NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 339

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2-AMINO-4-NITROPHENOL

(CAS NO. 99-57-0)

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

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2-AMINO-4-NITROPHENOL

(CAS NO. 99-57-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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P.O. Box 12233
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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).

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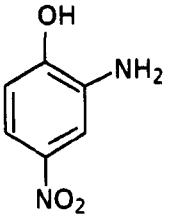

2-AMINO-4-NITROPHENOL

CAS No. 99-57-0

$C_6H_6O_3N_2$ Molecular weight 154.1

ABSTRACT

2-Amino-4-nitrophenol is used to color semipermanent hair dyes and in the manufacture of mordant dyes for leather, nylon, silk, wool, and fur. 2-Amino-4-nitrophenol was nominated by the National Cancer Institute for toxicology and carcinogenesis studies because of widespread human exposure associated with its manufacture and use. Toxicology and carcinogenesis studies were conducted by administering 2-amino-4-nitrophenol (98% pure) in corn oil by gavage, 5 days per week, to groups of F344/N rats and B6C3F$_1$ mice of each sex in 15-day, 13-week, and 2-year studies.

Fifteen-Day and Thirteen-Week Studies: During the 15-day studies, rats and mice received doses of 0, 313, 625, 1,250, 2,500, or 5,000 mg/kg. All rats that received 2,500 or 5,000 mg/kg and all female rats that received 1,250 mg/kg died before the end of the studies. Final mean body weights of chemically exposed rats surviving to the end of the studies were comparable to those of vehicle controls. Diarrhea was observed in all groups of exposed rats except those receiving 313 mg/kg. All mice that received 2,500 or 5,000 mg/kg, 2/5 males and all females that received 1,250 mg/kg, and 1/5 females that received 313 mg/kg died before the end of the studies. Final mean body weights of exposed mice surviving until the end of the studies were comparable to those of vehicle controls.

In 13-week studies, F344/N rats and B6C3F$_1$ mice of each sex received 2-amino-4-nitrophenol at doses of 0, 62.5, 125, 250, 500, or 1,000 mg/kg. All rats that received 1,000 mg/kg and 2/10 males and 2/10 females that received 500 mg/kg died before the end of the studies. The final mean body weight of male rats that received 500 mg/kg was reduced 10% compared with that of vehicle controls; final mean body weights of all other surviving exposed rat groups were comparable to those of vehicle controls. Diarrhea and lethargy were observed for rats that received 500 or 1,000 mg/kg. All male mice and most females that received 1,000 mg/kg and 4/10 females that received 500 mg/kg died before the end of the studies. Final mean body weights of chemically exposed mice were comparable to those of vehicle controls. No compound-related clinical signs were observed in mice during the studies.

Mineralization of the renal cortex and degeneration of the renal tubular epithelium were observed in male and female rats that received 1,000 mg/kg and in males that received 500 mg/kg. Degeneration and necrosis of the renal tubular epithelium was observed in 5/10 male and 3/10 female mice that received 1,000 mg/kg.

Body Weight and Survival in the Two-Year Studies: In the 2-year studies, rats and mice received 2-amino-4-nitrophenol at doses of 0, 125, or 250 mg/kg. Mean body weights of male rats that received 250 mg/kg were 8%-10% lower than those of vehicle controls throughout most of the 2-year study. Mean body weights of female rats were comparable to those of vehicle controls. Soft stools and occasional diarrhea were observed in chemically exposed rats starting 6 months after the beginning of the

studies. Survival of male rats that received 250 mg/kg was markedly lower than that of vehicle controls after week 89 (final survival: vehicle control, 32/50; 125 mg/kg group, 24/50; 250 mg/kg group, 10/50). Survival of female rats was comparable among all groups (final survival: 25/50; 27/50; 31/50).

Mean body weights of male and female mice that received 250 mg/kg were comparable to those of vehicle controls; the mean body weights of female mice that received 125 mg/kg were as much as 17% greater than that of vehicle controls. Survival of all mouse groups was comparable during the 2-year studies (final survival: male--28/50; 29/50; 23/50; female--28/50; 31/50; 30/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Pigmentation of the small and large intestines was present in exposed rats but not in vehicle controls. Ulcers and erosive lesions of the digestive tract were observed in male rats that received 250 mg/kg and to a lesser extent in male rats that received 125 mg/kg. A carcinoma of the colon occurred in one male rat that received 250 mg/kg; no other neoplasms were observed in the gastrointestinal tract of rats. No pigmentation, ulcers, or erosive lesions were found in the digestive tract of mice.

The severity of nephropathy was markedly greater in exposed male rats than in vehicle controls. Associated with the nephropathy were nonneoplastic lesions indicative of reduced renal function and secondary hyperparathyroidism, including parathyroid hyperplasia, mineralization of various organs, and fibrous osteodystrophy.

Renal tubular cell hyperplasia (1/50; 4/48; 5/50) and renal cortical (tubular cell) adenomas (0/50; 1/48; 3/50) occurred in male rats. Renal cortical adenomas are infrequently observed in male F344/N rats (historical incidence, 0.5%).

More preputial gland adenomas or carcinomas (combined) were observed in low dose male rats than in vehicle controls (3/50; 10/48; 3/50), whereas the incidences of clitoral gland neoplasms were decreased in dosed female rats (9/50; 6/50; 1/49).

Hemangiomas or hemangiosarcomas (combined) occurred in male mice that received 2-amino-4-nitrophenol (0/50; 1/50; 5/50); each tumor was present at a different site. The historical control incidence is 11% at the study laboratory and 6% in 2-year NTP studies.

Genetic Toxicology: 2-Amino-4-nitrophenol was mutagenic in *Salmonella typhimurium* strains TA98 and TA100 with metabolic activation. 2-Amino-4-nitrophenol was not mutagenic in strains TA1535 or TA1537. 2-Amino-4-nitrophenol was mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay without metabolic activation. It was not tested with activation. 2-Amino-4-nitrophenol induced sister chromatid exchanges (SCEs) and chromosomal aberrations in Chinese hamster ovary cells in the presence and absence of metabolic activation.

Audit: The data, documents, and pathology materials from the 2-year studies of 2-amino-4-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** of 2-amino-4-nitrophenol for male F344/N rats, as shown by increased incidences of renal cortical (tubular cell) adenomas. The incidences of renal tubular cell hyperplasia were also increased in male rats exposed to 2-amino-4-nitrophenol. The survival of male rats that received 2-amino-4-nitrophenol was reduced compared with survival of vehicle control male rats. There was *no evidence of carcinogenic activity* of 2-amino-4-nitrophenol for female F344/N rats or for male or female $B6C3F_1$ mice that received 125 or 250 mg/kg per day.

SUMMARY OF THE TWO-YEAR GAVAGE AND GENETIC TOXICOLOGY STUDIES OF 2-AMINO-4-NITROPHENOL

Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses			
125 or 250 mg/kg 2-amino-4-nitrophenol in corn oil, 5 d/wk	125 or 250 mg/kg 2-amino-4-nitrophenol in corn oil, 5 d/wk	125 or 250 mg/kg 2-amino-4-nitrophenol in corn oil, 5 d/wk	125 or 250 mg/kg 2-amino-4-nitrophenol in corn oil, 5 d/wk
Survival rates in the 2-year study			
32/50; 24/50; 10/50	25/50; 27/50; 31/50	28/50; 29/50; 23/50	28/50; 31/50; 30/50
Body weights in the 2-year study			
Exposed 8%-10% lower than vehicle controls	Exposed and vehicle controls comparable	Exposed and vehicle controls comparable	125 mg/kg group greater than vehicle controls
Nonneoplastic effects			
Chronic nephropathy; pigmentation of small and large intestines	Chronic nephropathy; pigmentation of small and large intestines	None	None
Neoplastic effects			
Renal cortical (tubular cell) adenomas	None	None	None
Level of evidence of carcinogenic activity			
Some evidence	No evidence	No evidence	No evidence
Genetic toxicology			
Mutagenic in *S. typhimurium* strains TA98 and TA100 with metabolic activation; not mutagenic in TA1535 or TA1537; mutagenic in mouse L5178Y lymphoma cells without activation; increased chromosomal aberrations and SCEs in Chinese hamster ovary cells with and without metabolic activation.			

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 11.

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.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 2-Amino-4-nitrophenol is based on the 13-week studies that began in April 1980 and ended in July 1980 and on the 2-year studies that began in January 1981 and ended in January 1983 at Physiological Research Laboratories (Minneapolis, Minnesota).

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The members of the Peer Review Panel who evaluated the draft Technical Report on 2-amino-4-nitrophenol on July 14, 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.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2-AMINO-4-NITROPHENOL

On July 14, 1987, the draft Technical Report on the toxicology and carcinogenesis studies of 2-amino-4-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.D. Irwin, NIEHS, introduced the studies of 2-amino-4-nitrophenol 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. Mirer, a principal reviewer, agreed with the conclusions proposed for male and female rats and female mice. He said that the conclusion of some evidence of carcinogenic activity for male rats was strengthened by the presence of a statistically significant increase in renal tumors despite sharply reduced survival in male rats. Dr. Mirer recommended changing the conclusion for male mice from no evidence to equivocal evidence of carcinogenic activity, based on significantly increased incidences of hemangiomas or hemangiosarcomas at multiple sites.

As a second principal reviewer, Dr. Chinchilli agreed with the conclusions but asked for more discussion about circulatory system tumors in male mice. Dr. Irwin responded that the occurrence of these tumors at separate sites and the similarity to historical control incidences at the study laboratory argued against an association with chemical administration.

As a third principal reviewer, Dr. Sivak agreed with the conclusions for female rats and male and female mice but thought that the conclusion for male rats should be changed from some evidence to equivocal evidence of carcinogenic activity, as the occurrence of renal tumors represented a marginal increase and the diagnosis depends on a continuum of lesions with a high probability of ambiguity. Dr. Irwin stated that the conclusion was based on a small but definite increase in a rare tumor type, a dose-response trend for the tumors, and a corresponding dose-related increase in renal tubular cell hyperplasia. Dr. J. Haseman, NIEHS, noted that there was reduced survival in high dose male rats and that these were late-appearing tumors in this study. Thus, an analysis based on animals' surviving until the appearance of the first tumor would further strengthen the significance of the observed increase in kidney neoplasms. At Dr. Scala's request, Dr. Haseman said that a supplemental analysis making this comparison would be added. [See page 37.] Dr. Sivak inquired about the stability of the dose mixtures over time in view of the propensity for *ortho* aminophenols to condense in solution. Dr. Irwin replied that the dose mixtures were evaluated and 2-amino-4-nitrophenol was shown to be stable in corn oil for at least 2 weeks.

In other discussion, Dr. Ashby noted that this might be the first mutagenic aromatic nitro compound to not produce liver tumors in either species. He commented on target organ toxicity (in this case, kidney) and possible implications concerning the relationship between tumor formation and mutagenicity. Dr. J. Huff, NIEHS, observed that nonneoplastic lesions were considered to be a factor in interpreting the findings for tumorigenicity.

Dr. Mirer moved that the Technical Report on 2-amino-4-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. Sivak seconded the motion, and the Technical Report was approved unanimously with nine votes.

I. INTRODUCTION

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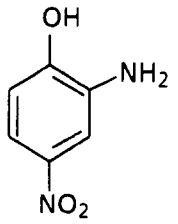


2-AMINO-4-NITROPHENOL

CAS No. 99-57-0

$C_6H_6O_3N_2$ Molecular weight 154.1

Anhydrous 2-amino-4-nitrophenol is an orange solid that melts at 142°-143° C and is soluble in ethanol and ether and sparingly soluble in water (Kirk-Othmer, 1978). It has been used as an intermediate in the manufacture of C.I. Mordant Brown 33 and C.I. Mordant Brown 1, which are used for dyeing leather, nylon, silk, wool, and fur. For this application, 2-amino-4-nitrophenol is converted to a diazonium salt and then coupled to other dye constituents via a diazo linkage. It has also been used in semipermanent hair dyes to produce gold-blond shades. For this application, 2-amino-4-nitrophenol is mixed unmodified with a blend of several other dyes in a shampoo base to produce the final color or tint desired. Semipermanent hair dyes utilize coloring agents that penetrate into the cortex of the hair shaft upon application and slowly diffuse out with subsequent washings. In general, color produced by semipermanent hair dyes is stable through five or six shampoo washings.

Data on current production for 2-amino-4-nitrophenol are not available; the most recent import data reported to the U.S. International Trade Commission were for the years 1979 and 1981, during which time the quantity imported was approximately 1.4×10^4 kg per year (USITC, 1980, 1982). 2-Amino-4-nitrophenol was reported in the U.S. Environmental Protection Agency TSCA inventory in 1980 (NIOSH, 1981).

The LD_{50} value for 2-amino-4-nitrophenol in rats was reported to be 246 mg/kg after intraperitoneal injection and greater than 4,000 mg/kg after oral administration. Percutaneous absorption through rat skin was determined after application 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% of the radioactivity administered in formulation 1 and 1.12% and 1.67% 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. By comparison, 5 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 chemical, since within 3 hours after oral administration, approximately 4% of the administered radioactivity was eliminated in the bile.

No long-term toxicity or carcinogenicity studies of 2-amino-4-nitrophenol were found in the literature. The long-term toxicity and carcinogenicity of a commercial hair coloring formulation containing the structural isomers 4-amino-2-nitrophenol and 2-amino-5-nitrophenol as well as 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; 4-amino-2-nitrophenol represented 0.11% and 2-amino-5-nitrophenol represented 0.15% by weight. Groups of 60 male or 60 female mice received 50 µl of the neat formulation three times per week for 20 months; they were then killed and necropsies were performed. 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 the dosed and control groups for hematologic analysis and urinalysis. Survival and mean body weights of

dosed and control animals did not differ significantly, and there were no significant differences between dosed and control groups in results of clinical chemical and hematologic analyses. The neoplasms observed in this study were considered characteristic of aging Swiss Webster mice and occurred at similar incidences in dosed and control animals.

4-Amino-2-nitrophenol and 2-amino-5-nitrophenol also have been evaluated in 2-year toxicology and carcinogenesis studies conducted by the NCI and the NTP. The 2-year studies of 4-amino-2-nitrophenol were conducted by feeding diets containing 1,250 or 2,500 ppm to groups of 50 F344/N rats and 50 B6C3F$_1$ mice of each sex (NCI, 1978). Survival and mean body weights of dosed animals were not significantly different from those of controls. 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; the increased incidence was attributed to chemical exposure. Transitional cell carcinomas of the urinary bladder also were observed in one low dose and two high dose female rats. Neoplasms found in mice were not associated with chemical exposure.

The 2-year studies of 2-amino-5-nitrophenol were conducted by administering the chemical, as a suspension, in corn oil by gavage; groups of 50 male and 50 female F344/N rats received doses of 100 or 200 mg/kg and groups of 50 male and 50 female B6C3F$_1$ mice received doses of 400 or 800 mg/kg (NTP, 1988a). Mean body weights of dosed male rats were 5%-10% lower than those of vehicle controls during the study; survival of male rats that received 200 mg/kg was significantly reduced compared with that of vehicle controls after week 75. Mean body weights of mice that received 800 mg/kg were 11%-13% lower than those of vehicle controls; survival of high dose mice of either sex was inadequate for evaluation of carcinogenic activity. Pancreatic acinar cell adenomas in male rats were the only chemically associated neoplasms observed in rats; no chemically associated neoplasms were found in mice.

As part of an investigation of the mutagenic activity of several hair dye components, 2-amino-4-nitrophenol was tested in the Salmonella plate incorporation assay over a dose range of 0-100 µg per plate (Ames et al., 1975). The results indicated that 2-amino-4-nitrophenol was mutagenic in *Salmonella typhimurium* strain TA1538 in the presence of human or rat liver S9. These results were confirmed by the experiments of Garner and Nutman (1977) who demonstrated the mutagenicity of 2-amino-4-nitrophenol in the presence of S9 and noted an increase in revertant colonies of strain TA1538 after treatment with 2-amino-4-nitrophenol in the absence of exogenous metabolic activation. The mutagenicity of 2-amino-4-nitrophenol in strains TA98 and TA1538 was further confirmed in a study that examined several aminonitrophenols (Shahin et al., 1982a).

In studies sponsored by the NTP at two independent laboratories, 2-amino-4-nitrophenol was tested in the Salmonella assay with a preincubation protocol with and without metabolic activation from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Zeiger et al., 1987; Appendix E, Table E1). In strain TA98, both laboratories observed possible mutagenic activity in the absence of S9 and clearly increased mutagenic activity in the presence of S9. One of the laboratories observed a significant increase in mutant colonies in strain TA100 exposed to 2-amino-4-nitrophenol in the presence of S9. No increase in revertant colonies was observed in strains TA1535 or TA1537. At concentrations of 25 µg/ml and greater, 2-amino-4-nitrophenol induced forward mutations at the TK locus in mouse lymphoma L5178Y cells in the absence of metabolic activation; it was not tested with S9 (Table E2). Significant increases in chromosomal aberrations and sister chromatid exchanges (SCEs) were observed in cultured Chinese hamster ovary (CHO) cells after incubation with 2-amino-4-nitrophenol both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Tables E3 and E4).

The in vivo mutagenicity of 2-amino-4-nitrophenol has been evaluated in two studies. In a dominant-lethal study, male Charles River CD rats received intraperitoneal injections of 20 mg/kg 2-amino-4-nitrophenol three times per week for 8 weeks and were then mated to

unexposed females (Burnett et al., 1977). 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 percentage of litters with resorptions. The ability of 2-amino-4-nitrophenol to induce micronuclei in bone marrow erythrocytes of male and female CFY rats was evaluated after oral administration of two doses of 2,500 mg/kg given 24 hours apart. The animals were killed 6 hours after the second dose, and the bone marrow cells were examined; no increase in micronucleated cells was observed (Hossack and Richardson, 1977).

The mutagenicity of the isomers 2-amino-5-nitrophenol and 4-amino-2-nitrophenol has also been examined. 2-Amino-5-nitrophenol was mutagenic in *S. typhimurium* strains TA1538 (Ames et al., 1975; Shahin et al., 1982a) and TA98 (Chiu et al., 1978; Shahin et al., 1982a) with and without S9. In NTP Salmonella assays, mutagenic activity was observed in TA98 and TA1537 with and without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9; weakly positive responses were observed in TA100 with and without S9, and possible mutagenic activity was detected in TA1535 in trials conducted in the presence of hamster liver S9 (Zeiger et al., 1987). 2-Amino-5-nitrophenol induced forward mutations in mouse L5178Y lymphoma cells in the absence of exogenous metabolic activation, and SCEs and chromosomal aberrations in cultured CHO cells with and without S9 (NTP, 1988a). 2-Amino-5-nitrophenol was negative in a dominant-lethal study reported by Burnett et al. (1977).

Commercial-grade 4-amino-2-nitrophenol induced mutations in Salmonella strains TA98 and TA1538 (Garner and Nutman, 1977; Dunkel and Simmon, 1980; Shahin et al., 1982b). However, 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 suggest that the mutagenic activity observed with commercial-grade material may have been due to impurities. In NTP assays, 99.6% pure 4-amino-2-nitrophenol induced reverse mutations in Salmonella strains TA97 and TA98 without S9 and forward mutations at the TK locus in mouse lymphoma L5178Y cells. 4-Amino-2-nitrophenol was negative in the dominant-lethal study of Burnett et al. (1977) and 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-4-nitrophenol and several other chemicals used in hair dyes were mutagenic in *S. typhimurium* prompted the National Cancer Institute to nominate several of these chemicals, including 2-amino-4-nitrophenol, for 2-year toxicology and carcinogenesis studies.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 2-AMINO-4-NITROPHENOL

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FIFTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

PROCUREMENT AND CHARACTERIZATION OF 2-AMINO-4-NITROPHENOL

2-Amino-4-nitrophenol was obtained in one lot (lot no. A8655) from Lowenstein Dyes, Cosmetics, Inc. (Brooklyn, New York). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, Missouri). (MRI reports on analyses performed in support of the studies on 2-amino-4-nitrophenol are on file at NIEHS.) Lot no. A8655 was obtained as brown, amorphous granules. Differential scanning calorimetry indicated an endotherm at 142°-145.5° C and an exotherm at 177°-200° 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-4-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. A8655 was greater than 98% pure. Results of elemental analyses agreed with the theoretical values. Water content by Karl Fischer titration was 0.5%. Titration of the phenolic group with tetrabutylammonium hydroxide indicated a purity of 98.1%. Titration of the amine group with perchloric acid indicated a purity of 97.1%. Thin-layer chromatography on silica gel plates indicated four trace impurities and two slight trace impurities with a hexanes:ethyl acetate:95% ethanol (60:35:5) solvent system and one trace impurity and two slight trace impurities with a chloroform:methanol (90:10) solvent system. Visualization was by ultraviolet light at 254 nm and a dimethylaminobenzaldehyde/tin chloride/hydrochloric acid spray (Touchstone and Dobbins, 1978). Four impurity peaks with a combined area totaling 0.07% of the major peak area were detected by high-performance liquid chromatography on a μBondapak C_{18} column. The mobile phase was aqueous 5 mM 1-heptane sulfonic acid containing 1% acetic acid:5 mM 1-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. Two impurity peaks with a combined area 0.12% of the major peak area were detected with a 40:60 solvent ratio. Results obtained with intermediate solvent ratios indicated that a total of six impurities with a total area 0.19% of the major peak area were detected by the two systems.

Stability studies performed at MRI by high-performance liquid chromatography on a μBondapak C_{18} column with a mobile phase of water:acetonitrile (70:30) at a flow rate of 2 ml/minute and with ultraviolet detection at 254 nm indicated that 2-amino-4-nitrophenol was stable as a bulk chemical when kept in the dark under nitrogen for 2 weeks at temperatures from −20° to 60° C. Further confirmation of bulk chemical stability was obtained at the study laboratory during the toxicity studies (storage at 25° C). Stability was determined by potentiometric titration in glacial acetic acid solution with 0.1 N perchloric acid and the high-performance liquid chromatographic system described above. No degradation was seen over the course of the studies. Chemical identity was confirmed by infrared spectroscopy.

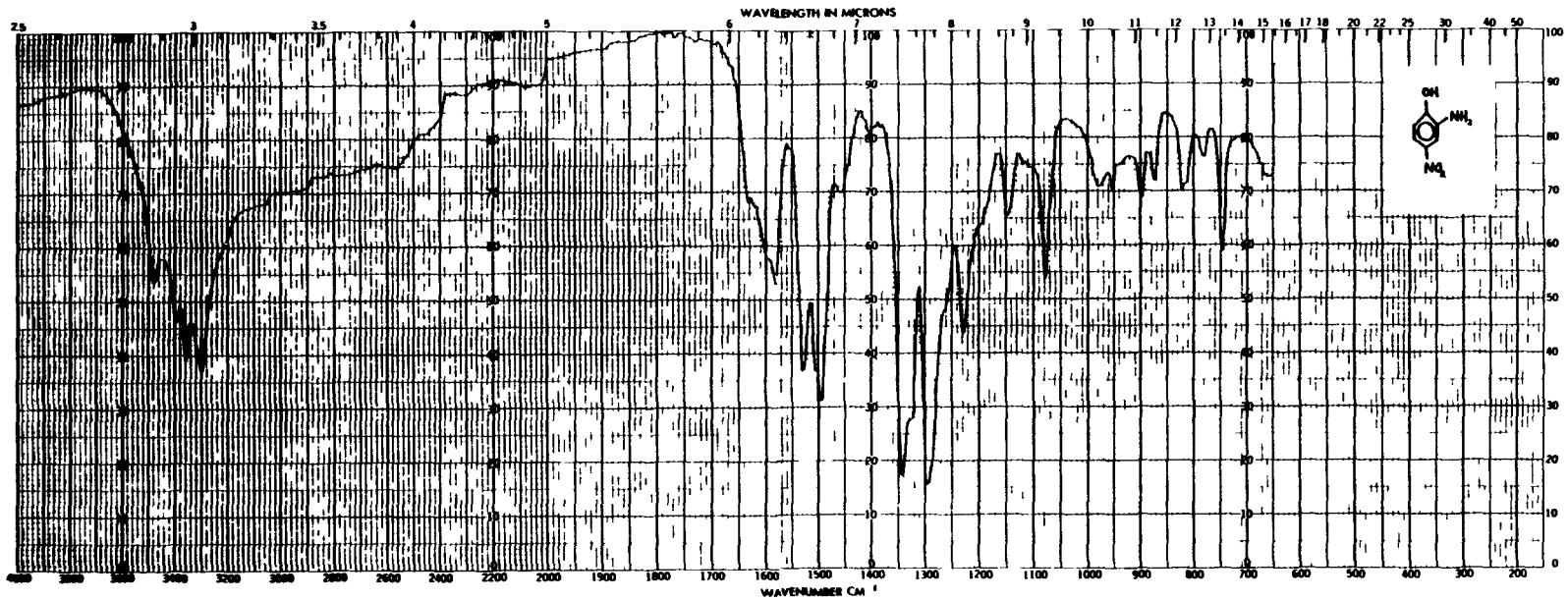


FIGURE 1. INFRARED ABSORPTION SPECTRUM OF 2-AMINO-4-NITROPHENOL (LOT NO. A8655)

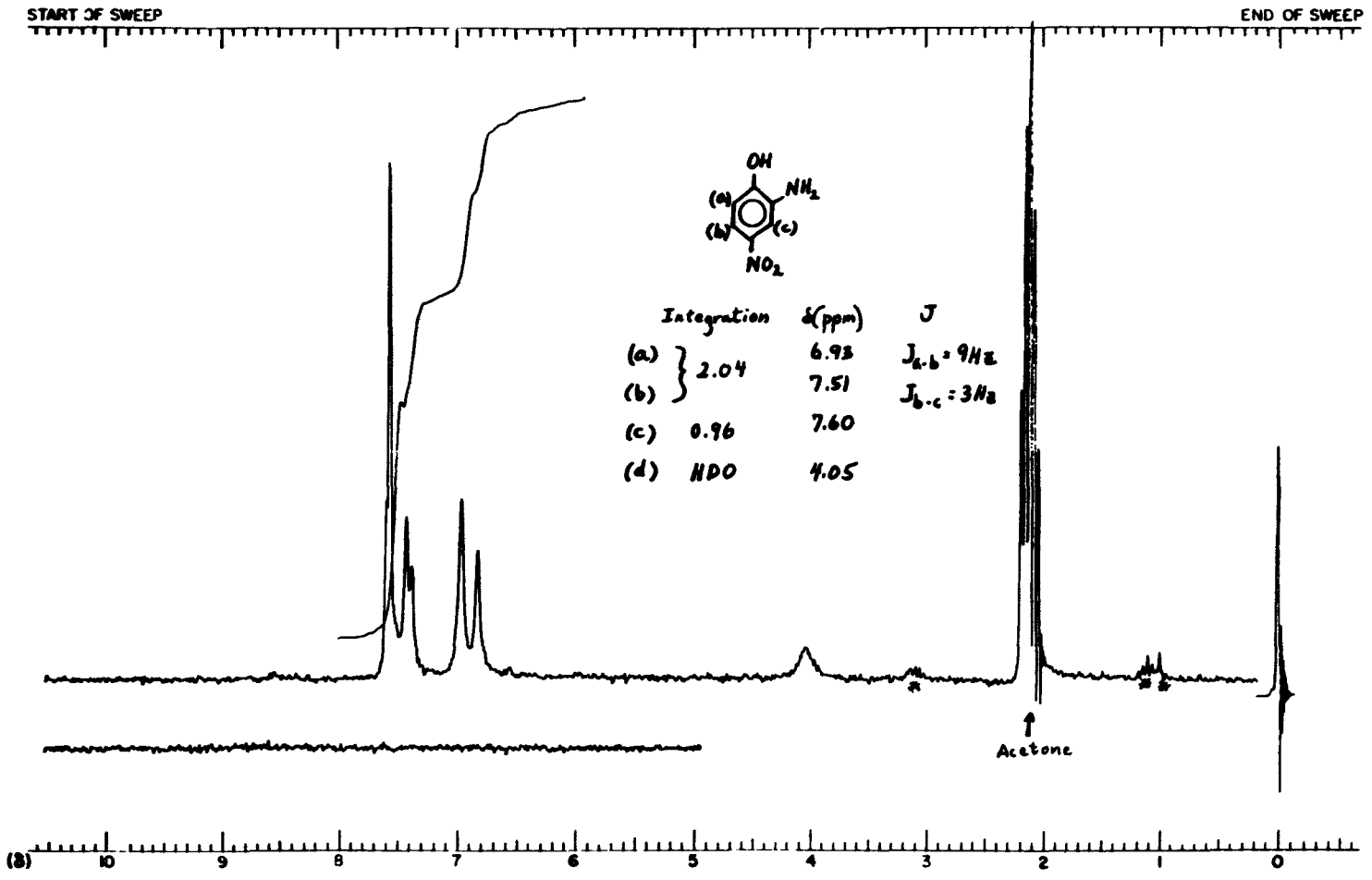


FIGURE 2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 2-AMINO-4-NITROPHENOL (LOT NO. A8655)

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

2-Amino-4-nitrophenol and corn oil were mixed to give suspensions at 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 on a μBondapak C_{18} column with a mobile phase of aqueous 1% acetic acid:1% acetic acid in methanol (60:40) at a flow rate of 1 ml/minute and ultraviolet detection at 254 nm. The results showed that 2-amino-4-nitrophenol was stable in corn oil for 14 days in the dark at 5° or 25° C or when exposed for 3 hours to air and light at room temperature. Suspensions were stored under nitrogen in foil-wrapped serum bottles at room temperature or 5° C for no longer than 2 weeks.

