49
6	31.0	48	31.4	101	49	30.9	100	49
7	32.4	48	32.7	101	49	31.9	98	48
8	33.4	48	34.5	103	49	33.0	99	48
9	34.4	48	34.7	101	49	33.9	99	45
10	34.7	48	34.9	101	49	34.0	98	45
11	35.2	48	35.4	101	49	34.6	98	45
12	35.6	48	35.5	100	49	34.2	96	45
16	37.0	48	37.8	102	49	35.5	96	44
21	38.0	48	38.7	102	49	36.0	95	44
25	39.1	48	39.3	101	49	36.9	94	26
29	40.1	48	39.1	98	49	36.8	92	24
34	41.5	48	40.3	97	49	38.2	92	21
39	43.5	48	41.5	95	49	39.1	90	20
43	43.2	47	42.8	99	49	39.6	92	20
47	44.0	47	43.2	98	49	40.1	91	20
52	44.6	46	43.7	98	49	40.3	90	20
56	45.0	46	44.5	99	49	41.0	91	20
61	46.6	46	46.4	100	48	41.5	89	19
65	46.5	46	46.7	100	48	42.5	91	18
69	45.8	44	46.6	102	48	41.6	91	18
74	46.3	44	47.4	102	48	43.1	93	17
78	46.2	44	47.3	102	47	43.6	94	16
82	46.0	44	47.6	103	47	44.1	96	15
87	45.8	42	47.2	103	46	44.1	96	15
91	45.0	41	47.7	106	43	44.1	98	14
95	43.8	38	47.1	108	42	43.3	99	14
100	43.6	34	47.6	109	36	42.3	97	13
103	44.1	31	47.1	107	36	42.1	95	12
FEMALE								
0	19.2	50	19.2	100	50	19.8	103	49
1	19.8	50	20.0	101	50	20.7	105	48
2	21.2	50	21.3	100	50	22.0	104	48
3	21.7	50	21.6	100	50	22.4	103	48
4	21.6	50	21.5	100	50	22.6	105	48
5	23.1	50	22.6	98	50	23.8	103	48
6	23.1	50	23.3	101	50	24.3	105	48
7	24.6	50	24.3	99	50	25.5	104	48
8	25.2	50	25.5	101	50	26.5	105	48
9	25.3	50	25.4	100	50	26.3	104	48
10	25.7	50	25.4	99	50	26.7	104	47
11	26.2	50	26.0	99	50	27.1	103	47
12	26.6	50	26.4	99	50	27.1	102	47
16	28.0	50	27.9	100	50	28.3	101	46
21	28.9	50	28.2	98	50	28.8	100	43
25	29.1	50	28.8	99	45	28.6	98	37
29	28.9	50	28.8	100	45	28.7	99	36
34	29.1	50	29.8	102	45	29.6	102	33
39	30.9	50	31.0	100	45	30.7	99	31
43	31.9	49	31.9	100	45	31.7	99	26
47	32.6	49	32.0	98	45	32.4	99	26
52	33.1	49	32.8	99	45	33.0	100	25
56	33.8	49	33.3	99	45	34.1	101	24
61	36.6	49	35.6	97	44	36.0	98	19
65	37.0	49	35.8	97	44	35.9	97	18
69	39.4	49	37.1	94	44	35.4	90	17
74	40.3	48	36.5	91	44	36.9	92	15
78	41.4	47	38.9	94	43	37.3	90	15
82	41.7	46	39.2	94	43	37.5	90	15
87	42.8	46	40.2	94	42	38.4	90	12
91	42.1	46	40.0	95	40	37.8	90	11
95	42.6	45	39.5	93	40	37.7	88	11
100	42.1	43	39.4	94	36	37.1	88	10
103	42.5	37	39.4	93	36	37.1	87	10

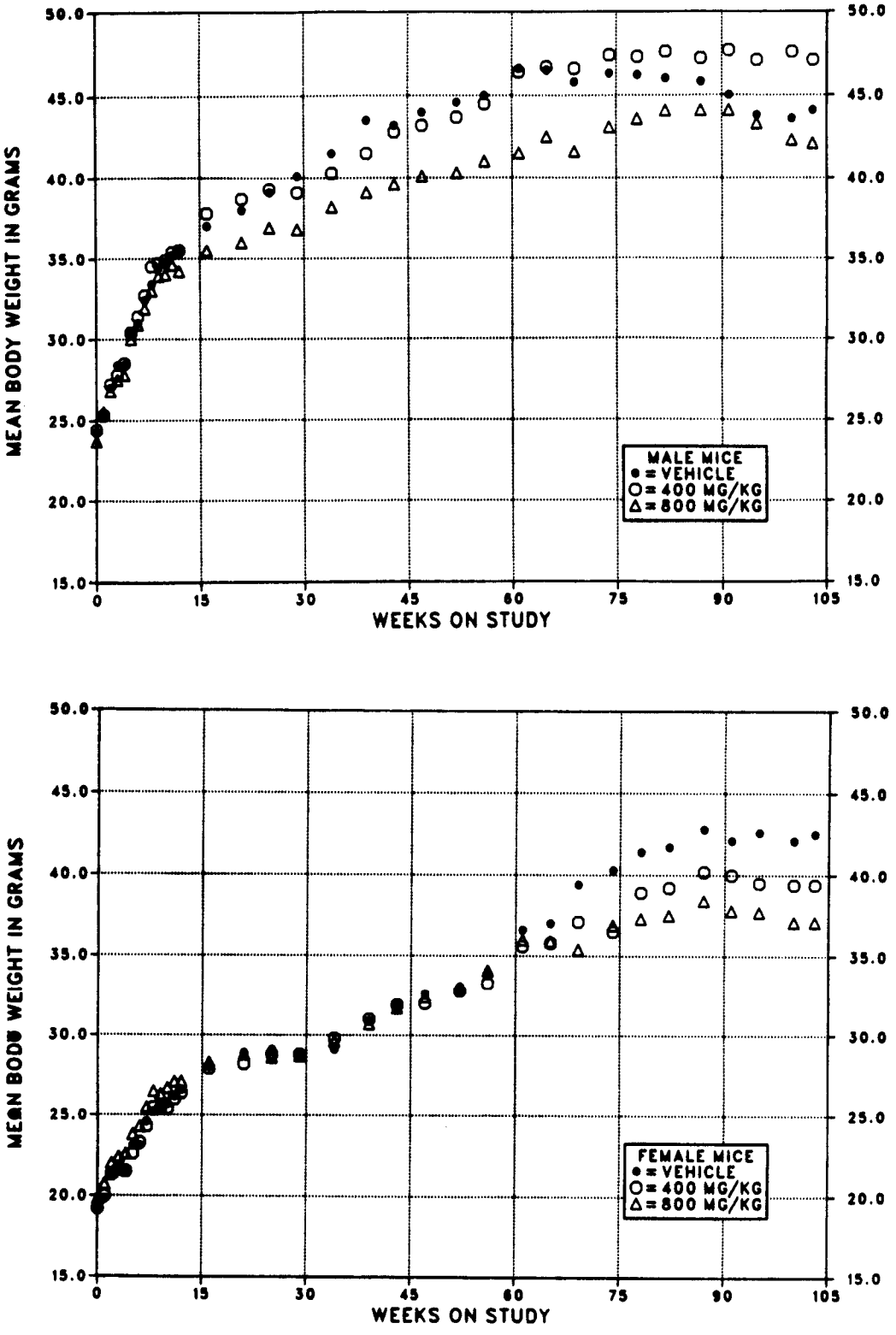


FIGURE 5. GROWTH CURVES FOR MICE ADMINISTERED 2-AMINO-5-NITROPHENOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered 2-amino-5-nitrophenol at the doses used in these studies and for vehicle controls are shown in Table 19 and in the Kaplan and Meier curves in Figure 6. Survival of high dose male mice after week 20 and high dose female mice after week 22 was significantly reduced compared with that of the vehicle controls. Of the 24 male mice that were dead by week 25, 18 died between weeks 22 and 25, but only 1 was recorded as an accidental death. Eighteen of the males dying by week 25 were located in four cages, and with a single exception, deaths of all male mice occurring by week 25 involved animals numbered 71-100. Five low dose and four high dose female mice drowned as a result of three separate incidents involving leakage or malfunction of the automatic watering system.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the cecum, colon, rectum, liver, circulatory system, and kidney.

Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes). Findings on nonneoplastic lesions are summarized in Table C4.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table D3 (footnotes). Findings on nonneoplastic lesions are summarized in Table D4.

TABLE 19. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	400 mg/kg	800 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	14	14	37
Accidentally killed	5	0	1
Killed at termination	31	36	12
Survival P values (c)	<0.001	0.971	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	12	9	35
Accidentally killed	1	5	4
Animals missing	0	0	1
Killed at termination	37	34	10
Died during termination period	0	2	0
Survival P values (c)	<0.001	0.861	<0.001

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

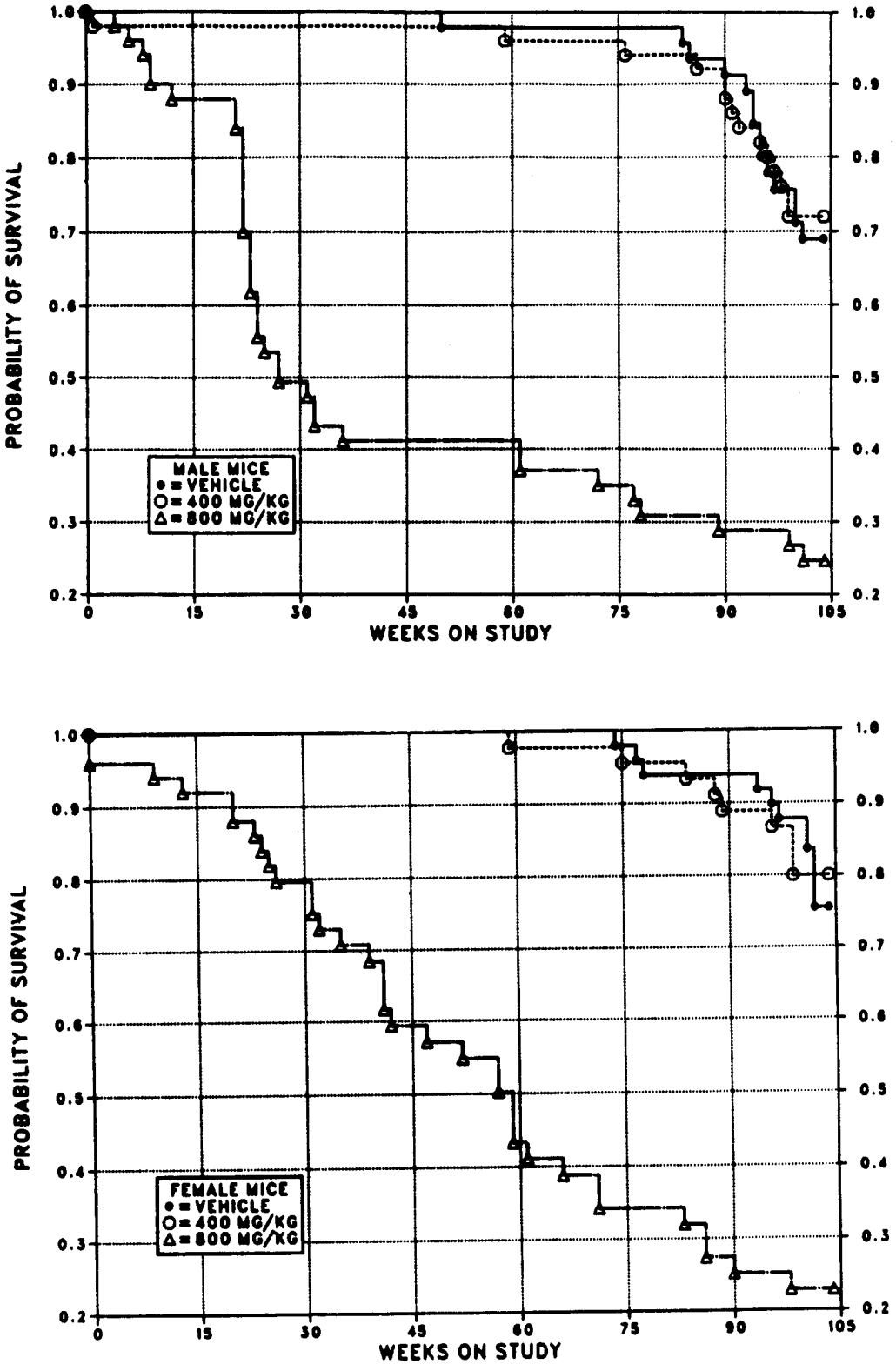


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED 2-AMINO-4-NITROPHENOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Cecum, Colon, or Rectum: Acute/chronic inflammation and pigmentation of the cecum and colon occurred at increased incidences in all groups of chemically exposed mice and were present in the rectum of male mice receiving 800 mg/kg (Table 20). Pigmentation was found at low incidence in the rectum of females receiving 800 mg/kg and mice of either sex receiving 400 mg/kg. The orange, granular pigment was found between stromal fibers of the lamina propria and/or submucosa of the cecum, colon, or rectum. Frequently associated with the pigmentation was a multifocal to diffuse acute/chronic inflammation (characterized by a cellular infiltrate containing macrophages and sometimes neutrophils); fibrosis; and, in some mice, hyperplasia of the overlying mucosal epithelium. Pigment was also present in the adventitia and muscularis of blood vessels in the lamina propria and submucosa and occasionally in vessels of the mesentery adjacent to the large intestine. Ulcers in the mucosa were found in the cecum and rectum of high dose male mice and in the cecum of high dose female mice but were not present in low dose or vehicle control mice. No neoplasms were found in the cecum, colon, or rectum of any chemically exposed or vehicle control mice.

TABLE 20. NUMBER OF MICE WITH SELECTED LESIONS OF THE CECUM, COLON, OR RECTUM IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL

Site/Lesion	Vehicle Control	400 mg/kg	800 mg/kg
MALE			
No. examined (a)	50	50	50
Cecum			
Acute/chronic inflammation	0	38	30
Chronic ulcer	0	0	6
Fibrosis	0	44	36
Pigmentation	0	47	44
Epithelial hyperplasia	0	7	2
Colon			
Acute/chronic inflammation	0	6	12
Ulcer	0	0	1
Fibrosis	0	27	17
Pigmentation	0	42	24
Epithelial hyperplasia	0	2	0
Rectum			
Acute/chronic inflammation	0	0	11
Ulcer	0	0	3
Fibrosis	0	0	13
Pigmentation	0	2	19
FEMALE			
No. examined (a)	50	50	49
Cecum			
Acute/chronic inflammation	0	12	29
Chronic ulcer	0	0	3
Fibrosis	0	26	31
Pigmentation	0	32	39
Epithelial hyperplasia	0	0	0
Colon			
Acute/chronic inflammation	0	2	7
Fibrosis	0	5	19
Pigmentation	0	7	24
Epithelial hyperplasia	0	0	0
Rectum			
Acute/chronic inflammation	1	0	0
Ulcer	0	0	0
Fibrosis	0	1	1
Pigmentation	0	1	4

(a) Number examined microscopically for cecum and colon and grossly for rectum

Liver: Cytoplasmic vacuolization was observed at increased incidences in high dose mice (male: vehicle control, 2/50; low dose, 1/50; high dose, 13/50; female: 2/50; 3/50; 9/49). Ten of the 13 high dose male mice with cytoplasmic vacuolization died at week 24 or earlier. Hepatocellular adenomas or carcinomas (combined) in male mice occurred with a significant negative trend; the incidence in the high dose group was significantly lower than that in the vehicle controls (Table 21).

Circulatory System: Hemangiosarcomas (vehicle control, 5/50; low dose, 0/50; high dose, 0/50) and hemangiomas or hemangiosarcomas (combined) (6/50; 0/50; 0/50) in male mice occurred with significant negative trends ($P<0.02$); the incidences of hemangiomas or hemangiosarcomas (combined) in dosed male mice were significantly lower than that in the vehicle controls ($P<0.05$).

Kidney: The incidences of tubular dilatation in high dose male and female mice were greater than those in the vehicle controls (male: vehicle control, 0/50; low dose, 0/50; high dose, 8/50; female: 0/50; 1/50; 4/49).

TABLE 21. ANALYSIS OF HEPATOCELLULAR TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (a)

	Vehicle Control	400 mg/kg	800 mg/kg
Adenoma			
Overall Rates	9/50 (18%)	9/50 (18%)	1/50 (2%)
Carcinoma			
Overall Rates	8/50 (16%)	7/50 (14%)	1/50 (2%)
Adenoma or Carcinoma			
Overall Rates	17/50 (34%)	16/50 (32%)	1/50 (2%)
Adjusted Rates	44.9%	37.3%	8.3%
Terminal Rates	11/31 (35%)	10/36 (28%)	1/12 (8%)
Week of First Observation	84	59	104
Life Table Tests	P=0.026N	P=0.341N	P=0.023N
Incidental Tumor Tests	P=0.032N	P=0.473N	P=0.029N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix C, Table C3 (*footnotes*).

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

2-Amino-5-nitrophenol was nominated and selected for toxicology and carcinogenesis studies as part of a study of chemicals used as coloring agents in hair dyeing formulations. Human exposure to 2-amino-5-nitrophenol associated with the use of hair dyes occurs primarily through contact with the skin, whereas occupational exposure may occur as a result of skin contact, inhalation, or accidental ingestion. Systemic exposure to 2-amino-5-nitrophenol resulting from dermal contact or oral ingestion was considered to pose the greatest risk of carcinogenicity to humans. In the present studies, oral administration was selected as the most effective way of achieving high systemic concentrations in rodents. A stability study of formulated feed mixtures conducted before the start of the toxicity studies indicated that 2-amino-5-nitrophenol was unstable in feed but could be prepared as a stable suspension in corn oil. Therefore, gavage was selected as the route of administration for the NTP studies.

Sixteen-day and 13-week studies were conducted to evaluate the short-term toxicity of 2-amino-5-nitrophenol. Reduced survival, reduced mean body weights, and the presence of perivasculitis in the cecum and colon in rats receiving doses of 400 mg/kg or more during the 13-week studies were the major factors guiding dose selection for the 2-year studies. Mean body weights of mice during the 13-week studies were only marginally affected by chemical exposure; therefore, dose selection for the 2-year studies was based on the reduced survival and the presence of perivasculitis of the cecum and colon in mice receiving 1,600 mg/kg during the 13-week studies.

Lesions of the cecum and colon, similar to those observed in the 13-week studies, were observed in all groups of rats and mice administered 2-amino-5-nitrophenol during the 2-year studies. The lesions were characterized as acute/chronic inflammation of the cecum and colon and were associated with the accumulation of an orange, granular pigment in the submucosa of the intestine, often adjacent to blood vessels. Focal ulceration of the intestinal mucosa was often present. A similar inflammatory lesion was found in the rectum of low and high dose male rats, high dose female rats, and high dose male mice. The increased incidences of bone marrow hyperplasia and lymphangiectasis observed in chemically exposed rats were considered a response to the inflammatory changes in the large intestine.

Neoplasms were observed in the small intestine of two male rats (one leiomyoma; one adenocarcinoma of the jejunum) and the large intestine of one male rat (one leiomyoma of the cecum) that received 100 mg/kg 2-amino-5-nitrophenol, and in the large intestine of two male rats (one lipoma and one osteosarcoma of the cecum) and one female rat (one leiomyoma of the cecum) that received 200 mg/kg. The low incidence of these tumors and their presence in both the small and large intestines make it unlikely that they are related to the nonneoplastic inflammatory lesions observed in the large intestine or to chemical exposure. Moreover, no intestinal neoplasms were found in mice that received doses of 2-amino-5-nitrophenol fourfold to eightfold higher than those administered to rats.

Unsubstituted or singly substituted aminophenols as a class are readily oxidized to darkly colored substances, and pigmentation of the intestinal wall has been observed in NTP studies of another related isomeric amino-nitrophenol. In 2-year studies, rats and mice received diets containing 4-amino-2-nitrophenol at 1,250 or 2,500 ppm (NCI, 1978). A high incidence of pigmentation was observed, but only in the small intestine, in all chemically exposed groups of rats and mice. No pigmentation was found in control animals.

The continuous exposure at relatively low concentrations which occurs with dietary administration is consistent with a large percentage of ingested chemical being absorbed through the small intestine and might explain why pigmentation was restricted to the small intestine in the 2-year studies of 4-amino-2-nitrophenol. The predominance of lesions in the large intestine in the present studies is consistent with the low aqueous solubility of 2-amino-5-nitrophenol and administration at higher doses as a suspension in corn oil. This would result in some of the parent compound traversing the small intestine and producing elevated chemical concentrations in the contents of the large intestine. Additional parent compound and metabolites excreted in the bile might also contribute to the contents of the large intestine.

Neoplasms of the exocrine pancreas occurred at increased incidences in chemically exposed male rats during the 2-year study. The incidence of pancreatic acinar cell adenomas was significantly increased in male rats receiving 100 mg/kg but not in male rats that received 200 mg/kg; however, the reduced survival of the latter group may be responsible for the low tumor incidence. The first acinar cell adenoma was observed in a male rat dying at week 80, but all other animals with this lesion died after week 98 or were found to have the neoplasm at study termination. At week 98, survival of male rats that received 200 mg/kg was only 12/50. With so few animals at risk during the latter part of the study, the sensitivity of this group for detecting a carcinogenic response was reduced.

Although the use of corn oil as a gavage vehicle has been associated with increased incidences of pancreatic acinar cell neoplasms among vehicle control male rats in other NTP studies (Boorman and Eustis, 1984; Haseman et al., 1985), in the present studies, only one adenoma and no carcinomas were observed in vehicle control male rats administered the same quantity of corn oil as chemically exposed animals. Moreover, the incidence of pancreatic acinar cell neoplasms was not increased in vehicle control male rats in three other corn oil gavage studies conducted concurrently with 2-amino-5-nitrophenol at the same laboratory (Table 22). The low incidence of acinar cell neoplasms among vehicle control male rats in all four studies is an indication that corn oil alone is not responsible for the increased incidence of these neoplasms.

In their analysis of previous NTP gavage studies that used corn oil as a vehicle, Haseman et al. (1985) found an apparent association between increased incidence of pancreatic acinar cell neoplasms in vehicle control male rats and maximum mean body weight. The significance of this association was due to two studies in which the maximum mean body weights of male rats (520.5 g and 511.5 g) were higher than in the other studies examined (body weight range of 430.0-497.3 g) and in which the incidence of acinar cell adenomas was much higher (14/50; 11/50) than in the other studies examined (next highest incidence, 5/49). When these two studies were excluded from the analysis, the association between maximum mean body weight and the incidence of pancreatic acinar cell adenomas was no longer significant. As illustrated in Table 22, the maximum mean body weights of vehicle control male rats in the 2-amino-4-nitrophenol (NTP, 1988a), 4-hexylresorcinol (NTP, 1988b), and 2-amino-5-nitrophenol studies fall in the same range as the two studies discussed by Haseman et al. (1985), but there is no association with increased incidences of acinar cell neoplasms.

Based on these considerations, the significant increase in the incidence of acinar cell adenomas in the pancreas of male rats that received 100 mg/kg is interpreted as being related to chemical exposure. This interpretation is further supported by the presence of pancreatic acinar cell adenomas in 3/13 (23%) high dose male rats that were still alive at week 98.

The incidences of adenomas or carcinomas (combined) of the preputial or clitoral gland were marginally increased in male and female rats that received 200 mg/kg 2-amino-5-nitrophenol during the 2-year studies. Although the differences between the chemically exposed and vehicle control animals were not statistically

TABLE 22. MAXIMUM MEAN BODY WEIGHTS AND COMBINED INCIDENCES OF PANCREATIC ACINAR CELL NEOPLASMS IN VEHICLE CONTROL MALE RATS IN STUDIES CONDUCTED CONCURRENTLY WITH 2-AMINO-5-NITROPHENOL

Chemical	Combined Incidence of Acinar Cell Neoplasms	Maximum Mean Body Weight (grams)
4-Hexylresorcinol (NTP, 1988b)	1/46	535
2-Mercaptobenzothiazole (NTP, 1988c)	2/50	523
2-Amino-4-nitrophenol (NTP, 1988a)	1/50	507
2-Amino-5-nitrophenol (current studies)	1/50	528

significant, the parallel increase in neoplasms arising from the same cell type in both the preputial and clitoral glands of high dose rats may be compound related. The poor survival of high dose male rats may have reduced the sensitivity of this group for detecting preputial gland tumors, since 20/23 rats (males and females combined) with adenomas or carcinomas (combined) of the preputial or clitoral gland died at week 96 or later or were found to have the neoplasms at study termination.

Survival of male and female mice receiving 800 mg/kg during the 2-year studies was considered inadequate for the evaluation of carcinogenicity. The high incidence of early deaths was apparently due to the toxicity of 2-amino-5-nitrophenol. Clinical signs indicative of toxicity (lethargy, prostration, and tremulous) were frequently noted shortly after gavage in mice that received 800 mg/kg and often resulted in moribund animals that were killed or found dead. Clinical signs related to compound administration (lethargy) were observed only occasionally in mice that received 400 mg/kg and were not observed in vehicle controls.

Eighteen high dose male mice dying by week 25 were housed in four cages, and 14/18 were killed when found moribund between weeks 20 and 25. There was no indication that these deaths were caused by improper preparation or administration of the gavage solutions, and a similar clustering of deaths was not seen in high dose females. One vehicle control male and one male and one female that received 800 mg/kg died from gavage trauma.

No compound-related neoplasms were found in mice receiving either 400 or 800 mg/kg 2-amino-5-nitrophenol. Pigmentation and inflammation of the large intestine occurred with similar incidences in males and females receiving 400 or 800 mg/kg (see Table 20) and were the most notable effects of chemical exposure in mice. Therefore, 400 mg/kg was considered to be an adequate challenge for evaluation of carcinogenicity but was not associated with reduced survival. Mean body weights of mice were not severely affected by chemical exposure and were never more than 13% lower than mean body weights of vehicle controls during the 2-year studies.

2-Amino-5-nitrophenol has been shown to be mutagenic in in vitro short-term tests with both bacteria and cultured mammalian cells. It induced mutations at the histidine locus of *S. typhimurium*, especially in the frameshift strains TA98, TA1537, and TA1538, and forward mutations at the TK locus of mouse lymphoma cells. It also induced aberrations and sister chromatid exchanges in Chinese hamster ovary cells. 2-Amino-5-nitrophenol produced a positive effect in all of these assay systems both in the presence and absence of metabolic activation, indicating that it is a direct-acting mutagen in vitro. In vivo mutagenicity data are limited to one negative dominant lethal study in which male rats were given intraperitoneal injections of 2-amino-5-nitrophenol three times per week for 8 weeks at individual doses that were approximately one-tenth of the LD_{50}.

Data Audit

The experimental and tabulated data for the NTP Technical Report on 2-amino-5-nitrophenol were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix H, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** for male F344/N rats that received 100 mg/kg 2-amino-5-nitrophenol, as shown by the increased incidence of acinar cell adenomas of the pancreas. Reduced survival of male F344/N rats that received 200 mg/kg decreased the sensitivity of this group for detecting a carcinogenic response. There was *no evidence of carcinogenic activity* for female rats that received 100 or 200 mg/kg per day. Marginally increased incidences of preputial or clitoral gland adenomas or carcinomas (combined) occurred in male and female F344/N rats administered 200 mg/kg 2-amino-5-nitrophenol. There was *no evidence of carcinogenic activity* for $B6C3F_1$ mice that received 400 mg/kg 2-amino-5-nitrophenol; reduced survival of $B6C3F_1$ mice that received 800 mg/kg caused this group to be considered inadequate for detecting a carcinogenic response.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

V. REFERENCES

V. REFERENCES

1. Ames, B.N.; Kammen, H.O.; Yamasaki, E. (1975) Hair dyes are mutagenic: Identification of a variety of mutagenic ingredients. Proc. Natl. Acad. Sci. USA. 72:2423-2427.

2. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons Inc., pp. 362-365.

3. Berenblum, I., Ed. (1969) Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2. Geneva: International Union Against Cancer.

4. Boorman, G.A.; Eustis, S.L. (1984) Proliferative lesions of the exocrine pancreas in male F344/N rats. Environ. Health Perspect. 56:213-217.

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

6. Burnett, C.; Loehr, R.; Corbett, J. (1977) Dominant lethal mutagenicity study on hair dyes. J. Toxicol. Environ. Health 2:657-662.

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

8. Clive, D.; Johnson, K.O.; Spector, J.F.S.; Batson, A.G.; Brown, M.M.M. (1979) Validation and characterization of the L5178Y/TK$^{+/-}$ mouse lymphoma mutagen assay system. Mutat. Res. 59:61-108.

9. Colour Index (1971) 3rd ed., Vol. 3. Yorkshire, England: Society of Dyers and Colourists, p. 3590.

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

11. Dunkel, V.C.; Zeiger, E.; Brusick, D.; McCoy, E.; McGregor, D.; Mortelmans, K.; Rosenkranz, H.S.; Simmon, V.F. (1985) Reproducibility of microbial mutagenicity assays. II. Testing of carcinogens and noncarcinogens in *Salmonella typhimurium* and *Escherichia coli*. Environ. Mutagen. 7(Suppl. 5):1-248.

12. Dunnett, C.W. (1955) A multiple comparison procedure for comparing several treatments with a control. J. Am. Stat. Assoc. 50:1096-1122.

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

14. Garner, R.C.; Nutman, C.A. (1977) Testing of some azo dyes and their reduction products for mutagenicity using *Salmonella typhimurium* TA 1538. Mutat. Res. 44:9-19.

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

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

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

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

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

20. Hofer, H.; Schwach, G.W.; Fenzl, C. (1982) Percutaneous absorption of 2-amino-4-nitrophenol in the rat. Food Chem. Toxicol. 20:921-923.

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

22. Jacobs, M.M.; Burnett, C.M.; Penicnak, A.J.; Herrera, J.A.; Morris, W.E.; Shubik, P.; Apaja, M.; Granroth, G. (1984) Evaluation of the toxicity and carcinogenicity of hair dyes in Swiss mice. Drug Chem. Toxicol. 7:573-586.

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

24. Kirk-Othmer Encyclopedia of Chemical Technology (1978) 3rd ed., Vol. 12. New York: John Wiley & Sons Inc., pp. 104-110.

25. Linhart, M.S.; Cooper, J.; Martin, R.L.; Page, N.; Peters, J. (1974) Carcinogenesis Bioassay Data System. Comput. Biomed. Res. 7:230-248.

26. Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

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

28. McConnell, E.E. (1983a) Pathology requirements for rodent two-year studies. I. A review of current procedures. Toxicol. Pathol. 11:60-64.

29. McConnell, E.E. (1983b) Pathology requirements for rodent two-year studies. II. Alternative approaches. Toxicol. Pathol. 11:65-76.

30. McConnell, E.E.; Solleveld, H.A.; Swenberg, J.A.; Boorman, G.A. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. 76:283-289.

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

32. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Technical Report No. 1. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health.

33. National Cancer Institute (NCI) (1978) Bioassay of 4-Amino-2-Nitrophenol for Possible Carcinogenicity. NCI Technical Report No. 94. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health.

34. National Institute for Occupational Safety and Health (NIOSH) (1981) Registry of Toxic Effects of Chemical Substances. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

35. National Institutes of Health (NIH) (1978) Open Formula Rat and Mouse Ration (NIH-07). Specification NIH-11-1335. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Bethesda, MD.

36. National Toxicology Program (NTP) (1988a) NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2-Amino-4-nitrophenol in F344/N Rats and B6C3F$_1$ Mice. NTP Technical Report No. 339. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health (in preparation).

37. National Toxicology Program (NTP) (1988b) NTP Technical Report on the Toxicology and Carcinogenesis Studies of 4-Hexylresorcinol in F344/N Rats and B6C3F$_1$ Mice. NTP Technical Report No. 330. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health (in preparation).

38. National Toxicology Program (NTP) (1988c) NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2-Mercaptobenzothiazole in F344/N Rats and B6C3F$_1$ Mice. NTP Technical Report No. 330. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health (in preparation).

39. Sadtler Standard Spectra, IR No. 18685; UV No. 6008; NMR No. 10012M. Philadelphia: Sadtler Research Laboratories.

40. Shahin, M.M.; Bugaut, A.; Kalopissis, G. (1982a) Mutagenicity of aminonitrophenol compounds in *Salmonella typhimurium*: A study of structural-activity relationships. Int. J. Cosmet. Sci. 4:25-35.

41. Shahin, M.M.; Bugaut, A.; Junino, A.; Kalopissis, G. (1982b) The nonmutagenicity of purified 4-amino-2-nitrophenol in *Salmonella typhimurium*. Carcinogenesis 3:809-813.

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

43. Touchstone, J.C.; Dobbins, M.F. (1978) Practice of Thin-Layer Chromatography, Spray No. 124. New York: Wiley-Interscience, p. 196.

44. U.S. International Trade Commission (USITC) (1982) Imports of Benzenoid Chemicals and Products 1981. USITC Publication No. 1272. Washington, DC: Government Printing Office.

45. Williams, G.M.; Laspia, M.F.; Dunkel, V.C. (1982) Reliability of the hepatocyte primary culture/DNA repair test in testing of coded carcinogens and noncarcinogens. Mutat. Res. 97:359-370.

46. Zeiger, E.; Anderson, B.; Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W. (1987) Salmonella mutagenicity tests. III. Results from the testing of 255 chemicals. Environ. Mutagen. 9(Suppl. 9):1-110.

APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Basal cell carcinoma		1 (2%)	
Trichoepithelioma	1 (2%)		1 (2%)
Keratoacanthoma	4 (8%)		
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibroma	6 (12%)	4 (8%)	1 (2%)
Fibrosarcoma	1 (2%)	2 (4%)	
Liposarcoma		1 (2%)	
Neurilemoma, malignant		1 (2%)	
RESPIRATORY SYSTEM			
#Trachea	(48)	(50)	(49)
Fibrosarcoma, metastatic	1 (2%)		
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	
Fibrosarcoma, metastatic	1 (2%)	1 (2%)	
Osteosarcoma, metastatic		1 (2%)	
Chordoma			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	8 (16%)	6 (12%)	4 (8%)
#Bone marrow	(50)	(50)	(50)
Sarcoma, NOS, unclear primary or metastatic	1 (2%)		
#Spleen	(50)	(50)	(50)
Sarcoma, NOS, unclear primary or metastatic	1 (2%)		
Fibrosarcoma, metastatic		1 (2%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Fibrosarcoma	1 (2%)		
#Endocardium	(50)	(50)	(50)
Neurilemoma			1 (2%)
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Papilloma, NOS		2 (4%)	
#Liver	(50)	(50)	(50)
Neoplastic nodule			2 (4%)
Sarcoma, NOS, unclear primary or metastatic	1 (2%)		
Fibrosarcoma, metastatic	1 (2%)	1 (2%)	
#Intrahepatic bile duct	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
#Pancreas	(50)	(50)	(49)
Acinar cell adenoma	1 (2%)	10 (20%)	3 (6%)
Acinar cell carcinoma		1 (2%)	
Fibrosarcoma, metastatic		1 (2%)	
#Esophagus	(50)	(50)	(49)
Papilloma, NOS		1 (2%)	
Fibrosarcoma, metastatic	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Stomach	(50)	(50)	(50)
Fibrosarcoma	1 (2%)		
#Small intestine	(50)	(50)	(50)
Leiomyoma		1 (2%)	
#Jejunum	(50)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	
#Cecum	(50)	(50)	(50)
Lipoma			1 (2%)
Leiomyoma		1 (2%)	
Osteosarcoma			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Sarcoma, NOS, unclear primary or metastatic	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(47)	(48)
Adenoma, NOS			1 (2%)
#Anterior pituitary	(48)	(47)	(48)
Adenoma, NOS	26 (54%)	17 (36%)	11 (23%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma			1 (2%)
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	19 (38%)	15 (30%)	12 (24%)
Pheochromocytoma, malignant	1 (2%)	1 (2%)	1 (2%)
#Thyroid	(49)	(49)	(49)
Follicular cell adenoma	1 (2%)	3 (6%)	1 (2%)
Follicular cell carcinoma	2 (4%)		1 (2%)
C-cell adenoma	8 (16%)	6 (12%)	6 (12%)
C-cell carcinoma	1 (2%)		
#Parathyroid	(33)	(41)	(38)
Adenoma, NOS			1 (3%)
#Pancreatic islets	(50)	(50)	(49)
Islet cell adenoma	2 (4%)		1 (2%)
Islet cell carcinoma		3 (6%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	2 (4%)	4 (8%)	
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS			4 (8%)
Adenoma, NOS	3 (6%)	2 (4%)	1 (2%)
#Prostate	(50)	(49)	(50)
Sarcoma, NOS, unclear primary or metastatic	1 (2%)		
#Testis	(50)	(49)	(50)
Interstitial cell tumor	42 (84%)	40 (82%)	39 (78%)
Mesothelioma, NOS	1 (2%)		3 (6%)
*Epididymis	(50)	(50)	(50)
Mesothelioma, NOS			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Meningioma	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteosarcoma		1 (2%)	
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
Mesothelioma, metastatic			1 (2%)
Osteosarcoma, metastatic		1 (2%)	
Lower leg			
Osteosarcoma		1	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	8	13
Moribund sacrifice	14	22	30
Terminal sacrifice	33	16	3
Dosing accident		4	4
TUMOR SUMMARY			
Total animals with primary tumors**	50	45	43
Total primary tumors	142	127	101
Total animals with benign tumors	50	45	40
Total benign tumors	116	106	82
Total animals with malignant tumors	14	20	11
Total malignant tumors	19	21	13
Total animals with secondary tumors##	1	4	1
Total secondary tumors	4	6	1
Total animals with tumors uncertain-- benign or malignant	2		5
Total uncertain tumors	2		6
Total animals with tumors uncertain-- primary or metastatic	1		
Total uncertain tumors	5		

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: VEHICLE CONTROL

ANIMAL NUMBER	1 0 5	1 0 4	1 2 2	1 1 5	1 4 4	1 1 4	1 2 5	1 1 3	1 4 3	1 4 7	1 1 8	1 0 8	1 1 9	1 2 1	1 2 4	1 3 1	1 2 6	1 0 1	1 0 2	1 0 3	1 0 6	1 0 7	1 0 9	1 1 0	1 1 1
WEEKS ON STUDY	0 7 1	0 8 2	0 8 4	0 8 6	0 8 6	0 8 9	0 8 9	0 9 0	0 9 0	0 9 5	0 9 6	0 9 8	1 0 0	1 0 0	1 0 2	1 0 2	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma																									
Keratoacanthoma											X						X								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS							X																		
Fibroma						X			X																
Fibrosarcoma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																		X							
Fibrosarcoma, metastatic													X												
Trachea	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic													X												
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, unclear primary or metastatic																	X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, unclear primary or metastatic																	X								
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma													X												
DIGESTIVE SYSTEM																									
Salivary gland	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, unclear primary or metastatic																	X								
Fibrosarcoma, metastatic													X												
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic													X												
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma											X														
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, unclear primary or metastatic																	X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X		X	X	X			X	X	X		X			X	X	X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma							X		X			X	X	X	X			X			X	X	X		
Pheochromocytoma, malignant			X																						
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
C-cell adenoma						X								X											
C-cell carcinoma																									
Parathyroid	+	+	−	+	−	+	−	−	+	+	−	+	−	+	−	+	+	+	+	+	−	−	−	+	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma										X															
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X	X	X	X	X				X	X	X			X	X	X	X		X	X	X	X	X	X	X
Mesothelioma, NOS														X											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, unclear primary or metastatic																	X								
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS			X																X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma	X																								
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS				X																					
Leukemia, mononuclear cell		X	X				X							X											

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	112	116	117	120	123	127	128	129	130	132	133	134	135	136	137	138	139	140	141	142	145	146	148	149	150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Trichoepithelioma																			X							1
Keratoacanthoma	X								X																	4
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma				X			X				X														X	6
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X														1
Alveolar/bronchiolar carcinoma					X																					2
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, unclear prim or metasta																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, unclear prim or metasta																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, unclear prim or metasta																										1
Fibrosarcoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma													X													1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, unclear prim or metasta																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X		X	X					X	X	X	X		X	X	X		X	X		X		X		X	26
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X		X	X				X		X							X			X			X	X	19
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma									X																	1
Follicular cell carcinoma							X									X										2
C-cell adenoma													X	X		X							X	X	X	8
C-cell carcinoma																		X								1
Parathyroid	−	+	−	+	−	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	−	+	+	+	+	33
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																			X							2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma										X													X			2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	42
Mesothelioma, NOS																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, unclear prim or metasta																										1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS													X													3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										1
Leukemia, mononuclear cell					X		X											X						X		8