Analyses for 2-amino-4-nitrophenol in dose mixtures by methanolic extraction and spectrophotometric quantitation (at 259 or 260 nm) were performed by the study and analytical chemistry laboratories to determine if the suspensions were formulated properly. Dose preparations were analyzed once during the 13-week studies. The results ranged from 90% to 103% of the target concentrations (Table 2). During the 2-year studies, the dose preparations were analyzed periodically, and concentrations varied from 93% to 109% of the target concentrations (Table 3). Because 39/39 dose mixtures analyzed were within 10% of the target concentrations, the dose mixtures were estimated to have been within specifications throughout the studies. Referee analyses were periodically performed by the analytical chemistry laboratory. Good agreement was generally found between the study and analytical chemistry laboratories (Table 4).

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF 2-AMINO-4-NITROPHENOL

Fifteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
2-Amino-4-nitrophenol was ground in a mortar with a pestle, passed through a 140-mesh sieve, and mixed with corn oil; the dose mixture was stirred with a magnetic stir bar for 15 min before being used	2-Amino-4-nitrophenol and corn oil were mixed (w/w), purged with nitrogen, and homogenized with a Polytron® at setting no. 5 for 15 sec, then setting no. 8 for 5 min	Same as 13-wk studies except 45 sec at setting no. 8
Maximum Storage Time		
	2 wk	2 wk
Storage Conditions		
4° C under nitrogen	4° C or room temperature under nitrogen	Room temperature or 5° C

TABLE 2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-4-NITROPHENOL

Concentration of 2-Amino-4-nitrophenol in Corn Oil (mg/ml)		Determined as a Percent of Target
Target	Determined (a)	
6.30	5.67	90.0
12.50	12.34	98.7
25.00	25.65	102.6
50.00	50.49	101.0
100.00	92.90	92.9
200.00	193.75	96.9

(a) Results of duplicate analysis; mix date: 4/21/80.

TABLE 3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-4-NITROPHENOL

Date Mixed	Concentration of 2-Amino-4-nitrophenol in Corn Oil for Target Concentration (mg/ml) (a)		
	12.5	25	50
01/07/81	12.4	23.4	46.8
04/16/81	12.4	26.2	51.2
05/21/81	12.9	--	--
05/23/81	--	23.7	49.6
07/02/81	12.7	(b) 23.6	52.1
08/27/81	12.7	25.0	48.8
11/25/81	13.6	26.5	51.3
12/17/81	12.7	24.8	49.4
03/09/82	13.3	26.3	51.7
03/30/82	12.6	23.8	52.9
06/29/82	13.5	25.8	48.5
07/29/82	12.1	24.5	48.1
10/28/82	12.2	23.2	50.6
11/18/82	12.2	25.9	47.0
Mean (mg/ml)	12.7	24.8	49.8
Standard deviation	0.49	1.21	1.96
Coefficient of variation (percent)	3.9	4.9	3.9
Range (mg/ml)	12.1-13.6	23.2-26.5	46.8-52.9
Number of samples	13	13	13

(a) Results of duplicate analysis
(b) Result of single analysis

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

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
01/07/81	50	46.8	50.0
07/02/81	12.5	12.7	12.4
06/29/82	25	25.8	20.1
07/29/82	25	24.5	24.2
10/28/82	12.5	12.2	11.7

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

FIFTEEN-DAY STUDIES

Male and female F344/N rats and male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 19 days before the studies began. Rats and mice were 7 weeks old when placed on study. Groups of five rats and five mice of each sex were administered 0, 313, 625, 1,250, 2,500, or 5,000 mg/kg 2-amino-4-nitrophenol in corn oil by gavage for 11 or 12 doses over 15 days. Rats and mice were observed twice per day and were weighed on day 1 and once per week thereafter. A necropsy was performed on all animals. Ten percent of the animals were examined histologically. Details of animal maintenance 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-4-nitrophenol and to determine the doses to be used in the 2-year studies.

Four-week-old male and female F344/N rats and 5- to 6-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 3 weeks, distributed to weight classes, and then assigned to cages according to a table of random numbers. The cages were assigned to dosed and vehicle control groups according to a second table of random numbers. Groups of 10 rats and 10 mice of each sex were administered 0, 62.5, 125, 250, 500, or 1,000 mg/kg 2-amino-4-nitrophenol 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; individual animal weights were recorded once per week. Moribund animals and those animals surviving to the end of the 13-week studies were humanely killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Liver weight to body weight ratios were determined at necropsy. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats and 50 mice of each sex were administered 0, 125, or 250 mg/kg 2-amino-4-nitrophenol in corn oil by gavage, 5 days per week for 103 weeks.

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 Harlan Industries (rats) or Charles River Breeding Laboratories (mice) under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facilities 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 16 days (rats) or 15 days (mice). Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were 45 days old and the mice 55 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-4-NITROPHENOL

Fifteen-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		
0, 313, 625, 1,250, 2,500, or 5,000 mg/kg 2-amino-4-nitrophenol in corn oil by gavage; dose vol--10 ml/kg	0, 62.5, 125, 250, 500, or 1,000 mg/kg 2-amino-4-nitrophenol in corn oil by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	0, 125, or 250 mg/kg 2-amino-4-nitrophenol in corn oil by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg
Date of First Dose		
7/30/79	4/28/80	Rats--1/8/81; mice--1/22/81
Date of Last Dose		
8/13/79	7/25/80	Rats--12/31/82; mice--1/14/83
Duration of Dosing		
5 d/wk (11 or 12 doses over 15 d)	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed 1 × wk	Same as 15-d studies	Observed 2 × d; weighed by cage 1 × wk for 12 (rats) or 13 (mice) wk and 1 × mo thereafter
Necropsy and Histologic Examination		
Necropsy performed on all animals; tissues from 10% of the animals examined histologically	Necropsy performed on all animals; histologic exam performed on animals dying before the end of the studies, animals with gross lesions, and all vehicle control and high dose animals; femur and kidney examined in all rats; kidney examined in all mice; liver weighed at necropsy	Necropsy performed on all animals; histologic exams performed on all male rats, vehicle control and high dose female rats, and male and female mice; liver examined in low dose female rats; liver and pancreas examined in low dose mice
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)	Rats--Harlan Industries (Indianapolis, IN); mice--Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory		
Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories
Method of Animal Identification		
Rats--tail mark; mice--ear punch	Toe clip	Toe clip and ear notch
Time Held Before Study		
19 d	20 d	Rats--16 d; mice--15 d
Age When Placed on Study		
7 wk	Rats--7 wk; mice--8-9 wk	Rats--6 wk; mice--7-8 wk
Age When Killed		
9 wk	Rats--20 wk; mice--22-23 wk	Rats--111 wk; mice--112-113 wk

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 2-AMINO-4-NITROPHENOL (Continued)

Fifteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Necropsy Dates		
8/15/79	Rats--7/28/80-7/29/80; mice--7/28/80-7/30/80	Rats--1/10/83-1/13/83; mice--1/24/83-1/27/83
Method of Animal Distribution		
Animals distributed to weight classes and assigned to groups according to two tables of random numbers	Animals distributed to weight classes and assigned to groups according to two tables of random numbers	Animals distributed to weight classes and assigned to groups according to two tables of random numbers
Feed		
Rodent Laboratory Chow 5001® meal (Ralston Purina Co., St. Louis, MO); available ad libitum	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding		
Aspen wood chips	Same as 15-d studies	Heat-treated aspen wood shavings (Minnesota Sawdust and Shavings Co., Anoka, MN)
Water		
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 15-d studies	Same as 15-d studies; water softened with sodium zeolite to < 1 grain/gal and filtered
Cages		
Polycarbonate (Lab Products, Inc.)	Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as 13-wk studies
Cage Filters		
		Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)
Animals per Cage		
5	5	5
Other Chemicals on Study in the Same Room		
		None
Animal Room Environment		
Temp--20.0°-21.1° C; hum--50%-70%; light 12 h/d	Temp--21.1°-24.4° C; hum--40%-60%; light 12 h/d	Temp--21.6°-26.7° C; hum--30%-80%; fluorescent light 12 h/d; 5-13 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.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded at least once per month. Body weights were recorded once per week for the first 12 (rats) or 13 (mice) 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 pathology 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: life table tests, incidental tumor analysis, and Fisher exact/Cochran-Armitage trend analyses. 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 administration of the study compound 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. The procedures described below also were used to evaluate selected nonneoplastic lesions.

Life Table Analyses--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 (1959) 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 Analyses--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.)

Fisher Exact/Cochran-Armitage Trend Analyses--In addition to survival-adjusted methods, 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 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

FIFTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FIFTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

FIFTEEN-DAY STUDIES

All rats that received 2,500 or 5,000 mg/kg died within 3 days, and only 1/5 males and no females that received 1,250 survived for 15 days (Table 6). Final mean body weights of rats that received 313 or 625 mg/kg were comparable to those of vehicle controls. Beginning with the first day of compound administration, diarrhea was observed in all groups of chemically exposed rats except those that received 313 mg/kg. Gross lesions observed at necropsy in chemically exposed rats were not clearly related to 2-amino-4-nitrophenol exposure.

THIRTEEN-WEEK STUDIES

All rats that received 1,000 mg/kg 2-amino-4-nitrophenol and 2/10 males and 2/10 females that received 500 mg/kg died during the first week of the studies (Table 7). All other early deaths were related to gavage trauma. Final mean body weights of chemically exposed rats were comparable to those of vehicle controls with the exception of males that received 500 mg/kg. Compound-related clinical signs included diarrhea and lethargy for rats that received 500 or 1,000 mg/kg.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FIFTEEN-DAY GAVAGE STUDIES OF 2-AMINO-4-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	128 ± 4	193 ± 3	+65 ± 2	--
313	5/5	136 ± 3	202 ± 5	+66 ± 4	105
625	5/5	148 ± 10	197 ± 13	+49 ± 4	102
1,250	(d) 1/5	130 ± 3	165	+39	85
2,500	(e) 0/5	136 ± 5	(f)	(f)	(f)
5,000	(g) 0/5	149 ± 3	(f)	(f)	(f)
FEMALE					
0	(h) 4/5	109 ± 4	147 ± 4	+37 ± 4	--
313	5/5	113 ± 6	141 ± 5	+28 ± 3	96
625	5/5	114 ± 4	145 ± 3	+31 ± 3	99
1,250	(i) 0/5	112 ± 4	(f)	(f)	(f)
2,500	(j) 0/5	116 ± 4	(f)	(f)	(f)
5,000	(j) 0/5	105 ± 3	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are 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: 2,5,10,12
(e) Day of death: 2,2,2,2,3
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: 1,2,2,2,3
(h) Day of death: 9
(i) Day of death: 2,2,4,5,5
(j) Day of death: 1,1,1,1,2

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-4-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	166 ± 3	357 ± 7	+191 ± 5	--
62.5	10/10	167 ± 3	370 ± 4	+203 ± 5	104
125	(d) 9/10	163 ± 3	367 ± 6	+204 ± 5	103
250	10/10	159 ± 4	351 ± 7	+192 ± 6	98
500	(e) 8/10	161 ± 3	322 ± 4	+162 ± 2	90
1,000	(e) 0/10	169 ± 3	(f)	(f)	(f)
FEMALE					
0	10/10	124 ± 2	198 ± 4	+74 ± 3	--
62.5	10/10	124 ± 2	197 ± 3	+73 ± 4	99
125	(d) 8/10	121 ± 2	201 ± 3	+80 ± 3	102
250	(d) 9/10	126 ± 2	208 ± 3	+82 ± 1	105
500	(e) 8/10	128 ± 1	208 ± 4	+81 ± 3	105
1,000	(e) 0/10	122 ± 2	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are 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) Deaths gavage related
(e) Week of death: all 1
(f) No data are reported due to the 100% mortality in this group.

Liver weight to body weight ratios of rats that received 500 mg/kg were significantly greater than those of vehicle controls; however, microscopic examination of the liver did not reveal any histopathologic changes attributable to chemical exposure (Table 8). Mild to severe mineralization of the renal cortex and mild to severe degeneration of the renal tubular epithelium were observed in male rats that received 500 or 1,000 mg/kg and in females that received 1,000 mg/kg (Table 9). Histopathologic lesions of the kidney resulting from exposure to 2-amino-4-nitrophenol were not found in rats that received 250 mg/kg. Osteomalacia of moderate severity was found in 1/10 males that received 500 mg/kg and 2/10 males that received 1,000 mg/kg; inflammation of the nonglandular portion of the stomach was observed in 2/10 males and 2/10 females that received 1,000 mg/kg.

Dose Selection Rationale: Doses of 125 and 250 mg/kg 2-amino-4-nitrophenol were selected for the 2-year studies in rats. Doses of 500 or 1,000 mg/kg were associated with adverse clinical signs, reduced survival, and compound-related toxicity of the kidney and were considered inappropriate for a 2-year study.

TABLE 8. ANALYSIS OF LIVER WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-4-NITROPHENOL (a)

Dose (mg/kg)	Number Examined	Final Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Final Body Weight (mg/g)
MALE				
0	10	357 ± 6.7	14,222 ± 795	39.7 ± 1.97
62.5	10	370 ± 4.0	15,508 ± 468	41.9 ± 1.05
125	9	367 ± 6.2	14,266 ± 525	38.8 ± 0.84
250	10	351 ± 6.6	14,904 ± 605	42.4 ± 1.54
500	8	(b) 322 ± 4.0	14,501 ± 295	(c) 45.0 ± 0.91
FEMALE				
0	10	198 ± 3.5	6,918 ± 255	34.9 ± 1.18
62.5	10	197 ± 3.4	6,818 ± 164	34.6 ± 0.63
125	8	201 ± 3.0	7,439 ± 240	36.9 ± 0.82
250	9	208 ± 3.3	(c) 7,738 ± 238	37.1 ± 0.78
500	8	208 ± 3.6	(b) 7,985 ± 212	(c) 38.4 ± 0.54

(a) Mean ± standard error; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) $P<0.01$
(c) $P<0.05$

TABLE 9. INCIDENCE OF SELECTED LESIONS IN RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-4-NITROPHENOL

Site/ Lesion	Male (mg/kg)				Female (mg/kg)		
	0	250	500	1,000	0	500	1,000
No. examined	10	10	9	10	10	10	10
Kidney							
Necrosis	0	0	4	10	0	0	7
Mineralization	0	0	4	10	0	0	4
Bone							
Osteomalacia	0	0	1	2	0	0	0
Stomach							
Inflammation/necrosis	0	0	0	2	0	0	2

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of male rats that received 250 mg/kg were never more than 10% lower than that of vehicle controls, and mean body weights of male rats that received 125 mg/kg were never more than 6% lower than that of vehicle controls (Table 10 and Figure 3). Mean body weights of chemically exposed female rats were comparable to those of vehicle controls throughout the studies. Soft stools and occasional diarrhea were observed in chemically exposed rats starting 6 months after the beginning of exposure to 2-amino-4-nitrophenol.

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-4-NITROPHENOL

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	125 mg/kg Av. Wt. (grams)	125 mg/kg Wt. (percent of veh. controls)	125 mg/kg No. of Survivors	250 mg/kg Av. Wt. (grams)	250 mg/kg Wt. (percent of veh. controls)	250 mg/kg No. of Survivors
MALE								
0	130	50	130	100	50	129	99	50
1	158	50	152	96	50	154	97	50
2	187	50	182	97	50	175	94	49
3	208	50	201	97	49	196	94	48
4	224	50	219	98	49	221	99	48
5	240	50	231	96	49	237	99	48
6	256	50	248	97	49	249	97	48
7	272	50	265	97	49	267	98	48
8	288	50	276	96	49	276	96	48
9	302	50	289	96	49	288	95	48
10	312	50	298	96	49	298	96	48
11	322	49	306	95	49	303	94	48
12	333	49	318	95	49	315	95	48
17	367	49	352	96	49	346	94	48
22	387	49	372	96	49	362	94	47
26	406	49	387	95	49	373	92	47
31	429	49	410	96	49	392	91	47
35	450	49	430	96	49	407	90	47
38	458	49	439	96	49	420	92	46
43	471	49	454	96	49	431	92	46
48	482	49	464	96	49	440	91	44
52	486	49	469	97	49	445	92	44
56	491	49	477	97	49	452	92	44
60	496	49	480	97	46	463	93	44
64	499	49	479	96	45	461	92	44
69	500	49	484	97	43	465	93	43
73	507	49	489	96	42	469	93	42
78	505	49	480	95	40	466	92	41
82	502	48	477	95	38	464	92	40
86	501	46	475	95	38	465	93	38
91	497	43	471	95	33	458	92	31
95	487	42	465	95	30	451	93	27
99	478	40	461	96	27	447	94	20
104	461	32	432	94	25	444	96	10
FEMALE								
0	105	50	104	99	50	103	98	50
1	117	50	115	98	50	117	100	50
2	132	50	133	101	50	131	99	50
3	141	50	141	100	49	137	97	50
4	149	50	154	103	49	151	101	49
5	159	49	155	97	49	155	97	49
6	160	49	161	101	49	158	99	49
7	167	49	172	103	49	166	99	49
8	171	48	171	100	49	168	98	49
9	177	48	177	100	46	176	99	48
10	179	47	178	99	46	177	99	48
11	183	46	183	100	46	182	99	48
12	186	46	186	100	46	187	101	48
17	200	46	200	100	45	198	99	48
22	210	46	209	100	43	209	100	47
26	214	46	216	101	43	215	100	46
31	227	46	229	101	43	224	99	43
35	234	46	237	101	43	232	99	43
38	239	46	242	101	43	237	99	43
43	247	46	249	101	43	244	99	43
48	255	46	255	100	43	249	98	43
52	262	46	263	100	43	253	97	43
56	275	44	273	99	43	261	95	43
60	287	44	285	99	42	273	95	43
64	297	44	295	99	41	280	94	43
69	305	42	306	100	39	294	96	43
73	313	42	317	101	39	300	96	43
78	319	42	319	100	39	308	97	42
82	324	42	330	102	37	313	97	40
86	328	42	335	102	36	320	98	39
91	331	38	335	101	33	322	97	37
95	334	33	336	101	31	326	98	33
99	332	31	335	101	29	328	99	32
104	326	26	338	104	27	326	100	31

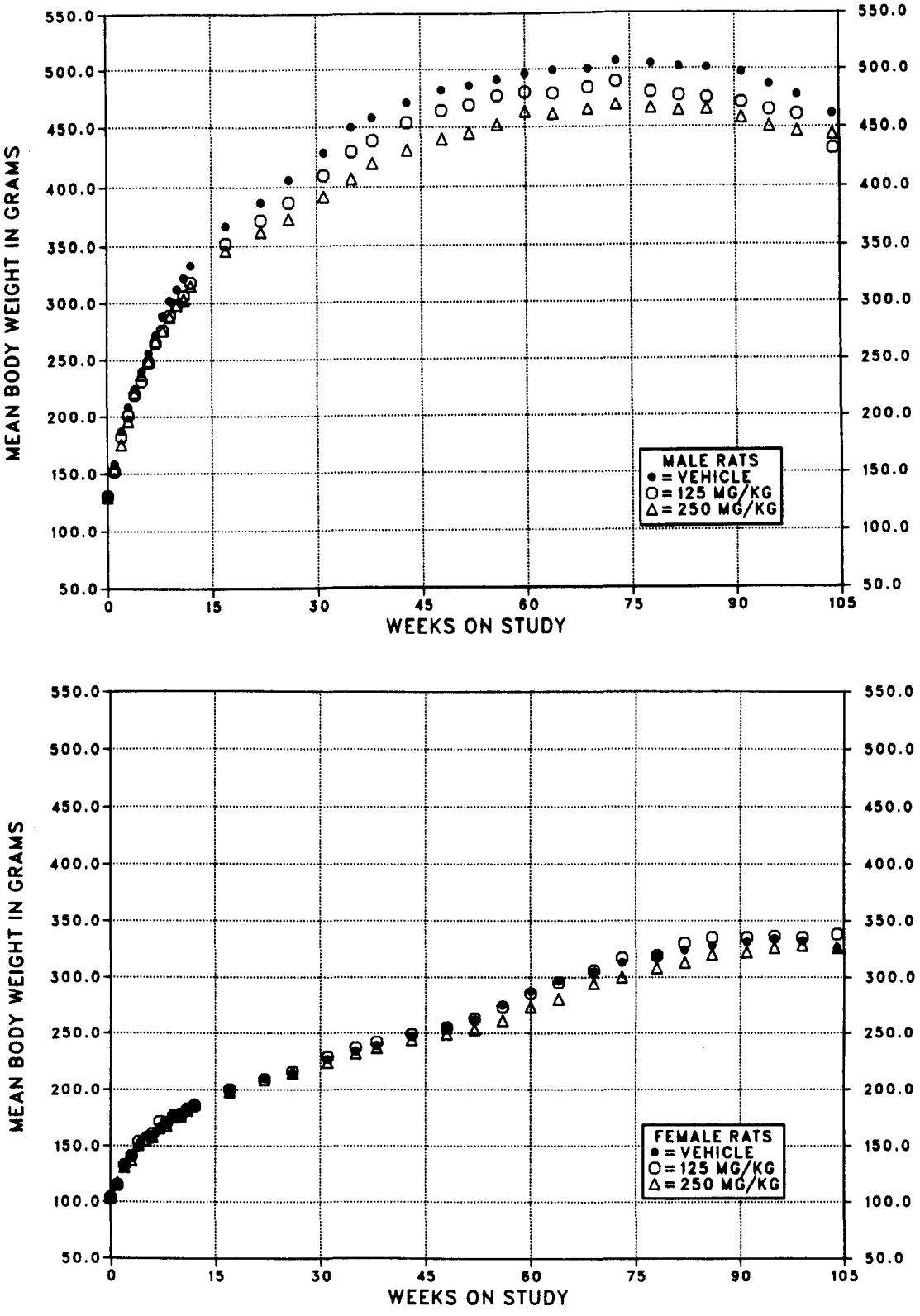


FIGURE 3. GROWTH CURVES FOR RATS ADMINISTERED 2-AMINO-4-NITROPHENOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered 2-amino-4-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 male rats exposed at 250 mg/kg was significantly lower than that of vehicle controls after week 89. Survival of chemically exposed female rats was comparable to survival of the vehicle controls throughout the study.

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 kidney, liver, preputial gland, clitoral gland, testis, tongue, parathyroid, bone, heart, multiple organs, and gastrointestinal tract.

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-4-NITROPHENOL

	Vehicle Control	125 mg/kg	250 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	17	23	35
Accidentally killed	1	3	5
Killed at termination	32	24	10
Survival P values (c)	<0.001	0.108	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	25	18	15
Accidentally killed	0	5	4
Killed at termination	24	27	31
Died during termination period	1	0	0
Survival P values (c)	0.135	0.525	0.154

(a) Terminal-kill period: week 105
(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.

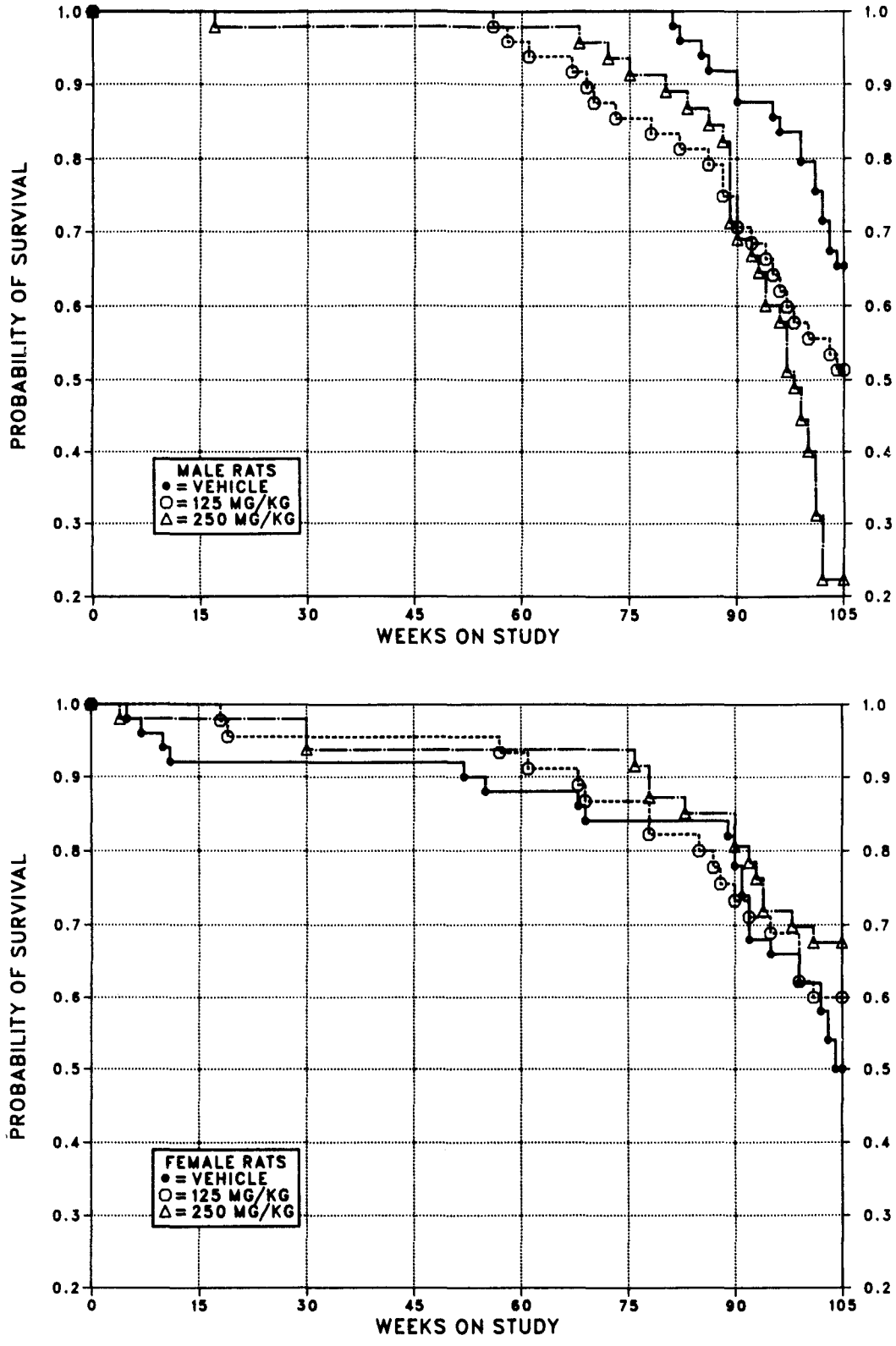


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED 2-AMINO-4-NITROPHENOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Kidney: Chronic nephropathy was present in nearly all chemically exposed male rats (Table 12). This spontaneous disease is characterized by varying degrees of tubular degeneration with atrophy of the epithelium and dilatation of the tubules, regeneration of tubular epithelium, thickening of the tubular basement membrane, interstitial fibrosis, chronic inflammation, and glomerulosclerosis. The severity of nephropathy in each rat was judged to be minimal, mild, moderate, or marked; the severity of nephropathy in chemically exposed male rats was greater than that observed in vehicle controls.

Hyperplasia of the renal tubular epithelium was observed in 1/50 vehicle control, 4/48 low dose, and 5/50 high dose male rats; renal cortical (tubular cell) adenomas were observed in 1/48 low dose and 3/50 high dose male rats (Table 13). Because of the reduced survival in the 250 mg/kg group, a direct comparison of the overall incidence of renal cortical adenomas may be misleading. Among male rats surviving until week 100 (when the first kidney tumor was observed), 3/20 animals in the 250 mg/kg group were found to have renal cortical adenomas compared with 0/39 vehicle controls. This difference is statistically significant (P = 0.035, Fisher exact test).

Hyperplasia and adenomas are part of a morphologic continuum and are distinguished largely on the basis of size, degree of cellular atypia, and loss of basement membrane dependency. The foci of tubular cell hyperplasia consisted of one to several cross sections of a single tubule filled with polygonal epithelial cells. This proliferative lesion was distinguished from tubular epithelial regeneration, a normal component of nephropathy, by the stratification of cells and loss of basement membrane dependency. The cortical adenomas consisted of solid masses of epithelial cells that lacked tubular arrangement or epithelial cells arranged in a complex papillary pattern. The incidence of epithelial hyperplasia of the renal pelvis was increased in exposed male rats (5/50; 17/48; 16/50).

TABLE 12. INCIDENCE AND SEVERITY OF NEPHROPATHY IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

Severity (a)	Vehicle Control	125 mg/kg	250 mg/kg
Absent	1/50	1/48	4/50
Minimal	0/50	0/48	0/50
Mild	20/50	11/48	5/50
Moderate	20/50	9/48	2/50
Marked	8/50	27/48	38/50

(a) The grade of severity is missing for one vehicle control and one high dose male rat.

TABLE 13. ANALYSIS OF RENAL CORTICAL LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (a)

	Vehicle Control	125 mg/kg	250 mg/kg
Tubular Cell Hyperplasia			
Overall Rates	1/50 (2%)	4/48 (8%)	5/50 (10%)
Adenoma (b)			
Overall Rates	0/50 (0%)	1/48 (2%)	3/50 (6%)
Adjusted Rates	0.0%	4.0%	16.7%
Terminal Rates	0/32 (0%)	0/24 (0%)	0/10 (0%)
Week of First Observation		104	100
Life Table Tests	P = 0.009	P = 0.445	P = 0.025
Incidental Tumor Tests	P = 0.170	P = 0.436	P = 0.240

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Historical incidence of tubular cell adenomas or adenocarcinomas (combined) at study laboratory: 0/149; historical incidence in NTP studies (mean ± SD): 9/1,695 (0.5% ± 0.9%)

Liver: Neoplastic nodules or hepatocellular carcinomas (combined) in male rats occurred with a significant positive trend; the incidence in the high dose group was significantly greater than that in the vehicle controls by the life table test (Table 14). These tumors were not considered to be life threatening in the present study, and the incidence in the high dose group was not significantly different from the vehicle control incidence by the incidental tumor test, the appropriate test of significance for nonfatal tumors. Two of the three neoplasms were neoplastic nodules, and there were no compound-related nonneoplastic lesions present in the liver of chemically exposed rats. Therefore, the presence of these neoplasms in high dose male rats was not considered to be related to chemical exposure.

Preputial Gland: The incidence of adenomas or carcinomas (combined) in male rats that received 125 mg/kg was significantly greater than that in vehicle controls (Table 15); the incidence in male rats that received 250 mg/kg was the same as that in vehicle controls.

TABLE 14. ANALYSIS OF LIVER TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	125 mg/kg	250 mg/kg
Neoplastic Nodule			
Overall Rates	0/50 (0%)	0/48 (0%)	2/50 (4%)
Hepatocellular Carcinoma			
Overall Rates	0/50 (0%)	0/48 (0%)	1/50 (2%)
Neoplastic Nodule or Hepatocellular Carcinoma (a)			
Overall Rates	0/50 (0%)	0/48 (0%)	3/50 (6%)
Adjusted Rates	0.0%	0.0%	16.4%
Terminal Rates	0/32 (0%)	0/24 (0%)	1/10 (10%)
Week of First Observation			94
Life Table Tests	P=0.011	(b)	P=0.035
Incidental Tumor Tests	P=0.046	(b)	P=0.109

(a) Historical incidence at study laboratory (mean ± SD): 3/149 (2% ± 3%); historical incidence in NTP studies: 58/1,697 (3% ± 3%)
(b) No P value is reported because no tumors were observed in the 125 mg/kg and vehicle control groups.

TABLE 15. ANALYSIS OF PREPUTIAL GLAND LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	125 mg/kg	250 mg/kg
Hyperplasia			
Overall Rates	0/50 (0%)	1/48 (2%)	2/50 (4%)
Adenoma			
Overall Rates	1/50 (2%)	5/48 (10%)	2/50 (4%)
Adjusted Rates	3.1%	17.3%	16.4%
Terminal Rates	1/32 (3%)	3/24 (13%)	1/10 (10%)
Week of First Observation	105	82	102
Life Table Tests	P=0.104	P=0.056	P=0.157
Incidental Tumor Tests	P=0.233	P=0.081	P=0.310
Carcinoma			
Overall Rates	2/50 (4%)	5/48 (10%)	1/50 (2%)
Adjusted Rates	6.3%	19.0%	2.4%
Terminal Rates	2/32 (6%)	3/24 (13%)	0/10 (0%)
Week of First Observation	105	98	80
Life Table Tests	P=0.357	P=0.116	P=0.711
Incidental Tumor Tests	P=0.592	P=0.115	P=0.689N
Adenoma or Carcinoma (a)			
Overall Rates	3/50 (6%)	10/48 (21%)	3/50 (6%)
Adjusted Rates	9.4%	34.4%	18.5%
Terminal Rates	3/32 (9%)	6/24 (25%)	1/10 (10%)
Week of First Observation	105	82	80
Life Table Tests	P=0.088	P=0.010	P=0.220
Incidental Tumor Tests	P=0.297	P=0.014	P=0.405

(a) Historical incidence at study laboratory (mean ± SD): 4/149 (3% ± 3%); historical incidence in NTP studies: 72/1,699 (4% ± 4%)

Clitoral Gland: Adenomas and adenomas, carcinomas, or squamous cell carcinomas (combined) in female rats occurred with significant negative trends; the incidences in the high dose group were significantly lower than those in the vehicle controls (Table 16).

Testis: Although the overall tumor incidences were similar, survival-adjusted analyses indicated that interstitial cell tumors in male rats occurred with a significant positive trend; the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 17). Testicular interstitial cell tumors are common in aging male F344 rats and are present at very high incidence in control animals. These neoplasms are generally not life threatening at 24 months of age, and most male rats (chemically exposed as well as controls) will develop this tumor during the latter part of a 2-year study. The marginal difference in the incidences of this neoplasm between chemically exposed and vehicle control male rats was not considered to be related to chemical exposure.

TABLE 16. ANALYSIS OF CLITORAL GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	125 mg/kg	250 mg/kg
Hyperplasia			
Overall Rates	1/50 (2%)	1/50 (2%)	0/49 (0%)
Adenoma			
Overall Rates	7/50 (14%)	3/50 (6%)	1/49 (2%)
Adjusted Rates	23.6%	9.6%	3.2%
Terminal Rates	5/25 (20%)	2/27 (7%)	1/31 (3%)
Week of First Observation	55	61	105
Life Table Tests	P=0.011N	P=0.151N	P=0.020N
Incidental Tumor Tests	P=0.011N	P=0.104N	P=0.025N
Carcinoma			
Overall Rates	2/50 (4%)	2/50 (4%)	0/49 (0%)
Squamous Cell Carcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	0/49 (0%)
Carcinoma or Squamous Cell Carcinoma			
Overall Rates	2/50 (4%)	3/50 (6%)	0/49 (0%)
Adenoma, Carcinoma, or Squamous Cell Carcinoma (a)			
Overall Rates	9/50 (18%)	6/50 (12%)	1/49 (2%)
Adjusted Rates	31.3%	20.5%	3.2%
Terminal Rates	7/25 (28%)	5/27 (19%)	1/31 (3%)
Week of First Observation	55	61	105
Life Table Tests	P=0.003N	P=0.256N	P=0.004N
Incidental Tumor Tests	P=0.003N	P=0.200N	P=0.006N

(a) Historical incidence at study laboratory (mean ± SD): 16/150 (11% ± 6%); historical incidence in NTP studies: 66/1,700 (4% ± 4%)

TABLE 17. ANALYSIS OF TESTICULAR INTERSTITIAL CELL TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (a)

	Vehicle Control	125 mg/kg	250 mg/kg
Overall Rates	39/50 (78%)	39/48 (81%)	36/48 (75%)
Adjusted Rates	92.8%	95.1%	100.0%
Terminal Rates	29/32 (91%)	22/24 (92%)	10/10 (100%)
Week of First Observation	85	57	72
Life Table Tests	P<0.001	P=0.034	P<0.001
Incidental Tumor Tests	P=0.024	P=0.059	P=0.017

(a) Historical incidence at study laboratory (mean ± SD): 121/149 (81% ± 17%); historical incidence in NTP studies: 1,465/1,695 (86% ± 10%)

Tongue: Squamous cell papillomas were observed in three low dose female rats. The historical incidence of oral cavity squamous cell neoplasms in female corn oil vehicle control F344/N rats is 6/1,700 (0.35%). No squamous cell neoplasms were present in the oral cavity of high dose female rats or of any male rats. Therefore, the presence of these neoplasms in low dose female rats is not obviously related to chemical exposure.

Parathyroid, Bone, Heart, and Multiple Organs: Hyperplasia of the parathyroid gland was observed at increased incidences ($P<0.01$) in chemically exposed male rats (male: vehicle control, 0/39; 125 mg/kg group, 2/36; 250 mg/kg group, 9/39; female: none observed). Parathyroid hyperplasia frequently accompanies severe renal disease, and the increased incidence observed in the present study is a consequence of the increased severity of nephropathy in exposed male rats. The increase of fibrous osteodystrophy of bone and metastatic calcification of the heart and other organs observed in exposed animals are associated with the disruption of calcium homeostasis and phosphate balance which accompanies severe renal disease (Table 18).

Gastrointestinal Tract: Minor erosive or ulcerative lesions were present in the gastrointestinal tract of chemically exposed rats (Table 19). The incidences of pigmentation of the small and large intestines were increased particularly in the groups that received 250 mg/kg. The pigment was often present within macrophages in the lamina propria of the intestine. Similar pigmentation was not present in the gastrointestinal tract of vehicle controls. A carcinoma of the colon was observed in one high dose male rat that received 250 mg/kg; however, no other neoplasms were found in the gastrointestinal tract of rats.

TABLE 18. NONNEOPLASTIC LESIONS ASSOCIATED WITH RENAL DISEASE AND HYPERPARATHYROIDISM IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

Lesion	Vehicle Control	125 mg/kg	250 mg/kg
Fibrous osteodystrophy	2/50	7/48	24/50
Metastatic calcification of the heart	0/50	4/48	8/49
Metastatic calcification of multiple organs	0/50	2/48	9/50

TABLE 19. NUMBER OF RATS WITH PIGMENTATION, EROSION, OR ULCERS OF THE GASTRO-INTESTINAL TRACT IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-4-NITROPHENOL

Site/Lesion	Vehicle Control	125 mg/kg	250 mg/kg
MALE			
No. examined microscopically	(a) 50	48	50
Glandular stomach			
Erosion	0	0	2
Forestomach			
Ulcer, NOS	0	1	5
Ulcer, acute	1	0	2
Ulcer, chronic	0	3	0
Duodenum			
Pigmentation	0	38	39
Ulcer, NOS	0	0	1
Ulcer, acute	0	1	0
Erosion	0	0	2
Ileum			
Pigmentation	0	0	31
Cecum			
Pigmentation	0	3	32
Ulcer, NOS	0	0	1
Ulcer, acute	0	0	2
Erosion	0	0	1
Colon			
Pigmentation	0	14	29
FEMALE			
No. examined microscopically	(a) 50	19	49
Glandular stomach			
Erosions	0	0	0
Forestomach			
Ulcer, NOS	1	1	0
Ulcer, acute	0	0	1
Ulcer, chronic	0	0	0
Duodenum			
Pigmentation	0	3	42
Ulcer, NOS	0	0	0
Ulcer, acute	0	0	0
Erosion	0	0	0
Ileum			
Pigmentation	0	0	19
Cecum			
Pigmentation	0	2	35
Ulcer, NOS	0	0	0
Ulcer, acute	0	0	0
Erosion	0	0	0
Colon	0	5	34

(a) Forty-nine examined for cecum and colon

FIFTEEN-DAY STUDIES

All mice that received 2,500 or 5,000 mg/kg and all females and 2/5 males that received 1,250 mg/kg died during the first 5 days of the studies (Table 20). Final mean body weights of exposed mice surviving to the end of the studies were comparable to those of vehicle controls.

TABLE 20. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FIFTEEN-DAY GAVAGE STUDIES OF 2-AMINO-4-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	27.6 ± 0.8	30.2 ± 1.0	+2.6 ± 0.4	--
313	(d) 3/5	25.2 ± 1.3	27.3 ± 2.2	+2.1 ± 0.7	90.4
625	(d) 4/5	25.8 ± 0.6	28.6 ± 0.4	+2.9 ± 0.5	94.7
1,250	(e) 3/5	26.1 ± 0.8	28.9 ± 1.6	+3.0 ± 0.3	95.7
2,500	(f) 0/5	26.2 ± 0.4	(g)	(g)	(g)
5,000	(h) 0/5	25.5 ± 1.0	(g)	(g)	(g)
FEMALE					
0	5/5	19.4 ± 0.5	20.4 ± 0.6	+1.0 ± 0.2	--
313	(i) 4/5	22.3 ± 0.7	23.6 ± 1.0	+1.0 ± 0.5	115.7
625	5/5	21.6 ± 0.4	22.0 ± 0.3	+0.4 ± 0.4	107.8
1,250	(j) 0/5	19.7 ± 0.5	(g)	(g)	(g)
2,500	(h) 0/5	22.1 ± 0.6	(g)	(g)	(g)
5,000	(h) 0/5	20.9 ± 0.1	(g)	(g)	(g)

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are 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) Deaths gavage related
(e) Day of death: 1,5
(f) Day of death: 1,1,1,2,2
(g) No data are reported due to the 100% mortality in this group.
(h) Day of death: all 1 (one male death gavage related)
(i) Day of death: 4
(j) Day of death: 1,1,1,1,5

THIRTEEN-WEEK STUDIES

Survival of male and female mice that received 1,000 mg/kg and females that received 500 mg/kg was reduced compared with that of vehicle controls (Table 21). Final mean body weights of chemically exposed mice were comparable to those of vehicle controls. No compound-related clinical signs were observed during the study. Liver weight to body weight ratios of males that received 1,000 mg/kg and females that received 62.5 mg/kg were significantly greater than those of vehicle controls (Table 22); however, microscopic examination did not reveal any histopathologic changes of the liver attributable to chemical exposure. Degeneration and necrosis of the renal tubular epithelium with some indication of regeneration were observed in 5/10 males and 3/10 females that received 1,000 mg/kg; there were no compound-related histopathologic lesions of the kidney in mice that received 500 mg/kg.

Dose Selection Rationale: Doses of 125 and 250 mg/kg 2-amino-4-nitrophenol were selected for the 2-year mouse studies. Exposure at 500 or 1,000 mg/kg for 13 weeks was associated with reduced survival and compound-related nephrotoxicity; these doses were considered inappropriate for a 2-year study.

TABLE 21. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-4-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	23.1 ± 0.3	36.9 ± 0.9	+13.8 ± 0.7	--
62.5	10/10	23.0 ± 0.3	37.7 ± 0.7	+14.7 ± 0.6	102.2
125	(d) 9/10	23.6 ± 0.2	38.1 ± 0.9	+14.5 ± 1.0	103.3
250	10/10	24.1 ± 0.3	39.2 ± 0.9	+15.1 ± 0.7	106.2
500	10/10	23.2 ± 0.3	39.4 ± 0.8	+16.2 ± 0.6	106.8
1,000	(e) 5/10	23.6 ± 0.4	35.8 ± 0.5	+12.3 ± 0.7	97.0
FEMALE					
0	10/10	18.8 ± 0.4	26.0 ± 0.6	+7.2 ± 0.6	--
62.5	10/10	18.2 ± 0.4	26.4 ± 0.9	+8.2 ± 0.6	101.5
125	10/10	17.7 ± 0.3	24.8 ± 0.6	+7.1 ± 0.6	95.4
250	10/10	18.7 ± 0.3	25.9 ± 0.6	+7.2 ± 0.5	99.6
500	(f) 6/10	18.4 ± 0.4	26.3 ± 0.9	+7.8 ± 0.8	101.2
1,000	(g) 1/10	18.3 ± 0.5	27.1	+6.6	104.2

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are 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: 8,8,8,9,10
(f) Week of death: 1,8,11 (one death gavage related)
(g) Week of death: 4,5,9,9,9,9,11,11,11

TABLE 22. ANALYSIS OF LIVER WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 2-AMINO-4-NITROPHENOL (a)

Dose (mg/kg)	Number Examined	Final Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Final Body Weight (mg/g)
MALE				
0	10	36.9 ± 0.88	1,855 ± 86	50.1 ± 1.54
62.5	10	37.7 ± 0.67	1,944 ± 76	51.5 ± 1.79
125	9	38.1 ± 0.92	1,849 ± 37	48.7 ± 1.33
250	10	39.2 ± 0.85	1,873 ± 56	47.7 ± 0.93
500	10	39.4 ± 0.79	2,085 ± 37	53.2 ± 1.61
1,000	5	35.8 ± 0.53	(b) 2,268 ± 152	(b) 63.5 ± 4.68
FEMALE				
0	10	26.0 ± 0.57	1,182 ± 48	45.4 ± 1.14
62.5	10	26.4 ± 0.89	(c) 1,384 ± 79	(c) 52.6 ± 3.07
125	10	24.8 ± 0.58	1,235 ± 43	49.8 ± 1.39
250	10	25.9 ± 0.61	1,291 ± 28	50.1 ± 1.12
500	6	26.3 ± 0.91	1,350 ± 58	51.5 ± 2.22
1,000	(d) 1	27.1	1,280	47.2

(a) Mean ± standard error; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) $P<0.01$
(c) $P<0.05$
(d) Not included in statistical analysis

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of chemically exposed males and mean body weights of females that received 250 mg/kg were comparable to those of vehicle controls; the mean body weight of females that received 125 mg/kg was up to 17% greater than that of vehicle controls (Table 23 and Figure 5). No compound-related clinical signs were observed in mice during the 2-year studies.

TABLE 23. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-4-NITROPHENOL

Weeks on Study	Vehicle Control		125 mg/kg			250 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	24.1	50	24.6	102	50	24.5	102	50
1	26.5	50	26.6	100	50	25.6	97	50
2	27.7	50	27.8	100	50	27.6	100	50
3	28.6	50	28.7	100	50	28.7	100	50
4	30.2	50	30.3	100	50	30.1	100	50
5	31.3	50	31.5	101	50	31.0	99	50
6	31.8	50	31.6	99	50	31.8	100	50
7	32.6	50	31.8	98	50	32.8	101	49
8	33.5	50	33.0	99	50	33.4	100	49
9	34.2	50	34.0	99	50	34.2	100	49
10	35.1	50	34.6	99	50	34.4	98	49
11	36.2	50	35.3	98	50	35.0	97	49
12	36.7	50	35.8	98	50	36.1	98	49
13	37.0	50	36.2	98	50	36.4	98	49
17	39.0	50	38.7	99	50	37.7	97	49
22	41.5	50	40.8	98	50	40.2	97	48
26	43.5	50	43.3	100	50	42.5	98	48
30	44.3	50	45.1	102	50	44.6	101	48
35	44.8	50	44.6	100	50	44.3	99	48
39	45.9	47	45.7	100	50	45.1	98	48
43	45.6	47	45.8	100	50	45.5	100	48
47	46.1	47	45.8	99	50	46.4	101	48
52	46.9	46	45.7	97	50	46.1	98	48
54	47.2	46	46.5	99	50	46.8	99	48
58	48.0	46	47.5	99	50	47.6	99	48
62	48.5	44	47.6	98	48	48.2	99	45
67	48.0	44	47.9	100	46	47.9	100	45
71	48.0	41	47.6	99	45	47.0	98	44
76	48.0	40	48.5	101	44	48.5	101	42
80	48.1	38	48.0	100	42	47.6	99	40
84	47.8	37	49.0	103	39	47.5	99	37
89	48.2	35	49.3	102	35	47.8	99	35
93	48.0	34	48.3	101	33	46.8	98	33
97	46.1	33	48.5	105	32	45.7	99	30
102	45.9	28	47.3	103	29	45.4	99	25
FEMALE								
0	18.2	50	18.5	102	50	18.0	99	50
1	19.9	49	19.9	100	50	19.0	95	50
2	19.9	49	20.4	103	50	19.9	100	50
3	20.8	49	20.8	100	50	20.5	99	50
4	21.6	49	22.1	102	50	21.3	99	50
5	22.6	49	22.8	101	50	21.8	96	50
6	22.1	49	22.5	102	50	21.7	98	50
7	22.6	47	22.9	101	50	22.1	98	50
8	23.4	47	23.4	100	50	22.8	97	50
9	23.9	47	24.4	102	50	23.6	99	50
10	23.9	47	24.8	104	50	23.6	99	48
11	24.6	47	25.4	103	50	23.9	97	46
12	24.8	47	26.3	106	50	24.3	98	46
13	24.7	47	26.5	107	50	24.5	99	46
17	26.3	47	27.5	105	50	25.8	98	46
22	27.5	47	29.6	108	50	27.1	99	43
26	29.6	47	32.9	111	50	29.9	101	43
30	31.3	47	34.2	109	50	30.7	98	43
35	32.2	47	35.4	110	50	31.0	96	43
39	32.6	46	35.3	108	50	31.3	96	42
43	33.5	46	36.6	109	50	31.9	95	42
47	33.7	46	36.7	109	50	32.2	96	42
52	35.2	46	38.0	108	50	33.1	94	42
54	36.1	46	39.1	108	50	33.2	92	41
58	35.7	46	39.4	110	49	34.7	97	41
62	36.6	45	40.6	111	49	35.5	97	39
67	37.1	44	42.2	114	49	36.5	98	39
71	37.9	42	41.7	110	49	36.1	95	38
76	38.3	41	42.9	112	49	37.7	98	37
80	39.3	41	44.7	114	49	39.3	100	37
84	39.7	41	45.3	114	47	40.1	101	37
89	39.1	40	45.8	117	43	40.1	103	36
93	40.6	36	45.3	112	40	40.1	99	36
97	39.7	34	44.9	113	40	41.4	104	32
102	41.4	28	46.4	112	33	41.6	100	30

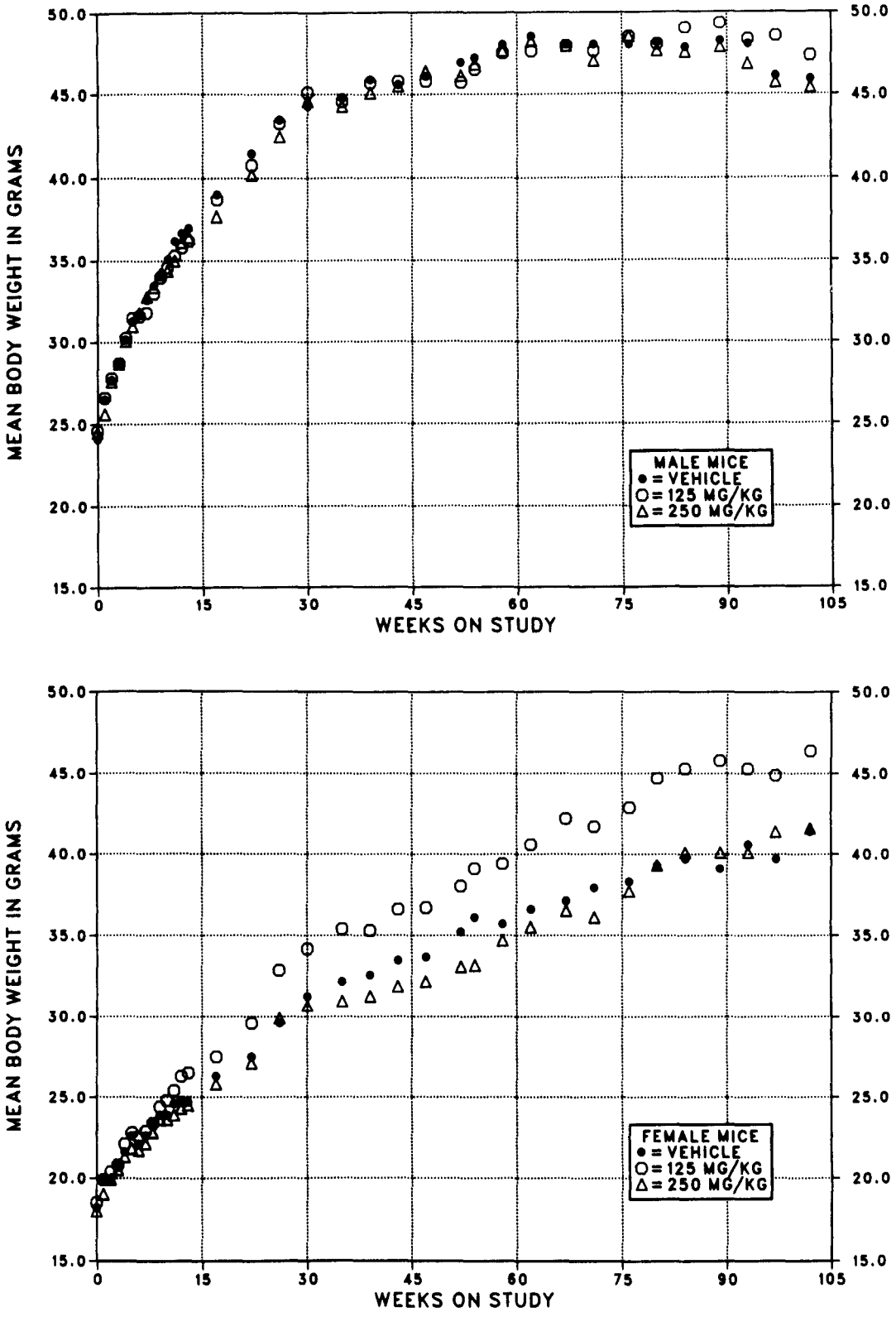


FIGURE 5. GROWTH CURVES FOR MICE ADMINISTERED 2-AMINO-4-NITROPHENOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered 2-amino-4-nitrophenol at the doses used in these studies and for vehicle controls are shown in Table 24 and in the Kaplan and Meier curves in Figure 6. No significant differences in survival were observed between chemically exposed and vehicle control animals. Three high dose female mice that died on the same day during week 19 exhibited chemical signs indicative of compound-related toxicity. The deaths of other female mice before week 60 did not appear to be compound related.

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 circulatory system, lung, kidney, and anterior pituitary gland.

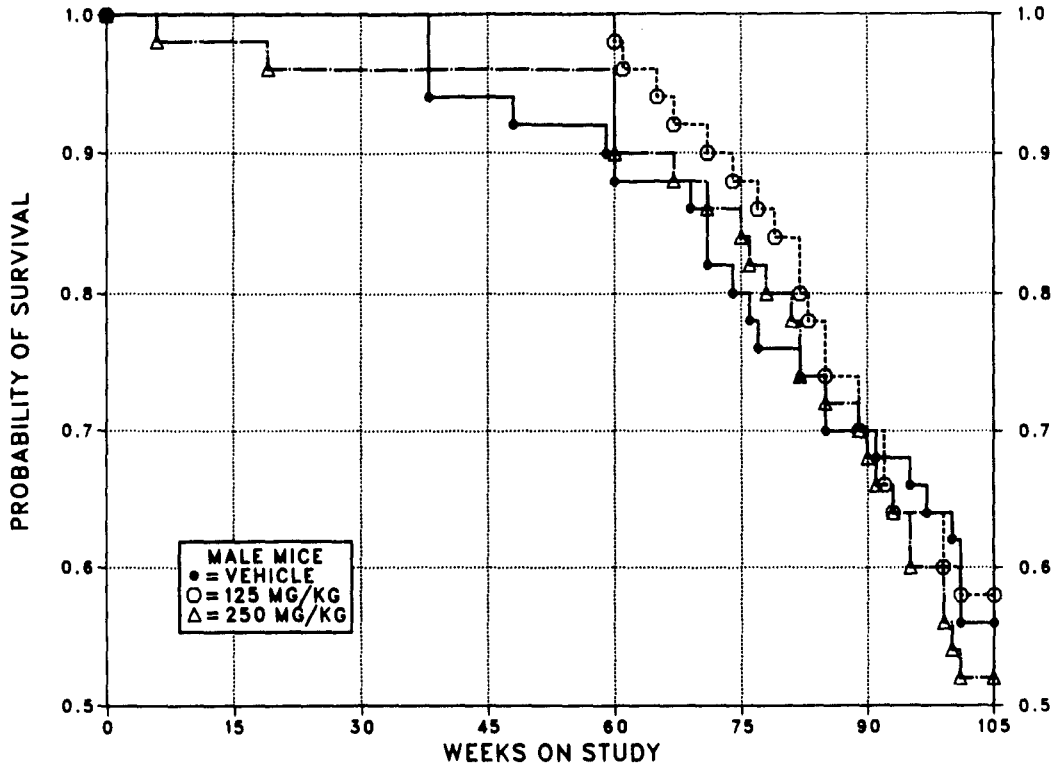
Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes). Historical incidences of tumors in corn oil vehicle control male mice are listed in Table C4. Findings on nonneoplastic lesions are summarized in Table C5.