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: LOW DOSE

ANIMAL NUMBER	0033	0036	0026	0115	0441	0443	0337	0002	0447	0220	0119	0110	0223	0007	0808	0006	0005	0440	0442	0229	0334	0444	0411	0116	0004
WEEKS ON STUDY	0004	0007	0008	0009	0009	0669	0711	0744	0779	0880	0882	0883	0883	0884	0887	0889	0900	0900	0911	0933	0955	0955	0966	0977	0999
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma											X						X								
Fibrosarcoma							X																		
Liposarcoma												X													
Neurilemoma, malignant																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma															X										
Fibrosarcoma, metastatic							X																		
Osteosarcoma, metastatic									X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic																									
Lymph nodes	+	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic							X																		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma										X															
Acinar cell carcinoma																							X		
Fibrosarcoma, metastatic																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS													X												
Leiomyoma																				X					
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS								X				X		X				X		X		X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X			X									X
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma						X																		X	
Parathyroid	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	−	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma										X															
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor						X	X	X	X	X	X		X		X	X	X		X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma									X																
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma, metastatic								X																	
Leukemia, mononuclear cell											X								X					X	
Lower leg, NOS																									
Osteosarcoma								X																	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0038	0030	0039	0050	0225	0112	0332	0445	0466	0001	0099	0113	0114	0117	0118	0221	0222	0224	0227	0228	0231	0333	0335	0348	0349	TOTAL:
WEEKS ON STUDY	099	100	100	101	102	103	103	103	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell carcinoma																X										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma															X					X						4
Fibrosarcoma													X													2
Liposarcoma																										1
Neurilemoma, malignant				X																						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Fibrosarcoma, metastatic																										1
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic													X													1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS		X												X												2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma		X	X	X				X		X		X								X		X			X	10
Acinar cell carcinoma																										1
Fibrosarcoma, metastatic													X													1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma, NOS																X										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Leiomyoma																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																								X		1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS			X	X	X		X			X						X		X	X			X	X			17
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X		X			X	X		X		X				X	X	X			X	X			X	15
Pheochromocytoma, malignant														X												1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma	X						X																	X		3
C-cell adenoma							X				X				X						X					6
Parathyroid	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	–	+	+	41
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell carcinoma							X			X															X	3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma						X	X	X																		4
Testis	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		40
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X		X																						2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS									X																	1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma, metastatic																										1
Leukemia, mononuclear cell	X			X																		X				6
Lower leg, NOS																										
Osteosarcoma																										1

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: HIGH DOSE

ANIMAL NUMBER	051	079	071	057	094	052	063	089	085	070	064	077	097	066	067	082	078	084	099	069	093	090	073	074	076
WEEKS ON STUDY	000	005	007	008	016	025	047	058	068	070	075	075	075	076	076	076	081	081	081	082	082	085	086	087	088
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Trichoepithelioma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Thymus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																								X	
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Neoplastic nodule									X																
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Osteosarcoma										X															
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																	X				X				X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma														X											
Pheochromocytoma																									
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
C-cell adenoma																	X	X							
Parathyroid	−	−	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	−	+
Adenoma, NOS																									
Pancreatic islets	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma												X													
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor									X	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Mesothelioma, NOS												X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS													X												
Adenoma, NOS																									
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	+	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS									X																
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, metastatic																									
Leukemia, mononuclear cell					X			X																	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	088	072	075	100	056	061	081	091	058	068	092	098	054	065	083	060	087	080	096	059	095	053	055	062	086	TOTAL:
WEEKS ON STUDY	088	089	091	091	093	093	093	093	095	096	096	096	098	099	099	100	100	101	102	102	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Trichoepithelioma									X																	1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																								X		1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma															X											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS								X																		1
Neoplastic nodule																X										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma													X								X	X				3
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																							X			1
Osteosarcoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS			X		X		X	X				X			X		X	X				X			12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma	X				X				X		X		X		X	X	X		X	X	X		X			12
Pheochromocytoma, malignant													X													1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																							X			1
Follicular cell carcinoma													X													1
C-cell adenoma				X							X				X					X						6
Parathyroid	+	–	–	+	+	+	+	+	+	+	+	+	–	–	+	+	–	–	+	+	+	+	+	–	+	38
Adenoma, NOS																							X			1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	39
Mesothelioma, NOS						X					X															3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS										X	X													X		4
Adenoma, NOS																	X									1
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS											X															1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, metastatic	X																									1
Leukemia, mononuclear cell															X							X				4

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	100 mg/kg	200 mg/kg
Skin: Keratoacanthoma			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	11.1%	0.0%	0.0%
Terminal Rates (c)	2/33 (6%)	0/16 (0%)	0/4 (0%)
Week of First Observation	96		
Life Table Tests (d)	P=0.113N	P=0.163N	P=0.439N
Incidental Tumor Tests (d)	P=0.019N	P=0.058N	P=0.083N
Cochran-Armitage Trend Test (d)	P=0.015N		
Fisher Exact Test (d)		P=0.059N	P=0.059N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	6/50 (12%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	16.1%	17.2%	25.0%
Terminal Rates (c)	4/33 (12%)	2/16 (13%)	1/4 (25%)
Week of First Observation	89	82	104
Life Table Tests (d)	P=0.515N	P=0.562	P=0.610N
Incidental Tumor Tests (d)	P=0.276N	P=0.563N	P=0.383N
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.370N	P=0.056N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	7/50 (14%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	19.0%	24.9%	25.0%
Terminal Rates (c)	5/33 (15%)	3/16 (19%)	1/4 (25%)
Week of First Observation	89	71	104
Life Table Tests (d)	P=0.540N	P=0.347	P=0.563N
Incidental Tumor Tests (d)	P=0.224N	P=0.545	P=0.345N
Cochran-Armitage Trend Test (d)	P=0.029N		
Fisher Exact Test (d)		P=0.500N	P=0.030N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	8/50 (16%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	20.8%	24.9%	25.0%
Terminal Rates (c)	5/33 (15%)	3/16 (19%)	1/4 (25%)
Week of First Observation	89	71	104
Life Table Tests (d)	P=0.417N	P=0.451	P=0.429N
Incidental Tumor Tests (d)	P=0.116N	P=0.559N	P=0.173N
Cochran-Armitage Trend Test (d)	P=0.015N		
Fisher Exact Test (d)		P=0.387N	P=0.015N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	9.1%	2.8%	0.0%
Terminal Rates (c)	3/33 (9%)	0/16 (0%)	0/4 (0%)
Week of First Observation	104	87	
Life Table Tests (d)	P=0.302N	P=0.532N	P=0.632N
Incidental Tumor Tests (d)	P=0.224N	P=0.475N	P=0.632N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	8/50 (16%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	19.8%	21.7%	34.3%
Terminal Rates (c)	4/33 (12%)	1/16 (6%)	1/4 (25%)
Week of First Observation	82	82	16
Life Table Tests (d)	P=0.306	P=0.483	P=0.372
Incidental Tumor Tests (d)	P=0.122N	P=0.350N	P=0.178N
Cochran-Armitage Trend Test (d)	P=0.141N		
Fisher Exact Test (d)		P=0.387N	P=0.178N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	1/50 (2%)	10/50 (20%)	3/49 (6%)
Adjusted Rates (b)	3.0%	44.2%	42.3%
Terminal Rates (c)	1/33 (3%)	5/16 (31%)	1/4 (25%)
Week of First Observation	104	80	98
Life Table Tests (d)	P<0.001	P<0.001	P=0.004
Incidental Tumor Tests (d)	P=0.061	P=0.002	P=0.117
Cochran-Armitage Trend Test (d)	P=0.291		
Fisher Exact Test (d)		P=0.004	P=0.301
Pancreas: Acinar Cell Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	11/50 (22%)	3/49 (6%)
Adjusted Rates (b)	3.0%	46.2%	42.3%
Terminal Rates (c)	1/33 (3%)	5/16 (31%)	1/4 (25%)
Week of First Observation	104	80	98
Life Table Tests (d)	P<0.001	P<0.001	P=0.004
Incidental Tumor Tests (d)	P=0.079	P=0.001	P=0.117
Cochran-Armitage Trend Test (d)	P=0.296		
Fisher Exact Test (d)		P=0.002	P=0.301
Pituitary Gland: Adenoma			
Overall Rates (a)	26/48 (54%)	17/47 (36%)	11/48 (23%)
Adjusted Rates (b)	64.1%	58.4%	60.7%
Terminal Rates (c)	18/32 (56%)	6/16 (38%)	1/4 (25%)
Week of First Observation	86	74	81
Life Table Tests (d)	P=0.099	P=0.406	P=0.081
Incidental Tumor Tests (d)	P=0.021N	P=0.158N	P=0.068N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.060N	P=0.002N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	19/50 (38%)	15/50 (30%)	12/50 (24%)
Adjusted Rates (b)	48.1%	62.5%	76.1%
Terminal Rates (c)	13/33 (39%)	8/16 (50%)	1/4 (25%)
Week of First Observation	89	83	88
Life Table Tests (d)	P=0.001	P=0.157	P=0.002
Incidental Tumor Tests (d)	P=0.551N	P=0.583N	P=0.409N
Cochran-Armitage Trend Test (d)	P=0.079N		
Fisher Exact Test (d)		P=0.264N	P=0.097N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	20/50 (40%)	16/50 (32%)	12/50 (24%)
Adjusted Rates (b)	49.1%	67.2%	76.1%
Terminal Rates (c)	13/33 (39%)	9/16 (56%)	1/4 (25%)
Week of First Observation	84	83	88
Life Table Tests (d)	P=0.002	P=0.140	P=0.004
Incidental Tumor Tests (d)	P=0.487N	P=0.580	P=0.282N
Cochran-Armitage Trend Test (d)	P=0.054N		
Fisher Exact Test (d)		P=0.266N	P=0.067N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	1/49 (2%)	3/49 (6%)	1/49 (2%)
Adjusted Rates (b)	3.0%	14.4%	25.0%
Terminal Rates (c)	1/33 (3%)	1/16 (6%)	1/4 (25%)
Week of First Observation	104	99	104
Life Table Tests (d)	P=0.083	P=0.130	P=0.256
Incidental Tumor Tests (d)	P=0.323	P=0.280	P=0.256
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.309	P=0.753N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	3/49 (6%)	2/49 (4%)
Adjusted Rates (b)	9.1%	14.4%	30.8%
Terminal Rates (c)	3/33 (9%)	1/16 (6%)	1/4 (25%)
Week of First Observation	104	99	98
Life Table Tests (d)	P=0.091	P=0.357	P=0.133
Incidental Tumor Tests (d)	P=0.382	P=0.539	P=0.304
Cochran-Armitage Trend Test (d)	P=0.412N		
Fisher Exact Test (d)		P=0.661N	P=0.500N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	8/49 (16%)	6/49 (12%)	6/49 (12%)
Adjusted Rates (b)	22.1%	27.3%	35.5%
Terminal Rates (c)	6/33 (18%)	3/16 (19%)	0/4 (0%)
Week of First Observation	89	69	81
Life Table Tests (d)	P=0.036	P=0.387	P=0.046
Incidental Tumor Tests (d)	P=0.542	P=0.564N	P=0.629
Cochran-Armitage Trend Test (d)	P=0.329N		
Fisher Exact Test (d)		P=0.387N	P=0.387N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	9/49 (18%)	6/49 (12%)	6/49 (12%)
Adjusted Rates (b)	25.0%	27.3%	35.5%
Terminal Rates (c)	7/33 (21%)	3/16 (19%)	0/4 (0%)
Week of First Observation	89	69	81
Life Table Tests (d)	P=0.052	P=0.464	P=0.056
Incidental Tumor Tests (d)	P=0.532N	P=0.486N	P=0.615N
Cochran-Armitage Trend Test (d)	P=0.235N		
Fisher Exact Test (d)		P=0.288N	P=0.288N
Pancreatic Islets: C-Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/49 (0%)
Adjusted Rates (b)	0.0%	16.9%	0.0%
Terminal Rates (c)	0/33 (0%)	2/16 (13%)	0/4 (0%)
Week of First Observation		103	
Life Table Tests (d)	P=0.152	P=0.035	(e)
Incidental Tumor Tests (d)	P=0.376	P=0.070	(e)
Cochran-Armitage Trend Test (d)	P=0.634		
Fisher Exact Test (d)		P=0.121	(e)
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/49 (2%)
Adjusted Rates (b)	5.4%	16.9%	2.5%
Terminal Rates (c)	1/33 (3%)	2/16 (13%)	0/4 (0%)
Week of First Observation	95	103	75
Life Table Tests (d)	P=0.275	P=0.245	P=0.682
Incidental Tumor Tests (d)	P=0.519N	P=0.417	P=0.384N
Cochran-Armitage Trend Test (d)	P=0.407N		
Fisher Exact Test (d)		P=0.500	P=0.508N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	6.1%	17.1%	0.0%
Terminal Rates (c)	2/33 (6%)	0/16 (0%)	0/4 (0%)
Week of First Observation	104	80	
Life Table Tests (d)	P=0.434	P=0.135	P=0.744N
Incidental Tumor Tests (d)	P=0.239N	P=0.392	P=0.744N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.339	P=0.247N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Preputial Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	8.0%	8.5%	10.0%
Terminal Rates (c)	2/33 (6%)	0/16 (0%)	0/4 (0%)
Week of First Observation	84	100	100
Life Table Tests (d)	P=0.509	P=0.630	P=0.653
Incidental Tumor Tests (d)	P=0.239N	P=0.486N	P=0.492N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Preputial Gland: Carcinoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	36.0%
Terminal Rates (c)	0/33 (0%)	0/16 (0%)	1/4 (25%)
Week of First Observation			75
Life Table Tests (d)	P<0.001	(e)	P=0.003
Incidental Tumor Tests (d)	P=0.015	(e)	P=0.073
Cochran-Armitage Trend Test (d)	P=0.015		
Fisher Exact Test (d)		(e)	P=0.059
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	8.0%	8.5%	42.4%
Terminal Rates (c)	2/33 (6%)	0/16 (0%)	1/4 (25%)
Week of First Observation	84	100	75
Life Table Tests (d)	P=0.011	P=0.630	P=0.013
Incidental Tumor Tests (d)	P=0.284	P=0.486N	P=0.287
Cochran-Armitage Trend Test (d)	P=0.274		
Fisher Exact Test (d)		P=0.500N	P=0.357
Testis: Interstitial Cell Tumor			
Overall Rates (a)	42/50 (84%)	40/49 (82%)	39/50 (78%)
Adjusted Rates (b)	93.2%	97.5%	100.0%
Terminal Rates (c)	30/33 (91%)	15/16 (94%)	4/4 (100%)
Week of First Observation	71	69	68
Life Table Tests (d)	P<0.001	P=0.001	P<0.001
Incidental Tumor Tests (d)	P=0.039	P=0.154	P=0.032
Cochran-Armitage Trend Test (d)	P=0.261N		
Fisher Exact Test (d)		P=0.482N	P=0.306N
All Sites: Mesothelioma			
Overall Rates (a)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	4.7%	0.0%	12.9%
Terminal Rates (c)	0/33 (0%)	0/16 (0%)	0/4 (0%)
Week of First Observation	86		75
Life Table Tests (d)	P=0.175	P=0.322N	P=0.208
Incidental Tumor Tests (d)	P=0.513N	P=0.143N	P=0.476N
Cochran-Armitage Trend Test (d)	P=0.390		
Fisher Exact Test (d)		P=0.247N	P=0.500
All Sites: Benign Tumors			
Overall Rates (a)	50/50 (100%)	45/50 (90%)	40/50 (80%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	33/33 (100%)	16/16 (100%)	4/4 (100%)
Week of First Observation	71	69	68
Life Table Tests (d)	P<0.001	P=0.003	P<0.001
Incidental Tumor Tests (d)	P=0.254N	(f)	P=0.669N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.029N	P=0.001N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
All Sites: Malignant Tumors			
Overall Rates (a)	14/50 (28%)	20/50 (40%)	11/50 (22%)
Adjusted Rates (b)	33.1%	61.1%	67.2%
Terminal Rates (c)	7/33 (21%)	6/16 (38%)	2/4 (50%)
Week of First Observation	71	71	16
Life Table Tests (d)	P=0.008	P=0.009	P=0.027
Incidental Tumor Tests (d)	P=0.185N	P=0.191	P=0.167N
Cochran-Armitage Trend Test (d)	P=0.293N		
Fisher Exact Test (d)		P=0.146	P=0.323N
All Sites: All Tumors			
Overall Rates (a)	50/50 (100%)	45/50 (90%)	43/50 (86%)
Adjusted Rates (b)	100%	100%	100%
Terminal Rates (c)	33/33 (100%)	16/16 (100%)	4/4 (100%)
Week of First Observation	71	69	16
Life Table Tests (d)	P<0.001	P=0.003	P<0.001
Incidental Tumor Tests (d)	P=0.722	(f)	P=0.909N
Cochran-Armitage Trend Test (d)	P=0.008N		
Fisher Exact Test (d)		P=0.029N	P=0.007N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the dosed and vehicle control groups.
(f) No P value is reported because the tumor incidences in the vehicle control and 100 mg/kg groups were 100% in each of the four time intervals during which tumors were observed.