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). Historical incidences of tumors in corn oil vehicle control female mice are listed in Table D4. Findings on nonneoplastic lesions are summarized in Table D5.

TABLE 24. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	125 mg/kg	250 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	22	21	27
Killed at termination	27	29	23
Died during termination period	1	0	0
Survival P values (c)	0.478	0.881	0.524
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	21	19	20
Accidentally killed	1	0	0
Killed at termination	28	31	30
Survival P values (c)	1.000	0.562	0.997

(a) Terminal-kill period: week 105
(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.



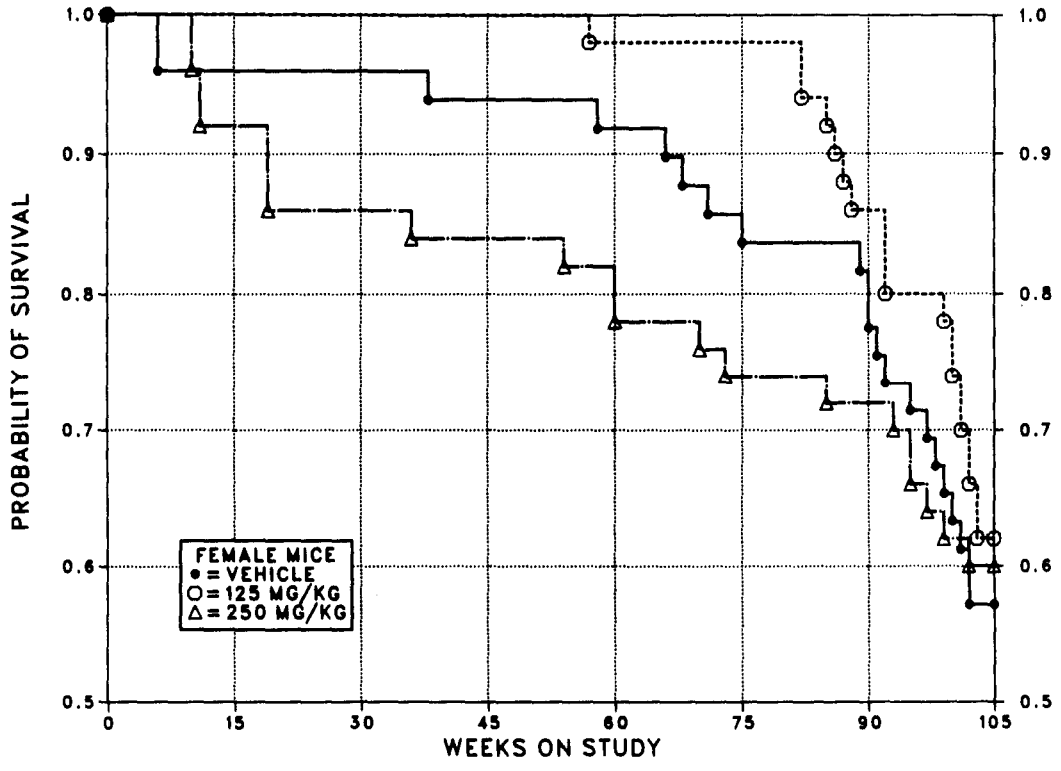


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED 2-AMINO-4-NITROPHENOL IN CORN OIL BY GAVAGE FOR TWO YEARS

Circulatory System: The incidence of hemangiomas or hemangiosarcomas (combined) in high dose male mice was significantly greater than that in vehicle controls (Table 25). Each tumor occurred at a different site (subcutaneous tissue, spleen, liver, lymph nodes, and pancreas).

Lung: Chronic bronchopneumonia and hyperplasia of the alveolar epithelium were observed at increased incidences in dosed male mice (chronic bronchopneumonia--male: vehicle control, 2/50; low dose, 10/32; high dose, 8/50; female: 4/49; 3/18; 1/49; alveolar epithelium hyperplasia--male: 1/50; 11/32; 3/50; female: 3/49; 3/18; 0/49). The lesions were focal, minimal to mild in severity, and morphologically similar in all animal groups. These lesions are indicative of a resolving viral infection and are consistent with the presence of positive titers for Sendai virus found in sentinel mice during the 2-year studies (Appendix F, Table F1).

Kidney: The incidence of renal tubule pigmentation in males that received 250 mg/kg was markedly greater than that found in vehicle control males (male: vehicle control, 4/50; low dose, 0/18 [32 kidneys not examined microscopically]; high dose, 25/50; female: none observed). The pigment consisted of yellow to brown material and was located in the lumen of the tubule. It did not resemble the study chemical or material derived from the study chemical. Usually, only one or two tubules were involved, and there was no difference in degree of severity or involvement between chemically exposed and vehicle control animals. There were no histopathologic changes in the tubular epithelium associated with the presence of pigment.

Anterior Pituitary Gland: The incidence of adenomas or adenocarcinomas (combined) in high dose female mice was significantly lower than that in vehicle controls (Table 26).

TABLE 25. ANALYSIS OF CIRCULATORY SYSTEM TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (a)

	Vehicle Control	125 mg/kg	250 mg/kg
Hemangioma			
Overall Rates	0/50 (0%)	(b) 1/50 (2%)	2/50 (4%)
Hemangiosarcoma			
Overall Rates	0/50 (0%)	(b) 0/50 (0%)	3/50 (6%)
Hemangioma or Hemangiosarcoma (c)			
Overall Rates	0/50 (0%)	(b) 1/50 (2%)	5/50 (10%)
Adjusted Rates	0.0%		18.3%
Terminal Rates	0/28 (0%)		3/23 (13%)
Week of First Observation			93
Life Table Test			P=0.024
Incidental Tumor Test			P=0.038

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix C, Table C3 (footnotes).
(b) Thirty-one spleens were examined microscopically.
(c) Historical incidence at study laboratory (mean ± SD): 16/149 (11% ± 10%); historical incidence in NTP studies: 101/1,743 (6% ± 5%)

TABLE 26. ANALYSIS OF ANTERIOR PITUITARY GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	125 mg/kg	250 mg/kg
Hyperplasia			
Overall Rates	5/49 (10%)	(a) 3/22 (14%)	8/49 (16%)
Adenoma			
Overall Rates	20/49 (41%)	(a) 10/22 (45%)	13/49 (27%)
Adjusted Rates	64.3%		40.5%
Terminal Rates	17/28 (61%)		11/30 (37%)
Week of First Observation	98		95
Life Table Test			P=0.059N
Incidental Tumor Test			P=0.071N
Adenocarcinoma			
Overall Rates	1/49 (2%)	(a) 0/22 (0%)	0/49 (0%)
Adenoma or Adenocarcinoma (b)			
Overall Rates	21/49 (43%)	(a) 10/22 (45%)	13/49 (27%)
Adjusted Rates	65.4%		40.5%
Terminal Rates	17/28 (61%)		11/30 (37%)
Week of First Observation	98		95
Life Table Test			P=0.040N
Incidental Tumor Test			P=0.048N

(a) Incomplete sampling of tissues
(b) Historical incidence of adenomas, adenocarcinomas, or carcinomas (combined) at study laboratory (mean ± SD): 47/147 (32% ± 9%); historical incidence in NTP studies: 329/1,562 (21% ± 10%)

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

2-Amino-4-nitrophenol was nominated and selected for toxicology and carcinogenesis studies as part of a study of chemicals used in hair dyes. Other aminonitrophenols that have been evaluated in NTP/NCI 2-year studies include 2-amino-5-nitrophenol (NTP, 1988a) and 4-amino-2-nitrophenol (NCI, 1978). Human exposure to 2-amino-4-nitrophenol associated with the use of hair dyes would involve primarily dermal contact, whereas occupational exposure could involve contact with skin, inhalation, or accidental ingestion. Systemic exposure was considered to pose the greatest risk of carcinogenesis to humans, and, for the present studies, oral administration was selected as the most effective way of achieving high systemic concentrations of 2-amino-4-nitrophenol in rodents. A stability study of formulated feed mixtures conducted before the start of the toxicity studies indicated that 2-amino-4-nitrophenol was unstable in feed at 25° C but could be prepared as a stable suspension in corn oil. Therefore, gavage was selected as the route of administration for these studies.

The short-term toxicity of 2-amino-4-nitrophenol was evaluated in 15-day and 13-week studies. Diarrhea, lethargy, reduced survival, and histopathologic lesions of the kidney were observed in rats and mice that received 1,000 mg/kg in the 13-week studies. Clinical signs of toxicity and histopathologic lesions of the kidney were also observed in rats that received 500 mg/kg; however, survival was improved at this dose. Animals that received doses of 250 mg/kg or lower during the 13-week studies did not exhibit clinical signs indicative of toxicity and had no gross or microscopic lesions attributable to chemical administration. Based on the results of the short-term studies, doses of 125 and 250 mg/kg were selected for the 2-year studies in both rats and mice.

Although the short-term studies indicated a potential for compound-related effects on the kidney in all groups of animals administered 2-amino-4-nitrophenol, kidney lesions were found only in male rats in the 2-year studies. Nephropathy was present at a markedly greater degree of severity in chemically exposed male rats than that observed in vehicle controls and may have contributed to the reduced survival of the 250 mg/kg group. Since there were no apparent histopathologic differences between the nephropathy present in chemically exposed animals and that present in vehicle controls, exposure to 2-amino-4-nitrophenol appears to have exacerbated the spontaneously occurring nephropathy.

Associated with the more severe nephropathy was a spectrum of nonneoplastic lesions characteristic of reduced renal function and renal secondary hyperparathyroidism. These included parathyroid hyperplasia, mineralization of the heart, fibrous osteodystrophy, and calcification of the heart and other organs. These lesions are well-known consequences of impaired renal function in both humans and experimental animals and involve a complex set of events leading to disruption of calcium and phosphorous homeostasis.

Progressive loss of renal function is accompanied by increased concentrations of serum phosphate and reduced levels of ionized calcium and 1,25-dihydroxyvitamin-D_3 in serum. Both calcium and 1,25-dihydroxyvitamin-D_3 are involved in the regulation of parathyroid hormone secretion (DeLuca and Schnoes, 1983; Silver et al., 1985), and, as their circulating levels decline, parathyroid hormone secretion is stimulated. Parathyroid hormone mobilizes calcium from bone and acts on the kidney to reduce tubular reabsorption of phosphate, increase tubular reabsorption of calcium, and restore normal calcium and phosphate levels. However, as renal function deteriorates, the ability of the kidney to respond to parathyroid hormone diminishes, phosphate levels remain increased, 1,25-dihydroxyvitamin-D_3 levels remain depressed, and intestinal absorption of calcium and parathyroid hormone sensitivity of the bone are reduced. This leads to a sustained increased level of parathyroid hormone secretion and, eventually, to parathyroid hyperplasia as well as to impaired calcification and excess production of fibrous connective tissue in bone. Precipitation of calcium phosphate is responsible for the mineralization of the heart and other tissues often observed in cases of renal failure (Slatopolsky and Whyte, 1985).

Increased incidences of renal cortical (tubular cell) adenomas and tubular cell hyperplasia

were observed in dosed male rats. Cortical or tubular cell adenomas are infrequently observed in male F344/N rats (historical corn oil vehicle control incidence of tubular cell neoplasms in NTP 2-year studies: 9/1,695, 0.5% ± 0.9%) and have not been observed in corn oil vehicle control male rats in any of the NTP 2-year studies conducted at the study laboratory, including three studies conducted concurrently with the present studies.

The pathogenesis of renal cortical epithelial neoplasms in rats is currently thought to involve a progression from tubular cell hyperplasia to tubular cell adenomas and, with increasing size, to adenocarcinomas or carcinomas (Hard, 1986). This progression was observed with tubular cell neoplasms induced in F344 rats exposed to *N*-(4'-fluoro-4-biphenylyl)acetamide in feed for 48 weeks, during which interim kills were performed to follow tumor development (Dees et al., 1980). Evidence of such a progression has also been found in other studies. Administration of tris(2,3-dibromopropyl)phosphate in feed for 2 years produced hyperplastic lesions of the proximal convoluted tubules and renal tubular cell adenocarcinomas and carcinomas in the kidneys of F344 rats and $B6C3F_1$ mice (Reznik, 1979). Increased incidences of tubular cell hyperplasia, adenomas, and adenocarcinomas were found in the kidney of male rats exposed to tetrachloroethylene by inhalation for 2 years (NTP, 1986). Moreover, studies in which tubular cell neoplasms were induced in Wistar rats exposed to dimethylnitrosamine have shown that once these neoplasms attain macroscopic dimensions (2 cm or larger), they have a high potential for metastasis (Hard, 1984).

The incidence of preputial gland adenomas or carcinomas (combined) in male rats that received 125 mg/kg was greater than that in vehicle controls; however, the incidence of these neoplasms in male rats that received 250 mg/kg was comparable to that in vehicle controls, and the incidence of clitoral gland adenomas or carcinomas (combined) in high dose female rats was significantly lower than that in vehicle controls. The survival of the 250 mg/kg group of males was reduced after week 89, but it is unlikely that this lower survival influenced the incidence of preputial gland neoplasms in this group. At week 82, when the first preputial gland neoplasm was recorded, 40/50 male rats were still alive in the 250 mg/kg group. In the present studies, the absence of a dose response for preputial gland neoplasms and of a parallel increase in the incidence of clitoral gland neoplasms argues against a compound-related effect on the preputial gland.

In the 2-year studies of 2-amino-5-nitrophenol (NTP, 1988a), an isomeric aminonitrophenol studied at the same laboratory concurrently with the present studies, the incidences of adenomas or carcinomas (combined) of the preputial or clitoral gland were increased in chemically exposed rats. Although these increases were not statistically significant, the parallel increase in the incidences of preputial and clitoral gland neoplasms was considered noteworthy, even though the evidence was insufficient to relate the increased incidences to chemical exposure.

Pigmentation was observed in the small and large intestines of rats administered 2-amino-4-nitrophenol in the 2-year studies; however, no pigmentation was present in the gastrointestinal tract of mice. Aminophenols, as a class, are readily oxidized to darkly colored substances, and similar pigmentation of the intestinal tract has been observed in NTP studies of two related isomers. In 2-year studies (NCI, 1978), rats and mice received diets containing 4-amino-2-nitrophenol at 1,250 or 2,500 ppm. A high incidence of pigmentation was observed in the small intestine of all groups of dosed animals, but no pigmentation was found in the large intestine. In 2-year studies of 2-amino-5-nitrophenol (NTP, 1988a), rats received doses of 100 or 200 mg/kg and mice received doses of 400 or 800 mg/kg in corn oil by gavage. Pigmentation and an associated inflammatory reaction were present in the large intestine of dosed rats and mice, but no pigmentation was present in the small intestine.

The continuous exposure to chemical at relatively low concentrations which occurs with dietary administration is consistent with most of ingested chemical being absorbed through the small intestine and might explain why pigmentation was not observed in the large intestine in the 2-year studies of 4-amino-2-nitrophenol

(NCI, 1978). In the 2-year studies of 2-amino-5-nitrophenol (NTP, 1988a) and in the present studies, the study chemicals were administered as suspensions in corn oil. Although mice were administered different doses in these two studies and rats received essentially the same doses, pigmentation was restricted to the large intestine in the 2-amino-5-nitrophenol studies but was present in both the small and large intestines in the present studies.

There were no compound-related neoplasms observed in female mice during the present 2-year study. The incidence of hemangiomas or hemangiosarcomas (combined) in male mice that received 250 mg/kg was significantly greater than that in vehicle controls (vehicle control, 0/50; 125 mg/kg, 1/50; 250 mg/kg, 5/50). The five animals in the 250 mg/kg group with hemangiomas or hemangiosarcomas each had one neoplasm that was located at a different site in each animal.

Hemangiomas and hemangiosarcomas are relatively common tumors in male $B6C3F_1$ mice; the historical incidence for these neoplasms in corn oil vehicle control male mice in NTP 2-year gavage studies is 101/1,743 (6% ± 5%). For gavage studies conducted at this study laboratory concurrently with the present studies, the incidences of hemangiomas or hemangiosarcomas, combined, were: 2-amino-5-nitrophenol--6/50; 4-hexylresorcinol--10/50; 2-mercaptobenzothiazole--0/49; total--16/149, 11% ± 10%) (NTP, 1988a,b,c).

Spontaneously occurring hemangiomas or hemangiosarcomas are usually found at low incidences at multiple anatomic sites. In the 2-amino-5-nitrophenol study, these neoplasms were found in six vehicle control male mice; they were present in the spleen of three animals, the heart of one animal, the liver of one animal, and the subcutis of one animal. In the 4-hexylresorcinol study, these neoplasms were present in 10 vehicle control male mice at seven different anatomic sites. However, in NTP studies in which the increased incidence of these neoplasms in male mice was considered to be associated with chemical exposure, a large increase in incidence was observed at one site (in one organ or tissue). In the propylene oxide inhalation study (NTP, 1985), hemangiomas or hemangiosarcomas (combined) were found in the subcutis of 1 low dose male mouse, the spleen of another low dose male mouse, and the nasal cavity of 10 high dose male mice. In the 1,3-butadiene study (NTP, 1984), hemangiomas or hemangiosarcomas (combined) were present in the heart of 16 low dose and 7 high dose male mice, and metastatic hemangiosarcomas were present in the liver of 16 low dose and 5 high dose animals.

Thus, although the six hemangiomas or hemangiosarcomas in the present study were in chemically exposed male mice and the incidence in high dose animals was significantly greater than the vehicle control incidence, their distribution among six separate anatomic sites is more indicative of spontaneously arising neoplasms than of an effect due to chemical exposure.

2-Amino-4-nitrophenol is both a gene mutagen and a clastogen. Exogeneous metabolic activation was not required for mutagenic activity in *S. typhimurium* strain TA98 or in cultured mouse lymphoma cells. Clastogenic and genotoxic activity in cultured Chinese hamster ovary cells was also observed in the absence as well as in the presence of rat liver S9. The mutagenic activity exhibited by 2-amino-4-nitrophenol in in vitro tests has not been demonstrated in vivo in the limited number of tests that have been conducted.

The experimental and tabulated data for the NTP Technical Report on 2-amino-4-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** of 2-amino-4-nitrophenol for male F344/N rats, as shown by increased incidences of renal cortical (tubular cell) adenomas. The incidences of renal tubular cell hyperplasia were also increased in male rats exposed to 2-amino-4-nitrophenol. The survival of male rats that received 2-amino-4-nitrophenol was reduced compared with survival of vehicle control male rats. There was *no evidence of carcinogenic activity* of 2-amino-4-nitrophenol for female F344/N rats or for male or female $B6C3F_1$ mice that received 125 or 250 mg/kg per day.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 8.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 11.

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(48)	(50)
Squamous cell papilloma		1 (2%)	1 (2%)
Squamous cell carcinoma		1 (2%)	
Basal cell tumor		1 (2%)	
Keratoacanthoma	1 (2%)	1 (2%)	1 (2%)
*Subcutaneous tissue	(50)	(48)	(50)
Sarcoma, NOS			1 (2%)
Fibroma	1 (2%)	5 (10%)	3 (6%)
Fibrosarcoma		1 (2%)	
Lipoma	1 (2%)		
Neurofibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(48)	(49)
Alveolar/bronchiolar adenoma	4 (8%)	2 (4%)	
Alveolar/bronchiolar carcinoma	2 (4%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(48)	(50)
Malignant lymphoma, lymphocytic type	2 (4%)	1 (2%)	
Malignant lymphoma, histiocytic type			1 (2%)
Leukemia, mononuclear cell	13 (26%)	7 (15%)	4 (8%)
#Spleen	(50)	(48)	(50)
Sarcoma, NOS	1 (2%)	1 (2%)	
#Mandibular lymph node	(50)	(48)	(50)
Histiocytic sarcoma		1 (2%)	
CIRCULATORY SYSTEM			
#Glandular stomach	(50)	(48)	(50)
Hemangiosarcoma		1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(47)	(47)
Neurilemoma, malignant			1 (2%)
#Liver	(50)	(48)	(50)
Neoplastic nodule			2 (4%)
Hepatocellular carcinoma			1 (2%)
Histiocytic sarcoma		1 (2%)	
#Pancreas	(50)	(48)	(50)
Acinar cell adenoma	1 (2%)	2 (4%)	2 (4%)
Acinar cell carcinoma			1 (2%)
#Colon	(49)	(48)	(50)
Carcinoma, NOS			1 (2%)
URINARY SYSTEM			
#Kidney/cortex	(50)	(48)	(50)
Adenoma, NOS		1 (2%)	3 (6%)
Lipoma	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(45)	(50)
Adenoma, NOS	20 (42%)	18 (40%)	18 (36%)
Adenocarcinoma, NOS	1 (2%)		
#Adrenal medulla	(50)	(48)	(50)
Pheochromocytoma	30 (60%)	27 (56%)	20 (40%)
Pheochromocytoma, malignant	4 (8%)	2 (4%)	2 (4%)
Ganglioneuroma		1 (2%)	
#Thyroid	(50)	(47)	(47)
Follicular cell adenoma		1 (2%)	1 (2%)
Follicular cell carcinoma	2 (4%)		
C-cell adenoma	4 (8%)	5 (11%)	5 (11%)
C-cell carcinoma	2 (4%)	1 (2%)	
#Pancreatic islets	(50)	(48)	(50)
Islet cell adenoma	3 (6%)	1 (2%)	3 (6%)
Islet cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(48)	(50)
Adenocarcinoma, NOS	1 (2%)		
Fibroadenoma	4 (8%)		2 (4%)
*Preputial gland	(50)	(48)	(50)
Carcinoma, NOS	2 (4%)	5 (10%)	1 (2%)
Adenoma, NOS	1 (2%)	5 (10%)	2 (4%)
#Testis	(50)	(48)	(48)
Interstitial cell tumor	39 (78%)	39 (81%)	36 (75%)
#Tunica albuginea	(50)	(48)	(48)
Mesothelioma, NOS		1 (2%)	
NERVOUS SYSTEM			
#Brain	(50)	(48)	(50)
Histiocytic sarcoma		1 (2%)	
Ependymoma	1 (2%)		
#Cerebellum	(50)	(48)	(50)
Sarcoma, NOS		1 (2%)	
*Spinal cord	(50)	(48)	(50)
Neurilemoma, malignant	1 (2%)		
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(48)	(50)
Squamous cell carcinoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(48)	(50)
Neurilemoma, metastatic			1 (2%)
BODY CAVITIES			
*Tunica vaginalis	(50)	(48)	(50)
Mesothelioma, NOS	2 (4%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(48)	(50)
Mesothelioma, malignant	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	11	13
Moribund sacrifice	15	12	22
Terminal sacrifice	32	24	10
Dosing accident	1	3	5
TUMOR SUMMARY			
Total animals with primary tumors**	48	45	42
Total primary tumors	147	135	113
Total animals with benign tumors	48	45	41
Total benign tumors	110	110	97
Total animals with malignant tumors	26	19	14
Total malignant tumors	35	24	14
Total animals with secondary tumors##			1
Total secondary tumors			1
Total animals with tumors uncertain--benign or malignant	2	1	2
Total uncertain tumors	2	1	2

* Number of animals receiving complete necropsy examination; 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-4-NITROPHENOL: VEHICLE CONTROL

ANIMAL NUMBER	103	109	135	124	142	106	110	116	120	127	136	121	123	132	148	119	122	114	101	102	104	105	107	108	111
WEEKS ON STUDY	011	081	082	085	086	090	090	095	096	099	099	101	101	102	102	103	103	104	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																			X						
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Lipoma																									
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X		X			
Alveolar/bronchiolar carcinoma																						X			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS														X											
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X			X	X		X	X			X		X		X				X		X		X	X
Adenocarcinoma, NOS							X																		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma				X	X		X	X		X	X	X				X		X		X	X		X	X	X
Pheochromocytoma, malignant										X			X	X			X								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma										X												X			
C-cell carcinoma																									
Parathyroid	+	+	+	+	−	−	+	+	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma							X																		
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS													X												
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				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
Carcinoma, NOS																									
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ependymoma										X															
Spinal cord	N	+	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma, malignant						X																			
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, 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	N	N
Mesothelioma, malignant																								X	
Malignant lymphoma, lymphocytic type								X										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 A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	112	113	115	117	118	125	126	128	129	130	131	133	134	137	138	139	140	141	143	144	145	146	147	149	150	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																					X					1
Lipoma														X												1
Neurofibrosarcoma											X															1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X		X								4
Alveolar/bronchiolar carcinoma	X																									2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																		X								1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma										X																1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS										X		X	X			X				X		X		X	X	20
Adenocarcinoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X	X		X	X	X		X		X	X	X	X			X	X		X		X			X	X	30
Pheochromocytoma, malignant																										4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma	X																							X		2
C-cell adenoma				X								X														4
C-cell carcinoma			X																		X					2
Parathyroid	+	+	−	+	+	−	+	+	+	+	−	+	+	+	−	−	+	+	+	−	+	+	+	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma										X									X							3
Islet cell carcinoma			X																							1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma				X				X	X									X								4
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	39
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																	2
Adenoma, NOS					X																					1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ependymoma																										1
Spinal cord	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
Neurilemoma, malignant																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, 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
Mesothelioma, malignant																										1
Malignant lymphoma, lymphocytic type																										2
Leukemia, *mononuclear cell*	X	X		X	X												X									13

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL: LOW DOSE

ANIMAL NUMBER	0023	0035	0021	0005	0014	0447	0034	0028	0119	0445	0442	0444	0449	0255	0268	0441	0448	0115	0337	0443	0550	0333	0331	0006	0339
WEEKS ON STUDY	0003	0056	0057	0058	0061	0667	0669	0700	0733	0778	0822	0822	0866	0888	0888	0900	0900	0922	0944	0955	0966	0977	0988	1000	1033
INTEGUMENTARY SYSTEM																									
Skin	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																									
Basal cell tumor																									
Keratoacanthoma																									
Subcutaneous tissue	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma											X				X		X								
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X						X		
Trachea	+	A	+	B	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS														X											
Lymph nodes	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Thymus	+	A	−	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	A	+	B	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Liver	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X												
Bile duct	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Small intestine	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Urinary bladder	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	A	+	B	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+
Adenoma, NOS			X			X	X		X			X								X				X	X
Adrenal	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma												X			X	X		X	X	X					
Pheochromocytoma, malignant																					X		X	X	
Ganglioneuroma																X									
Thyroid	+	A	+	B	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																					X				
C-cell adenoma																									
C-cell carcinoma																									
Parathyroid	+	A	−	B	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+
Pancreatic islets	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testis	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X					X		X	X			X	X	X	X	X	X	X	X	X	X	X	X
Mesothelioma, NOS																									
Prostate	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	A	N	B	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											X							X							
NERVOUS SYSTEM																									
Brain	+	A	+	B	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Sarcoma, NOS								X																	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	A	N	B	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type										X															
Leukemia, mononuclear cell																		X							X

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

ANIMAL NUMBER	030	001	002	003	004	007	008	009	010	011	012	013	016	017	018	020	022	024	027	029	032	036	038	040	046	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Squamous cell papilloma														X												1
Squamous cell carcinoma								X																		1
Basal cell tumor																X										1
Keratoacanthoma		X																								1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Fibroma								X							X											5
Fibrosarcoma																			X							1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, NOS																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinar cell adenoma					X																X					2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																				X						1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS	X	X				X			X				X	X	X	X	X	X								18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma	X	X		X	X			X		X	X	X		X		X	X	X	X	X	X	X	X	X	X	27
Pheochromocytoma, malignant																					X					2
Ganglioneuroma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																										1
C-cell adenoma			X							X	X			X											X	5
C-cell carcinoma				X																						1
Parathyroid	+	+	+	–	+	–	–	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	–	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																					X					1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	39
Mesothelioma, NOS																					X					1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	*48
Carcinoma, NOS	X										X			X								X				5
Adenoma, NOS			X	X		X																				5
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Sarcoma, 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	*48
Malignant lymphoma, lymphocytic type																										1
Leukemia, mononuclear cell				X		X			X		X			X												7

* Animals necropsied

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL: HIGH DOSE

ANIMAL NUMBER	080	055	088	084	092	093	089	091	060	095	096	082	054	057	066	067	069	097	085	072	100	077	087	081	052
WEEKS ON STUDY	002	003	017	037	045	045	068	072	075	080	083	086	088	089	089	089	089	089	090	092	093	094	094	096	097
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																X									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																							X		
Hepatocellular carcinoma																									X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									X
Acinar cell carcinoma																									
Esophagus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																					X				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS							X		X		X				X					X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma								X													X	X	X	X	X
Pheochromocytoma, malignant																			X						
Thyroid	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma																			X						
Parathyroid	+	–	–	–	+	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Fibroadenoma																						X			
Testis	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–
Interstitial cell tumor								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
Carcinoma, NOS										X															
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	N
Squamous cell carcinoma																									
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
Neurilemoma, metastatic																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, histiocytic type																				X					
Leukemia, mononuclear cell																							X		

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

ANIMAL NUMBER	065	099	083	071	079	059	074	056	068	075	094	053	063	073	078	051	058	061	062	064	070	076	086	090	098	TOTAL:
WEEKS ON STUDY	097	097	098	099	099	100	100	101	101	101	101	102	102	102	102	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Squamous cell papilloma																										1
Keratoacanthoma																									X	1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Sarcoma, NOS																					X					1
Fibroma									X							X										3
RESPIRATORY SYSTEM																										
Lungs and bronchi	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Neurilemoma, malignant																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																						X				2
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma										X																2
Acinar cell carcinoma		X																								1
Esophagus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS							X				X	X														3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X	X			X		X	X	X	X		X			X			X		X		X		X	X		18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X	X	X	X		X	X	X				X	X	X		X			X	X		X			20
Pheochromocytoma, malignant										X																2
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma				X																						1
C-cell adenoma							X					X									X		X			5
Parathyroid	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma				X											X		X									3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma						X																				2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	36
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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
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
Squamous cell carcinoma														X												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	*50
Neurilemoma, metastatic																										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, histiocytic type																										1
Leukemia, mononuclear cell	X															X	X									4

* Animals necropsied

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	125 mg/kg	250 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	1/50 (2%)	5/48 (10%)	3/50 (6%)
Adjusted Rates (b)	3.1%	15.5%	17.9%
Terminal Rates (c)	1/32 (3%)	2/24 (8%)	1/10 (10%)
Week of First Observation	105	82	94
Life Table Tests (d)	P=0.067	P=0.060	P=0.074
Incidental Tumor Tests (d)	P=0.219	P=0.097	P=0.206
Cochran-Armitage Trend Test (d)	P=0.265		
Fisher Exact Test (d)		P=0.093	P=0.309
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	2/50 (4%)	6/48 (13%)	4/50 (8%)
Adjusted Rates (b)	6.3%	19.4%	27.0%
Terminal Rates (c)	2/32 (6%)	3/24 (13%)	2/10 (20%)
Week of First Observation	105	82	94
Life Table Tests (d)	P=0.042	P=0.071	P=0.043
Incidental Tumor Tests (d)	P=0.139	P=0.108	P=0.117
Cochran-Armitage Trend Test (d)	P=0.291		
Fisher Exact Test (d)		P=0.121	P=0.339
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	2/48 (4%)	0/49 (0%)
Adjusted Rates (b)	12.5%	6.3%	0.0%
Terminal Rates (c)	4/32 (13%)	0/24 (0%)	0/10 (0%)
Week of First Observation	105	90	
Life Table Tests (d)	P=0.155N	P=0.481N	P=0.291N
Incidental Tumor Tests (d)	P=0.081N	P=0.431N	P=0.291N
Cochran-Armitage Trend Test (d)	P=0.039N		
Fisher Exact Test (d)		P=0.359N	P=0.061N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	2/48 (4%)	0/49 (0%)
Adjusted Rates (b)	15.6%	6.3%	0.0%
Terminal Rates (c)	5/32 (16%)	0/24 (0%)	0/10 (0%)
Week of First Observation	105	90	
Life Table Tests (d)	P=0.098N	P=0.351N	P=0.223N
Incidental Tumor Tests (d)	P=0.049N	P=0.309N	P=0.223N
Cochran-Armitage Trend Test (d)	P=0.018N		
Fisher Exact Test (d)		P=0.235N	P=0.030N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	13/50 (26%)	7/48 (15%)	4/50 (8%)
Adjusted Rates (b)	33.3%	26.2%	25.7%
Terminal Rates (c)	7/32 (22%)	5/24 (21%)	2/10 (20%)
Week of First Observation	85	92	94
Life Table Tests (d)	P=0.327N	P=0.312N	P=0.438N
Incidental Tumor Tests (d)	P=0.039N	P=0.252N	P=0.047N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.125N	P=0.016N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	0/50 (0%)	0/48 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	16.4%
Terminal Rates (c)	0/32 (0%)	0/24 (0%)	1/10 (10%)
Week of First Observation			94
Life Table Tests (d)	P=0.011	(e)	P=0.035
Incidental Tumor Tests (d)	P=0.046	(e)	P=0.109
Cochran-Armitage Trend Test (d)	P=0.038		
Fisher Exact Test (d)		(e)	P=0.121

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Pancreas: Acinar Cell Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	2/48 (4%)	3/50 (6%)
Adjusted Rates (b)	3.1%	8.3%	12.8%
Terminal Rates (c)	1/32 (3%)	2/24 (8%)	0/10 (0%)
Week of First Observation	105	105	97
Life Table Tests (d)	P=0.050	P=0.399	P=0.104
Incidental Tumor Tests (d)	P=0.172	P=0.399	P=0.359
Cochran-Armitage Trend Test (d)	P=0.223		
Fisher Exact Test (d)		P=0.485	P=0.309
Kidney/Cortex: Adenoma			
Overall Rates (a)	0/50 (0%)	1/48 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	4.0%	16.7%
Terminal Rates (c)	0/32 (0%)	0/24 (0%)	0/10 (0%)
Week of First Observation		104	100
Life Table Tests (d)	P=0.009	P=0.445	P=0.025
Incidental Tumor Tests (d)	P=0.170	P=0.436	P=0.240
Cochran-Armitage Trend Test (d)	P=0.062		
Fisher Exact Test (d)		P=0.490	P=0.121
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	20/48 (42%)	18/45 (40%)	18/50 (36%)
Adjusted Rates (b)	49.6%	53.4%	72.3%
Terminal Rates (c)	12/31 (39%)	9/23 (39%)	5/10 (50%)
Week of First Observation	81	57	68
Life Table Tests (d)	P=0.018	P=0.342	P=0.015
Incidental Tumor Tests (d)	P=0.431N	P=0.422N	P=0.463N
Cochran-Armitage Trend Test (d)	P=0.318N		
Fisher Exact Test (d)		P=0.519N	P=0.356N
Anterior Pituitary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	21/48 (44%)	18/45 (40%)	18/50 (36%)
Adjusted Rates (b)	50.7%	53.4%	72.3%
Terminal Rates (c)	12/31 (39%)	9/23 (39%)	5/10 (50%)
Week of First Observation	81	57	68
Life Table Tests (d)	P=0.028	P=0.404	P=0.024
Incidental Tumor Tests (d)	P=0.327N	P=0.339N	P=0.347N
Cochran-Armitage Trend Test (d)	P=0.248N		
Fisher Exact Test (d)		P=0.438N	P=0.282N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	30/50 (60%)	27/48 (56%)	20/50 (40%)
Adjusted Rates (b)	72.6%	81.3%	72.8%
Terminal Rates (c)	21/32 (66%)	18/24 (75%)	4/10 (40%)
Week of First Observation	85	82	72
Life Table Tests (d)	P=0.032	P=0.218	P=0.044
Incidental Tumor Tests (d)	P=0.256N	P=0.304	P=0.174N
Cochran-Armitage Trend Test (d)	P=0.029N		
Fisher Exact Test (d)		P=0.432N	P=0.036N
Adrenal Gland: Malignant Pheochromocytoma			
Overall Rates (a)	4/50 (8%)	2/48 (4%)	2/50 (4%)
Adjusted Rates (b)	10.2%	7.4%	8.5%
Terminal Rates (c)	0/32 (0%)	1/24 (4%)	0/10 (0%)
Week of First Observation	99	96	90
Life Table Tests (d)	P=0.584N	P=0.506N	P=0.637
Incidental Tumor Tests (d)	P=0.110N	P=0.488N	P=0.107N
Cochran-Armitage Trend Test (d)	P=0.254N		
Fisher Exact Test (d)		P=0.359N	P=0.339N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	33/50 (66%)	28/48 (58%)	22/50 (44%)
Adjusted Rates (b)	74.8%	82.0%	75.3%
Terminal Rates (c)	21/32 (66%)	18/24 (75%)	4/10 (40%)
Week of First Observation	85	82	72
Life Table Tests (d)	P=0.034	P=0.307	P=0.039
Incidental Tumor Tests (d)	P=0.106N	P=0.414	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test (d)		P=0.283N	P=0.022N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	4/50 (8%)	5/47 (11%)	5/47 (11%)
Adjusted Rates (b)	11.6%	20.8%	31.6%
Terminal Rates (c)	3/32 (9%)	5/24 (21%)	2/10 (20%)
Week of First Observation	99	105	90
Life Table Tests (d)	P=0.039	P=0.315	P=0.070
Incidental Tumor Tests (d)	P=0.131	P=0.321	P=0.274
Cochran-Armitage Trend Test (d)	P=0.393		
Fisher Exact Test (d)		P=0.460	P=0.460
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	6/47 (13%)	5/47 (11%)
Adjusted Rates (b)	17.7%	25.0%	31.6%
Terminal Rates (c)	5/32 (16%)	6/24 (25%)	2/10 (20%)
Week of First Observation	99	105	90
Life Table Tests (d)	P=0.098	P=0.402	P=0.150
Incidental Tumor Tests (d)	P=0.241	P=0.408	P=0.413
Cochran-Armitage Trend Test (d)	P=0.482N		
Fisher Exact Test (d)		P=0.576	P=0.544N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	3/50 (6%)	1/48 (2%)	3/50 (6%)
Adjusted Rates (b)	8.3%	4.2%	20.2%
Terminal Rates (c)	2/32 (6%)	1/24 (4%)	1/10 (10%)
Week of First Observation	90	105	99
Life Table Tests (d)	P=0.230	P=0.410N	P=0.247
Incidental Tumor Tests (d)	P=0.466	P=0.357N	P=0.555
Cochran-Armitage Trend Test (d)	P=0.593		
Fisher Exact Test (d)		P=0.324N	P=0.661
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	1/48 (2%)	3/50 (6%)
Adjusted Rates (b)	11.4%	4.2%	20.2%
Terminal Rates (c)	3/32 (9%)	1/24 (4%)	1/10 (10%)
Week of First Observation	90	105	99
Life Table Tests (d)	P=0.352	P=0.274N	P=0.330
Incidental Tumor Tests (d)	P=0.592	P=0.234N	P=0.632
Cochran-Armitage Trend Test (d)	P=0.413N		
Fisher Exact Test (d)		P=0.194N	P=0.500N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	4/50 (8%)	0/48 (0%)	2/50 (4%)
Adjusted Rates (b)	12.5%	0.0%	8.3%
Terminal Rates (c)	4/32 (13%)	0/24 (0%)	0/10 (0%)
Week of First Observation	105		94
Life Table Tests (d)	P=0.541N	P=0.104N	P=0.572
Incidental Tumor Tests (d)	P=0.368N	P=0.104N	P=0.596N
Cochran-Armitage Trend Test (d)	P=0.223N		
Fisher Exact Test (d)		P=0.064N	P=0.339N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Preputial Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	5/48 (10%)	2/50 (4%)
Adjusted Rates (b)	3.1%	17.3%	16.4%
Terminal Rates (c)	1/32 (3%)	3/24 (13%)	1/10 (10%)
Week of First Observation	105	82	102
Life Table Tests (d)	P=0.104	P=0.056	P=0.157
Incidental Tumor Tests (d)	P=0.233	P=0.081	P=0.310
Cochran-Armitage Trend Test (d)	P=0.413		
Fisher Exact Test (d)		P=0.093	P=0.500
Preputial Gland: Carcinoma			
Overall Rates (a)	2/50 (4%)	5/48 (10%)	1/50 (2%)
Adjusted Rates (b)	6.3%	19.0%	2.4%
Terminal Rates (c)	2/32 (6%)	3/24 (13%)	0/10 (0%)
Week of First Observation	105	98	80
Life Table Tests (d)	P=0.357	P=0.116	P=0.711
Incidental Tumor Tests (d)	P=0.592	P=0.115	P=0.689N
Cochran-Armitage Trend Test (d)	P=0.413N		
Fisher Exact Test (d)		P=0.201	P=0.500N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	10/48 (21%)	3/50 (6%)
Adjusted Rates (b)	9.4%	34.4%	18.5%
Terminal Rates (c)	3/32 (9%)	6/24 (25%)	1/10 (10%)
Week of First Observation	105	82	80
Life Table Tests (d)	P=0.088	P=0.010	P=0.220
Incidental Tumor Tests (d)	P=0.297	P=0.014	P=0.405
Cochran-Armitage Trend Test (d)	P=0.564		
Fisher Exact Test (d)		P=0.030	P=0.661
Testis: Interstitial Cell Tumor			
Overall Rates (a)	39/50 (78%)	39/48 (81%)	36/48 (75%)
Adjusted Rates (b)	92.8%	95.1%	100.0%
Terminal Rates (c)	29/32 (91%)	22/24 (92%)	10/10 (100%)
Week of First Observation	85	57	72
Life Table Tests (d)	P<0.001	P=0.034	P<0.001
Incidental Tumor Tests (d)	P=0.024	P=0.059	P=0.017
Cochran-Armitage Trend Test (d)	P=0.409N		
Fisher Exact Test (d)		P=0.442	P=0.455N
All Sites: Mesothelioma			
Overall Rates (a)	3/50 (6%)	1/48 (2%)	0/50 (0%)
Adjusted Rates (b)	7.8%	4.2%	0.0%
Terminal Rates (c)	1/32 (3%)	1/24 (4%)	0/10 (0%)
Week of First Observation	90	105	
Life Table Tests (d)	P=0.174N	P=0.417N	P=0.294N
Incidental Tumor Tests (d)	P=0.073N	P=0.361N	P=0.099N
Cochran-Armitage Trend Test (d)	P=0.062N		
Fisher Exact Test (d)		P=0.324N	P=0.121N
All Sites: Benign Tumors			
Overall Rates (a)	48/50 (96%)	45/48 (94%)	41/50 (82%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	32/32 (100%)	24/24 (100%)	10/10 (100%)
Week of First Observation	81	57	68
Life Table Tests (d)	P<0.001	P=0.069	P<0.001
Incidental Tumor Tests (d)	P=0.453N	P=0.702	P=0.541N
Cochran-Armitage Trend Test (d)	P=0.013N		
Fisher Exact Test (d)		P=0.481N	P=0.026N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
All Sites: Malignant Tumors			
Overall Rates (a)	26/50 (52%)	19/48 (40%)	14/50 (28%)
Adjusted Rates (b)	58.8%	56.1%	54.9%
Terminal Rates (c)	14/32 (44%)	10/24 (42%)	3/10 (30%)
Week of First Observation	85	70	80
Life Table Tests (d)	P=0.335	P=0.532N	P=0.320
Incidental Tumor Tests (d)	P=0.016N	P=0.233N	P=0.021N
Cochran-Armitage Trend Test (d)	P=0.009N		
Fisher Exact Test (d)		P=0.151N	P=0.012N
All Sites: All Tumors			
Overall Rates (a)	48/50 (96%)	45/48 (94%)	42/50 (84%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	32/32 (100%)	24/24 (100%)	10/10 (100%)
Week of First Observation	81	57	68
Life Table Tests (d)	P<0.001	P=0.069	P<0.001
Incidental Tumor Tests (d)	P=0.601	P=0.702	P=0.716N
Cochran-Armitage Trend Test (d)	P=0.026N		
Fisher Exact Test (d)		P=0.481N	P=0.046N

(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 125 mg/kg and vehicle control groups.

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

Study	Incidence in Vehicle Controls		
	Adenoma	Adenocarcinoma	Adenoma or Adenocarcinoma
Historical Incidence at Physiological Research Laboratories			
2-Amino-5-nitrophenol	0/50	0/50	0/50
4-Hexylresorcinol	0/49	0/49	0/49
2-Mercaptobenzothiazole	0/50	0/50	0/50
TOTAL	0/149 (0.0%)	0/149 (0.0%)	0/149 (0.0%)
SD (b)	0.00%	0.00%	0.00%
Range (c)			
High	0/50	0/50	0/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	3/1,695 (0.2%)	(d) 6/1,695 (0.4%)	(d) 9/1,695 (0.5%)
SD (b)	0.58%	0.78%	0.90%
Range (c)			
High	1/50	1/48	1/48
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two adenocarcinomas, NOS

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

Study	Incidence in Vehicle Controls		
	Neoplastic Nodule	Hepatocellular Carcinoma	Neoplastic Nodule or Hepatocellular Carcinoma
Historical Incidence at Physiological Research Laboratories			
2-Amino-5-nitrophenol	0/50	0/50	0/50
4-Hexylresorcinol	0/49	0/49	0/49
2-Mercaptobenzothiazole	3/50	0/50	3/50
TOTAL	3/149 (2.0%)	0/149 (0.0%)	3/149 (2.0%)
SD (b)	3.46%	0.00%	3.46%
Range (c)			
High	3/50	0/50	3/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	47/1,697 (2.8%)	11/1,697 (0.6%)	58/1,697 (3.4%)
SD (b)	3.04%	1.18%	3.43%
Range (c)			
High	7/50	2/50	7/50
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4c. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Physiological Research Laboratories			
2-Amino-5-nitrophenol	3/50	0/50	3/50
4-Hexylresorcinol	0/49	0/49	0/49
2-Mercaptobenzothiazole	0/50	1/50	1/50
TOTAL	3/149 (2.0%)	1/149 (0.7%)	4/149 (2.7%)
SD (b)	3.46%	1.15%	3.06%
Range (c)			
High	3/50	1/50	3/50
Low	0/50	0/50	0/49
Overall Historical Incidence			
TOTAL	33/1,699 (1.9%)	(d) 39/1,699 (2.3%)	(d) 72/1,699 (4.2%)
SD (b)	3.17%	2.42%	4.11%
Range (c)			
High	7/50	5/50	9/50
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes three squamous cell carcinomas and seven adenocarcinomas, NOS

TABLE A4d. HISTORICAL INCIDENCE OF TESTICULAR INTERSTITIAL CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls
Historical Incidence at Physiological Research Laboratories	
2-Amino-5-nitrophenol	42/50
4-Hexylresorcinol	31/49
2-Mercaptobenzothiazole	48/50
TOTAL	121/149 (81.2%)
SD (b)	16.56%
Range (c)	
High	48/50
Low	31/49
Overall Historical Incidence	
TOTAL	(d) 1,465/1,695 (86.4%)
SD (b)	9.52%
Range (c)	
High	48/50
Low	31/49

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one malignant interstitial cell tumor

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(48)	(50)
Epidermal inclusion cyst	1 (2%)	1 (2%)	
Ulcer, NOS		1 (2%)	
Ulcer, acute			1 (2%)
Inflammation, active chronic	1 (2%)		1 (2%)
Hyperkeratosis		1 (2%)	1 (2%)
*Subcutaneous tissue	(50)	(48)	(50)
Hematoma, NOS		1 (2%)	
Abscess, NOS	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(48)	(50)
Foreign body, NOS		1 (2%)	
Hemorrhage	2 (4%)	2 (4%)	5 (10%)
Inflammation, acute	1 (2%)	1 (2%)	2 (4%)
Inflammation, active chronic	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute/chronic		1 (2%)	2 (4%)
Inflammation, chronic	3 (6%)	15 (31%)	7 (14%)
Foreign material, NOS	1 (2%)		
*Nasal turbinate	(50)	(48)	(50)
Inflammation, chronic			1 (2%)
#Lung/bronchiole	(50)	(48)	(49)
Inflammation, acute		1 (2%)	
#Lung	(50)	(48)	(49)
Emphysema, alveolar		1 (2%)	5 (10%)
Congestion, NOS	2 (4%)	11 (23%)	11 (22%)
Edema, NOS	1 (2%)	3 (6%)	9 (18%)
Hemorrhage	9 (18%)	8 (17%)	11 (22%)
Bronchopneumonia, acute		1 (2%)	2 (4%)
Pneumonia, interstitial chronic	6 (12%)	5 (10%)	7 (14%)
Bronchopneumonia, chronic	6 (12%)	2 (4%)	1 (2%)
Cholesterol deposit	1 (2%)		2 (4%)
Foreign material, NOS			6 (12%)
Hyperplasia, alveolar epithelium	4 (8%)	1 (2%)	
Histiocytosis	16 (32%)	6 (13%)	10 (20%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(48)	(50)
Hyperplasia, megakaryocytic		1 (2%)	
#Spleen	(50)	(48)	(50)
Granuloma, NOS		1 (2%)	
Fibrosis	2 (4%)	4 (8%)	2 (4%)
Fibrosis, focal	1 (2%)		1 (2%)
Pigmentation, NOS	46 (92%)	37 (77%)	45 (90%)
Atrophy, NOS		2 (4%)	1 (2%)
Hyperplasia, lymphoid		3 (6%)	1 (2%)
Hematopoiesis	43 (86%)	35 (73%)	35 (70%)
#Splenic capsule	(50)	(48)	(50)
Fibrosis	1 (2%)	1 (2%)	1 (2%)
#Splenic follicles	(50)	(48)	(50)
Atrophy, 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-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(50)	(48)	(50)
Congestion, NOS		1 (2%)	
Hemorrhage		1 (2%)	
Inflammation, chronic		1 (2%)	
Plasmacytosis	4 (8%)	3 (6%)	
Hyperplasia, lymphoid		1 (2%)	1 (2%)
#Mesenteric lymph node	(50)	(48)	(50)
Congestion, NOS		1 (2%)	
Inflammation, acute			1 (2%)
#Liver	(50)	(48)	(50)
Hematopoiesis	3 (6%)		1 (2%)
#Adrenal cortex	(50)	(48)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Thymus	(50)	(47)	(48)
Embryonal duct cyst	1 (2%)		1 (2%)
Congestion, NOS		2 (4%)	
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#Heart	(50)	(48)	(49)
Calcification, metastatic		4 (8%)	8 (16%)
#Heart/atrium	(50)	(48)	(49)
Mineralization	1 (2%)		1 (2%)
Thrombosis, NOS		1 (2%)	
Thrombus, organized	1 (2%)		
Thrombus, mural	1 (2%)		
*Pulmonary artery	(50)	(48)	(50)
Mineralization	3 (6%)	2 (4%)	1 (2%)
*Pulmonary vein	(50)	(48)	(50)
Mineralization	2 (4%)		3 (6%)
*Vena cava	(50)	(48)	(50)
Mineralization	3 (6%)		1 (2%)
*Mesentery	(50)	(48)	(50)
Periarteritis			1 (2%)
#Testis	(50)	(48)	(48)
Periarteritis	1 (2%)		3 (6%)
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(47)	(47)
Inflammation, acute			2 (4%)
Inflammation, active chronic	1 (2%)		
Inflammation, chronic	1 (2%)	6 (13%)	3 (6%)
Atrophy, NOS	7 (14%)	7 (15%)	2 (4%)
#Liver	(50)	(48)	(50)
Accessory structure		1 (2%)	
Congestion, NOS	2 (4%)	1 (2%)	
Abscess, NOS			1 (2%)
Granuloma, NOS	4 (8%)		
Peliosis hepatis	1 (2%)		
Necrosis, NOS			1 (2%)
Necrosis, coagulative		1 (2%)	2 (4%)
Metamorphosis, fatty	19 (38%)	6 (13%)	4 (8%)
Cytoplasmic vacuolization	1 (2%)	1 (2%)	1 (2%)
Focal cellular change	44 (88%)	40 (83%)	40 (80%)
Hepatocytomegaly	4 (8%)		
Hyperplasia, NOS	3 (6%)	1 (2%)	
Angiectasis	2 (4%)	1 (2%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver/centrilobular	(50)	(48)	(50)
Congestion, NOS			1 (2%)
Necrosis, NOS		1 (2%)	
Necrosis, coagulative	1 (2%)		
Metamorphosis, fatty	3 (6%)		
Cytoplasmic vacuolization			1 (2%)
#Liver/periportal	(50)	(48)	(50)
Inflammation, chronic	4 (8%)	32 (67%)	4 (8%)
Metamorphosis, fatty	2 (4%)	2 (4%)	
#Bile duct	(50)	(48)	(50)
Hyperplasia, NOS	44 (88%)	41 (85%)	34 (68%)
#Pancreas	(50)	(48)	(50)
Cystic ducts	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, acute	1 (2%)		
Abscess, NOS			1 (2%)
Inflammation, chronic		5 (10%)	
Focal cellular change			1 (2%)
Atrophy, NOS	9 (18%)	4 (8%)	2 (4%)
#Pancreatic acinus	(50)	(48)	(50)
Focal cellular change		1 (2%)	
Atrophy, NOS	14 (28%)	15 (31%)	8 (16%)
Hyperplasia, NOS	12 (24%)	14 (29%)	13 (26%)
Hyperplasia, focal	2 (4%)		
#Esophagus	(50)	(48)	(48)
Inflammation, acute			2 (4%)
Ulcer, acute			1 (2%)
#Stomach	(50)	(48)	(50)
Inflammation, active chronic		1 (2%)	2 (4%)
#Gastric fundal gland	(50)	(48)	(50)
Dilatation, NOS	32 (64%)	32 (67%)	29 (58%)
#Glandular stomach	(50)	(48)	(50)
Mineralization	2 (4%)		2 (4%)
Inflammation, acute	1 (2%)		
Inflammation, chronic		1 (2%)	
Erosion			2 (4%)
Calcification, metastatic			1 (2%)
#Forestomach	(50)	(48)	(50)
Ulcer, NOS		1 (2%)	5 (10%)
Inflammation, acute	1 (2%)		
Ulcer, acute	1 (2%)		2 (4%)
Inflammation, active chronic	1 (2%)	2 (4%)	4 (8%)
Inflammation, chronic		2 (4%)	
Ulcer, chronic		3 (6%)	
Hyperkeratosis		1 (2%)	
#Duodenum	(50)	(48)	(50)
Ulcer, NOS			1 (2%)
Ulcer, acute		1 (2%)	
Erosion			2 (4%)
Pigmentation, NOS		38 (79%)	39 (78%)
#Ileum	(50)	(48)	(50)
Pigmentation, NOS			31 (62%)
#Colon	(49)	(48)	(50)
Pigmentation, NOS		14 (29%)	29 (58%)
#Cecum	(49)	(48)	(50)
Edema, NOS		1 (2%)	
Hemorrhage			1 (2%)
Ulcer, NOS			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Cecum (Continued)	(49)	(48)	(50)
Inflammation, acute			1 (2%)
Ulcer, acute			2 (4%)
Inflammation, active chronic			1 (2%)
Erosion			1 (2%)
Pigmentation, NOS		3 (6%)	32 (64%)
Hyperplasia, epithelial			1 (2%)
Polyp, inflammatory			1 (2%)
Angiectasis		1 (2%)	
*Rectum	(50)	(48)	(50)
Pigmentation, NOS			3 (6%)
URINARY SYSTEM			
#Kidney	(50)	(48)	(50)
Congestion, NOS		2 (4%)	2 (4%)
Hemorrhage			1 (2%)
Nephropathy	49 (98%)	47 (98%)	46 (92%)
Hyperplasia, tubular cell	1 (2%)	4 (8%)	5 (10%)
#Kidney/cortex	(50)	(48)	(50)
Cyst, NOS	3 (6%)	3 (6%)	
#Kidney/tubule	(50)	(48)	(50)
Mineralization	40 (80%)	25 (52%)	37 (74%)
Pigmentation, NOS	48 (96%)	47 (98%)	47 (94%)
#Kidney/pelvis	(50)	(48)	(50)
Hemorrhage		1 (2%)	
Inflammation, acute			5 (10%)
Hyperplasia, epithelial	5 (10%)	17 (35%)	16 (32%)
#Urinary bladder	(50)	(48)	(46)
Calculus, gross observation only		1 (2%)	
Calculus, microscopic examination		1 (2%)	1 (2%)
Hemorrhage		1 (2%)	
Inflammation, acute			1 (2%)
*Urethra	(50)	(48)	(50)
Calculus, microscopic examination	1 (2%)	7 (15%)	2 (4%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(45)	(50)
Hemorrhagic cyst		1 (2%)	
#Anterior pituitary	(48)	(45)	(50)
Cyst, NOS	8 (17%)	1 (2%)	5 (10%)
Multiple cysts		1 (2%)	
Hemorrhage		1 (2%)	
Hemorrhagic cyst	1 (2%)		
Lymphocytic inflammatory infiltrate			1 (2%)
Pigmentation, NOS	1 (2%)	1 (2%)	
Hyperplasia, NOS	12 (25%)	15 (33%)	12 (24%)
Hyperplasia, focal	1 (2%)		
#Adrenal	(50)	(48)	(50)
Hypertrophy, focal	1 (2%)		
#Adrenal cortex	(50)	(48)	(50)
Accessory structure	3 (6%)	1 (2%)	
Metamorphosis, fatty	28 (56%)	26 (54%)	32 (64%)
Pigmentation, NOS		2 (4%)	
Cytoplasmic vacuolization			2 (4%)
Focal cellular change		1 (2%)	
Hyperplasia, NOS	11 (22%)	8 (17%)	11 (22%)
Hyperplasia, focal	1 (2%)		
#Adrenal medulla	(50)	(48)	(50)
Hemorrhage	2 (4%)		
Hyperplasia, NOS	15 (30%)	11 (23%)	12 (24%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(47)	(47)
Embryonal duct cyst	1 (2%)		2 (4%)
Mineralization	4 (8%)		
Cystic follicles	13 (26%)	10 (21%)	16 (34%)
Hemorrhage			1 (2%)
Pigmentation, NOS	7 (14%)	3 (6%)	7 (15%)
Hyperplasia, C-cell	21 (42%)	18 (38%)	10 (21%)
Hyperplasia, follicular cell	1 (2%)	2 (4%)	
#Parathyroid	(39)	(36)	(39)
Hyperplasia, NOS		2 (6%)	9 (23%)
#Pancreatic islets	(50)	(48)	(50)
Hyperplasia, NOS	4 (8%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(48)	(50)
Hyperplasia, cystic	28 (56%)	22 (46%)	27 (54%)
*Penis	(50)	(48)	(50)
Hyperkeratosis			1 (2%)
*Preputial gland	(50)	(48)	(50)
Cystic ducts	1 (2%)	2 (4%)	
Inflammation, suppurative	2 (4%)	1 (2%)	
Inflammation, active chronic	1 (2%)	10 (21%)	7 (14%)
Inflammation, chronic		17 (35%)	5 (10%)
Hyperplasia, NOS		1 (2%)	2 (4%)
#Prostate	(50)	(48)	(48)
Inflammation, active chronic	22 (44%)	27 (56%)	17 (35%)
Inflammation, chronic		2 (4%)	
Hyperplasia, NOS	1 (2%)	1 (2%)	
*Seminal vesicle	(50)	(48)	(50)
Inflammation, suppurative		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, active chronic	2 (4%)		2 (4%)
Atrophy, NOS	3 (6%)	5 (10%)	2 (4%)
#Testis	(50)	(48)	(48)
Cyst, NOS	1 (2%)		
Hypoplasia, NOS		1 (2%)	1 (2%)
Atrophy, NOS	39 (78%)	35 (73%)	33 (69%)
Hyperplasia, interstitial cell	44 (88%)	41 (85%)	36 (75%)
#Tunica albuginea	(50)	(48)	(48)
Mineralization			1 (2%)
#Testis/tubule	(50)	(48)	(48)
Mineralization	27 (54%)	24 (50%)	19 (40%)
Degeneration, NOS	1 (2%)		1 (2%)
Oligospermia	2 (4%)	1 (2%)	2 (4%)
Metaplasia, squamous			1 (2%)
*Scrotum	(50)	(48)	(50)
Steatitis	8 (16%)	1 (2%)	2 (4%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(48)	(50)
Hemorrhage	1 (2%)		4 (8%)
#Brain	(50)	(48)	(50)
Compression, NOS	3 (6%)	2 (4%)	1 (2%)
Mineralization	1 (2%)		1 (2%)
Hemorrhage		2 (4%)	2 (4%)
Malacia	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
*Eye	(50)	(48)	(50)
Hemorrhage		1 (2%)	
Retinopathy	2 (4%)	2 (4%)	1 (2%)
Cataract	2 (4%)	2 (4%)	1 (2%)
*Eye/sclera	(50)	(48)	(50)
Mineralization		2 (4%)	
*Eye/lacrimal gland	(50)	(48)	(50)
Atrophy, NOS			1 (2%)
*Nasolacrimal duct	(50)	(48)	(50)
Hemorrhage	5 (10%)	7 (15%)	3 (6%)
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, active chronic	1 (2%)	1 (2%)	6 (12%)
Inflammation, chronic	2 (4%)	31 (65%)	6 (12%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(48)	(50)
Fibrous osteodystrophy	2 (4%)	7 (15%)	22 (44%)
*Vertebra	(50)	(48)	(50)
Hyperplasia, stromal	1 (2%)		
*Femur	(50)	(48)	(50)
Fibrous osteodystrophy			2 (4%)
BODY CAVITIES			
*Pleura	(50)	(48)	(50)
Inflammation, active chronic			1 (2%)
*Pericardium	(50)	(48)	(50)
Inflammation, chronic	1 (2%)		
*Mesentery	(50)	(48)	(50)
Hemorrhage		1 (2%)	
Steatitis	6 (12%)	3 (6%)	1 (2%)
Inflammation, chronic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(48)	(50)
Inflammation, acute			1 (2%)
Inflammation, active chronic	1 (2%)		1 (2%)
Inflammation, chronic	44 (88%)	4 (8%)	32 (64%)
Calcification, metastatic		2 (4%)	9 (18%)
Pigmentation, NOS			2 (4%)
Atrophy, NOS			1 (2%)
Hyperplasia, NOS	5 (10%)		1 (2%)
Adipose tissue			
Steatitis		1	
SPECIAL MORPHOLOGY SUMMARY			
No necropsy performed		1	
Autolysis/no necropsy		1	