TABLE A4a. HISTORICAL INCIDENCE OF PANCREATIC ACINAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls	
	Adenoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.		
Overall Historical Incidence		
TOTAL	78/1,381 (5.6%)	(b) 80/1,381 (5.8%)
SD (c)	7.86%	8.00%
Range (d)		
High	14/50	14/50
Low	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks; does not include 22/50 observed in the benzyl acetate study for which multiple sections were examined.
(b) One adenoma, NOS, one carcinoma, NOS, and one adenocarcinoma, NOS, were also observed; the inclusion of these tumors would not affect the reported range.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	30/1,450 (2.1%)	(b) 35/1,450 (2.4%)	(b) 65/1,450 (4.5%)
SD (c)	3.27%	2.53%	4.33%
Range (d)			
High	7/50	5/50	9/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes 26 carcinomas, NOS, 3 squamous cell carcinomas, and 6 adenocarcinomas
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)	3 (6%)	3 (6%)
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	1 (2%)
*Nasal turbinate	(50)	(50)	(50)
Hemorrhage		3 (6%)	
Inflammation, acute/chronic	32 (64%)	29 (58%)	23 (46%)
#Lung	(50)	(50)	(50)
Congestion, NOS		6 (12%)	4 (8%)
Edema, NOS			1 (2%)
Hemorrhage			1 (2%)
Inflammation, chronic focal	5 (10%)	5 (10%)	2 (4%)
Calcification, NOS		1 (2%)	1 (2%)
Foreign material, NOS		3 (6%)	1 (2%)
Bronchiolization	2 (4%)		
Histiocytosis			2 (4%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(50)
Hyperplasia, NOS	5 (10%)	21 (42%)	37 (74%)
Hyperplasia, reticulum cell	1 (2%)		1 (2%)
#Spleen	(50)	(50)	(50)
Fibrosis, focal	1 (2%)	2 (4%)	3 (6%)
Pigmentation, NOS			1 (2%)
Hemosiderosis	1 (2%)	2 (4%)	2 (4%)
Atrophy, NOS			1 (2%)
Hematopoiesis	3 (6%)		2 (4%)
#Splenic capsule	(50)	(50)	(50)
Hyperplasia, mesothelial			1 (2%)
#Lymph node	(49)	(47)	(48)
Pigmentation, NOS	1 (2%)		
#Small intestine	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Jejunum	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
#Ileum	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Colon	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
CIRCULATORY SYSTEM			
#Lymph node	(49)	(47)	(48)
Lymphangiectasis	1 (2%)	15 (32%)	22 (46%)
#Lung	(50)	(50)	(50)
Perivasculitis	6 (12%)	4 (8%)	2 (4%)
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	43 (86%)	37 (74%)	33 (66%)
Calcification, NOS		1 (2%)	1 (2%)
*Artery	(50)	(50)	(50)
Perivasculitis			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
*Pulmonary artery	(50)	(50)	(50)
Calcification, NOS	2 (4%)	3 (6%)	1 (2%)
#Testis	(50)	(49)	(50)
Perivasculitis	1 (2%)		
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Hyperplasia, epithelial		5 (10%)	
#Salivary gland	(49)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Inflammation with fibrosis	1 (2%)		
Atrophy, focal		1 (2%)	
#Liver	(50)	(50)	(50)
Congenital malformation, NOS		3 (6%)	1 (2%)
Inflammation, multifocal			1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	8 (16%)	6 (12%)	5 (10%)
Degeneration, cystic	1 (2%)		1 (2%)
Degeneration, lipoid	1 (2%)	2 (4%)	1 (2%)
Necrosis, NOS			1 (2%)
Necrosis, focal			1 (2%)
Focal cellular change	34 (68%)	28 (56%)	21 (42%)
Hepatocytomegaly	1 (2%)		
Hyperplasia, focal	1 (2%)	1 (2%)	
Angiectasis			1 (2%)
#Hepatic capsule	(50)	(50)	(50)
Fibrosis, focal			1 (2%)
#Intrahepatic bile duct	(50)	(50)	(50)
Multiple cysts		1 (2%)	
Hyperplasia, NOS	28 (56%)	31 (62%)	17 (34%)
#Pancreas	(50)	(50)	(49)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal	2 (4%)		
#Pancreatic acinus	(50)	(50)	(49)
Atrophy, focal	20 (40%)	10 (20%)	8 (16%)
Hyperplasia, NOS	2 (4%)	3 (6%)	6 (12%)
Hyperplasia, focal	1 (2%)		
#Esophagus	(50)	(50)	(49)
Dilatation, NOS		1 (2%)	
#Stomach	(50)	(50)	(50)
Ulcer, perforated	1 (2%)		
#Gastric mucosa	(50)	(50)	(50)
Multiple cysts	1 (2%)		1 (2%)
Calcification, NOS	1 (2%)	3 (6%)	4 (8%)
Hyperplasia, epithelial	1 (2%)		
#Cardiac stomach	(50)	(50)	(50)
Ulcer, NOS		3 (6%)	3 (6%)
Inflammation, acute	1 (2%)		1 (2%)
Eosinophilic leukocytic infiltrate			1 (2%)
Inflammation with fibrosis		4 (8%)	1 (2%)
Hyperplasia, epithelial	11 (22%)	12 (24%)	9 (18%)
#Gastric fundus	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
#Small intestine	(50)	(50)	(50)
Hyperplasia, epithelial			1 (2%)
Polyp, inflammatory		1 (2%)	
#Duodenum	(50)	(50)	(50)
Pigmentation, NOS			4 (8%)
#Jejunum	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Ileum	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
#Colon	(50)	(50)	(50)
Multiple cysts			1 (2%)
Ulcer, NOS		4 (8%)	10 (20%)
Inflammation, acute/chronic		10 (20%)	24 (48%)
Pigmentation, NOS		43 (86%)	39 (78%)
#Cecum	(50)	(50)	(50)
Ulcer, NOS		3 (6%)	5 (10%)
Abscess, NOS			1 (2%)
Inflammation, acute/chronic		12 (24%)	17 (34%)
Pigmentation, NOS		44 (88%)	42 (84%)
*Rectum	(50)	(50)	(50)
Ulcer, NOS		9 (18%)	21 (42%)
Inflammation, acute/chronic		15 (30%)	11 (22%)
Pigmentation, NOS		42 (84%)	37 (74%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cyst, NOS		1 (2%)	1 (2%)
Multiple cysts		1 (2%)	
Pyelonephritis, NOS		1 (2%)	1 (2%)
Abscess, chronic	2 (4%)		
Nephropathy	47 (94%)	43 (86%)	41 (82%)
Nephrosis, NOS			1 (2%)
Calcification, NOS	1 (2%)	2 (4%)	2 (4%)
#Kidney/capsule	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
#Urinary bladder	(50)	(49)	(50)
Calculus, gross observation only	1 (2%)		
Cast, NOS			1 (2%)
Inflammation, chronic			1 (2%)
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder/submucosa	(50)	(49)	(50)
Inflammation, acute	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary	(48)	(47)	(48)
Hematoma, NOS	1 (2%)		
#Anterior pituitary	(48)	(47)	(48)
Cyst, NOS	2 (4%)	2 (4%)	2 (4%)
Multiple cysts	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, NOS	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, focal	2 (4%)	1 (2%)	
#Adrenal cortex	(50)	(50)	(50)
Degeneration, lipoid	6 (12%)	11 (22%)	6 (12%)
Lipoidosis		1 (2%)	
Hyperplasia, focal	7 (14%)		
Angiectasis	4 (8%)	4 (8%)	
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, NOS	4 (8%)	2 (4%)	5 (10%)
#Thyroid	(49)	(49)	(49)
Cyst, NOS	1 (2%)		
Hyperplasia, C-cell	21 (43%)	15 (31%)	10 (20%)
#Parathyroid	(33)	(41)	(38)
Hyperplasia, NOS	1 (3%)	5 (12%)	3 (8%)
#Pancreatic islets	(50)	(50)	(49)
Hyperplasia, NOS	1 (2%)		1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, cystic	1 (2%)	5 (10%)	3 (6%)
*Preputial gland	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)	3 (6%)
Inflammation, acute/chronic	31 (62%)	29 (58%)	5 (10%)
Inflammation, chronic	1 (2%)		1 (2%)
#Prostate	(50)	(49)	(50)
Inflammation, acute/chronic	26 (52%)	23 (47%)	23 (46%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Inflammation, NOS			1 (2%)
Atrophy, NOS	14 (28%)	11 (22%)	10 (20%)
#Testis	(50)	(49)	(50)
Calcification, NOS			1 (2%)
Atrophy, NOS	6 (12%)	2 (4%)	2 (4%)
Hyperplasia, interstitial cell	19 (38%)	18 (37%)	16 (32%)
*Scrotum	(50)	(50)	(50)
Necrosis, fat	2 (4%)	3 (6%)	2 (4%)
NERVOUS SYSTEM			
#Cerebrum	(50)	(50)	(50)
Necrosis, hemorrhagic	1 (2%)		
#Brain	(50)	(50)	(50)
Hydrocephalus, NOS		1 (2%)	
Epidermal inclusion cyst		1 (2%)	
Hemorrhage	1 (2%)	2 (4%)	
SPECIAL SENSE ORGANS			
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	6 (12%)	35 (70%)	11 (22%)
*Eye/lens, cortex	(50)	(50)	(50)
Cataract	7 (14%)	34 (68%)	10 (20%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)	4 (8%)	1 (2%)
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Cyst, NOS			1 (2%)
*Mesentery	(50)	(50)	(50)
Inflammation, acute			1 (2%)
Inflammation, acute/chronic			1 (2%)
Inflammation granulomatous focal	1 (2%)		
Necrosis, fat	3 (6%)	2 (4%)	1 (2%)
ALL OTHER SYSTEMS			
Site unknown			
Abscess, NOS			1

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL MORPHOLOGY SUMMARY			
None			

• Number of animals receiving necropsy examinations; all gross lesions including masses examined microscopically.
Number of animals examined microscopically at this site

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Papilloma, NOS	2 (4%)	1 (2%)	
Basal cell tumor		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	2 (4%)	1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(23)	(50)
Adenocarcinoma, NOS, metastatic		2 (9%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	9 (18%)	6 (12%)	11 (22%)
#Lymph node	(50)	(49)	(49)
Sarcoma, NOS		1 (2%)	
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Esophagus	(50)	(12)	(50)
Squamous cell carcinoma	1 (2%)		
#Cecum	(50)	(50)	(50)
Leiomyoma			1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(46)	(48)
Adenoma, NOS		1 (2%)	
#Anterior pituitary	(50)	(46)	(48)
Adenoma, NOS	30 (60%)	30 (65%)	29 (60%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma		1 (2%)	1 (2%)
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	1 (2%)	2 (4%)	4 (8%)
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(50)	(12)	(49)
Follicular cell adenoma			1 (2%)
C-cell adenoma	4 (8%)	1 (8%)	3 (6%)
C-cell carcinoma	2 (4%)	1 (8%)	1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS			1 (2%)
Adenocarcinoma, NOS	1 (2%)	3 (6%)	1 (2%)
Fibroadenoma	10 (20%)	12 (24%)	13 (26%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	2 (4%)	
Adenoma, NOS	2 (4%)	1 (2%)	7 (14%)
#Uterus	(50)	(21)	(50)
Adenocarcinoma, NOS		1 (5%)	
Sarcoma, NOS		1 (5%)	
Leiomyosarcoma			1 (2%)
Endometrial stromal polyp	12 (24%)	10 (48%)	11 (22%)
Deciduoma		1 (5%)	
#Ovary	(50)	(11)	(50)
Gonadal stromal tumor	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(13)	(50)
Granular cell tumor, benign	1 (2%)		
Oligodendroglioma	1 (2%)		
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Peritoneum	(50)	(50)	(50)
Fibrosarcoma	1 (2%)		
*Mesentery	(50)	(50)	(50)
Lipoma	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	
Pheochromocytoma, metastatic	1 (2%)		
Sarcoma, NOS, unclear primary or metastatic		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	7	6
Moribund sacrifice	17	9	11
Terminal sacrifice	30	32	29
Dosing accident		2	4

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	46	45	38
Total primary tumors	83	79	85
Total animals with benign tumors	40	41	35
Total benign tumors	65	62	71
Total animals with malignant tumors	15	14	13
Total malignant tumors	17	16	14
Total animals with secondary tumors##	1	3	
Total secondary tumors	1	3	
Total animals with tumors uncertain--benign or malignant	1		
Total uncertain tumors	1		
Total animals with tumors uncertain--primary or metastatic		1	
Total uncertain tumors		1	

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: VEHICLE CONTROL

ANIMAL NUMBER	13 2	13 0	11 9	11 7	11 8	13 4	10 8	12 7	15 0	10 7	13 3	14 1	14 8	13 9	14 2	14 4	12 9	13 6	12 4	14 7	10 1	10 2	10 3	10 4	10 5
WEEKS ON STUDY	03 9	04 1	05 3	07 5	07 9	08 0	08 1	08 6	08 8	08 9	08 9	09 0	09 3	10 1	10 1	10 1	10 2	10 2	10 3	10 3	10 4	10 4	10 4	10 4	10 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma			X																						
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X		X	X			X	X		X			X		X	X	X	X	X	X	X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																					X				
Pheochromocytoma, malignant								X																	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell adenoma															X										X
C-cell carcinoma										X									X						
Parathyroid	−	−	+	−	−	−	−	−	−	+	+	+	+	+	−	+	+	+	+	−	+	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS		X																							
Fibroadenoma						X															X		X		X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																				X					
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp					X		X						X							X	X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gonadal stromal tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, benign																									
Oligodendroglioma							X																		
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Lipoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pheochromocytoma, metastatic								X																	
Leukemia, mononuclear cell				X	X			X		X	X			X							X			X	

+ Tissue examined microscopically
− Required tissue not examined microscopically
X Tumor incidence
N Necropsy, no autolysis, no microscopic examination
S Animal missexed
No tissue information submitted
C Necropsy, no histology due to protocol
A Autolysis
M Animal missing
B No necropsy performed

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	1 0 6	1 0 9	1 1 0	1 1 1	1 1 2	1 1 3	1 1 4	1 1 5	1 1 6	1 2 0	1 2 1	1 2 2	1 2 3	1 2 5	1 2 6	1 2 8	1 3 1	1 3 5	1 3 7	1 3 8	1 4 0	1 4 3	1 4 5	1 4 6	1 4 9	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS														X						X						2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma											X															2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X		X		X	X	X		X	X	X				X		X	X		X		X	X		30
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										1
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma				X																		X				4
C-cell carcinoma																										2
Parathyroid	–	–	+	+	+	+	+	–	–	+	+	+	–	–	+	+	+	+	+	+	+	+	+	–	–	31
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma	X				X					X			X					X					X			10
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Adenoma, NOS				X			X																			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp			X			X		X				X			X	X						X				12
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gonadal stromal tumor								X																		1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, benign																			X							1
Oligodendroglioma																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma				X																						1
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Lipoma									X																	1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pheochromocytoma, metastatic																										1
Leukemia, mononuclear cell															X											9

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: LOW DOSE

ANIMAL NUMBER	041	101	021	031	012	039	014	035	004	033	006	028	040	043	007	038	026	045	001	002	003	005	008	009	011
WEEKS ON STUDY	045	060	060	063	068	078	080	080	083	088	090	092	094	096	098	099	100	101	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	+	+
Papilloma, NOS																									X
Basal cell tumor	X																								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	+	+
Fibroma																								X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	−	+	+	+	−	−	+	+	+	−	+	−	−	−	−	−	+	−
Adenocarcinoma, NOS, metastatic									X							X									
Trachea	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	+	−	−	−	−	−	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	−	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−
Lymph nodes	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																X									
Thymus	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	−	+	+	+	+	−	+	−	+	+	+	+	−	−	+	−	+	−
Bile duct	+	+	+	+	+	+	+	−	+	+	+	+	−	+	−	+	+	+	+	−	−	+	−	+	−
Pancreas	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Esophagus	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Small intestine	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	+	−	−	−	−	−	−
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+
Adenoma, NOS						X	X			X		X	X		X	X	X		X	X			@	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																								X	
Thyroid	+	+	+	+	+	+	+	−	−	+	+	−	−	−	−	−	−	+	−	−	−	−	−	−	+
C-cell adenoma																		X							
C-cell carcinoma																									X
Parathyroid	−	+	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	N	+	N	N	+	N	N	N	+	N	+	N	+	N
Adenocarcinoma, NOS									X				X			X									
Fibroadenoma													X							X		X			
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																								X	
Uterus	+	+	+	+	+	+	+	−	+	+	+	−	−	+	+	−	−	+	+	−	−	−	+	−	−
Adenocarcinoma, NOS							X																		
Sarcoma, NOS					X																				
Endometrial stromal polyp		X	X								X			X	X			X						
Deciduoma																									
Ovary	+	+	+	+	+	+	+	−	+	+	+	−	−	−	−	−	−	+	−	−	−	−	−	−	−
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−	−	−	−	−	−	−
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic							X																		
Sarcoma, NOS, unclear primary or metastatic								X																	
Leukemia, mononuclear cell									X	X	X			X											

@ : Multiple occurrence of morphology

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0113	0115	0116	0117	0118	0119	0220	0222	0223	0224	0225	0227	0229	0230	0232	0234	0236	0237	0242	0244	0246	0247	0248	0249	0250	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	*50
Papilloma, NOS																										1
Basal cell tumor																										1
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	+	–	+	–	–	+	+	–	–	–	–	+	+	–	–	–	–	–	+	–	–	–	–	+	23
Adenocarcinoma, NOS, metastatic																										2
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	13
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Liver	+	–	–	+	+	–	+	–	–	–	+	+	+	+	–	–	+	+	–	+	–	+	+	–	–	31
Bile duct	+	–	–	+	+	–	+	–	–	–	+	+	+	+	–	–	+	+	–	+	–	+	+	–	–	31
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	12
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
Small intestine	–	–	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	13
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	46
Adenoma, NOS	X	X	X	X	X		X	X	X	X	X	X			X	X		X	X	X			X	X	X	30
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																					X					1
Pheochromocytoma																									X	2
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	12
C-cell adenoma																										1
C-cell carcinoma																										1
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	+	N	+	N	N	+	N	+	N	N	N	+	N	+	+	N	N	+	N	N	N	N	*50
Adenocarcinoma, NOS																										3
Fibroadenoma	X			X		X			X		X				X		X	X			X					12
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS									X												X					2
Adenoma, NOS																										1
Uterus	+	–	+	–	+	–	–	–	–	–	–	+	–	–	+	–	–	–	–	–	+	–	–	–	–	21
Adenocarcinoma, NOS																										1
Sarcoma, NOS																										1
Endometrial stromal polyp	X		X												X						X					10
Deciduoma					X																					1
Ovary	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	13
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																	X									1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS, metastatic																										1
Sarcoma, NOS, unclear prim or metasta																										1
Leukemia, mononuclear cell	X													X												6

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: HIGH DOSE

ANIMAL NUMBER	0080	0076	1000	0054	0062	0098	0070	0099	0079	0074	0068	0060	0053	0098	0077	0064	0057	0059	0089	0065	0089	0051	0052	0055	0056
WEEKS ON STUDY	0001	0002	0002	0007	0009	0009	0048	0062	0069	0073	0078	0089	0092	0092	0093	0095	0096	0098	0100	0101	0103	0104	0104	0104	0104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Small intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X	X		X	X	X	X		X	X	X	X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																							X		
Thyroid	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma																									
C-cell carcinoma																						X			
Parathyroid	+	+	+	+	−	−	+	+	+	−	−	+	+	+	+	−	+	+	+	−	+	+	+	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Fibroadenoma																	X	X		X					
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS										X										X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma														X											
Endometrial stromal polyp																X			X		X			X	X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell								X											X			X	X		

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	058	061	063	066	067	071	072	073	075	078	081	082	083	084	085	086	087	088	090	091	092	093	094	095	097	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma													X													1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X	X	X	X		X	X		X	X	X		X			X	X	X	X	X	X		X			29
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																X										1
Pheochromocytoma											X				X	X										4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma			X																							1
C-cell adenoma	X				X					X																3
C-cell carcinoma																										1
Parathyroid	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	40
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS											X															1
Adenocarcinoma, NOS											X															1
Fibroadenoma		X	X		X		X		X				X		X	X			X				X			13
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS					X								X		X							X	X			7
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Endometrial stromal polyp	X									X				X	X	X					X					11
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X	X	X			X							X					X		X		11