* Number of animals receiving complete necropsy examination; 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-4-NITROPHENOL

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(49)
Squamous cell papilloma	2 (4%)		1 (2%)
Squamous cell carcinoma	1 (2%)		
Trichoepithelioma		2 (4%)	
*Subcutaneous tissue	(50)	(50)	(49)
Fibroma	1 (2%)	1 (2%)	
Fibrosarcoma			1 (2%)
Chordoma		1 (2%)	
Neurofibroma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(28)	(49)
Squamous cell carcinoma, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma			1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)
C-cell carcinoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(49)
Malignant lymphoma, lymphocytic type	1 (2%)		
Leukemia, mononuclear cell	6 (12%)	8 (16%)	9 (18%)
#Liver	(50)	(50)	(49)
Leukemia, mononuclear cell		1 (2%)	
#Thymus	(45)	(19)	(49)
Thymoma, benign		1 (5%)	
Malignant lymphoma, histiocytic type			1 (2%)
CIRCULATORY SYSTEM			
#Heart	(50)	(24)	(49)
Neurilemoma, malignant	2 (4%)		
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(49)
Squamous cell papilloma		3 (6%)	
#Liver	(50)	(50)	(49)
Neoplastic nodule		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(19)	(49)
Lipoma	1 (2%)		
#Urinary bladder	(48)	(18)	(47)
Transitional cell papilloma			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(43)	(49)
Adenoma, NOS	22 (45%)	25 (58%)	27 (55%)
Adenocarcinoma, NOS	2 (4%)		
#Adrenal	(50)	(20)	(49)
Cortical adenoma	2 (4%)		1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(50)	(20)	(49)
Pheochromocytoma	7 (14%)	2 (10%)	5 (10%)
Pheochromocytoma, malignant	2 (4%)		
#Thyroid	(47)	(20)	(48)
Follicular cell adenoma	2 (4%)	1 (5%)	2 (4%)
Follicular cell carcinoma		1 (5%)	2 (4%)
C-cell adenoma	3 (6%)		3 (6%)
C-cell carcinoma	2 (4%)		2 (4%)
#Pancreatic islets	(50)	(20)	(49)
Islet cell adenoma		1 (5%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(49)
Adenoma, NOS	1 (2%)		3 (6%)
Adenocarcinoma, NOS	1 (2%)	1 (2%)	
Fibroadenoma	20 (40%)	16 (32%)	13 (27%)
*Clitoral gland	(50)	(50)	(49)
Carcinoma, NOS	2 (4%)	2 (4%)	
Squamous cell carcinoma		1 (2%)	
Adenoma, NOS	7 (14%)	3 (6%)	1 (2%)
#Uterus	(49)	(28)	(48)
Endometrial stromal polyp	13 (27%)	10 (36%)	12 (25%)
#Ovary	(49)	(21)	(48)
Granulosa cell tumor		1 (5%)	
NERVOUS SYSTEM			
#Brain	(50)	(19)	(49)
Astrocytoma	1 (2%)		
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	6	6
Moribund sacrifice	17	12	9
Terminal sacrifice	24	27	31
Dosing accident		5	4

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	42	39	39
Total primary tumors	102	83	86
Total animals with benign tumors	39	38	38
Total benign tumors	81	66	70
Total animals with malignant tumors	17	14	13
Total malignant tumors	21	15	16
Total animals with secondary tumors##	1		1
Total secondary tumors	1		1
Total animals with tumors uncertain--benign or malignant		2	
Total uncertain tumors		2	

* Number of animals receiving complete necropsy examination; 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-4-NITROPHENOL: VEHICLE CONTROL

ANIMAL NUMBER	13 37	14 42	13 32	12 21	11 12	11 16	11 14	10 07	11 13	10 06	10 08	14 49	15 00	10 03	13 80	13 35	10 05	11 15	12 28	12 20	14 43	13 34	13 39	10 02	14 47
WEEKS ON STUDY	00 05	00 07	01 10	01 11	05 52	05 55	06 88	06 69	08 89	09 00	09 00	09 91	09 91	09 92	09 92	09 92	09 95	09 99	09 99	10 02	10 02	10 03	10 03	10 04	10 04
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma							X																		
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic							X																		
Alveolar/bronchiolar carcinoma																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X					X		X	X			X	X		X			X		X	X
Adenocarcinoma, NOS																							X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																							X		
Pheochromocytoma									X	X				X						X					
Pheochromocytoma, malignant														X											
Thyroid	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma												X													
C-cell adenoma																	X							X	
C-cell carcinoma																									
Parathyroid	−	+	−	−	+	−	+	−	+	−	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Fibroadenoma								X	X	X							X	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																									
Adenoma, NOS						X			X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Endometrial stromal polyp							X	X		X					X	X								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
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, lymphocytic type																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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	101	104	109	110	111	117	118	119	122	123	124	125	126	127	129	131	133	136	138	140	141	144	145	146	148	TOTAL:
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma				X				X																		2
Squamous cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																						X				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, malignant													X					X								2
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma									X																	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X	X						X		X			X	X		X			X	X	X		X	X		22
Adenocarcinoma, NOS															X											2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma									X																	2
Pheochromocytoma													X					X					X			7
Pheochromocytoma, malignant																						X				2
Thyroid	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma							X																			2
C-cell adenoma														X												3
C-cell carcinoma													X										X			2
Parathyroid	+	+	+	+	+	–	+	+	–	+	–	+	–	+	+	+	+	–	+	+	+	–	+	–	+	34
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																			X							1
Adenocarcinoma, NOS													X													1
Fibroadenoma	X				X		X	X		X		X		X		X	X	X		X	X					20
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	X						X	X				X											X			7
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp									X	X							X	X		X		X	X			13
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																				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
Malignant lymphoma, lymphocytic type																										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-4-NITROPHENOL: LOW DOSE

ANIMAL NUMBER	0022	0029	0032	0041	0006	0038	0034	0036	0003	0030	0033	0008	0009	0047	0028	0018	0050	0048	0010	0002	0014	0042	0011	0001	0004
WEEKS ON STUDY	0003	0009	0009	0009	0113	0118	0119	0557	0661	0668	0669	0778	0778	0885	0887	0888	0990	0992	0995	0999	0999	0999	1001	1005	1005
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	N	+
Trichoepithelioma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	N	+
Fibroma																						X			
Chordoma																							X		
Neurofibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−
Trachea	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	−	−	−	+	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	−
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	−	+
Thymus	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−
Thymoma, benign																									
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
Squamous cell papilloma																			X					X	
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Leukemia, mononuclear cell																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−
Pheochromocytoma																							X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−
Follicular cell adenoma																									
Follicular cell carcinoma																		X							
Parathyroid	+	−	+	−	+	−	+	+	−	−	−	+	−	−	+	−	+	+	−	−	−	−	−	−	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	−	−
Islet cell adenoma													X												
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	N	+
Adenocarcinoma, NOS															X										
Fibroadenoma														X		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																									
Squamous cell carcinoma																									
Adenoma, NOS									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	−	−
Endometrial stromal polyp								X						X											
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−
Granulosa cell tumor																									
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		X	X			

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

ANIMAL NUMBER	0005	0007	0012	0013	0015	0016	0017	0019	0020	0021	0023	0024	0025	0026	0027	0031	0035	0037	0039	0040	0043	0044	0045	0046	0049	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	N	N	+	N	+	N	N	N	N	N	N	N	+	N	+	N	N	N	+	N	N	N	N	N	*50
Trichoepithelioma														X		X										2
Subcutaneous tissue	+	N	N	+	N	+	N	N	N	N	N	N	N	+	N	+	N	N	N	+	N	N	N	N	N	*50
Fibroma																										1
Chordoma																										1
Neurofibroma													X													1
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	–	–	–	–	–	–	+	+	–	–	–	–	+	+	–	–	–	–	–	+	–	–	–	–	28
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	18
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19
Spleen	+	–	–	–	–	–	–	+	–	–	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–	26
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	21
Thymus	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19
Thymoma, benign				X																						1
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	24
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
Squamous cell papilloma																						X				3
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																					X					1
Leukemia, mononuclear cell																X										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	20
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	20
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19
URINARY SYSTEM																										
Kidney	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	18
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	–	+	+	+	+	–	–	–	+	+	–	+	+	+	+	+	+	+	+	+	+	43
Adenoma, NOS	X	X	X	X		X	X		X				X	X			X		X	X			X		X	25
Adrenal	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	20
Pheochromocytoma				X																						2
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	20
Follicular cell adenoma																					X					1
Follicular cell carcinoma																										1
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Pancreatic islets	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	20
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	N	+	N	N	N	N	N	+	+	N	N	N	+	+	+	+	+	+	N	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma		X	X	X		X						X						X	X	X	X	X			X	16
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
Squamous cell carcinoma													X													1
Adenoma, NOS			X																					X		3
Uterus	+	+	–	–	+	–	–	–	–	–	+	–	–	–	+	–	+	+	–	–	–	–	–	+	–	28
Endometrial stromal polyp	X	X									X				X		X	X						X		10
Ovary	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	21
Granulosa cell tumor				X																						1
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19
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																		8

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL: HIGH DOSE

ANIMAL NUMBER	072	076	083	067	061	065	093	063	066	071	079	056	059	099	095	051	086	097	052	053	054	055	057	058	060
WEEKS ON STUDY	004	009	119	223	030	030	030	076	078	078	083	090	090	092	093	094	094	098	101	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									X
Subcutaneous tissue	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma									X																
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
C-cell carcinoma, metastatic																									
Trachea	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	–	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, histiocytic type																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	–	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Transitional cell papilloma																							X		
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS											X			X			X	X			X	X		X	X
Adrenal	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																X		X							
Thyroid	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																		X							
Follicular cell carcinoma																									
C cell adenoma																									
C-cell carcinoma																									
Parathyroid	–	+	+	+	+	–	A	+	–	+	+	+	–	–	+	–	+	+	–	–	+	–	+	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																						X			
Fibroadenoma								X		X			X		X							X	X	X	
Preputial/clitoral gland	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Uterus	+	+	+	+	–	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp									X		X				X										X
Ovary	+	+	+	+	–	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	A	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	X		X						

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

ANIMAL NUMBER	0682	0684	0688	0689	0700	0703	0704	0705	0707	0708	0710	0801	0802	0804	0805	0807	0808	0809	0901	0902	0904	0906	0908	0910	TOTAL:
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Squamous cell papilloma																									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibrosarcoma																									1
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	49
Alveolar/bronchiolar adenoma																									1
Alveolar/bronchiolar carcinoma																		X							1
C-cell carcinoma, metastatic											X														1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, histiocytic type								X																	1
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Transitional cell papilloma																									1
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X	X	X	X	X	X		X	X	X	X		X	X	X	X		X	X	X		X		X	27
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																						X			1
Pheochromocytoma																		X	X					X	5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																								X	2
Follicular cell carcinoma		X																X							2
C cell adenoma								X		X									X						3
C-cell carcinoma											X				X										2
Parathyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	–	35
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenoma, NOS													X		X										3
Fibroadenoma	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	*49
Adenoma, NOS						X																			1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endometrial stromal polyp					X	X	X	X	X							X			X			X			12
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	*49
Leukemia, mononuclear cell		X							X			X													9

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	125 mg/kg	250 mg/kg
Skin: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/49 (2%)
Adjusted Rates (b)	10.1%	0.0%	3.2%
Terminal Rates (c)	2/25 (8%)	0/27 (0%)	1/31 (3%)
Week of First Observation	68		105
Life Table Tests (d)	P=0.146N	P=0.118N	P=0.252N
Incidental Tumor Tests (d)	P=0.137N	P=0.077N	P=0.251N
Cochran-Armitage Trend Test (d)	P=0.180N		
Fisher Exact Test (d)		P=0.121N	P=0.316N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	6/50 (12%)	(e,f) 9/50 (18%)	9/49 (18%)
Adjusted Rates (b)	18.3%		23.3%
Terminal Rates (c)	2/25 (8%)		3/31 (10%)
Week of First Observation	90		76
Life Table Test (d)			P=0.351
Incidental Tumor Test (d)			P=0.126
Fisher Exact Test (d)			P=0.274
Tongue: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/49 (0%)
Adjusted Rates (b)	0.0%	10.3%	0.0%
Terminal Rates (c)	0/25 (0%)	2/27 (7%)	0/31 (0%)
Week of First Observation		95	
Life Table Tests (d)	P=0.602N	P=0.128	(g)
Incidental Tumor Tests (d)	P=0.620	P=0.096	(g)
Cochran-Armitage Trend Test (d)	P=0.634		
Fisher Exact Test (d)		P=0.121	(g)
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	22/49 (45%)	25/43 (58%)	27/49 (55%)
Adjusted Rates (b)	61.5%	79.2%	76.9%
Terminal Rates (c)	12/25 (48%)	16/22 (73%)	23/31 (74%)
Week of First Observation	52	69	83
Life Table Tests (d)	P=0.454	P=0.193	P=0.484
Incidental Tumor Tests (d)	P=0.145	P=0.029	P=0.201
Cochran-Armitage Trend Test (d)	P=0.181		
Fisher Exact Test (d)		P=0.145	P=0.210
Anterior Pituitary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	24/49 (49%)	25/43 (58%)	27/49 (55%)
Adjusted Rates (b)	65.7%	79.2%	76.9%
Terminal Rates (c)	13/25 (52%)	16/22 (73%)	23/31 (74%)
Week of First Observation	52	69	83
Life Table Tests (d)	P=0.464N	P=0.303	P=0.505N
Incidental Tumor Tests (d)	P=0.257	P=0.056	P=0.330
Cochran-Armitage Trend Test (d)	P=0.306		
Fisher Exact Test (d)		P=0.252	P=0.343
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	7/50 (14%)	(e) 2/20 (10%)	5/49 (10%)
Adjusted Rates (b)	21.1%		14.9%
Terminal Rates (c)	3/25 (12%)		3/31 (10%)
Week of First Observation	89		94
Life Table Test (d)			P=0.318N
Incidental Tumor Test (d)			P=0.527N
Fisher Exact Test (d)			P=0.394N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	8/50 (16%)	(e) 2/20 (10%)	5/49 (10%)
Adjusted Rates (b)	24.7%		14.9%
Terminal Rates (c)	4/25 (16%)		3/31 (10%)
Week of First Observation	89		94
Life Table Test (d)			P=0.219N
Incidental Tumor Test (d)			P=0.392N
Fisher Exact Test (d)			P=0.290N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	2/47 (4%)	(e) 2/20 (10%)	4/48 (8%)
Adjusted Rates (b)	6.6%		12.4%
Terminal Rates (c)	1/24 (4%)		3/31 (10%)
Week of First Observation	91		98
Life Table Test (d)			P=0.414
Incidental Tumor Test (d)			P=0.318
Fisher Exact Test (d)			P=0.349
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/47 (6%)	(e) 0/20 (0%)	3/48 (6%)
Adjusted Rates (b)	10.4%		9.7%
Terminal Rates (c)	1/24 (4%)		3/31 (10%)
Week of First Observation	95		105
Life Table Test (d)			P=0.573N
Incidental Tumor Test (d)			P=0.657
Fisher Exact Test (d)			P=0.651N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/47 (11%)	(e) 0/20 (0%)	5/48 (10%)
Adjusted Rates (b)	18.2%		16.1%
Terminal Rates (c)	3/24 (13%)		5/31 (16%)
Week of First Observation	95		105
Life Table Test (d)			P=0.490N
Incidental Tumor Test (d)			P=0.575N
Fisher Exact Test (d)			P=0.616N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	20/50 (40%)	16/50 (32%)	13/49 (27%)
Adjusted Rates (b)	59.0%	49.1%	35.9%
Terminal Rates (c)	12/25 (48%)	11/27 (41%)	9/31 (29%)
Week of First Observation	69	85	76
Life Table Tests (d)	P=0.040N	P=0.264N	P=0.050N
Incidental Tumor Tests (d)	P=0.104N	P=0.407N	P=0.111N
Cochran-Armitage Trend Test (d)	P=0.093N		
Fisher Exact Test (d)		P=0.266N	P=0.113N
Mammary Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	0/50 (0%)	3/49 (6%)
Adjusted Rates (b)	4.0%	0.0%	9.7%
Terminal Rates (c)	1/25 (4%)	0/27 (0%)	3/31 (10%)
Week of First Observation	105		105
Life Table Tests (d)	P=0.225	P=0.485N	P=0.384
Incidental Tumor Tests (d)	P=0.225	P=0.485N	P=0.384
Cochran-Armitage Trend Test (d)	P=0.171		
Fisher Exact Test (d)		P=0.500N	P=0.301

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/49 (6%)
Adjusted Rates (b)	8.0%	2.8%	9.7%
Terminal Rates (c)	2/25 (8%)	0/27 (0%)	3/31 (10%)
Week of First Observation	105	87	105
Life Table Tests (d)	P=0.467	P=0.500N	P=0.599
Incidental Tumor Tests (d)	P=0.424	P=0.536N	P=0.599
Cochran-Armitage Trend Test (d)	P=0.391		
Fisher Exact Test (d)		P=0.500N	P=0.490
Clitoral Gland: Adenoma			
Overall Rates (a)	7/50 (14%)	3/50 (6%)	1/49 (2%)
Adjusted Rates (b)	23.6%	9.6%	3.2%
Terminal Rates (c)	5/25 (20%)	2/27 (7%)	1/31 (3%)
Week of First Observation	55	61	105
Life Table Tests (d)	P=0.011N	P=0.151N	P=0.020N
Incidental Tumor Tests (d)	P=0.011N	P=0.104N	P=0.025N
Cochran-Armitage Trend Test (d)	P=0.019N		
Fisher Exact Test (d)		P=0.159N	P=0.032N
Clitoral Gland: Carcinoma or Squamous Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/49 (0%)
Adjusted Rates (b)	8.0%	11.1%	0.0%
Terminal Rates (c)	2/25 (8%)	3/27 (11%)	0/31 (0%)
Week of First Observation	105	105	
Life Table Tests (d)	P=0.148N	P=0.536	P=0.192N
Incidental Tumor Tests (d)	P=0.148N	P=0.536	P=0.192N
Cochran-Armitage Trend Test (d)	P=0.207N		
Fisher Exact Test (d)		P=0.500	P=0.253N
Clitoral Gland: Adenoma, Carcinoma, or Squamous Cell Carcinoma			
Overall Rates (a)	9/50 (18%)	6/50 (12%)	1/49 (2%)
Adjusted Rates (b)	31.3%	20.5%	3.2%
Terminal Rates (c)	7/25 (28%)	5/27 (19%)	1/31 (3%)
Week of First Observation	55	61	105
Life Table Tests (d)	P=0.003N	P=0.256N	P=0.004N
Incidental Tumor Tests (d)	P=0.003N	P=0.200N	P=0.006N
Cochran-Armitage Trend Test (d)	P=0.008N		
Fisher Exact Test (d)		P=0.288N	P=0.009N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	13/49 (27%)	(e) 10/28 (36%)	12/48 (25%)
Adjusted Rates (b)	38.9%		34.3%
Terminal Rates (c)	7/25 (28%)		9/31 (29%)
Week of First Observation	68		78
Life Table Test (d)			P=0.349N
Incidental Tumor Test (d)			P=0.508N
Fisher Exact Test (d)			P=0.524N
All Sites: Benign Tumors			
Overall Rates (a)	39/50 (78%)	38/50 (76%)	38/49 (78%)
Adjusted Rates (b)	88.5%	92.7%	92.6%
Terminal Rates (c)	20/25 (80%)	24/27 (89%)	28/31 (90%)
Week of First Observation	52	57	76
Life Table Tests (d)	P=0.175N	P=0.492N	P=0.194N
Incidental Tumor Tests (d)	P=0.457	P=0.465	P=0.556
Cochran-Armitage Trend Test (d)	P=0.526N		
Fisher Exact Test (d)		P=0.500N	P=0.574N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
All Sites: Malignant Tumors			
Overall Rates (a)	17/50 (34%)	14/50 (28%)	13/49 (27%)
Adjusted Rates (b)	49.8%	39.2%	34.3%
Terminal Rates (c)	9/25 (36%)	6/27 (22%)	7/31 (23%)
Week of First Observation	68	69	76
Life Table Tests (d)	P=0.159N	P=0.365N	P=0.170N
Incidental Tumor Tests (d)	P=0.397N	P=0.539N	P=0.377N
Cochran-Armitage Trend Test (d)	P=0.240N		
Fisher Exact Test (d)		P=0.333N	P=0.278N
All Sites: All Tumors			
Overall Rates (a)	42/50 (84%)	39/50 (78%)	39/49 (80%)
Adjusted Rates (b)	91.3%	95.1%	92.8%
Terminal Rates (c)	21/25 (84%)	25/27 (93%)	28/31 (90%)
Week of First Observation	52	57	76
Life Table Tests (d)	P=0.101N	P=0.373N	P=0.119N
Incidental Tumor Tests (d)	P=0.480N	P=0.602N	P=0.546N
Cochran-Armitage Trend Test (d)	P=0.334N		
Fisher Exact Test (d)		P=0.306N	P=0.380N

(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) Incomplete sampling of tissues
(f) Only 26 spleens were examined microscopically.
(g) No P value is reported because no tumors were observed in the 250 mg/kg and vehicle control groups.

TABLE B4a. HISTORICAL INCIDENCE OF CLITORAL GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Physiological Research Laboratories			
2-Amino-5-nitrophenol	2/50	1/50	3/50
4-Hexylresorcinol	1/50	3/50	4/50
2-Mercaptobenzothiazole	5/50	4/50	9/50
TOTAL	8/150 (5.3%)	8/150 (5.3%)	16/150 (10.7%)
SD (b)	4.16%	3.06%	6.43%
Range (c)			
High	5/50	4/50	9/50
Low	1/50	1/50	3/50
Overall Historical Incidence			
TOTAL	32/1,700 (1.9%)	(d) 34/1,700 (2.0%)	(d) 66/1,700 (3.9%)
SD (b)	2.31%	2.31%	3.62%
Range (c)			
High	5/50	4/50	9/50
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one adenocarcinoma, NOS

TABLE B4b. HISTORICAL INCIDENCE OF ORAL CAVITY TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

No oral cavity tumors have been observed in 150 corn oil vehicle control female F344/N rats at Physiological Research Laboratories.