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control		100 mg/kg	200 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia				
Overall Rates (a)	9/50 (18%)	(b,f)	6/50 (12%)	11/50 (22%)
Adjusted Rates (c)	22.1%			34.7%
Terminal Rates (d)	3/30 (10%)			9/29 (31%)
Week of First Observation	75			62
Life Table Test (e)				P=0.346
Incidental Tumor Test (e)				P=0.262
Fisher Exact Test (e)				P=0.401
Pituitary Gland: Adenoma				
Overall Rates (a)	30/50 (60%)		30/46 (65%)	29/48 (60%)
Adjusted Rates (c)	72.6%		78.4%	80.3%
Terminal Rates (d)	19/30 (63%)		22/30 (73%)	21/28 (75%)
Week of First Observation	53		78	89
Life Table Tests (e)	P=0.445		P=0.551	P=0.483
Incidental Tumor Tests (e)	P=0.202		P=0.324	P=0.238
Cochran-Armitage Trend Test (e)	P=0.522			
Fisher Exact Test (e)			P=0.376	P=0.565
Adrenal Gland: Pheochromocytoma				
Overall Rates (a)	1/50 (2%)		2/50 (4%)	4/50 (8%)
Adjusted Rates (c)	3.3%		6.3%	13.8%
Terminal Rates (d)	1/30 (3%)		2/32 (6%)	4/29 (14%)
Week of First Observation	104		104	104
Life Table Tests (e)	P=0.105		P=0.523	P=0.167
Incidental Tumor Tests (e)	P=0.105		P=0.523	P=0.167
Cochran-Armitage Trend Test (e)	P=0.118			
Fisher Exact Test (e)			P=0.500	P=0.181
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma				
Overall Rates (a)	2/50 (4%)		2/50 (4%)	4/50 (8%)
Adjusted Rates (c)	5.6%		6.3%	13.8%
Terminal Rates (d)	1/30 (3%)		2/32 (6%)	4/29 (14%)
Week of First Observation	86		104	104
Life Table Tests (e)	P=0.234		P=0.681N	P=0.317
Incidental Tumor Tests (e)	P=0.196		P=0.686N	P=0.255
Cochran-Armitage Trend Test (e)	P=0.252			
Fisher Exact Test (e)			P=0.691	P=0.339
Thyroid Gland: C-Cell Adenoma				
Overall Rates (a)	4/50 (8%)	(f)	1/12 (8%)	3/49 (6%)
Adjusted Rates (c)	12.4%			10.3%
Terminal Rates (d)	3/30 (10%)			3/29 (10%)
Week of First Observation	101			104
Life Table Test (e)				P=0.530N
Incidental Tumor Test (e)				P=0.526N
Fisher Exact Test (e)				P=0.512N
Thyroid Gland: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	6/50 (12%)	(f)	2/12 (17%)	4/49 (8%)
Adjusted Rates (c)	17.2%			13.8%
Terminal Rates (d)	3/30 (10%)			4/29 (14%)
Week of First Observation	89			104
Life Table Test (e)				P=0.404N
Incidental Tumor Test (e)				P=0.461N
Fisher Exact Test (e)				P=0.384N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Mammary Gland: Fibroadenoma			
Overall Rates (a)	10/50 (20%)	12/50 (24%)	13/50 (26%)
Adjusted Rates (c)	31.6%	36.1%	40.3%
Terminal Rates (d)	9/30 (30%)	11/32 (34%)	10/29 (34%)
Week of First Observation	80	94	96
Life Table Tests (e)	P=0.228	P=0.465	P=0.266
Incidental Tumor Tests (e)	P=0.205	P=0.436	P=0.232
Cochran-Armitage Trend Test (e)	P=0.277		
Fisher Exact Test (e)		P=0.405	P=0.318
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	10/50 (20%)	12/50 (24%)	14/50 (28%)
Adjusted Rates (c)	31.6%	36.1%	43.5%
Terminal Rates (d)	9/30 (30%)	11/32 (34%)	11/29 (38%)
Week of First Observation	80	94	96
Life Table Tests (e)	P=0.162	P=0.465	P=0.194
Incidental Tumor Tests (e)	P=0.142	P=0.436	P=0.165
Cochran-Armitage Trend Test (e)	P=0.206		
Fisher Exact Test (e)		P=0.405	P=0.241
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	(g) 1/50 (2%)
Adjusted Rates (c)	2.0%	7.7%	3.4%
Terminal Rates (d)	0/30 (0%)	0/32 (0%)	1/29 (3%)
Week of First Observation	41	83	104
Life Table Tests (e)	P=0.578	P=0.306	P=0.745
Incidental Tumor Tests (e)	P=0.588N	P=0.179	P=0.639N
Cochran-Armitage Trend Test (e)	P=0.610		
Fisher Exact Test (e)		P=0.309	P=0.753N
Clitoral Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	7/50 (14%)
Adjusted Rates (c)	6.7%	3.1%	21.9%
Terminal Rates (d)	2/30 (7%)	1/32 (3%)	5/29 (17%)
Week of First Observation	104	104	73
Life Table Tests (e)	P=0.029	P=0.477N	P=0.068
Incidental Tumor Tests (e)	P=0.035	P=0.477N	P=0.089
Cochran-Armitage Trend Test (e)	P=0.036		
Fisher Exact Test (e)		P=0.500N	P=0.080
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	7/50 (14%)
Adjusted Rates (c)	9.6%	9.4%	21.9%
Terminal Rates (d)	2/30 (7%)	3/32 (9%)	5/29 (17%)
Week of First Observation	103	104	73
Life Table Tests (e)	P=0.091	P=0.638N	P=0.139
Incidental Tumor Tests (e)	P=0.102	P=0.660N	P=0.165
Cochran-Armitage Trend Test (e)	P=0.107		
Fisher Exact Test (e)		P=0.661N	P=0.159
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	12/50 (24%)	(f) 10/21 (48%)	11/50 (22%)
Adjusted Rates (c)	33.9%		34.1%
Terminal Rates (d)	8/30 (27%)		8/29 (28%)
Week of First Observation	79		95
Life Table Test (e)			P=0.556N
Incidental Tumor Test (e)			P=0.547
Fisher Exact Test (e)			P=0.500N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
All Sites: Benign Tumors			
Overall Rates (a)	40/50 (80%)	41/50 (82%)	35/50 (70%)
Adjusted Rates (c)	92.9%	89.0	89.7%
Terminal Rates (d)	27/30 (90%)	27/32 (84%)	25/29 (86%)
Week of First Observation	53	45	73
Life Table Test (e)	P=0.329N	P=0.535N	P=0.353N
Incidental Tumor Test (e)	P=0.432N	P=0.498	P=0.584N
Cochran-Armitage Trend	P=0.141N		
Fisher Exact Test (e)		P=0.500	P=0.178N
All Sites: Malignant Tumors			
Overall Rates (a)	15/50 (30%)	14/50 (28%)	13/50 (26%)
Adjusted Rates (c)	34.1%	33.7%	39.6%
Terminal Rates (d)	4/30 (13%)	6/32 (19%)	10/29 (34%)
Week of First Observation	41	68	62
Life Table Test (e)	P=0.455N	P=0.492N	P=0.495N
Incidental Tumor Test (e)	P=0.522	P=0.581N	P=0.562N
Cochran-Armitage Trend	P=0.369N		
Fisher Exact Test (e)		P=0.500N	P=0.412N
All Sites: All Tumors			
Overall Rates (a)	46/50 (92%)	45/50 (90%)	38/50 (76%)
Adjusted Rates (c)	95.8%	91.8%	92.7%
Terminal Rates (d)	28/30 (93%)	28/32 (88%)	26/29 (90%)
Week of First Observation	41	45	62
Life Table Test (e)	P=0.198N	P=0.411N	P=0.213N
Incidental Tumor Test (e)	P=0.143N	P=0.520N	P=0.232N
Cochran-Armitage Trend	P=0.015N		
Fisher Exact Test (e)		P=0.500N	P=0.028N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Only 12 spleens examined microscopically
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(f) Incomplete sampling of tissues
(g) An adenoma was also observed in this animal.

TABLE B4. HISTORICAL INCIDENCE OF CLITORAL GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	21/1,450 (1.4%)	(b) 22/1,450 (1.5%)	(b) 43/1,450 (3.0%)
SD (c)	1.84%	1.66%	2.31%
Range (d)			
High	4/50	3/50	5/50
Low	0/50	0/50	0/50

(a) Data as of August 30, 1985, for studies of at least 104 weeks
(b) Includes one adenocarcinoma, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)	1 (2%)	
Inflammation, acute	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal turbinate	(50)	(50)	(50)
Congestion, acute			1 (2%)
Inflammation, NOS			2 (4%)
Inflammation, acute/chronic	33 (66%)	2 (4%)	31 (62%)
#Lung	(50)	(23)	(50)
Congestion, NOS	1 (2%)	1 (4%)	4 (8%)
Pneumonia, aspiration			2 (4%)
Inflammation, chronic focal	3 (6%)	2 (9%)	2 (4%)
Inflammation, granulomatous focal	1 (2%)		
Foreign material, NOS			4 (8%)
Alveolar macrophages		2 (9%)	
Bronchiolization	1 (2%)	1 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(50)
Fibrosis			1 (2%)
Hypoplasia, NOS	1 (2%)	1 (2%)	
Hyperplasia, NOS	3 (6%)	5 (10%)	10 (20%)
Hyperplasia, erythroid	1 (2%)	1 (2%)	
Hyperplasia, reticulum cell	7 (14%)	5 (10%)	3 (6%)
#Spleen	(50)	(12)	(50)
Fibrosis, focal			1 (2%)
Hemosiderosis	2 (4%)		2 (4%)
Hematopoiesis	2 (4%)	1 (8%)	
#Lymph node	(50)	(49)	(49)
Abscess, NOS			1 (2%)
Pigmentation, NOS			3 (6%)
Angiectasis		1 (2%)	
#Colon	(50)	(50)	(50)
Hyperplasia, lymphoid			2 (4%)
#Cecum	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Thymus	(48)	(10)	(49)
Congestion, acute			1 (2%)
CIRCULATORY SYSTEM			
#Lymph node	(50)	(49)	(49)
Lymphangiectasis		16 (33%)	23 (47%)
Embolus, septic		1 (2%)	
#Mesenteric lymph node	(50)	(49)	(49)
Lymphangiectasis			1 (2%)
#Lung	(50)	(23)	(50)
Perivasculitis	7 (14%)		8 (16%)
#Myocardium	(50)	(10)	(50)
Degeneration, NOS	38 (76%)	4 (40%)	32 (64%)
*Pulmonary artery	(50)	(50)	(50)
Calcification, NOS			2 (4%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
*Rectum	(50)	(50)	(50)
Lymphangiectasis			2 (4%)
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Hyperplasia, epithelial		2 (4%)	
#Salivary gland	(50)	(10)	(50)
Fibrosis		1 (10%)	
#Liver	(50)	(31)	(50)
Congenital malformation, NOS		1 (3%)	
Inflammation, chronic focal	9 (18%)	4 (13%)	13 (26%)
Degeneration, lipoid	3 (6%)	2 (6%)	1 (2%)
Necrosis, zonal		1 (3%)	
Focal cellular change	41 (82%)	18 (58%)	35 (70%)
Hepatocytomegaly	1 (2%)		1 (2%)
Angiectasis	1 (2%)		
#Intrahepatic bile duct	(50)	(31)	(50)
Hyperplasia, NOS	7 (14%)	1 (3%)	5 (10%)
#Pancreas	(50)	(11)	(50)
Inflammation with fibrosis			1 (2%)
#Pancreatic acinus	(50)	(11)	(50)
Atrophy, focal	5 (10%)	1 (9%)	9 (18%)
#Esophagus	(50)	(12)	(50)
Inflammation, acute		1 (8%)	
#Gastric mucosa	(50)	(11)	(49)
Multiple cysts	1 (2%)		1 (2%)
#Cardiac stomach	(50)	(11)	(49)
Inflammation, NOS			1 (2%)
Inflammation, acute		1 (9%)	
Ulcer, acute			1 (2%)
Inflammation, acute/chronic	1 (2%)		
Hyperplasia, epithelial	3 (6%)	2 (18%)	1 (2%)
#Duodenum	(50)	(13)	(49)
Inflammation, acute/chronic		1 (8%)	
Pigmentation, NOS			2 (4%)
#Colon	(50)	(50)	(50)
Multiple cysts			1 (2%)
Ulcer, NOS		2 (4%)	4 (8%)
Abscess, NOS			1 (2%)
Inflammation, acute/chronic		17 (34%)	16 (32%)
Erosion			1 (2%)
Pigmentation, NOS		39 (78%)	38 (76%)
#Cecum	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	3 (6%)
Inflammation, acute/chronic		25 (50%)	6 (12%)
Inflammation, granulomatous			1 (2%)
Pigmentation, NOS		43 (86%)	42 (84%)
*Rectum	(50)	(50)	(50)
Multiple cysts			2 (4%)
Ulcer, NOS			24 (48%)
Inflammation, focal			1 (2%)
Inflammation, acute/chronic			14 (28%)
Inflammation, chronic		1 (2%)	
Pigmentation, NOS			41 (82%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hamartoma	1 (2%)		
Hydronephrosis		1 (2%)	
Cyst, NOS		2 (4%)	
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Nephropathy	19 (38%)	24 (48%)	26 (52%)
#Kidney/tubule	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
#Urinary bladder	(50)	(10)	(48)
Inflammation, chronic focal	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(46)	(48)
Cyst, NOS	2 (4%)	13 (28%)	1 (2%)
Multiple cysts	14 (28%)	2 (4%)	8 (17%)
Hyperplasia, NOS	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	2 (4%)	1 (2%)	
#Adrenal/capsule	(50)	(50)	(50)
Hyperplasia, focal	1 (2%)		
#Adrenal cortex	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
Degeneration, lipoid	12 (24%)	9 (18%)	12 (24%)
Necrosis, focal	1 (2%)	1 (2%)	
Calcification, focal	1 (2%)		1 (2%)
Atrophy, NOS			1 (2%)
Hyperplasia, focal	5 (10%)		2 (4%)
Angiectasis	17 (34%)	4 (8%)	11 (22%)
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, NOS		1 (2%)	1 (2%)
#Thyroid	(50)	(12)	(49)
Cyst, NOS	2 (4%)		
Hyperplasia, cystic			1 (2%)
Hyperplasia, C-cell	20 (40%)	1 (8%)	13 (27%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, cystic	9 (18%)		6 (12%)
*Clitoral gland	(50)	(50)	(50)
Cyst, NOS	1 (2%)	1 (2%)	2 (4%)
Inflammation, acute/chronic	4 (8%)		8 (16%)
Abscess, chronic	1 (2%)		
#Uterus	(50)	(21)	(50)
Dilatation, NOS			1 (2%)
Cyst, NOS		4 (19%)	2 (4%)
Multiple cysts			3 (6%)
#Uterus/endometrium	(50)	(21)	(50)
Hyperplasia, cystic			1 (2%)
#Ovary	(50)	(11)	(50)
Cyst, NOS	5 (10%)	2 (18%)	1 (2%)
Multiple cysts	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(13)	(50)
Calcification, focal			1 (2%)
#Cerebellum	(50)	(13)	(50)
Angiectasis			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	13 (26%)	41 (82%)	25 (50%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract			1 (2%)
*Eye/lens, cortex	(50)	(50)	(50)
Cataract	6 (12%)	40 (80%)	18 (36%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Inflammation, acute/chronic			2 (4%)
Necrosis, fat	8 (16%)	8 (16%)	3 (6%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Sebaceous adenoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma		2 (4%)	
Fibrosarcoma	2 (4%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)	
Hepatocellular carcinoma, metastatic	2 (4%)	1 (2%)	
Alveolar/bronchiolar adenoma	6 (12%)	5 (10%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)	3 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undifferentiated type	1 (2%)	2 (4%)	2 (4%)
Malignant lymphoma, histiocytic type		1 (2%)	
Malignant lymphoma, mixed type	2 (4%)	3 (6%)	
#Lymph node	(50)	(49)	(49)
Malignant lymphoma, mixed type		1 (2%)	
#Mandibular lymph node	(50)	(49)	(49)
Malignant lymphoma, lymphocytic type		1 (2%)	
#Jejunum	(50)	(50)	(50)
Malignant lymphoma, mixed type		1 (2%)	
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma, metastatic	1 (2%)		
#Spleen	(50)	(50)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma	2 (4%)		
#Heart	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		
#Liver	(50)	(50)	(50)
Hemangiosarcoma	2 (4%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Bile duct carcinoma		1 (2%)	
Hepatocellular adenoma	9 (18%)	9 (18%)	1 (2%)
Hepatocellular carcinoma	8 (16%)	7 (14%)	1 (2%)
Mixed hepato/cholangio carcinoma	1 (2%)		
#Forestomach	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	2 (4%)	
URINARY SYSTEM			
None			

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(50)	(49)
Adenoma, NOS	1 (2%)	1 (2%)	
#Adrenal medulla	(49)	(47)	(50)
Pheochromocytoma	2 (4%)		
#Pancreatic islets	(50)	(50)	(50)
Islet cell adenoma	1 (2%)		
Islet cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
None			
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	3 (6%)	3 (6%)
Adenocarcinoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Bile duct carcinoma, metastatic		1 (2%)	
Mixed hepato/cholangiocarcinoma, metastatic	1 (2%)		
Fibrosarcoma, metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	10	5	15
Moribund sacrifice	4	9	22
Terminal sacrifice	31	36	12
Dosing accident	1		1
Accidentally killed, nda	4		
TUMOR SUMMARY			
Total animals with primary tumors**	31	32	8
Total primary tumors	44	44	9
Total animals with benign tumors	20	20	5
Total benign tumors	23	23	5
Total animals with malignant tumors	18	19	4
Total malignant tumors	21	21	4
Total animals with secondary tumors##	5	3	
Total secondary tumors	5	3	

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: VEHICLE CONTROL

ANIMAL NUMBER	11133	11109	11197	11741	14343	10868	12685	14848	14646	10161	11164	11142	12255	13311	12242	10037	10742	10202	10404	10505	10808	10941	11144
WEEKS ON STUDY	00105	00055	04040	05050	06068	06884	08585	09090	09393	09494	09494	09595	09595	09696	09797	10000	10001	10104	10404	10404	10404	10404	10404
INTEGUMENTARY SYSTEM																							
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma								X															
RESPIRATORY SYSTEM																							
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																	X						
Alveolar/bronchiolar adenoma													X		X					X	X		
Alveolar/bronchiolar carcinoma																			X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																							
Hemangiosarcoma																							
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	−	−	+	+	+	+	−	+	−	−	+	+	−	+	+	−	+
CIRCULATORY SYSTEM																							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							
DIGESTIVE SYSTEM																							
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma										X	X								X				
Hepatocellular carcinoma							X						X		X		X				X		
Mixed hepato/cholangiocarcinoma															X								
Hemangiosarcoma				X								X											
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	N	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																						X	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																							
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																							
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X
Adrenal	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																							
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	+	+	−	+	+	−	+	+	−	+	+	+	−	+	−	+	+	+	−	+	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																							
Islet cell carcinoma																							
REPRODUCTIVE SYSTEM																							
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																							
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																							
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS															X							X	
ALL OTHER SYSTEMS																							
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mixed hepato/cholangiocarcinoma, metastatic															X								
Fibrosarcoma, metastatic								X															
Hemangiosarcoma, metastatic				X																			
Malignant lymphoma, undifferentiated type																	X						
Malignant lymphoma, mixed type											X		X										

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	112	115	118	120	121	122	123	127	128	129	130	132	133	134	135	136	137	138	139	140	144	145	147	149	150	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma										X																2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																							X			2
Alveolar/bronchiolar adenoma										X			X													6
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																X										1
Hemangiosarcoma			X								X															2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																							X			1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X			X			X				X						X		9
Hepatocellular carcinoma			X																X		X	X				8
Mixed hepato/cholangiocarcinoma																										1
Hemangiosarcoma																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma														X									X			2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	–	+	–	+	+	–	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	–	+	+	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma					X																					1
Islet cell carcinoma																			X							1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mixed hepato/cholangiocarcinoma meta																										1
Fibrosarcoma, metastatic																										1
Hemangiosarcoma, metastatic																										1
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, mixed type																										2

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: LOW DOSE

ANIMAL NUMBER	0050	0038	0118	0119	0443	0447	0035	0007	0032	0006	0400	0411	0110	0445	0001	0002	0003	0004	0005	0098	0099	0111	0112	0113	0114
WEEKS ON STUDY	001	059	076	086	090	090	091	092	095	096	097	098	099	099	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
Hepatocellular carcinoma, metastatic										X															
Alveolar/bronchiolar adenoma					X									X					X			X			
Alveolar/bronchiolar carcinoma											X	X									X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																							X		
Malignant lymphoma, mixed type																									
Thymus	+	+	+	+	+	+	+	+	−	−	+	−	−	+	+	+	+	+	−	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct carcinoma													X												
Hepatocellular adenoma																							X		
Hepatocellular carcinoma		X		X	X					X		X	X												
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																						X			
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																			X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	+	+	−	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Adenocarcinoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Bile duct carcinoma, metastatic													X												
Malignant lymphoma, undifferentiated type							X	X																	
Malignant lymphoma, histiocytic type						X																			
Malignant lymphoma, mixed type									X																

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	0 1 5	0 1 6	0 1 7	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 1	0 3 3	0 3 4	0 3 6	0 3 7	0 3 9	0 4 2	0 4 4	0 4 6	0 4 8	0 4 9	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sebaceous adenoma																	X									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma						X									X											2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic			X																							1
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma				X																						5
Alveolar/bronchiolar carcinoma																										3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type																						X				1
Thymus	+	–	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	–	+	–	+	–	+	–	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct carcinoma																										1
Hepatocellular adenoma	X							X		X				X				X	X		X		X			9
Hepatocellular carcinoma																									X	7
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma	X														X											2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Adrenal	+	–	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	–	+	+	+	–	+	–	–	–	–	+	–	–	–	–	+	–	–	+	–	–	+	+	–	+	30
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS												X										X			X	3
Adenocarcinoma, NOS			X																							1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Bile duct carcinoma, metastatic																										1
Malignant lymphoma, undiffer type																										2
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type														X									X			3

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: HIGH DOSE

ANIMAL NUMBER	0096	0068	1000	0994	0999	0778	0888	0997	0711	0773	0774	0776	0779	0880	0886	0995	0772	0884	0889	0998	0775	0991	0993	0992	0777
WEEKS ON STUDY	004	006	008	009	009	012	021	021	022	022	022	022	022	022	022	022	023	023	023	023	024	024	024	025	027
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	N	+	+	N	+	+	N	+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	−	−	+	−	+	+	+	−	+	+	−	+	+	+	+	+	−	−	−	+	−	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undifferentiated type																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	0 8 2	0 6 1	0 6 2	0 8 3	0 6 6	0 5 4	0 8 7	0 6 0	0 5 5	0 5 8	0 5 6	0 5 1	0 6 7	0 5 2	0 5 3	0 5 7	0 5 9	0 6 3	0 6 4	0 6 5	0 6 9	0 7 0	0 8 1	0 8 5	0 9 0	TOTAL. TISSUES TUMORS
WEEKS ON STUDY	0 2 7	0 3 1	0 3 2	0 3 2	0 3 6	0 6 1	0 6 1	0 7 2	0 7 7	0 7 8	0 8 9	0 9 9	1 0 1	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X									1
Alveolar/bronchiolar carcinoma												X														1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	–	+	+	+	+	–	+	+	+	+	–	+	+	+	–	–	+	+	+	+	+	–	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																			X							1
Hepatocellular carcinoma																			X							1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
Parathyroid	+	+	+	+	–	–	–	–	+	+	–	–	+	+	–	–	+	+	+	+	+	+	–	+	–	28
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS														X	X	X										3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undiffer type																					X				X	2