Overall Historical Incidence

	No. Examined	No. of Tumors	Site	Diagnosis
		1	Palate	Squamous cell papilloma
		4	Tongue	Squamous cell papilloma
		1	Dorsum of tongue	Squamous cell papilloma
TOTAL	1,700	6 (0.4%)		

(a) Data as of August 7, 1986, for studies of at least 104 weeks; no more than two tumors have been observed in any corn oil vehicle control group.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(49)
Inflammation, active chronic	2 (4%)		
Ulcer, chronic	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(49)
Hemorrhage			1 (2%)
Inflammation, active chronic	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(49)
Hemorrhage	2 (4%)	2 (4%)	3 (6%)
Inflammation, acute			1 (2%)
Inflammation, active chronic			4 (8%)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Inflammation, chronic	12 (24%)	7 (14%)	11 (22%)
Foreign material, NOS			1 (2%)
*Nasal turbinate	(50)	(50)	(49)
Inflammation, chronic			1 (2%)
#Trachea	(49)	(18)	(48)
Inflammation, acute		1 (6%)	
#Lung	(50)	(28)	(49)
Emphysema, alveolar		4 (14%)	2 (4%)
Congestion, NOS	7 (14%)	9 (32%)	6 (12%)
Edema, NOS	5 (10%)	4 (14%)	4 (8%)
Hemorrhage	18 (36%)	11 (39%)	17 (35%)
Pneumonia, aspiration	1 (2%)		1 (2%)
Bronchopneumonia, acute	1 (2%)		1 (2%)
Pneumonia, interstitial chronic	6 (12%)	3 (11%)	6 (12%)
Bronchopneumonia, chronic	6 (12%)		
Granuloma, NOS	1 (2%)		
Cholesterol deposit	3 (6%)		
Foreign material, NOS	1 (2%)	1 (4%)	4 (8%)
Hyperplasia, alveolar epithelium		1 (4%)	
Histiocytosis	13 (26%)	6 (21%)	8 (16%)
HEMATOPOIETIC SYSTEM			
#Spleen	(50)	(26)	(49)
Infarct, NOS	1 (2%)		1 (2%)
Pigmentation, NOS	48 (96%)	22 (85%)	47 (96%)
Atrophy, NOS			1 (2%)
Hematopoiesis	44 (88%)	17 (65%)	43 (88%)
#Splenic capsule	(50)	(26)	(49)
Fibrosis	1 (2%)		
#Mandibular lymph node	(50)	(21)	(48)
Plasmacytosis	4 (8%)		1 (2%)
Hyperplasia, lymphoid			1 (2%)
#Mesenteric lymph node	(50)	(21)	(48)
Congestion, NOS	2 (4%)		
Pigmentation, NOS		1 (5%)	
Hyperplasia, lymphoid		1 (5%)	
#Liver	(50)	(50)	(49)
Hematopoiesis	2 (4%)		1 (2%)
#Thymus	(45)	(19)	(49)
Congestion, NOS	1 (2%)		
Hemorrhage			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM			
#Heart	(50)	(24)	(49)
Mineralization			1 (2%)
Hemorrhage		1 (4%)	
Endocardiosis			1 (2%)
#Heart/atrium	(50)	(24)	(49)
Thrombus, organized	1 (2%)		
*Pulmonary artery	(50)	(50)	(49)
Mineralization	2 (4%)	1 (2%)	
*Pulmonary vein	(50)	(50)	(49)
Mineralization		1 (2%)	
*Vena cava	(50)	(50)	(49)
Mineralization	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(19)	(48)
Inflammation, active chronic		1 (5%)	2 (4%)
Inflammation, chronic			1 (2%)
Atrophy, NOS	4 (8%)	1 (5%)	4 (8%)
#Liver	(50)	(50)	(49)
Accessory structure	4 (8%)		
Congestion, NOS		2 (4%)	
Inflammation, acute	1 (2%)		
Inflammation, chronic		6 (12%)	
Granuloma, NOS	13 (26%)	15 (30%)	27 (55%)
Fibrosis			1 (2%)
Necrosis, NOS	1 (2%)		
Necrosis, coagulative	2 (4%)	1 (2%)	1 (2%)
Metamorphosis, fatty	6 (12%)	3 (6%)	1 (2%)
Cytoplasmic vacuolization			1 (2%)
Focal cellular change	45 (90%)	43 (86%)	42 (86%)
Hepatocytomegaly	1 (2%)	1 (2%)	
Hyperplasia, focal	2 (4%)		
Angiectasis	2 (4%)		
#Hepatic capsule	(50)	(50)	(49)
Fibrosis		1 (2%)	
#Liver/centrilobular	(50)	(50)	(49)
Congestion, NOS	1 (2%)		1 (2%)
Necrosis, coagulative			2 (4%)
#Liver/periportal	(50)	(50)	(49)
Inflammation, chronic	13 (26%)	11 (22%)	20 (41%)
Metamorphosis, fatty	6 (12%)	2 (4%)	1 (2%)
#Bile duct	(50)	(50)	(49)
Hyperplasia, NOS	34 (68%)	26 (52%)	32 (65%)
#Pancreas	(50)	(20)	(49)
Inflammation, chronic			2 (4%)
#Pancreatic acinus	(50)	(20)	(49)
Atrophy, NOS	15 (30%)	4 (20%)	19 (39%)
Hyperplasia, NOS	19 (38%)	6 (30%)	21 (43%)
Hyperplasia, focal		1 (5%)	
#Esophageal adventitia	(49)	(20)	(49)
Hemorrhage		1 (5%)	
#Gastric fundal gland	(50)	(19)	(49)
Dilatation, NOS	25 (50%)	11 (58%)	35 (71%)
#Forestomach	(50)	(19)	(49)
Ulcer, NOS	1 (2%)	1 (5%)	
Ulcer, acute			1 (2%)
Inflammation, active chronic	1 (2%)		
Hyperkeratosis		1 (5%)	
#Duodenum	(50)	(19)	(49)
Ectopia		1 (5%)	
Pigmentation, NOS		3 (16%)	42 (86%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Ileum	(50)	(19)	(49)
Pigmentation, NOS			19 (39%)
#Colon	(49)	(19)	(49)
Pigmentation, NOS		5 (26%)	34 (69%)
#Cecum	(49)	(19)	(49)
Inflammation, active chronic			1 (2%)
Pigmentation, NOS		2 (11%)	35 (71%)
*Rectum	(50)	(50)	(49)
Pigmentation, NOS			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(19)	(49)
Cyst, NOS	1 (2%)		
Congestion, NOS			3 (6%)
Hemorrhage	1 (2%)	1 (5%)	
Pyelonephritis, acute	1 (2%)		
Nephropathy	36 (72%)	8 (42%)	40 (82%)
Hyperplasia, tubular cell	3 (6%)	1 (5%)	1 (2%)
#Kidney/cortex	(50)	(19)	(49)
Cyst, NOS	1 (2%)		
#Kidney/tubule	(50)	(19)	(49)
Mineralization	35 (70%)	7 (37%)	33 (67%)
Pigmentation, NOS	46 (92%)	13 (68%)	47 (96%)
#Kidney/pelvis	(50)	(19)	(49)
Mineralization			1 (2%)
Hemorrhage		2 (11%)	1 (2%)
Hyperplasia, epithelial	1 (2%)		
#Urinary bladder	(48)	(18)	(47)
Inflammation, acute			1 (2%)
#Urinary bladder/mucosa	(48)	(18)	(47)
Cytoplasmic vacuolization			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(43)	(49)
Cyst, NOS	17 (35%)	10 (23%)	17 (35%)
Multiple cysts		2 (5%)	
Hemorrhage	2 (4%)		
Hemorrhagic cyst	4 (8%)	3 (7%)	
Pigmentation, NOS	2 (4%)	1 (2%)	
Hyperplasia, NOS	8 (16%)	9 (21%)	5 (10%)
#Adrenal cortex	(50)	(20)	(49)
Necrosis, NOS			1 (2%)
Infarct, acute			1 (2%)
Metamorphosis, fatty	21 (42%)	5 (25%)	16 (33%)
Cytoplasmic vacuolization		1 (5%)	
Hyperplasia, NOS	14 (28%)	5 (25%)	13 (27%)
#Adrenal medulla	(50)	(20)	(49)
Hyperplasia, NOS	9 (18%)		9 (18%)
#Thyroid	(47)	(20)	(48)
Embryonal duct cyst			1 (2%)
Mineralization			1 (2%)
Cystic follicles	7 (15%)	3 (15%)	4 (8%)
Hyperplasia, C-cell	26 (55%)	3 (15%)	18 (38%)
#Pancreatic islets	(50)	(20)	(49)
Hyperplasia, NOS			2 (4%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(49)
Inflammation, active chronic		1 (2%)	
Hyperplasia, cystic	45 (90%)	12 (24%)	39 (80%)
*Clitoral gland	(50)	(50)	(49)
Inflammation, active chronic	5 (10%)	2 (4%)	
Inflammation, chronic			1 (2%)
Hyperplasia, NOS	1 (2%)	1 (2%)	
*Vagina	(50)	(50)	(49)
Epidermal inclusion cyst	1 (2%)		
#Uterus	(49)	(28)	(48)
Prolapse		2 (7%)	
Hydrometra	1 (2%)	2 (7%)	1 (2%)
Cyst, NOS	1 (2%)		
Hemorrhage			1 (2%)
Hematoma, NOS	1 (2%)		
Hematoma, organized		2 (7%)	
Inflammation, acute			1 (2%)
#Uterus/endometrium	(49)	(28)	(48)
Edema, NOS		1 (4%)	
Inflammation, active chronic			1 (2%)
Hyperplasia, cystic	6 (12%)	3 (11%)	9 (19%)
Metaplasia, squamous		1 (4%)	
#Ovary	(49)	(21)	(48)
Parovarian cyst		2 (10%)	1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(19)	(49)
Hemorrhage	1 (2%)		1 (2%)
*Choroid plexus	(50)	(50)	(49)
Mineralization	1 (2%)		
#Brain	(50)	(19)	(49)
Compression, NOS	8 (16%)	2 (11%)	1 (2%)
Mineralization	1 (2%)		
Hydrocephalus, internal	1 (2%)		
Hemorrhage	3 (6%)	2 (11%)	3 (6%)
*Olfactory sensory epithelium	(50)	(50)	(49)
Inflammation, acute			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(49)
Mineralization		2 (4%)	
Hemorrhage	1 (2%)	3 (6%)	2 (4%)
Retinopathy	3 (6%)	7 (14%)	2 (4%)
Cataract	1 (2%)	4 (8%)	2 (4%)
Phthisis bulbi	1 (2%)	1 (2%)	1 (2%)
*Eye/lacrimal gland	(50)	(50)	(49)
Atrophy, NOS		1 (2%)	
*Nasolacrimal duct	(50)	(50)	(49)
Hemorrhage	3 (6%)	4 (8%)	3 (6%)
Inflammation, acute			1 (2%)
Inflammation, active chronic	4 (8%)	1 (2%)	6 (12%)
Inflammation, chronic	6 (12%)	7 (14%)	7 (14%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(49)
Fibrous osteodystrophy			2 (4%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Mesentery	(50)	(50)	(49)
Steatitis	8 (16%)	9 (18%)	5 (10%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(49)
Inflammation, chronic	29 (58%)	10 (20%)	21 (43%)
Calcification, metastatic			1 (2%)
Hyperplasia, NOS	1 (2%)		
SPECIAL MORPHOLOGY SUMMARY			
Autolysis/no necropsy			1

* Number of animals receiving complete necropsy examination; 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-4-NITROPHENOL

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-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)
Squamous cell carcinoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	2 (4%)
Fibroma	2 (4%)	6 (12%)	4 (8%)
Fibrosarcoma	3 (6%)	5 (10%)	6 (12%)
Neurofibrosarcoma	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Adenocarcinoma, NOS, invasive			2 (4%)
#Lung	(50)	(32)	(50)
Adenocarcinoma, NOS, metastatic			2 (4%)
Alveolar/bronchiolar adenoma	4 (8%)	4 (13%)	3 (6%)
Alveolar/bronchiolar carcinoma	6 (12%)	4 (13%)	3 (6%)
Pheochromocytoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undifferentiated type	2 (4%)		
Malignant lymphoma, mixed type	2 (4%)	5 (10%)	3 (6%)
Mast cell sarcoma	1 (2%)		
#Spleen	(50)	(31)	(50)
Sarcoma, NOS, metastatic			1 (2%)
#Mesenteric lymph node	(49)	(22)	(50)
Malignant lymphoma, mixed type		1 (5%)	
#Peyer's patch	(50)	(20)	(50)
Malignant lymphoma, mixed type			1 (2%)
#Thymus	(41)	(17)	(45)
Alveolar/bronchiolar carcinoma, invasive	1 (2%)		
CIRCULATORY SYSTEM			
*Abdominal cavity	(50)	(50)	(50)
Hemangioma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Hemangioma			1 (2%)
#Spleen	(50)	(31)	(50)
Hemangiosarcoma			1 (2%)
#Mesenteric lymph node	(49)	(22)	(50)
Hemangiosarcoma			1 (2%)
#Heart	(50)	(21)	(49)
Alveolar/bronchiolar carcinoma, metastatic	1 (2%)		
#Liver	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
#Pancreas	(50)	(48)	(50)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Ameloblastoma			1 (2%)
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	8 (16%)	11 (22%)	3 (6%)
Hepatocellular carcinoma	8 (16%)	8 (16%)	7 (14%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Duodenum	(50)	(20)	(50)
Adenocarcinoma, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(18)	(50)
Tubular cell adenoma			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(18)	(47)
Adenoma, NOS	2 (4%)		
#Adrenal	(49)	(18)	(50)
Cortical adenoma	1 (2%)		2 (4%)
#Adrenal medulla	(49)	(18)	(50)
Pheochromocytoma	2 (4%)		3 (6%)
Pheochromocytoma, malignant			1 (2%)
#Thyroid	(50)	(17)	(49)
Follicular cell adenoma	1 (2%)		
REPRODUCTIVE SYSTEM			
None			
NERVOUS SYSTEM			
#Brain/meninges	(50)	(18)	(50)
Meningioma	1 (2%)		
#Brain	(50)	(18)	(50)
Meningioma, invasive	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye/ciliary body	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)	3 (6%)	1 (2%)
Adenocarcinoma, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Neurofibrosarcoma, invasive		1 (2%)	
BODY CAVITIES			
*Pleura	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive	1 (2%)		
*Pericardium	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	2	10
Moribund sacrifice	18	19	17
Terminal sacrifice	27	29	23
TUMOR SUMMARY			
Total animals with primary tumors**	34	39	35
Total primary tumors	47	51	48
Total animals with benign tumors	19	22	17
Total benign tumors	21	25	20
Total animals with malignant tumors	24	22	25
Total malignant tumors	26	26	28
Total animals with secondary tumors##	2	1	4
Total secondary tumors	4	1	7

* 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-4-NITROPHENOL: VEHICLE CONTROL

ANIMAL NUMBER	11 17	13 38	14 46	14 41	11 16	10 03	13 33	10 05	13 30	13 36	10 01	11 11	13 37	12 20	12 24	15 50	12 25	13 35	11 10	11 12	12 21	12 28	10 02	10 04	10 06
WEEKS ON STUDY	03 38	03 38	03 38	04 48	05 59	06 00	06 99	07 71	07 71	07 74	07 76	07 77	08 22	08 55	08 55	09 51	09 55	09 97	10 00	10 01	10 11	10 11	10 05	10 55	10 55
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+
Fibroma																									
Fibrosarcoma											X										X	X			
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X		X																			
Alveolar/bronchiolar carcinoma																		X							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	−	+
Alveolar/bronchiolar carcinoma, invasive																		X							
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic																		X							
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X	X					X			X				X
Hepatocellular carcinoma						X		X		X			X	X	X										
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																					X				
Adrenal	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																							X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																					X				
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma																X									
Meningioma, invasive																X									
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																									
BODY CAVITIES																									
Pleura	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
Alveolar/bronchiolar carcinoma, invasive																		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
Sarcoma, NOS					X																				
Malignant lymphoma, undifferentiated type												X								X					
Malignant lymphoma, mixed type																	X								
Mast cell sarcoma																									

+: 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	107	108	109	113	114	115	118	119	122	123	126	127	129	131	132	134	139	140	142	143	144	145	147	148	149	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma	X										X															2
Fibrosarcoma																										3
Neurofibrosarcoma																X										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X					X						4
Alveolar/bronchiolar carcinoma				X		X										X				X		X				6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	+	41
Alveolar/bronchiolar carcinoma, invasiv																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metasta																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X	X						X																8
Hepatocellular carcinoma					X							X														8
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS														X												1
Large intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+		48
Adenoma, NOS						X																				2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma												X														1
Pheochromocytoma									X																	2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Parathyroid	+	–	+	+	+	+	+	+	–	–	+	+	+	+	+	–	+	+	+	+	–	+	+	+	–	38
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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma																										1
Meningioma, invasive																										1
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
BODY CAVITIES																										
Pleura	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
Alveolar/bronchiolar carcinoma, invasiv																										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
Sarcoma, NOS																										1
Malignant lymphoma, undifferentia type																										2
Malignant lymphoma, mixed type														X												2
Mast cell sarcoma																		X								1

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL: LOW DOSE

ANIMAL NUMBER	00003	00113	00336	00333	00330	00116	00448	00114	00004	00117	00332	00118	00440	00445	00447	00055	00299	00002	00101	00422	00297	00068	00078	00088	00099
WEEKS ON STUDY	06001	06061	06065	06067	07071	07074	07077	07079	08082	08082	08083	08085	08085	08089	08089	09092	09092	09093	09099	09099	10101	10105	10105	10105	10105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	N	N	+	N
Squamous cell carcinoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	N	N	+	N
Sarcoma, NOS										X															
Fibroma																								X	
Fibrosarcoma	X							X				X					X		X						
Neurofibrosarcoma																					X				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	−	+	−
Alveolar/bronchiolar adenoma																						X		X	
Alveolar/bronchiolar carcinoma																		X							
Trachea	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	−	−	−
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	−	−	−	−
Malignant lymphoma, mixed type																			X						
Thymus	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma			X				X																		X
Hepatocellular carcinoma							X		X				X			X		X							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	N	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	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															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
Neurofibrosarcoma, invasive																					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
Hemangioma																									
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, mixed type				X										X	X					X					

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

ANIMAL NUMBER	010	011	012	015	019	020	021	022	023	024	025	026	028	031	034	035	037	038	039	041	043	045	046	049	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	N	+	N	N	N	N	+	+	N	N	N	N	N	+	N	N	+	+	+	N	N	N	N	N	N	*50
Squamous cell carcinoma								X																		1
Subcutaneous tissue	N	+	N	N	N	N	+	+	N	N	N	N	N	+	N	N	+	+	+	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
Fibroma		X					X	X						X			X									6
Fibrosarcoma																										5
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	−	+	+	+	+	−	−	−	−	−	−	−	+	+	−	−	+	−	+	+	+	−	−	+	−	32
Alveolar/bronchiolar adenoma				X	X																					4
Alveolar/bronchiolar carcinoma													X				X		X							4
Trachea	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	17
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	18
Spleen	−	+	+	+	+	+	−	−	−	+	−	+	+	−	−	−	−	+	−	−	−	+	+	−	−	31
Lymph nodes	−	−	−	−	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	22
Malignant lymphoma, mixed type																										1
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	17
CIRCULATORY SYSTEM																										
Heart	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	+	−	−	−	21
DIGESTIVE SYSTEM																										
Salivary gland	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	19
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X			X					X			X	X	X		X					X			11
Hepatocellular carcinoma								X									X				X					8
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	48
Esophagus	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	19
Stomach	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	18
Small intestine	−	−	+	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	20
Large intestine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	18
URINARY SYSTEM																										
Kidney	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	18
Urinary bladder	−	−	−	−	−	−	−	+	−	−	−	+	+	−	−	−	−	−	−	+	−	−	−	−	−	22
ENDOCRINE SYSTEM																										
Pituitary	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	18
Adrenal	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	18
Thyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	17
Parathyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	11
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	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	18
Prostate	+	−	−	−	−	−	+	−	−	−	+	−	−	+	−	−	−	−	−	−	−	+	−	−	+	24
NERVOUS SYSTEM																										
Brain	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	18
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		3
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
Neurofibrosarcoma, invasive																										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
Hemangioma	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
Malignant lymphoma, mixed type						X																				5

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL: HIGH DOSE

ANIMAL NUMBER	0096	0091	0076	0077	0082	1000	0062	0056	0051	0080	0090	0084	0088	0066	0086	0095	0057	0065	0069	0098	0073	0081	0055	0079	0063
WEEKS ON STUDY	0006	0019	0060	0060	0060	0067	0711	0755	0776	0781	0811	0822	0822	0855	0899	0900	0911	0933	0955	0955	0999	0999	1000	1011	1022
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Sarcoma, NOS																X			X						
Fibroma																									
Fibrosarcoma							X		X						X					X			X		
Hemangioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic														X										X	
Alveolar/bronchiolar adenoma																			X						
Alveolar/bronchiolar carcinoma																						X			X
Pheochromocytoma, metastatic										X															
Trachea	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive														X										X	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																			X						
Hemangiosarcoma																		X							
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																			X						
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
Ameloblastoma																					X				
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma											X	X	X				X						X		
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Pheochromocytoma, malignant										X															
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	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Eye	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											
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																									X
Adenocarcinoma, NOS																								X	
BODY CAVITIES																									
Pericardium	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											
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, mixed type						X																			

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

ANIMAL NUMBER	071	058	052	053	054	059	060	061	064	067	068	070	072	074	075	078	083	085	087	089	092	093	094	097	099	TOTAL:
WEEKS ON STUDY	102	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										2
Fibroma									X			X	X									X				4
Fibrosarcoma					X																					6
Hemangioma																	X									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										2
Alveolar/bronchiolar adenoma															X							X				3
Alveolar/bronchiolar carcinoma																					X					3
Pheochromocytoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	*50
Adenocarcinoma, NOS, invasive																										2
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic																										1
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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
Ameloblastoma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																				X	X				X	3
Hepatocellular carcinoma																	X					X				7
Hemangiosarcoma												X														1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																	X									1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type											X															1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma								X																		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma	X																							X		2
Pheochromocytoma	X			X																		X				3
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	−	−	+	+	−	−	−	+	+	−	+	+	+	+	−	+	−	+	−	−	−	+	−	+	+	27
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																										
Eye	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
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																										1
Adenocarcinoma, NOS																										1
BODY CAVITIES																										
Pericardium	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
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, mixed type								X				X														3

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	125 mg/kg	250 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	7.1%	20.7%	17.4%
Terminal Rates (c)	2/28 (7%)	6/29 (21%)	4/23 (17%)
Week of First Observation	105	105	105
Life Table Tests (d)	P=0.190	P=0.140	P=0.246
Incidental Tumor Tests (d)	P=0.190	P=0.140	P=0.246
Cochran-Armitage Trend Test (d)	P=0.290		
Fisher Exact Test (d)		P=0.134	P=0.339
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (b)	8.8%	12.2%	17.1%
Terminal Rates (c)	0/28 (0%)	0/29 (0%)	1/23 (4%)
Week of First Observation	76	60	71
Life Table Tests (d)	P=0.189	P=0.384	P=0.225
Incidental Tumor Tests (d)	P=0.361	P=0.428	P=0.382
Cochran-Armitage Trend Test (d)	P=0.195		
Fisher Exact Test (d)		P=0.357	P=0.243
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	4/50 (8%)	7/50 (14%)	8/50 (16%)
Adjusted Rates (b)	12.0%	17.2%	22.1%
Terminal Rates (c)	1/28 (4%)	0/29 (0%)	1/23 (4%)
Week of First Observation	76	60	71
Life Table Tests (d)	P=0.141	P=0.295	P=0.162
Incidental Tumor Tests (d)	P=0.329	P=0.335	P=0.326
Cochran-Armitage Trend Test (d)	P=0.146		
Fisher Exact Test (d)		P=0.262	P=0.178
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	11/50 (22%)	10/50 (20%)
Adjusted Rates (b)	15.3%	30.4%	32.2%
Terminal Rates (c)	2/28 (7%)	6/29 (21%)	5/23 (22%)
Week of First Observation	76	60	71
Life Table Tests (d)	P=0.084	P=0.113	P=0.098
Incidental Tumor Tests (d)	P=0.160	P=0.118	P=0.168
Cochran-Armitage Trend Test (d)	P=0.117		
Fisher Exact Test (d)		P=0.086	P=0.131
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	6/50 (12%)	13/50 (26%)	12/50 (24%)
Adjusted Rates (b)	18.6%	34.3%	36.3%
Terminal Rates (c)	3/28 (11%)	6/29 (21%)	5/23 (22%)
Week of First Observation	76	60	71
Life Table Tests (d)	P=0.064	P=0.089	P=0.072
Incidental Tumor Tests (d)	P=0.149	P=0.093	P=0.148
Cochran-Armitage Trend Test (d)	P=0.087		
Fisher Exact Test (d)		P=0.062	P=0.096
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	(e) 4/32 (13%)	3/50 (6%)
Adjusted Rates (b)	11.1%		11.5%
Terminal Rates (c)	2/28 (7%)		2/23 (9%)
Week of First Observation	48		95
Life Table Test (d)			P=0.558N
Incidental Tumor Test (d)			P=0.574N
Fisher Exact Test (d)			P=0.500N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	6/50 (12%)	(e) 4/32 (13%)	3/50 (6%)
Adjusted Rates (b)	20.3%		11.1%
Terminal Rates (c)	5/28 (18%)		1/23 (4%)
Week of First Observation	97		99
Life Table Test (d)			P=0.327N
Incidental Tumor Test (d)			P=0.219N
Fisher Exact Test (d)			P=0.244N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	(e) 8/32 (25%)	6/50 (12%)
Adjusted Rates (b)	27.1%		21.7%
Terminal Rates (c)	6/28 (21%)		3/23 (13%)
Week of First Observation	48		95
Life Table Test (d)			P=0.391N
Incidental Tumor Test (d)			P=0.306N
Fisher Exact Test (d)			P=0.288N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	2/50 (4%)	(e,f) 6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	6.4%		15.0%
Terminal Rates (c)	1/28 (4%)		3/23 (13%)
Week of First Observation	95		67
Life Table Test (d)			P=0.278
Incidental Tumor Test (d)			P=0.316
Fisher Exact Test (d)			P=0.339
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	4/50 (8%)	(e,f) 6/50 (12%)	4/50 (8%)
Adjusted Rates (b)	11.7%		15.0%
Terminal Rates (c)	1/28 (4%)		3/23 (13%)
Week of First Observation	77		67
Life Table Test (d)			P=0.578
Incidental Tumor Test (d)			P=0.629N
Fisher Exact Test (d)			P=0.643N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	0/50 (0%)	(e,f) 0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%		10.1%
Terminal Rates (c)	0/28 (0%)		1/23 (4%)
Week of First Observation			93
Life Table Test (d)			P=0.108
Incidental Tumor Test (d)			P=0.167
Fisher Exact Test (d)			P=0.121
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	0/50 (0%)	(e,f) 1/50 (2%)	5/50 (10%)
Adjusted Rates (b)	0.0%		18.3%
Terminal Rates (c)	0/28 (0%)		3/23 (13%)
Week of First Observation			93
Life Table Test (d)			P=0.024
Incidental Tumor Test (d)			P=0.038
Fisher Exact Test (d)			P=0.028
Liver: Hepatocellular Adenoma			
Overall Rates (a)	8/50 (16%)	11/50 (22%)	3/50 (6%)
Adjusted Rates (b)	23.7%	34.0%	13.0%
Terminal Rates (c)	4/28 (14%)	9/29 (31%)	3/23 (13%)
Week of First Observation	77	65	105
Life Table Tests (d)	P=0.159N	P=0.346	P=0.154N
Incidental Tumor Tests (d)	P=0.122N	P=0.310	P=0.096N
Cochran-Armitage Trend Test (d)	P=0.102N		
Fisher Exact Test (d)		P=0.305	P=0.100N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	8/50 (16%)	8/50 (16%)	7/50 (14%)
Adjusted Rates (b)	20.3%	21.5%	21.0%
Terminal Rates (c)	2/28 (7%)	3/29 (10%)	2/23 (9%)
Week of First Observation	60	77	81
Life Table Tests (d)	P=0.490N	P=0.555N	P=0.536N
Incidental Tumor Tests (d)	P=0.282N	P=0.364N	P=0.287N
Cochran-Armitage Trend Test (d)	P=0.445N		
Fisher Exact Test (d)		P=0.607N	P=0.500N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	15/50 (30%)	18/50 (36%)	10/50 (20%)
Adjusted Rates (b)	38.3%	49.7%	32.2%
Terminal Rates (c)	6/28 (21%)	12/29 (41%)	5/23 (22%)
Week of First Observation	60	65	81
Life Table Tests (d)	P=0.265N	P=0.406	P=0.272N
Incidental Tumor Tests (d)	P=0.113N	P=0.490	P=0.088N
Cochran-Armitage Trend Test (d)	P=0.160N		
Fisher Exact Test (d)		P=0.335	P=0.178N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	2/49 (4%)	(e) 0/18 (0%)	3/50 (6%)
Adjusted Rates (b)	7.1%		12.2%
Terminal Rates (c)	2/28 (7%)		2/23 (9%)
Week of First Observation	105		102
Life Table Test (d)			P=0.422
Incidental Tumor Test (d)			P=0.474
Fisher Exact Test (d)			P=0.509
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	2/49 (4%)	(e) 0/18 (0%)	4/50 (8%)
Adjusted Rates (b)	7.1%		14.3%
Terminal Rates (c)	2/28 (7%)		2/23 (9%)
Week of First Observation	105		78
Life Table Test (d)			P=0.280
Incidental Tumor Test (d)			P=0.326
Fisher Exact Test (d)			P=0.348
Harderian Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	3.6%	9.4%	3.8%
Terminal Rates (c)	1/28 (4%)	2/29 (7%)	0/23 (0%)
Week of First Observation	105	89	102
Life Table Tests (d)	P=0.566	P=0.321	P=0.730
Incidental Tumor Tests (d)	P=0.577N	P=0.394	P=0.729N
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.309	P=0.753
Harderian Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	3.6%	9.4%	7.4%
Terminal Rates (c)	1/28 (4%)	2/29 (7%)	0/23 (0%)
Week of First Observation	105	89	101
Life Table Tests (d)	P=0.351	P=0.321	P=0.453
Incidental Tumor Tests (d)	P=0.470	P=0.394	P=0.596
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.309	P=0.500

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
All Sites: Benign Tumors			
Overall Rates (a)	19/50 (38%)	22/50 (44%)	17/50 (34%)
Adjusted Rates (b)	54.4%	67.9%	62.4%
Terminal Rates (c)	13/28 (46%)	19/29 (66%)	13/23 (57%)
Week of First Observation	48	65	95
Life Table Tests (d)	P=0.466	P=0.406	P=0.523
Incidental Tumor Tests (d)	P=0.514N	P=0.310	P=0.510N
Cochran-Armitage Trend Test (d)	P=0.379N		
Fisher Exact Test (d)		P=0.342	P=0.418N
All Sites: Malignant Tumors			
Overall Rates (a)	24/50 (48%)	22/50 (44%)	25/50 (50%)
Adjusted Rates (b)	55.3%	48.6%	59.0%
Terminal Rates (c)	9/28 (32%)	6/29 (21%)	7/23 (30%)
Week of First Observation	59	60	67
Life Table Tests (d)	P=0.373	P=0.380N	P=0.389
Incidental Tumor Tests (d)	P=0.223N	P=0.140N	P=0.284N
Cochran-Armitage Trend Test (d)	P=0.460		
Fisher Exact Test (d)		P=0.421N	P=0.500
All Sites: All Tumors			
Overall Rates (a)	34/50 (68%)	39/50 (78%)	35/50 (70%)
Adjusted Rates (b)	77.0%	84.7%	81.0%
Terminal Rates (c)	18/28 (64%)	22/29 (76%)	15/23 (65%)
Week of First Observation	48	60	67
Life Table Tests (d)	P=0.267	P=0.353	P=0.301
Incidental Tumor Tests (d)	P=0.389N	P=0.388	P=0.414N
Cochran-Armitage Trend Test (d)	P=0.456		
Fisher Exact Test (d)		P=0.184	P=0.500

(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) Incomplete sampling of tissues
(f) Only 31 spleens were examined microscopically.