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	400 mg/kg	800 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	17.6%	12.7%	8.3%
Terminal Rates (c)	4/31 (13%)	3/36 (8%)	1/12 (8%)
Week of First Observation	95	90	104
Life Table Tests (d)	P=0.251N	P=0.409N	P=0.347N
Incidental Tumor Tests (d)	P=0.327N	P=0.497N	P=0.416N
Cochran-Armitage Trend Test (d)	P=0.049N		
Fisher Exact Test (d)		P=0.500N	P=0.056N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	3.2%	7.6%	7.1%
Terminal Rates (c)	1/31 (3%)	1/36 (3%)	0/12 (0%)
Week of First Observation	104	97	99
Life Table Tests (d)	P=0.332	P=0.359	P=0.544
Incidental Tumor Tests (d)	P=0.188	P=0.242	P=0.463
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.309	P=0.753
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	8/50 (16%)	2/50 (4%)
Adjusted Rates (b)	20.7%	19.6%	14.9%
Terminal Rates (c)	5/31 (16%)	4/36 (11%)	1/12 (8%)
Week of First Observation	95	90	99
Life Table Tests (d)	P=0.443N	P=0.604N	P=0.494N
Incidental Tumor Tests (d)	P=0.532	P=0.463	P=0.608N
Cochran-Armitage Trend Test (d)	P=0.078N		
Fisher Exact Test (d)		P=0.500	P=0.080N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	2/50 (4%)	5/50 (10%)	0/50 (0%)
Adjusted Rates (b)	5.1%	13.2%	0.0%
Terminal Rates (c)	0/31 (0%)	4/36 (11%)	0/12 (0%)
Week of First Observation	94	95	
Life Table Tests (d)	P=0.553N	P=0.272	P=0.482N
Incidental Tumor Tests (d)	P=0.546	P=0.163	P=0.630N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.218	P=0.248N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	3/50 (6%)	9/50 (18%)	2/50 (4%)
Adjusted Rates (b)	7.9%	21.5%	16.7%
Terminal Rates (c)	0/31 (0%)	5/36 (14%)	2/12 (17%)
Week of First Observation	94	90	104
Life Table Tests (d)	P=0.212	P=0.100	P=0.445
Incidental Tumor Tests (d)	P=0.133	P=0.058	P=0.303
Cochran-Armitage Trend Test (d)	P=0.432N		
Fisher Exact Test (d)		P=0.061	P=0.500N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	5/50 (10%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	13.8%	0.0%	0.0%
Terminal Rates (c)	3/31 (10%)	0/36 (0%)	0/12 (0%)
Week of First Observation	50		
Life Table Tests (d)	P=0.018N	P=0.027N	P=0.183N
Incidental Tumor Tests (d)	P=0.004N	P=0.055N	P=0.063N
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Test (d)		P=0.029N	P=0.029N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	400 mg/kg	800 mg/kg
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	6/50 (12%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	16.9%	0.0%	0.0%
Terminal Rates (c)	4/31 (13%)	0/36 (0%)	0/12 (0%)
Week of First Observation	50		
Life Table Tests (d)	P=0.009N	P=0.013N	P=0.137N
Incidental Tumor Tests (d)	P=0.002N	P=0.028N	P=0.047N
Cochran-Armitage Trend Test (d)	P=0.003N		
Fisher Exact Test (d)		P=0.014N	P=0.014N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	9/50 (18%)	9/50 (18%)	1/50 (2%)
Adjusted Rates (b)	26.4%	25.0%	8.3%
Terminal Rates (c)	7/31 (23%)	9/36 (25%)	1/12 (8%)
Week of First Observation	93	104	104
Life Table Tests (d)	P=0.149N	P=0.476N	P=0.171N
Incidental Tumor Tests (d)	P=0.178N	P=0.533N	P=0.199N
Cochran-Armitage Trend Test (d)	P=0.012N		
Fisher Exact Test (d)		P=0.602	P=0.008N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	8/50 (16%)	7/50 (14%)	1/50 (2%)
Adjusted Rates (b)	21.8%	15.6%	8.3%
Terminal Rates (c)	4/31 (13%)	1/36 (3%)	1/12 (8%)
Week of First Observation	84	59	104
Life Table Tests (d)	P=0.177N	P=0.410N	P=0.227N
Incidental Tumor Tests (d)	P=0.206N	P=0.544N	P=0.295N
Cochran-Armitage Trend Test (d)	P=0.018N		
Fisher Exact Test (d)		P=0.500N	P=0.015N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	17/50 (34%)	16/50 (32%)	1/50 (2%)
Adjusted Rates (b)	44.9%	37.3%	8.3%
Terminal Rates (c)	11/31 (35%)	10/36 (28%)	1/12 (8%)
Week of First Observation	84	59	104
Life Table Tests (d)	P=0.026N	P=0.341N	P=0.023N
Incidental Tumor Tests (d)	P=0.032N	P=0.473N	P=0.029N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.500N	P<0.001N
Harderian Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	5.9%	8.3%	25.0%
Terminal Rates (c)	1/31 (3%)	3/36 (8%)	3/12 (25%)
Week of First Observation	96	104	104
Life Table Tests (d)	P=0.102	P=0.566	P=0.129
Incidental Tumor Tests (d)	P=0.083	P=0.509	P=0.098
Cochran-Armitage Trend Test (d)	P=0.412		
Fisher Exact Test (d)		P=0.500	P=0.500
Harderian Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	5.9%	11.1%	25.0%
Terminal Rates (c)	1/31 (3%)	4/36 (11%)	3/12 (25%)
Week of First Observation	96	104	104
Life Table Tests (d)	P=0.092	P=0.407	P=0.129
Incidental Tumor Tests (d)	P=0.076	P=0.356	P=0.098
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.339	P=0.500

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	400 mg/kg	800 mg/kg
All Sites: Benign Tumors			
Overall Rates (a)	20/50 (40%)	20/50 (40%)	5/50 (10%)
Adjusted Rates (b)	54.9%	52.4%	41.7%
Terminal Rates (c)	15/31 (48%)	18/36 (50%)	5/12 (42%)
Week of First Observation	93	90	104
Life Table Tests (d)	P=0.162N	P=0.358N	P=0.212N
Incidental Tumor Tests (d)	P=0.239N	P=0.482N	P=0.287N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.581N	P<0.001N
All Sites: Malignant Tumors			
Overall Rates (a)	18/50 (36%)	19/50 (38%)	4/50 (8%)
Adjusted Rates (b)	42.8%	40.0%	30.4%
Terminal Rates (c)	8/31 (26%)	8/36 (22%)	3/12 (25%)
Week of First Observation	50	59	99
Life Table Tests (d)	P=0.213N	P=0.490N	P=0.212N
Incidental Tumor Tests (d)	P=0.207N	P=0.438	P=0.205N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.500	P<0.001N
All Sites All Tumors			
Overall Rates (a)	31/50 (62%)	32/50 (64%)	8/50 (16%)
Adjusted Rates (b)	73.3%	66.7%	61.3%
Terminal Rates (c)	20/31 (65%)	20/36 (56%)	7/12 (58%)
Week of First Observation	50	59	99
Life Table Tests (d)	P=0.133N	P=0.374N	P=0.138N
Incidental Tumor Tests (d)	P=0.125N	P=0.556	P=0.124N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.500	P<0.001N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Abscess, NOS	1 (2%)		
Inflammation, chronic		1 (2%)	1 (2%)
Fibrosis		2 (4%)	
Pigmentation, NOS	1 (2%)		
Melanin		1 (2%)	
Hyperplasia, epithelial	1 (2%)		
Hyperplasia, basal cell		2 (4%)	
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal turbinate	(50)	(50)	(50)
Inflammation, acute serous	1 (2%)		
#Lung	(50)	(50)	(50)
Congestion, NOS	3 (6%)	2 (4%)	4 (8%)
Hemorrhage	2 (4%)	1 (2%)	
Pneumonia, lipid		2 (4%)	2 (4%)
Pneumonia, aspiration	4 (8%)	1 (2%)	
Alveolar macrophages	4 (8%)	3 (6%)	1 (2%)
Hyperplasia, alveolar epithelium	2 (4%)	2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemoid reaction	1 (2%)		
#Bone marrow	(50)	(49)	(49)
Hypoplasia, NOS		1 (2%)	
Atrophy, NOS	2 (4%)		
Angiectasis	1 (2%)		
Hyperplasia, granulocytic	1 (2%)	2 (4%)	2 (4%)
#Spleen	(50)	(50)	(50)
Infarct, acute			1 (2%)
Hyperplasia, lymphoid	7 (14%)	5 (10%)	2 (4%)
Hematopoiesis	5 (10%)	5 (10%)	2 (4%)
#Lymph node	(50)	(49)	(49)
Plasma cell infiltrate	1 (2%)		
#Mandibular lymph node	(50)	(49)	(49)
Plasma cell infiltrate	1 (2%)		
Necrosis, NOS			1 (2%)
Pigmentation, NOS			1 (2%)
Angiectasis		1 (2%)	
Hyperplasia, lymphoid	6 (12%)	1 (2%)	
Mastocytosis		1 (2%)	
#Mesenteric lymph node	(50)	(49)	(49)
Congestion, NOS	1 (2%)	2 (4%)	
Edema, NOS			2 (4%)
Hemorrhage	5 (10%)	1 (2%)	1 (2%)
Inflammation, acute		1 (2%)	
Inflammation, acute diffuse	1 (2%)		
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic			1 (2%)
Inflammation, granulomatous		1 (2%)	
Pigmentation, NOS		2 (4%)	2 (4%)
Hyperplasia, NOS		2 (4%)	2 (4%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
#Mesenteric lymph node (Continued)	(50)	(49)	(49)
Angiectasis	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	5 (10%)	2 (4%)	5 (10%)
#Renal lymph node	(50)	(49)	(49)
Hyperplasia, lymphoid	1 (2%)		
#Lung	(50)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	
#Salivary gland	(50)	(49)	(49)
Hyperplasia, lymphoid	16 (32%)	14 (29%)	5 (10%)
#Liver	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Pancreas	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Ileum	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Cecum	(50)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)		
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	3 (6%)	1 (2%)	
#Prostate	(50)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)		
#Thymus	(40)	(36)	(42)
Cyst, NOS	1 (3%)		
Atrophy, NOS		1 (3%)	
Hyperplasia, lymphoid			5 (12%)
CIRCULATORY SYSTEM			
*Perilymphatic tissue	(50)	(50)	(50)
Inflammation with fibrosis		1 (2%)	
Pigmentation, NOS		1 (2%)	
#Heart	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
Inflammation, chronic diffuse		1 (2%)	
Degeneration, NOS			1 (2%)
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		
*Vein	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
Pigmentation, NOS		1 (2%)	1 (2%)
*Pulmonary vein	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
*Hepatic vein	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
*Renal vein	(50)	(50)	(50)
Thrombus, organized		1 (2%)	
#Testis	(50)	(48)	(50)
Thrombosis, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(49)	(49)
Inflammation, acute	1 (2%)		
Inflammation with fibrosis	1 (2%)		
Calcification, focal	1 (2%)	1 (2%)	
Atrophy, NOS	1 (2%)	1 (2%)	
Atrophy, focal		1 (2%)	
#Liver	(50)	(50)	(50)
Congestion, NOS	1 (2%)		
Hemorrhage	1 (2%)		
Inflammation, acute focal	1 (2%)		
Inflammation, acute diffuse		1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)		
Necrosis, NOS	1 (2%)		1 (2%)
Necrosis, focal			1 (2%)
Necrosis, diffuse		1 (2%)	
Infarct, NOS	1 (2%)		
Amyloidosis	1 (2%)		
Metamorphosis, fatty	1 (2%)		
Cytoplasmic vacuolization	1 (2%)	1 (2%)	
Focal cellular change	1 (2%)		
Angiectasis	1 (2%)		
#Liver/centrilobular	(50)	(50)	(50)
Hepatocytomegaly			1 (2%)
#Liver/hepatocytes	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
Cytoplasmic vacuolization	1 (2%)		13 (26%)
*Gallbladder	(50)	(50)	(50)
Hyperplasia, epithelial	1 (2%)		
#Pancreas	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
#Pancreatic acinus	(50)	(50)	(50)
Hyperplasia, focal		1 (2%)	
#Esophagus	(49)	(50)	(50)
Foreign body, NOS	1 (2%)		
Inflammation, acute	1 (2%)		
#Glandular stomach	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Multiple cysts	1 (2%)	4 (8%)	
Inflammation, acute/chronic	2 (4%)	3 (6%)	1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	1 (2%)	2 (4%)	
Hyperplasia, NOS		1 (2%)	
#Forestomach	(50)	(50)	(50)
Inflammation, necrotizing		1 (2%)	
Inflammation, acute focal		1 (2%)	
Abscess, NOS			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Ulcer, chronic			1 (2%)
Hyperkeratosis		2 (4%)	1 (2%)
#Ileum	(50)	(50)	(50)
Necrosis, focal			1 (2%)
#Colon	(50)	(50)	(50)
Inflammation, acute/chronic		6 (12%)	12 (24%)
Ulcer, chronic			1 (2%)
Fibrosis		26 (52%)	17 (34%)
Fibrosis, focal		1 (2%)	
Pigmentation, NOS		42 (84%)	24 (48%)
Hyperplasia, epithelial		2 (4%)	
#Cecum	(50)	(50)	(50)
Inflammation, acute/chronic		38 (76%)	30 (60%)
Ulcer, chronic			6 (12%)
Fibrosis		44 (88%)	36 (72%)
Calcification, focal			1 (2%)
Pigmentation, NOS		47 (94%)	44 (88%)
Hyperplasia, epithelial		7 (14%)	2 (4%)
*Rectum	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
Ulcer, acute			1 (2%)
Inflammation, acute/chronic			11 (22%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
*Rectum (Continued)	(50)	(50)	(50)
Ulcer, chronic			1 (2%)
Inflammation with fibrosis			1 (2%)
Fibrosis			12 (24%)
Pigmentation, NOS		2 (4%)	19 (38%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hydronephrosis	1 (2%)		
Cyst, NOS	1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)		
Glomerulonephritis, chronic	2 (4%)	4 (8%)	
Pyelonephritis, chronic	1 (2%)		
Cytoplasmic vacuolization	1 (2%)		
Metaplasia, osseous	1 (2%)		
#Kidney/glomerulus	(50)	(50)	(50)
Amyloidosis	1 (2%)		
#Kidney/tubule	(50)	(50)	(50)
Mineralization		1 (2%)	3 (6%)
Dilatation, NOS			8 (16%)
Cast, NOS			2 (4%)
Cyst, NOS	2 (4%)	2 (4%)	1 (2%)
Glomerulonephritis, chronic		1 (2%)	
Cytoplasmic vacuolization	1 (2%)		5 (10%)
Regeneration, NOS	22 (44%)	30 (60%)	11 (22%)
#Kidney/pelvis	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
#Urinary bladder	(49)	(50)	(48)
Distention			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Hypertrophy, focal	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(50)	(49)
Cyst, NOS	2 (4%)	1 (2%)	
Multiple cysts	1 (2%)	3 (6%)	
Hyperplasia, focal	2 (4%)		
#Adrenal/capsule	(49)	(47)	(50)
Hyperplasia, stromal	30 (61%)	31 (66%)	15 (30%)
#Adrenal cortex	(49)	(47)	(50)
Hypertrophy, focal	6 (12%)		
Hyperplasia, focal	1 (2%)	1 (2%)	
#Adrenal medulla	(49)	(47)	(50)
Hyperplasia, focal	2 (4%)		
#Thyroid	(50)	(50)	(48)
Cystic follicles	1 (2%)		
Atrophy, NOS	2 (4%)	1 (2%)	
Hyperplasia, follicular cell		1 (2%)	
#Pancreatic islets	(50)	(50)	(50)
Cytoplasmic vacuolization			1 (2%)
Hyperplasia, NOS	3 (6%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibrosis			1 (2%)
*Prepuce	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
*Preputial gland	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Multiple cysts			1 (2%)
Cystic ducts	6 (12%)	10 (20%)	6 (12%)
Inflammation, suppurative		3 (6%)	
Inflammation, acute/chronic	3 (6%)	2 (4%)	
Inflammation, chronic	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic focal		2 (4%)	1 (2%)
Inflammation, chronic diffuse	1 (2%)		
Inflammation, chronic suppurative	7 (14%)	4 (8%)	2 (4%)
Inflammation with fibrosis	1 (2%)		
Hyperplasia, NOS	1 (2%)		
#Prostate	(50)	(50)	(49)
Hemorrhage			1 (2%)
Inflammation, suppurative		1 (2%)	
Inflammation, acute diffuse	1 (2%)		
Inflammation, chronic		1 (2%)	1 (2%)
Inflammation, chronic focal	1 (2%)		
*Seminal vesicle	(50)	(50)	(50)
Distention	20 (40%)	20 (40%)	11 (22%)
Inflammation, chronic		1 (2%)	
#Testis	(50)	(48)	(50)
Inflammation, granulomatous			1 (2%)
Degeneration, NOS			2 (4%)
Calcification, focal			1 (2%)
Atrophy, NOS			1 (2%)
Hyperplasia, interstitial cell			1 (2%)
Angiectasis	1 (2%)		
#Testis/tubule	(50)	(48)	(50)
Degeneration, NOS	2 (4%)		2 (4%)
Calcification, focal	1 (2%)		1 (2%)
*Epididymis	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	1 (2%)
Degeneration, NOS	1 (2%)		1 (2%)
NERVOUS SYSTEM			
*Ependymal cell	(50)	(50)	(50)
Cytoplasmic vacuolization			1 (2%)
#Brain	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Perivascular cuffing	1 (2%)		
Calcification, focal	27 (54%)	24 (48%)	7 (14%)
Cytoplasmic vacuolization			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Atrophy, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Joint of lower extremity	(50)	(50)	(50)
Ankylosis	15 (30%)	12 (24%)	2 (4%)
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Pigmentation, NOS		1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
Adipose tissue			
Lymphocytic inflammatory infiltrate		1	
Necrosis, fat	2		
Pigmentation, NOS	1		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported	1		2

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(49)
Fibrosarcoma	1 (2%)	2 (4%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(49)
Adenocarcinoma, NOS, invasive	1 (2%)		
#Lung	(50)	(50)	(49)
Adenocarcinoma, NOS, metastatic	1 (2%)		
Hepatocellular carcinoma, metastatic		1 (2%)	
Alveolar/bronchiolar adenoma	2 (4%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma	2 (4%)	3 (6%)	
Fibrosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(49)
Malignant lymphoma, NOS	4 (8%)		1 (2%)
Malignant lymphoma, undifferentiated type	4 (8%)	3 (6%)	
Malignant lymphoma, mixed type	2 (4%)	5 (10%)	2 (4%)
#Spleen	(50)	(50)	(49)
Malignant lymphoma, mixed type	1 (2%)		
#Mandibular lymph node	(50)	(50)	(49)
Malignant lymphoma, mixed type		1 (2%)	
#Mesenteric lymph node	(50)	(50)	(49)
Malignant lymphoma, mixed type			1 (2%)
#Thymus	(46)	(44)	(46)
Malignant lymphoma, NOS			1 (2%)
CIRCULATORY SYSTEM			
*Mediastinum	(50)	(50)	(49)
Hemangiosarcoma	1 (2%)		
#Spleen	(50)	(50)	(49)
Hemangiosarcoma	2 (4%)	1 (2%)	1 (2%)
#Liver	(50)	(50)	(49)
Hemangiosarcoma		1 (2%)	
#Uterus	(50)	(50)	(49)
Hemangiosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(49)
Hepatocellular adenoma	4 (8%)	2 (4%)	1 (2%)
Hepatocellular carcinoma	1 (2%)	1 (2%)	
#Forestomach	(50)	(50)	(48)
Squamous cell papilloma	1 (2%)		1 (2%)
URINARY SYSTEM			
None			

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(50)	(46)
Adenoma, NOS		1 (2%)	
#Anterior pituitary	(49)	(50)	(46)
Adenoma, NOS	13 (27%)	13 (26%)	2 (4%)
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(49)
Adenoma, NOS		1 (2%)	
Adenocarcinoma, NOS	1 (2%)	1 (2%)	
Adenosquamous carcinoma	1 (2%)		
#Uterus	(50)	(50)	(49)
Adenocarcinoma, NOS		1 (2%)	
Histiocytic sarcoma		1 (2%)	
#Uterus/endometrium	(50)	(50)	(49)
Adenoma, NOS		1 (2%)	
#Ovary	(50)	(50)	(44)
Granulosa cell tumor	1 (2%)		
Teratoma, benign	1 (2%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(49)
Adenoma, NOS		1 (2%)	
Adenocarcinoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(49)
Fibrosarcoma, invasive	1 (2%)		
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(49)
Histiocytic sarcoma, metastatic		1 (2%)	
Adipose tissue			
Adenocarcinoma, NOS, metastatic		1	

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	5	25
Moribund sacrifice	8	6	10
Terminal sacrifice	37	34	10
Dosing accident			1
Accidentally killed, nda	1	5	3
Animal missing			1
TUMOR SUMMARY			
Total animals with primary tumors**	29	30	8
Total primary tumors	44	41	11
Total animals with benign tumors	18	20	5
Total benign tumors	21	21	5
Total animals with malignant tumors	19	17	6
Total malignant tumors	22	20	6
Total animals with secondary tumors##	2	4	
Total secondary tumors	3	4	
Total animals with tumors uncertain-- benign or malignant	1		
Total uncertain tumors	1		

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: VEHICLE CONTROL

ANIMAL NUMBER	150	110	114	129	139	142	149	108	132	111	113	118	130	101	102	103	104	105	106	107	109	112	115	116	117
WEEKS ON STUDY	040	074	077	078	094	096	097	101	101	102	102	102	102	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic								X																	
Alveolar/bronchiolar adenoma									X																
Alveolar/bronchiolar carcinoma					X																				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive								X																	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Malignant lymphoma, mixed type														X											
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X									X	X				X			
Hepatocellular carcinoma											X														
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																				X					
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X												X			X				X	X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	+	+	+	+	−	+	−	+	+	+	−	−	−	+	−	+	−	+	+	−	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Adenosquamous carcinoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor														X											
Teratoma, benign																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS								X																	
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, invasive														X											
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma							X																		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS									X			X													
Malignant lymphoma, undifferentiated type				X														X							
Malignant lymphoma, mixed type							X																X		

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	119	120	121	122	123	124	125	126	127	128	131	133	134	135	136	137	138	140	141	143	144	145	146	147	148	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma					X																					2
Alveolar/bronchiolar carcinoma	X																									2
Trachea	+	+	+	+	+	+	+	+	+	+	~	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS, invasive																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma															X											2
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	~	+	+	+	+	+	+	+	+	+	~	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										4
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	~	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X	X						X			X	X						X	X						13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	~	+	+	+	+	+	+	+	+	+	+	+	~	+	+	+	+	+	~	+	+	+	+	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																									X	1
Adenosquamous carcinoma							X																			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma			X																							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor																										1
Teratoma, benign					X																					1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS																										1
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, invasive																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS															X		X									4
Malignant lymphoma, undiffer type									X										X							4
Malignant lymphoma, mixed type																										2

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: LOW DOSE

ANIMAL NUMBER	0191	0411	0433	0444	0455	0355	0277	0399	0466	0177	0488	0113	0224	0332	0001	0002	0003	0004	0005	0006	0007	0008	0009	0110	0111
WEEKS ON STUDY	0222	0244	0244	0244	0244	0559	0775	0884	0888	0899	0966	0999	0999	0999	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma												X	X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic								X																	
Alveolar/bronchiolar adenoma															X				X						
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic												X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																X									
Thymus	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																X				X					
Hepatocellular carcinoma								X																	
Hemangiosarcoma														X											
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS														X	X			X							X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X												
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	−	−	+	−	+	+	+	−	−	−	+	+	+	−	+	+	+	+	−	+	−	−	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS											X														
Adenocarcinoma, NOS														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Histiocytic sarcoma							X																		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Histiocytic sarcoma, metastatic							X																		
Malignant lymphoma, undifferentiated type										X					X										
Malignant lymphoma, mixed type						X					X														
Adipose tissue																									
Adenocarcinoma, NOS, metastatic																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	012	014	015	016	018	020	021	022	023	025	026	028	029	030	031	033	034	036	037	038	040	042	047	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma		X																								1
Alveolar/bronchiolar carcinoma																									X	3
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																		X								1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																										1
Thymus	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										2
Hepatocellular carcinoma																										1
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS			X	X	X			X	X			X			X				X	X		X				14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	+	–	–	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	–	–	–	+	30
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																								X		1
Adenocarcinoma, NOS		X																								1
Histiocytic sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS					X																					1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Histiocytic sarcoma, metastatic																										1
Malignant lymphoma, undiffer type	X																									3
Malignant lymphoma, mixed type											X							X				X				5
Adipose tissue																										
Adenocarcinoma, NOS, metastatic		X																								1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL: HIGH DOSE

ANIMAL NUMBER	0054	0065	0074	0075	0053	0066	0094	0089	0081	0051	0052	0055	0078	0087	0064	0071	0060	0069	0067	0088	0063	0068	0096	0093	0058
WEEKS ON STUDY	0000	0000	0099	0113	0220	0220	0230	0233	0244	0255	0255	0255	0255	0266	0311	0311	0312	0315	0338	0339	0411	0411	0411	0422	0447
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	–	+	+
Malignant lymphoma, NOS																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Hepatocellular adenoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	N	+	+	+	+	+	+	+	N	N	+	M	+	N	+	+	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Esophagus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	–	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Urinary bladder	–	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	M	+	+	+	–	–	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Thyroid	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Parathyroid	–	–	–	+	–	–	–	–	+	–	+	+	–	+	+	–	+	M	+	–	+	+	–	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Ovary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N
Malignant lymphoma, NOS																									
Malignant lymphoma, mixed type																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	0085	0059	0062	0073	0076	1000	0083	0079	0086	0090	0095	0096	0557	0599	0992	0861	0770	0772	0772	0880	0882	0884	0891	0997	0998	TOTAL TISSUES TUMORS
WEEKS ON STUDY	0552	0557	0557	0559	0559	0559	0601	0606	0711	0711	0803	0806	0886	0900	0908	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																X										1
Trachea	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																	X									1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type														X												1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	46
Malignant lymphoma, NOS																		X								1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																					X					1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	N	N	N	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma																		X								1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	+	+	+	+	+	+	+	46
Adenoma, NOS													X												X	2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	–	+	–	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	–	+	30
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	–	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	44
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malignant lymphoma, NOS											X															1
Malignant lymphoma, mixed type													X												X	2

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	400 mg/kg	800 mg/kg
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/49 (0%)
Adjusted Rates (b)	4.8%	8.3%	0.0%
Terminal Rates (c)	1/37 (3%)	3/36 (8%)	0/10 (0%)
Week of First Observation	94	104	
Life Table Tests (d)	P=0.543N	P=0.477	P=0.566N
Incidental Tumor Tests (d)	P=0.600N	P=0.420	P=0.644N
Cochran-Armitage Trend Test (d)	P=0.207N		
Fisher Exact Test (d)		P=0.500	P=0.253N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	1/49 (2%)
Adjusted Rates (b)	9.6%	11.1%	10.0%
Terminal Rates (c)	2/37 (5%)	4/36 (11%)	1/10 (10%)
Week of First Observation	94	104	104
Life Table Tests (d)	P=0.598	P=0.609	P=0.705N
Incidental Tumor Tests (d)	P=0.517	P=0.522	P=0.664
Cochran-Armitage Trend Test (d)	P=0.152N		
Fisher Exact Test (d)		P=0.643N	P=0.187N
Hematopoietic System: Malignant Lymphoma, Undifferentiated Type			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	0/49 (0%)
Adjusted Rates (b)	10.1%	7.9%	0.0%
Terminal Rates (c)	3/37 (8%)	2/36 (6%)	0/10 (0%)
Week of First Observation	78	89	
Life Table Tests (d)	P=0.245N	P=0.526N	P=0.320N
Incidental Tumor Tests (d)	P=0.052N	P=0.379N	P=0.139N
Cochran-Armitage Trend Test (d)	P=0.050N		
Fisher Exact Test (d)		P=0.500N	P=0.061N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	3/50 (6%)	6/50 (12%)	3/49 (6%)
Adjusted Rates (b)	7.6%	15.3%	24.0%
Terminal Rates (c)	2/37 (5%)	4/36 (11%)	1/10 (10%)
Week of First Observation	97	59	86
Life Table Tests (d)	P=0.074	P=0.222	P=0.108
Incidental Tumor Tests (d)	P=0.130	P=0.142	P=0.204
Cochran-Armitage Trend Test (d)	P=0.562		
Fisher Exact Test (d)		P=0.243	P=0.651
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	11/50 (22%)	9/50 (18%)	5/49 (10%)
Adjusted Rates (b)	26.1%	22.5%	37.0%
Terminal Rates (c)	7/37 (19%)	6/36 (17%)	2/10 (20%)
Week of First Observation	78	59	83
Life Table Tests (d)	P=0.306	P=0.462N	P=0.245
Incidental Tumor Tests (d)	P=0.455N	P=0.512N	P=0.632N
Cochran-Armitage Trend Test (d)	P=0.076N		
Fisher Exact Test (d)		P=0.402N	P=0.093N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	1/49 (2%)
Adjusted Rates (b)	9.8%	5.3%	10.0%
Terminal Rates (c)	2/37 (5%)	1/36 (3%)	1/10 (10%)
Week of First Observation	97	99	104
Life Table Tests (d)	P=0.470N	P=0.373N	P=0.699N
Incidental Tumor Tests (d)	P=0.615	P=0.535N	P=0.664
Cochran-Armitage Trend Test (d)	P=0.122N		
Fisher Exact Test (d)		P=0.339N	P=0.188N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	400 mg/kg	800 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	1/49 (2%)
Adjusted Rates (b)	10.2%	5.6%	10.0%
Terminal Rates (c)	3/37 (8%)	2/36 (6%)	1/10 (10%)
Week of First Observation	101	104	104
Life Table Tests (d)	P=0.460N	P=0.362N	P=0.699N
Incidental Tumor Tests (d)	P=0.505N	P=0.408N	P=0.703
Cochran-Armitage Trend Test (d)	P=0.122N		
Fisher Exact Test (d)		P=0.339N	P=0.187N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	1/49 (2%)
Adjusted Rates (b)	12.4%	7.8%	10.0%
Terminal Rates (c)	3/37 (8%)	2/36 (6%)	1/10 (10%)
Week of First Observation	101	84	104
Life Table Tests (d)	P=0.399N	P=0.394N	P=0.608N
Incidental Tumor Tests (d)	P=0.302N	P=0.321N	P=0.694N
Cochran-Armitage Trend Test (d)	P=0.073N		
Fisher Exact Test (d)		P=0.357N	P=0.107N
Pituitary Gland: Adenoma			
Overall Rates (a)	13/49 (27%)	13/50 (26%)	2/46 (4%)
Adjusted Rates (b)	34.7%	35.0%	18.7%
Terminal Rates (c)	12/36 (33%)	12/36 (33%)	1/8 (13%)
Week of First Observation	74	99	86
Life Table Tests (d)	P=0.399N	P=0.583	P=0.401N
Incidental Tumor Tests (d)	P=0.241N	P=0.539	P=0.100N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P=0.567N	P=0.003N
All Sites: Benign Tumors			
Overall Rates (a)	18/50 (36%)	20/50 (40%)	5/49 (10%)
Adjusted Rates (b)	44.5%	51.2%	44.3%
Terminal Rates (c)	15/37 (41%)	17/36 (47%)	4/10 (40%)
Week of First Observation	74	96	86
Life Table Tests (d)	P=0.427	P=0.355	P=0.595
Incidental Tumor Tests (d)	P=0.492	P=0.224	P=0.372N
Cochran-Armitage Trend Test (d)	P=0.003N		
Fisher Exact Test (d)		P=0.418	P=0.002N
All Sites: Malignant Tumors			
Overall Rates (a)	19/50 (38%)	17/50 (34%)	6/49 (12%)
Adjusted Rates (b)	41.9%	38.5%	44.8%
Terminal Rates (c)	11/37 (30%)	9/36 (25%)	3/10 (30%)
Week of First Observation	78	59	83
Life Table Tests (d)	P=0.462	P=0.515N	P=0.449
Incidental Tumor Tests (d)	P=0.298N	P=0.490	P=0.492N
Cochran-Armitage Trend Test (d)	P=0.003N		
Fisher Exact Test (d)		P=0.418N	P=0.003N
All Sites: All Tumors			
Overall Rates (a)	29/50 (58%)	30/50 (60%)	8/49 (16%)
Adjusted Rates (b)	62.8%	68.1%	60.6%
Terminal Rates (c)	20/37 (54%)	22/36 (61%)	5/10 (50%)
Week of First Observation	74	59	83
Life Table Tests (d)	P=0.453	P=0.396	P=0.567
Incidental Tumor Tests (d)	P=0.255N	P=0.213	P=0.240N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.500	P<0.001N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(49)
Ulcer, NOS	1 (2%)		
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Ulcer, chronic	1 (2%)		
Inflammation with fibrosis			1 (2%)
Fibrosis, focal			1 (2%)
Pigmentation, NOS		1 (2%)	
Acanthosis	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(49)
Foreign body, NOS	1 (2%)		
Inflammation, suppurative	1 (2%)		
Inflammation, chronic focal	1 (2%)		
*Nasal turbinate	(50)	(50)	(49)
Inflammation, suppurative	1 (2%)		1 (2%)
#Lung/bronchus	(50)	(50)	(49)
Foreign body, NOS		1 (2%)	
#Lung/bronchiole	(50)	(50)	(49)
Foreign body, NOS		1 (2%)	
#Lung	(50)	(50)	(49)
Congestion, NOS		4 (8%)	7 (14%)
Edema, NOS			1 (2%)
Hemorrhage	2 (4%)	1 (2%)	3 (6%)
Pneumonia, lipid			1 (2%)
Pneumonia, aspiration		1 (2%)	1 (2%)
Pneumonia, interstitial chronic	1 (2%)		
Alveolar macrophages	1 (2%)	1 (2%)	
Hyperplasia, alveolar epithelium	2 (4%)		
#Lung/alveoli	(50)	(50)	(49)
Foreign body, NOS			1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(50)	(49)
Fibrosis		1 (2%)	
Atrophy, NOS	1 (2%)		
Hyperplasia, granulocytic	1 (2%)		3 (6%)
#Spleen	(50)	(50)	(49)
Congestion, NOS			1 (2%)
Angiectasis		1 (2%)	
Hyperplasia, lymphoid	9 (18%)	15 (30%)	3 (6%)
Hematopoiesis	6 (12%)	5 (10%)	2 (4%)
#Lymph node	(50)	(50)	(49)
Inflammation, chronic diffuse	1 (2%)		
Hyperplasia, lymphoid		1 (2%)	
#Mandibular lymph node	(50)	(50)	(49)
Angiectasis			1 (2%)
Hyperplasia, lymphoid	3 (6%)	4 (8%)	
Mastocytosis			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(50)	(50)	(49)
Hemorrhage			2 (4%)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, diffuse	1 (2%)		
Angiectasis		2 (4%)	
Hyperplasia, lymphoid	2 (4%)	5 (10%)	2 (4%)
#Renal lymph node	(50)	(50)	(49)
Inflammation, acute/chronic	1 (2%)		
#Lung	(50)	(50)	(49)
Hyperplasia, lymphoid	3 (6%)	1 (2%)	1 (2%)
#Salivary gland	(47)	(49)	(49)
Hyperplasia, lymphoid	10 (21%)	10 (20%)	5 (10%)
#Liver	(50)	(50)	(49)
Hyperplasia, lymphoid	4 (8%)	2 (4%)	1 (2%)
Hematopoiesis			1 (2%)
#Pancreas	(50)	(50)	(49)
Hyperplasia, lymphoid			1 (2%)
#Glandular stomach	(50)	(50)	(48)
Hyperplasia, lymphoid	5 (10%)		
#Small intestine	(50)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)		
#Cecum	(50)	(50)	(49)
Hyperplasia, lymphoid		3 (6%)	
#Kidney	(50)	(50)	(49)
Hyperplasia, lymphoid	9 (18%)	6 (12%)	3 (6%)
#Urinary bladder	(50)	(50)	(44)
Hyperplasia, lymphoid	3 (6%)	4 (8%)	2 (5%)
#Pancreatic islets	(50)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)		
CIRCULATORY SYSTEM			
*Lymphatic vessels	(50)	(50)	(49)
Pigmentation, NOS		1 (2%)	1 (2%)
#Heart	(50)	(50)	(49)
Mineralization			1 (2%)
Inflammation, acute			2 (4%)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal	2 (4%)		
#Heart/atrium	(50)	(50)	(49)
Thrombosis, NOS			1 (2%)
#Myocardium	(50)	(50)	(49)
Inflammation, acute			1 (2%)
Inflammation, chronic focal		1 (2%)	
Fibrosis		1 (2%)	1 (2%)
Degeneration, NOS			1 (2%)
Calcification, focal		1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(47)	(49)	(49)
Atrophy, NOS			2 (4%)
#Liver	(50)	(50)	(49)
Inflammation, acute	1 (2%)		
Inflammation, acute/chronic	2 (4%)	1 (2%)	1 (2%)
Necrosis, focal	1 (2%)		
Basophilic cyto change			1 (2%)
Focal cellular change	2 (4%)		
Angiectasis	1 (2%)		
#Liver/hepatocytes	(50)	(50)	(49)
Cytoplasmic vacuolization	2 (4%)	3 (6%)	9 (18%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(50)	(50)	(49)
Multiple cysts	1 (2%)		
Inflammation, acute necrotizing	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Atrophy, NOS	2 (4%)		1 (2%)
#Glandular stomach	(50)	(50)	(48)
Cyst, NOS	1 (2%)	2 (4%)	
Multiple cysts	6 (12%)	3 (6%)	
Inflammation, acute/chronic	2 (4%)		
Inflammation, chronic	4 (8%)	2 (4%)	
Inflammation, chronic focal	5 (10%)		
Inflammation with fibrosis	1 (2%)		
Calcification, focal	1 (2%)	1 (2%)	
Hyperplasia, epithelial	1 (2%)		1 (2%)
#Forestomach	(50)	(50)	(48)
Cyst, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic	1 (2%)	1 (2%)	
Acanthosis	1 (2%)		
#Ileum	(50)	(50)	(49)
Inflammation, acute/chronic			1 (2%)
Pigmentation, NOS			1 (2%)
#Colon	(50)	(50)	(49)
Inflammation, acute/chronic		2 (4%)	7 (14%)
Inflammation, chronic			1 (2%)
Fibrosis		5 (10%)	19 (39%)
Pigmentation, NOS		7 (14%)	24 (49%)
#Cecum	(50)	(50)	(49)
Inflammation, acute/chronic		12 (24%)	29 (59%)
Ulcer, chronic			3 (6%)
Erosion			1 (2%)
Fibrosis		26 (52%)	31 (63%)
Pigmentation, NOS		32 (64%)	39 (80%)
*Rectum	(50)	(50)	(49)
Inflammation, acute/chronic	1 (2%)		
Fibrosis		1 (2%)	1 (2%)
Pigmentation, NOS		1 (2%)	4 (8%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Hydronephrosis	1 (2%)		
Multiple cysts	1 (2%)		
Glomerulonephritis, chronic	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic focal	1 (2%)		
Metaplasia, osseous			1 (2%)
#Perirenal tissue	(50)	(50)	(49)
Inflammation, suppurative		1 (2%)	
#Kidney/tubule	(50)	(50)	(49)
Mineralization	1 (2%)		
Dilatation, NOS		1 (2%)	4 (8%)
Degeneration, hyaline		1 (2%)	
Necrosis, NOS		1 (2%)	
Regeneration, NOS	9 (18%)	4 (8%)	1 (2%)
#Urinary bladder	(50)	(50)	(44)
Inflammation, chronic diffuse			1 (2%)
Metaplasia, squamous		1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(50)	(46)
Cyst, NOS	2 (4%)	1 (2%)	
Multiple cysts	1 (2%)	1 (2%)	1 (2%)
Pigmentation, NOS	1 (2%)		
Focal cellular change			2 (4%)
Hyperplasia, NOS	9 (18%)	1 (2%)	
Hyperplasia, focal	9 (18%)	8 (16%)	3 (7%)
Angiectasis	11 (22%)	8 (16%)	
#Adrenal/capsule	(50)	(50)	(49)
Hyperplasia, stromal	50 (100%)	50 (100%)	40 (82%)
#Adrenal cortex	(50)	(50)	(49)
Congestion, NOS			1 (2%)
Hemorrhage			3 (6%)
Cytoplasmic vacuolization	1 (2%)	2 (4%)	
#Thyroid	(50)	(50)	(48)
Cystic follicles	1 (2%)	2 (4%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Atrophy, NOS	1 (2%)		
Hyperplasia, epithelial	3 (6%)		
Hyperplasia, follicular cell	1 (2%)		
#Pancreatic islets	(50)	(50)	(49)
Hyperplasia, focal		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(49)
Multiple cysts			1 (2%)
#Uterus	(50)	(50)	(49)
Dilatation, NOS	1 (2%)	2 (4%)	6 (12%)
Multiple cysts		1 (2%)	
Inflammation, suppurative		1 (2%)	1 (2%)
#Uterus/endometrium	(50)	(50)	(49)
Cyst, NOS	1 (2%)		
Multiple cysts	1 (2%)		
Inflammation, suppurative		1 (2%)	
Hyperplasia, cystic	43 (86%)	41 (82%)	31 (63%)
#Ovary	(50)	(50)	(44)
Cyst, NOS	7 (14%)	4 (8%)	2 (5%)
Multiple cysts	1 (2%)	2 (4%)	1 (2%)
Hemorrhage	1 (2%)		
Hematoma, organized		1 (2%)	
Hemorrhagic cyst		1 (2%)	
Abscess, NOS	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Fibrosis			1 (2%)
Angiectasis	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(49)
Perivascular cuffing	3 (6%)		1 (2%)
#Brain	(50)	(50)	(49)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Perivascular cuffing	3 (6%)		
Calcification, focal	25 (50%)	21 (42%)	3 (6%)
*Spinal cord	(50)	(50)	(49)
Degeneration, myelin		1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-5-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(49)
Osteosclerosis			1 (2%)
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
Adipose tissue			
Inflammation, chronic		1	
Inflammation, granulomatous	1	1	
Reaction, foreign body		1	
Inflammation with fibrosis		1	
Necrosis, fat	3	3	
SPECIAL MORPHOLOGY SUMMARY			
Animal missing/no necropsy			1

* Number of animals receiving complete necropsy examinations; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX E

GENETIC TOXICOLOGY OF

2-AMINO-5-NITROPHENOL

TABLE E1. MUTAGENICITY OF 2-AMINO-5-NITROPHENOL IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA100	0	184 ± 11.5	85 ± 4.4	207 ± 8.4	185 ± 17.4	192 ± 7.5	147 ± 9.3
	100	184 ± 3.7	80 ± 3.2	248 ± 7.6	209 ± 11.2	176 ± 9.9	173 ± 6.0
	333	200 ± 8.5	123 ± 10.3	245 ± 15.9	240 ± 9.2	209 ± 4.1	171 ± 3.2
	1,000	232 ± 10.3	137 ± 9.4	296 ± 11.0	281 ± 4.1	248 ± 10.3	190 ± 4.6
	3,333	248 ± 7.0	141 ± 12.5	305 ± 23.7	282 ± 16.0	268 ± 3.0	161 ± 8.5
	10,000	154 ± 15.7	67 ± 2.4	199 ± 22.9	146 ± 8.7	138 ± 21.7	67 ± 8.9
	Trial summary	Weakly positive	Weakly positive	Weakly positive	Weakly positive	Weakly positive	Negative
	Positive control (c)	918 ± 111.3	420 ± 29.4	1,746 ± 39.4	2,371 ± 193.6	1,759 ± 182.6	567 ± 20.7
TA1537	0	8 ± 4.3	3 ± 1.2	8 ± 2.0	3 ± 0.3	8 ± 1.9	5 ± 0.9
	100	10 ± 1.5	4 ± 1.2	10 ± 2.1	6 ± 0.9	8 ± 1.2	4 ± 0.3
	333	12 ± 2.0	6 ± 0.6	24 ± 1.5	8 ± 0.9	16 ± 1.3	8 ± 1.8
	1,000	34 ± 6.7	13 ± 1.8	43 ± 5.9	17 ± 2.2	26 ± 4.9	12 ± 2.4
	3,333	34 ± 6.8	22 ± 1.2	40 ± 9.5	35 ± 6.2	25 ± 5.0	23 ± 2.3
	10,000	10 ± 2.5	3 ± 0.3	10 ± 4.4	14 ± 4.1	7 ± 1.2	2 ± 0.9
	Trial summary	Positive	Weakly positive	Positive	Positive	Weakly positive	Weakly positive
	Positive control (c)	149 ± 46.9	59 ± 18.6	72 ± 11.5	31 ± 9.1	69 ± 3.5	39 ± 3.8
TA98	0	18 ± 2.9	14 ± 1.5	23 ± 4.5	25 ± 1.3	21 ± 3.0	23 ± 1.5
	100	39 ± 1.9	20 ± 2.6	36 ± 1.5	17 ± 1.2	25 ± 3.1	18 ± 1.8
	333	63 ± 3.8	46 ± 7.3	74 ± 7.3	33 ± 2.3	49 ± 2.3	22 ± 1.0
	1,000	123 ± 7.7	54 ± 2.9	110 ± 7.2	41 ± 7.0	73 ± 4.9	50 ± 1.8
	3,333	265 ± 14.5	93 ± 25.1	183 ± 13.3	112 ± 6.3	165 ± 17.8	87 ± 4.4
	10,000	241 ± 5.8	154 ± 15.4	166 ± 50.2	193 ± 20.0	154 ± 38.1	113 ± 7.2
	Trial summary	Positive	Positive	Positive	Positive	Positive	Positive
	Positive control (c)	147 ± 14.0	74 ± 10.4	1,302 ± 109.6	565 ± 86.0	742 ± 27.2	368 ± 53.8

Strain	Dose (µg/plate)	Revertants/plate (b) −S9 Trial 1	−S9 Trial 2	−S9 Trial 3	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (hamster) Trial 3	+S9 (rat) Trial 1	+S9 (rat) Trial 2	+S9 (rat) Trial 3
TA1535	0	9 ± 1.5	3 ± 0.3	8 ± 1.2	9 ± 0.7	5 ± 0.6	8 ± 1.3	15 ± 1.9	5 ± 0.3	13 ± 0.3
	100	8 ± 1.7	1 ± 0.6	6 ± 2.3	14 ± 1.8	5 ± 1.5	12 ± 1.5	11 ± 1.0	5 ± 1.2	14 ± 2.9
	333	8 ± 1.5	7 ± 3.0	13 ± 1.5	17 ± 1.2	3 ± 1.2	15 ± 3.0	14 ± 1.9	5 ± 2.1	16 ± 2.2
	1,000	8 ± 1.7	4 ± 0.9	13 ± 1.8	15 ± 2.3	4 ± 0.9	17 ± 2.8	19 ± 0.9	4 ± 0.6	16 ± 0.3
	3,333	7 ± 1.2	3 ± 0.3	10 ± 4.6	19 ± 0.9	4 ± 1.5	10 ± 0.3	15 ± 0.7	5 ± 0.7	12 ± 3.8
	10,000	8 ± 1.0	2 ± 0.6	7 ± 3.8	9 ± 0.9	3 ± 1.5	3 ± 0.9	10 ± 3.5	3 ± 1.5	0 ± 0.3
	Trial summary	Negative	Negative	Negative	Equivocal	Negative	Equivocal	Negative	Negative	Negative
	Positive control (c)	882 ± 51.8	125 ± 14.3	117 ± 8.4	122 ± 1.7	144 ± 3.8	131 ± 29.6	151 ± 9.9	134 ± 10.9	43 ± 4.2

(a) Study performed at Case Western Reserve University. The detailed protocol is presented in Haworth et al. (1983). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE E2. MUTAGENICITY OF 2-AMINO-5-NITROPHENOL IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
Trial 1					
Dimethyl sulfoxide		90.0 ± 6.6	100.0 ± 1.0	84.0 ± 4.6	31.3 ± 0.9
2-Amino-5-nitrophenol	(d) 12.5	72.0 ± 1.0	81.0 ± 7.0	132.0 ± 1.0	(e) 61.0 ± 1.0
	(d) 25	69.0 ± 2.0	77.5 ± 1.5	125.5 ± 1.5	(e) 60.5 ± 1.5
	(d) 50	66.0 ± 3.0	45.0 ± 1.0	151.5 ± 8.5	(e) 76.5 ± 0.5
	(d) 100	67.0 ± 6.0	26.0 ± 2.0	152.5 ± 0.5	(e) 77.0 ± 7.0
	200	54.7 ± 3.3	11.0 ± 2.1	153.3 ± 34.4	(e) 92.0 ± 15.2
	(d) 300	59.0 ± 1.0	6.0 ± 1.0	239.0 ± 6.0	(e) 135.5 ± 1.5
	400	Lethal	--	--	--
Methyl methanesulfonate (f)	5	62	47	562	305
	10	33	12	517	520
Trial 2					
Dimethyl sulfoxide (g)		98.0 ± 5.6	100.0 ± 4.7	90.0 ± 6.3	31.3 ± 2.8
2-Amino-5-nitrophenol	12.5	84.7 ± 10.3	80.3 ± 6.7	99.7 ± 6.8	40.3 ± 4.3
	25	85.3 ± 5.4	60.3 ± 4.9	165.0 ± 6.0	(e) 65.0 ± 5.3
	50	76.0 ± 9.0	38.3 ± 1.8	179.0 ± 22.9	(e) 80.3 ± 14.3
	100	76.3 ± 4.9	26.3 ± 1.5	158.3 ± 22.1	(e) 68.7 ± 4.7
	200	79.7 ± 4.7	11.3 ± 0.7	204.7 ± 6.4	(e) 86.0 ± 4.4
	300	Lethal	--	--	--
Methyl methanesulfonate	5	75.0 ± 5.6	61.7 ± 8.4	365.0 ± 23.7	(e) 163.0 ± 1.7

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate, unless otherwise specified; the average for the three tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency. Studies were performed without metabolic activation.

(b) Mean ± standard error of three replicate plates for approximately 3×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered mutagenic. If only one of these responses is significant, the call is "questionable"; the absence of both trend and peak response results in a "negative" call.

(c) Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.

(d) Data presented are the average of two tests.

(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6

(f) Data are the results of a single test.

(g) Data presented are the average of four tests.

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 2-AMINO-5-NITROPHENOL (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
-S9 (c)								
Trial 1--Summary: Positive								
Dimethyl sulfoxide		50	1,026	416	0.41	8.3	25.5	--
2-Amino-5-nitrophenol	4	50	1,032	477	0.46	9.5	25.5	114.5
	13.3	50	1,029	582	0.57	11.6	25.5	139.8
	40	50	1,034	751	0.73	15.0	25.5	180.7
	133.3	0					(d) 31.0	
Mitomycin C	0.001	50	1,020	711	0.70	14.2	25.5	171.1
	0.010	5	102	198	1.94	39.6	25.5	477.1
+S9 (e)								
Trial 1--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,037	405	0.39	8.1	25.5	--
2-Amino-5-nitrophenol	133.3	50	1,029	385	0.37	7.7	25.5	95.1
	400	50	1,033	411	0.40	8.2	25.5	101.2
	1,300	50	1,020	606	0.59	12.1	(d) 31.0	149.4
	4,000	0						
Cyclophosphamide	0.3	50	1,041	610	0.59	12.2	25.5	150.6
	2	5	105	203	1.93	40.6	25.5	501.2
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,026	428	0.42	8.6	25.5	--
2-Amino-5-nitrophenol	907	50	1,006	715	0.71	14.3	25.5	166.3
	1,010	50	1,006	656	0.65	13.1	(d) 32.8	152.3
	1,240	50	1,015	848	0.84	17.0	(d) 32.8	197.7
	1,500	0						
Cyclophosphamide	0.3	50	1,026	603	0.59	12.1	25.5	140.7
	2	5	105	159	1.51	31.8	25.5	369.8

(a) Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) or (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.
(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second-division cells available for analysis.
(e) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY 2-AMINO-5-NITROPHENOL (a)

Trial 1					Trial 2				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
−S9 (b)--Harvest time 10.5 h					−S9 (b)--Harvest time 20.8 h (c)				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	1	0.01	1		100	5	0.05	2
2-Amino-5-nitrophenol					2-Amino-5-nitrophenol				
405	96	4	0.04	4	49.5	100	12	0.12	11
450	85	5	0.06	5	100.5	100	14	0.14	13
500	71	1	0.01	1	149.9	100	25	0.25	20
1,000	0								
Summary: Negative					Summary: Positive				
Mitomycin C					Mitomycin C				
0.500	50	31	0.62	38	0.062	50	73	1.46	58
+S9 (d)--Harvest time 23.0 h (c)									
Dimethyl sulfoxide									
	100	0	0.00	0					
2-Amino-5-nitrophenol									
905	100	31	0.31	22					
1,000	100	33	0.33	21					
1,240	0								
Summary: Positive									
Cyclophosphamide									
10	50	49	0.98	50					

(a) Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) or (d). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) Because of significant chemically induced cell cycle delay, incubation time before addition of colcemid was lengthened to provide sufficient metaphases at harvest.
(d) In the presence of S9, cells were incubated with study compound or solvent (dimethyl sulfoxide) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX F

SENTINEL ANIMAL PROGRAM

APPENDIX F. SENTINEL ANIMAL PROGRAM

I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect 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 viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus)	MHV (mouse hepatitis virus)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	*M. pul.* (*Mycoplasma pulmonis*)

II. Results

Results are presented in Table F1.

TABLE F1. MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-5-NITROPHENOL (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	--	None positive
12	3/10	Sendai
18	4/9	Sendai
	1/9	KRV
24	10/10	Sendai
	10/10	(b) *M. pul.*
MICE		
6	--	None positive
12	6/10	Sendai
18	1/9	GDVII
	6/9	Sendai
24	8/9	Sendai

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.
(b) Further evaluation of this assay has indicated that it is not specific for *M. pulmonis* and that these results are considered false positive.

APPENDIX G

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

Pelleted Diet: April 1981 to April 1983

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE G1. 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
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

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

TABLE G2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamin		
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 activity
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
Mineral		
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 G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.8 ± 0.87	22.2-25.3	24
Crude fat (percent by weight)	5.0 ± 0.45	4.2-5.7	24
Crude fiber (percent by weight)	3.3 ± 0.23	2.9-3.8	24
Ash (percent by weight)	6.4 ± 0.37	5.7-7.1	24
Essential Amino Acid (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.94 ± 0.065	1.85-1.99	4
Lysine	1.279 ± 0.075	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acid (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008		1
Vitamin			
Vitamin A (IU/kg)	11,183 ± 2,211	8,400-18,000	24
Vitamin D (IU/kg)	4,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm)	16.4 ± 2.17	13.0-21.0	(b) 23
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.20	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 ± 120.0	3,200-3,430	4
Mineral			
Calcium (percent)	0.22 ± 0.11	1.08-1.53	24
Phosphorus (percent)	0.97 ± 0.04	0.88-1.1	24
Potassium (percent)	0.862 ± 0.10	0.772-0.970	3
Chloride (percent)	0.546 ± 0.10	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409-523	4
Manganese (ppm)	90.6 ± 8.20	81.7-99.4	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One to four batches of feed analyzed for nutrients reported in this table were manufactured during 1983-1985.
(b) One batch (7/22/81) was not analyzed for thiamine.

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.46 ± 0.10	<0.29-0.70	24
Cadmium (ppm) (a)	<0.1		24
Lead (ppm)	0.95 ± 0.76	0.33-3.37	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.29 ± 0.07	0.13-0.40	24
Aflatoxins (ppb) (b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	10.24 ± 4.1	3.8-22.0	24
Nitrite nitrogen (ppm) (c)	2.0 ± 1.6	<0.4-6.9	24
BHA (ppm) (d)	6.1 ± 4.9	<0.4-17.0	24
BHT (ppm) (d)	3.3 ± 2.6	0.9-12.0	24
Aerobic plate count (CFU/g) (e)	39,879 ± 27,920	4,900-88,000	24
Coliform (MPN/g) (f)	15.5 ± 22.7	<3-93	23
Coliform (MPN/g) (g)	34.0 ± 93.4	<3-460	24
E. coli (MPN/g) (h)	<3		24
Total nitrosamines (ppb) (i, j)	3.7 ± 2.7	0.8-9.3	23
Total nitrosamines (ppb) (j,k)	15.2 ± 56.4	0.8-279.5	24
N-Nitrosodimethylamine (ppb) (j,l)	2.7 ± 2.5	0.8-8.3	23
N-Nitrosodimethylamine (ppb) (j,m)	14.1 ± 56.3	0.8-278.0	24
N-Nitrosopyrrolidine (ppb)	1.2 ± 0.5	<0.9-2.9	24
Pesticide (ppm) (c)			
α-BHC (a,n)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a)	<0.01		24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (o)	<0.05	0.09 (8/26/81)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (a)	<0.1		24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (p)	0.09 ± 0.06	<0.05-0.27	24
Endosulfan I (q)	<0.01		18
Endosulfan II (q)	<0.01		18
Endosulfan sulfate (q)	<0.03		18

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) CFU = colony-forming unit
(f) MPN = most probable number. Mean, standard deviation, and range exclude one very high value of 460 obtained for the batch produced on 9/23/82.
(g) Mean, standard deviation, and range include the very high value given in footnote (f).
(h) All values were less than 3 MPN/g.
(i) Mean, standard deviation, and range exclude one very high value of 279.5 obtained for the batch produced on 4/27/81.
(j) All values were corrected for percent recovery.
(k) Mean, standard deviation, and range include the very high value given in footnote (i).
(l) Mean, standard deviation, and range exclude one very high value of 278.0 for the batch produced on 4/27/81.
(m) Mean, standard deviation, and range include the very high value listed in footnote (l).
(n) BHC = hexachlorocyclohexane or benzene hexachloride
(o) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(p) Ten batches contained more than 0.05 ppm.
(q) Six batches were not analyzed for endosulfan I, endosulfan II, or endosulfan sulfate.

APPENDIX H

DATA AUDIT SUMMARY

APPENDIX H. DATA AUDIT SUMMARY

The experimental data, documents, pathology materials, and draft Technical Report for the 2-year toxicology and carcinogenesis studies of 2-amino-5-nitrophenol in F344/N rats and B6C3F$_1$ mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations of the Food and Drug Administration (implemented by the NTP beginning on October 1, 1981). The laboratory experiments were conducted for the NTP by Physiological Research Laboratories (Minneapolis, Minnesota) under a subcontract with Tracor Jitco, Inc., through February 1983 and then under contract with the NIEHS. Exposure to the chemical began in May 1981 for both rats and mice. The retrospective audit was conducted for the NTP during July and August 1986 by Argus Research Laboratories, P.A. Wennerberg, Principal Investigator. Other individuals involved in the audit are listed in the full audit report, which is on file at the NIEHS. The audit included a review of:

(1) All inlife records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) Clinical observations recorded during the last 6 months of life and all body weights for a random 10% sample of the study animals.
(3) All inlife records concerning environmental conditions, palpable masses, mortality, animal identification, and correlation of final inlife observation of masses, dates of death, and disposition with necropsy records.
(4) All chemistry records, including chromatograms, Midwest Research Institute reports and raw data, receipt reports, chemical use and dose preparation records, analytical records, and correspondence.
(5) All postmortem records for individual animals concerning identification, disposition codes, condition codes, and correlation between gross observations and microscopic diagnoses.
(6) Inventory and labeling for all wet tissue bags.
(7) Wet tissues from a random 20% sample of the study animals and from animals that had a gross observation without a corresponding microscopic diagnosis to verify animal identification and to examine for untrimmed lesions.
(8) Slides and blocks of tissues from all vehicle control and high dose animals to examine for proper match and inventory.

Review of the toxicology data, the analytical chemistry data, and the pathology materials revealed no discrepancies that would influence interpretation of the study results. The minor discrepancies identified in this audit were adequately resolved or were considered not to affect the interpretation of these 2-year carcinogenesis studies of 2-amino-5-nitrophenol. Thus, the records examined in the audit support the data and results presented in the NTP Technical Report.

* U. S. GOVERNMENT PRINTING OFFICE:1988-201-778:61213

NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PUBLISHED AS OF JANUARY 1988

TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl 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)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
281	H.C. 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(hydroxymethy)phosphonium Sulfate and Tetrakis(hydroxymethy)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
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
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate

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