TABLE C4. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at Physiological Research Laboratories			
2-Amino-5-nitrophenol	1/50	5/50	6/50
4-Hexylresorcinol	6/50	4/50	10/50
2-Mercaptobenzothiazole	0/49	0/49	0/49
TOTAL	7/149 (4.7%)	9/149 (6.0%)	16/149 (10.7%)
SD (b)	6.43%	5.29%	10.07%
Range (c)			
High	6/50	5/50	10/50
Low	0/49	0/49	0/49
Overall Historical Incidence			
TOTAL	19/1,743 (1.1%)	84/1,743 (4.8%)	101/1,743 (5.8%)
SD (b)	2.24%	4.20%	4.94%
Range (c)			
High	6/50	7/50	10/50
Low	0/50	0/50	0/50

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-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%)	
Ulcer, NOS		2 (4%)	
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, active chronic	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic			4 (8%)
Ulcer, chronic			4 (8%)
Hyperplasia, epithelial		1 (2%)	1 (2%)
Hyperkeratosis		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Mineralization	1 (2%)		
Steatitis		2 (4%)	
Inflammation, acute			1 (2%)
Abscess, NOS	3 (6%)		1 (2%)
Inflammation, active chronic	1 (2%)	1 (2%)	
Inflammation, chronic	2 (4%)		1 (2%)
Granuloma, foreign body	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Hemorrhage	6 (12%)	1 (2%)	2 (4%)
Lymphocytic inflammatory infiltrate	5 (10%)	5 (10%)	5 (10%)
Inflammation, acute	1 (2%)		4 (8%)
Inflammation, active chronic	1 (2%)		
#Tracheal gland	(50)	(17)	(49)
Inflammation, acute	1 (2%)		
#Lung/bronchiole	(50)	(32)	(50)
Hyperplasia, epithelial			1 (2%)
#Lung	(50)	(32)	(50)
Foreign body, NOS	1 (2%)		
Mineralization		1 (3%)	1 (2%)
Congestion, NOS	4 (8%)		9 (18%)
Edema, NOS	1 (2%)		
Hemorrhage	8 (16%)	5 (16%)	11 (22%)
Lymphocytic inflammatory infiltrate	4 (8%)	3 (9%)	4 (8%)
Bronchopneumonia, acute			1 (2%)
Abscess, NOS	2 (4%)		
Pneumonia, interstitial chronic	1 (2%)		1 (2%)
Bronchopneumonia, chronic	2 (4%)	10 (31%)	8 (16%)
Cholesterol deposit		4 (13%)	
Hyperplasia, alveolar epithelium	1 (2%)	11 (34%)	3 (6%)
Histiocytosis	7 (14%)	13 (41%)	9 (18%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(18)	(50)
Fibrosis	1 (2%)		
Necrosis, NOS	1 (2%)		
Pigmentation, NOS	1 (2%)		
Hyperplasia, granulocytic	35 (71%)	13 (72%)	25 (50%)
Hyperplasia, megakaryocytic	1 (2%)		
#Spleen	(50)	(31)	(50)
Inflammation, acute		1 (3%)	1 (2%)
Infarct, acute	1 (2%)		
Amyloidosis	1 (2%)		
Pigmentation, NOS	41 (82%)	16 (52%)	45 (90%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM			
#Spleen (Continued)	(50)	(31)	(50)
Histiocytosis			1 (2%)
Hyperplasia, reticulum cell	1 (2%)		1 (2%)
Hyperplasia, lymphoid	13 (26%)	8 (26%)	7 (14%)
Hematopoiesis	46 (92%)	24 (77%)	47 (94%)
#Mandibular lymph node	(49)	(22)	(50)
Pigmentation, NOS	1 (2%)		2 (4%)
Histiocytosis			2 (4%)
Plasmacytosis	1 (2%)		1 (2%)
Hyperplasia, lymphoid	1 (2%)		3 (6%)
#Thoracic lymph node	(49)	(22)	(50)
Plasmacytosis		1 (5%)	
Hyperplasia, lymphoid	1 (2%)		
#Pancreatic lymph node	(49)	(22)	(50)
Hyperplasia, lymphoid		1 (5%)	
#Mesenteric lymph node	(49)	(22)	(50)
Congestion, NOS		1 (5%)	4 (8%)
Inflammation, chronic			1 (2%)
Necrosis, NOS		1 (5%)	
Histiocytosis	2 (4%)		1 (2%)
Erythrophagocytosis			1 (2%)
Hyperplasia, lymphoid	2 (4%)		4 (8%)
#Liver	(50)	(50)	(50)
Hyperplasia, reticulum cell	1 (2%)		
Hematopoiesis	16 (32%)	2 (4%)	20 (40%)
#Thymus	(41)	(17)	(45)
Embryonal duct cyst	1 (2%)		
Ultimobranchial cyst	1 (2%)		
Cyst, NOS	1 (2%)	1 (6%)	
Multiple cysts	2 (5%)	2 (12%)	3 (7%)
Hemorrhage			1 (2%)
Necrosis, NOS	1 (2%)		
Atrophy, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#Heart	(50)	(21)	(49)
Mineralization	1 (2%)	1 (5%)	
Inflammation, active chronic	1 (2%)		
Inflammation, chronic	4 (8%)	1 (5%)	3 (6%)
#Heart/atrium	(50)	(21)	(49)
Thrombosis, NOS			1 (2%)
*Artery	(50)	(50)	(50)
Periarteritis		1 (2%)	
#Pancreas	(50)	(48)	(50)
Periarteritis		1 (2%)	
*Mesentery	(50)	(50)	(50)
Periarteritis	1 (2%)		
#Testis	(50)	(18)	(50)
Periarteritis			1 (2%)
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Dysplasia, NOS	1 (2%)		
*Root of tooth	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		1 (2%)
Inflammation, active chronic	2 (4%)		2 (4%)
Inflammation, chronic	1 (2%)		1 (2%)
*Periodontal tissues	(50)	(50)	(50)
Inflammation, active chronic			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Salivary gland	(50)	(19)	(50)
Lymphocytic inflammatory infiltrate	3 (6%)	2 (11%)	1 (2%)
Atrophy, NOS		1 (5%)	3 (6%)
#Liver	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, acute	3 (6%)		3 (6%)
Inflammation, active chronic			2 (4%)
Inflammation, chronic		6 (12%)	1 (2%)
Fibrosis	1 (2%)		
Necrosis, coagulative	2 (4%)	5 (10%)	4 (8%)
Necrosis, ischemic	1 (2%)		
Infarct, NOS		2 (4%)	
Infarct, acute	1 (2%)		
Metamorphosis, fatty	4 (8%)	1 (2%)	1 (2%)
Cytoplasmic vacuolization		3 (6%)	1 (2%)
Focal cellular change	2 (4%)	1 (2%)	
Hepatocytomegaly	2 (4%)	1 (2%)	5 (10%)
Regeneration, NOS	1 (2%)		
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, coagulative	1 (2%)		
Metamorphosis, fatty	2 (4%)		4 (8%)
#Liver/periportal	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Metamorphosis, fatty			2 (4%)
*Gallbladder	(50)	(50)	(50)
Cyst, NOS	3 (6%)		1 (2%)
Multiple cysts	1 (2%)		1 (2%)
Inflammation, acute	3 (6%)	1 (2%)	1 (2%)
#Bile duct	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Multiple cysts			1 (2%)
#Pancreas	(50)	(48)	(50)
Lymphocytic inflammatory infiltrate		14 (29%)	1 (2%)
#Pancreatic acinus	(50)	(48)	(50)
Focal cellular change	1 (2%)	2 (4%)	
Atrophy, NOS	4 (8%)	1 (2%)	2 (4%)
Hyperplasia, NOS	2 (4%)		1 (2%)
#Esophagus	(50)	(19)	(50)
Ulcer, acute	1 (2%)		
#Gastric fundal gland	(50)	(18)	(50)
Dilatation, NOS	8 (16%)	2 (11%)	4 (8%)
#Glandular stomach	(50)	(18)	(50)
Mineralization	1 (2%)		1 (2%)
Inflammation, acute	2 (4%)	1 (6%)	
Inflammation, active chronic	3 (6%)		1 (2%)
Hyperplasia, epithelial	2 (4%)	2 (11%)	3 (6%)
#Forestomach	(50)	(18)	(50)
Multiple cysts	1 (2%)		
Ulcer, chronic	1 (2%)		
#Duodenum	(50)	(20)	(50)
Cyst, NOS		1 (5%)	1 (2%)
Inflammation, chronic	1 (2%)		
Hyperplasia, epithelial			1 (2%)
#Cecum	(47)	(18)	(50)
Inflammation, acute			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(18)	(50)
Hemorrhage	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)	3 (17%)	2 (4%)
Pyelonephritis, acute	1 (2%)	1 (6%)	
Pyelonephritis, acute/chronic	1 (2%)		
Inflammation, chronic	2 (4%)		
Nephropathy	2 (4%)		2 (4%)
Hyperplasia, tubular cell	33 (66%)	8 (44%)	31 (62%)
#Kidney/cortex	(50)	(18)	(50)
Cyst, NOS	1 (2%)		1 (2%)
Hemorrhage	2 (4%)		
Metaplasia, osseous	3 (6%)		5 (10%)
#Kidney/glomerulus	(50)	(18)	(50)
Necrosis, NOS			1 (2%)
#Kidney/tubule	(50)	(18)	(50)
Mineralization	27 (54%)	11 (61%)	21 (42%)
Dilatation, NOS	3 (6%)	1 (6%)	
Necrosis, NOS	6 (12%)	1 (6%)	1 (2%)
Pigmentation, NOS	4 (8%)		25 (50%)
Cytoplasmic vacuolization	42 (84%)	13 (72%)	25 (50%)
Regeneration, NOS	4 (8%)		2 (4%)
#Urinary bladder	(50)	(22)	(50)
Calculus, microscopic examination	1 (2%)		
Inflammation, active chronic		2 (9%)	
Inflammation, chronic		1 (5%)	
*Urethra	(50)	(50)	(50)
Calculus, microscopic examination	10 (20%)	4 (8%)	16 (32%)
Inflammation, chronic			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(18)	(47)
Cyst, NOS	4 (8%)		3 (6%)
Multiple cysts	3 (6%)		1 (2%)
Congestion, NOS			1 (2%)
Hyperplasia, NOS	3 (6%)		2 (4%)
#Adrenal/capsule	(49)	(18)	(50)
Inflammation, chronic			1 (2%)
Hyperplasia, NOS	47 (96%)	15 (83%)	48 (96%)
#Adrenal cortex	(49)	(18)	(50)
Degeneration, lipoid	1 (2%)		
Pigmentation, NOS	3 (6%)		6 (12%)
Hyperplasia, NOS	3 (6%)		4 (8%)
Hyperplasia, focal	1 (2%)		
#Adrenal medulla	(49)	(18)	(50)
Focal cellular change	1 (2%)		
Hyperplasia, NOS	2 (4%)	1 (6%)	4 (8%)
Hyperplasia, focal		1 (6%)	
#Thyroid	(50)	(17)	(49)
Cystic follicles	20 (40%)	2 (12%)	15 (31%)
Hyperplasia, C-cell		1 (6%)	1 (2%)
Hyperplasia, follicular cell	1 (2%)		1 (2%)
#Thyroid follicle	(50)	(17)	(49)
Atrophy, NOS	8 (16%)	1 (6%)	5 (10%)
#Pancreatic islets	(50)	(48)	(50)
Hyperplasia, NOS	24 (48%)	14 (29%)	13 (26%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Penis	(50)	(50)	(50)
Calculus, gross observation only		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Impaction, NOS		1 (2%)	
Cystic ducts		2 (4%)	1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)	2 (4%)
Inflammation, acute			1 (2%)
Inflammation, active chronic	2 (4%)	2 (4%)	2 (4%)
Inflammation, chronic	6 (12%)	8 (16%)	6 (12%)
#Prostate	(50)	(24)	(49)
Inflammation, acute		1 (4%)	
Inflammation, active chronic	1 (2%)	1 (4%)	
Inflammation, chronic		1 (4%)	
Hyperplasia, NOS			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	13 (26%)	11 (22%)	12 (24%)
Cyst, NOS			1 (2%)
Inflammation, active chronic	1 (2%)	1 (2%)	
#Testis	(50)	(18)	(50)
Atrophy, NOS	10 (20%)	4 (22%)	4 (8%)
Hyperplasia, interstitial cell		1 (6%)	1 (2%)
#Testis/tubule	(50)	(18)	(50)
Mineralization	2 (4%)	3 (17%)	5 (10%)
*Epididymis	(50)	(50)	(50)
Mineralization			1 (2%)
Inflammation, active chronic		1 (2%)	
Granuloma, spermatic	1 (2%)		
*Scrotum	(50)	(50)	(50)
Steatitis		2 (4%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(18)	(50)
Cyst, NOS	1 (2%)		
#Third ventricle	(50)	(18)	(50)
Granuloma, NOS			1 (2%)
Cholesterol deposit			1 (2%)
#Brain	(50)	(18)	(50)
Mineralization	26 (52%)	8 (44%)	18 (36%)
Congestion, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(50)	(50)	(50)
Hemorrhage	1 (2%)		4 (8%)
Lymphocytic inflammatory infiltrate		2 (4%)	
Polyp, NOS			1 (2%)
*Middle ear	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Knee joint	(50)	(50)	(50)
Ankylosis		1 (2%)	
*Tarsal joint	(50)	(50)	(50)
Ankylosis	21 (42%)	20 (40%)	17 (34%)
Osteoarthritis			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Pleura	(50)	(50)	(50)
Foreign body, NOS	3 (6%)		
Inflammation, acute	3 (6%)		
*Pleural mesothelium	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)		
*Pericardium	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, active chronic	1 (2%)		
*Mesentery	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Steatitis	1 (2%)	1 (2%)	
Abscess, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	43 (86%)	12 (24%)	45 (90%)
Inflammation, active chronic		1 (2%)	1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
None			

* Number of animals receiving complete necropsy examination; 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-4-NITROPHENOL

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	49
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(49)	(50)	(49)
Sebaceous adenocarcinoma	1 (2%)		
Fibrosarcoma	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(50)	(49)
Adenocarcinoma, NOS, invasive		1 (2%)	
Sebaceous adenocarcinoma, invasive	1 (2%)		
#Lung	(49)	(18)	(49)
Alveolar/bronchiolar adenoma	2 (4%)		1 (2%)
Alveolar/bronchiolar carcinoma		2 (11%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(49)
Malignant lymphoma, lymphocytic type	1 (2%)		
Malignant lymphoma, histiocytic type		1 (2%)	
Malignant lymphoma, mixed type	6 (12%)	5 (10%)	11 (22%)
Myelomonocytic leukemia		1 (2%)	
Granulocytic leukemia		1 (2%)	
#Spleen	(49)	(21)	(49)
Malignant lymphoma, mixed type	1 (2%)	2 (10%)	1 (2%)
#Liver	(49)	(50)	(49)
Malignant lymphoma, mixed type			1 (2%)
#Peyer's patch	(49)	(14)	(49)
Malignant lymphoma, mixed type		1 (7%)	1 (2%)
#Jejunum	(49)	(14)	(49)
Malignant lymphoma, mixed type			1 (2%)
#Ovary	(47)	(21)	(44)
Malignant lymphoma, mixed type	1 (2%)		
CIRCULATORY SYSTEM			
#Spleen	(49)	(21)	(49)
Hemangiosarcoma		1 (5%)	
#Mesenteric lymph node	(49)	(16)	(49)
Hemangiosarcoma, metastatic		1 (6%)	
#Uterus	(49)	(48)	(49)
Hemangioma		2 (4%)	1 (2%)
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(49)
Hepatocellular adenoma	1 (2%)	2 (4%)	3 (6%)
Hepatocellular carcinoma	2 (4%)		1 (2%)
#Forestomach	(49)	(10)	(49)
Squamous cell carcinoma		1 (10%)	
URINARY SYSTEM			
None			

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(22)	(49)
Adenoma, NOS		1 (5%)	
#Anterior pituitary	(49)	(22)	(49)
Adenoma, NOS	20 (41%)	10 (45%)	13 (27%)
Adenocarcinoma, NOS	1 (2%)		
Neurilemoma, malignant		1 (5%)	
#Adrenal medulla	(48)	(10)	(49)
Pheochromocytoma			1 (2%)
#Thyroid	(47)	(10)	(46)
Follicular cell adenoma	2 (4%)		
REPRODUCTIVE SYSTEM			
#Uterus	(49)	(48)	(49)
Leiomyoma		1 (2%)	
Endometrial stromal polyp	1 (2%)		
#Ovary	(47)	(21)	(44)
Granulosa cell tumor	1 (2%)		
Teratoma, benign			1 (2%)
Teratoma, NOS	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(49)	(15)	(49)
Neurilemoma, invasive		1 (7%)	
#Third ventricle	(49)	(15)	(49)
Lipoma			1 (2%)
#Brain	(49)	(15)	(49)
Adenocarcinoma, NOS, invasive	1 (2%)	1 (7%)	
Neurilemoma, invasive		1 (7%)	
SPECIAL SENSE ORGANS			
*Harderian gland	(49)	(50)	(49)
Adenocarcinoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Skull	(49)	(50)	(49)
Adenocarcinoma, NOS, invasive		1 (2%)	
*Lumbar vertebra	(49)	(50)	(49)
Osteosarcoma			1 (2%)
*Skeletal muscle	(49)	(50)	(49)
Fibrosarcoma, invasive		1 (2%)	
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
Cranial cavity			
Sebaceous adenocarcinoma, invasive	1		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	5	10
Moribund sacrifice	18	14	10
Terminal sacrifice	28	31	30
Dosing accident	1		
TUMOR SUMMARY			
Total animals with primary tumors**	32	27	29
Total primary tumors	42	34	41
Total animals with benign tumors	22	14	19
Total benign tumors	26	16	21
Total animals with malignant tumors	14	16	19
Total malignant tumors	14	18	20
Total animals with secondary tumors##	2	4	
Total secondary tumors	3	7	
Total animals with tumors uncertain-- benign or malignant	2		
Total uncertain tumors	2		

* 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-4-NITROPHENOL: VEHICLE CONTROL

ANIMAL NUMBER	12 26	12 25	13 30	11 19	14 48	11 12	11 11	11 10	14 55	14 42	14 46	14 47	12 22	10 06	10 04	13 32	12 28	12 21	12 27	11 17	13 36	13 38	10 01	10 02	10 03
WEEKS ON STUDY	00 01	00 06	00 06	03 38	05 38	06 66	06 68	07 71	07 75	08 89	09 90	09 90	09 91	09 92	09 95	09 97	09 98	09 99	10 00	10 01	10 02	10 02	10 05	10 05	10 05
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenocarcinoma										X															
Fibrosarcoma							X																		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	–	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Nasal cavity	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous adenocarcinoma, invasive										X															
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma									X																
Bile duct	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	A	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Stomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	A	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																	X		X		X				X
Adenocarcinoma, NOS																				X					
Adrenal	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	–	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Follicular cell adenoma																			X						
Parathyroid	+	–	+	+	A	–	+	+	+	+	+	+	–	+	+	–	+	+	+	–	–	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Uterus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Ovary	+	–	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
Teratoma, NOS									X																
Malignant lymphoma, mixed type																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive																				X					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type												X													
Malignant lymphoma, mixed type															X	X					X	X	X		
Cranial cavity					A																				
Sebaceous adenocarcinoma, invasive										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	105	107	108	109	113	114	115	116	118	120	123	124	129	131	133	134	135	137	139	140	141	143	144	149	150	TOTAL:
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Sebaceous adenocarcinoma																										1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma						X															X					2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Sebaceous adenocarcinoma, invasive																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type									X																	1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma						X																				1
Hepatocellular carcinoma						X																				2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X	X	X		X		X	X		X	X	X	X		X		X		X			X	X		X	20
Adenocarcinoma, NOS																										1
Adrenal	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																			X							2
Parathyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	40
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp																			X							1
Ovary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Granulosa cell tumor		X																								1
Teratoma, NOS																										1
Malignant lymphoma, mixed type					X																					1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, invasive																										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	*49
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type																									X	6
Cranial cavity																										
Sebaceous adenocarcinoma, invasive																										1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL: LOW DOSE

ANIMAL NUMBER	0007	0004	0022	0119	0220	0133	0155	0227	0228	0250	0117	0440	0449	0223	0444	0001	0110	0009	0330	0002	0003	0005	0006	0008	0111
WEEKS ON STUDY	057	082	082	085	086	087	088	092	092	092	099	100	100	101	101	102	102	103	103	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
Fibrosarcoma													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	+	+	−	−	+	−	−	−	−	+
Alveolar/bronchiolar carcinoma									X																
Trachea	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Nasal cavity	+	+	+	+	+	+	+	+	+	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, invasive												X													
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	−	−	+	−	−	−	−	−	+
Hemangiosarcoma														X											
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	−	−	−	+	−	−	−	−	−	+
Hemangiosarcoma, metastatic														X											
Thymus	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−	−	+	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Squamous cell carcinoma								X																	
Small intestine	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−
Urinary bladder	+	+	+	+	−	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	−	−	−	−	+	+	+	+	−	−	−	−	−	−	−
Adenoma, NOS							X									X		X							
Neurilemoma, malignant						X																			
Adrenal	+	+	−	+	+	+	+	+	+	+	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−
Thyroid	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Parathyroid	+	+	+	+	−	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+
Leiomyoma																									
Hemangioma																									
Ovary	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	−	−	−	−	−	+	+	−	−	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	+	+	−	−	−	−	−	−	−
Adenocarcinoma, NOS, invasive												X													
Neurilemoma, invasive					@X																				
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																									
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
Adenocarcinoma, NOS, invasive												X													
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												
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, histiocytic type																			X						
Malignant lymphoma, mixed type							X		X						X										X
Myelomonocytic leukemia			X																						
Granulocytic leukemia		X																							

@: Multiple occurrence of morphology

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

ANIMAL NUMBER	0121	0141	0161	0181	0201	0241	0251	0261	0291	0311	0321	0331	0341	0351	0361	0371	0381	0391	0411	0421	0431	0445	0461	0471	0481	TOTAL:
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
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	N	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	18
Alveolar/bronchiolar carcinoma																						X				2
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Nasal 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
Adenocarcinoma, NOS, invasive																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Spleen	–	+	–	–	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–	–	–	+	–	–	+	21
Hemangiosarcoma																										1
Malignant lymphoma, mixed type																						X			X	2
Lymph nodes	–	–	+	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	16
Hemangiosarcoma, metastatic																										1
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X					X																2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	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
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	12
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Squamous cell carcinoma																										1
Small intestine	–	–	–	–	–	–	+	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	14
Malignant lymphoma, mixed type														X												1
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
URINARY SYSTEM																										
Kidney	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
Urinary bladder	–	–	–	–	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	11
ENDOCRINE SYSTEM																										
Pituitary	–	+	–	+	–	–	–	–	–	+	+	–	+	+	+	–	–	+	–	–	–	–	–	–	–	22
Adenoma, NOS		X		X						X	X		X	X	X			X								11
Neurilemoma, malignant																										1
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
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
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyoma										X																1
Hemangioma																					X	X				2
Ovary	–	–	–	–	+	–	–	–	–	–	+	–	–	+	–	+	–	–	–	–	–	–	–	–	+	21
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	15
Adenocarcinoma, NOS, invasive																										1
Neurilemoma, invasive																										1
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																										
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
Adenocarcinoma, NOS, invasive																										1
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
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, histiocytic type																										1
Malignant lymphoma, mixed type								X																		5
Myelomonocytic leukemia																										1
Granulocytic leukemia																										1

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL: HIGH DOSE

ANIMAL NUMBER	05 56	09 97	07 76	09 91	07 73	09 92	09 93	10 00	09 99	08 87	09 00	06 67	09 96	08 84	06 69	05 58	08 85	07 77	06 62	05 51	05 52	05 53	05 54	05 55	05 57
WEEKS ON STUDY	01 00	01 00	01 01	01 01	01 01	01 01	01 01	03 36	05 54	06 00	06 00	07 00	07 73	08 85	09 93	09 95	09 95	09 97	09 99	10 02	10 05	10 05	10 05	10 05	10 05
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	−	+	−	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	A	+	+	−	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	−	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Malignant lymphoma, mixed type																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	N	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	−	+	+	−	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																							X		
Large intestine	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																	X			X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	−	+	−	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	−	+	+	−	−	−	−	+	+	−	A	−	−	−	+	−	−	−	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									X
Ovary	+	+	−	+	+	+	−	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	−	+	−
Teratoma, benign	X																								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	A	N	N	+	N	N	N X	N	N	N	N	N	N	N
Osteosarcoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, mixed type													X		X	X	X			X					

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

ANIMAL NUMBER	059	060	061	063	064	065	066	068	070	071	072	074	075	078	079	080	081	082	083	086	088	089	094	095	098	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																	X		X			X				3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type											X															1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma					X				X				X													3
Hepatocellular carcinoma																X										1
Malignant lymphoma, mixed type	X																									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type																						X				2
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS				X	X	X					X		X	X				X				X	X	X	X	13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																	X									1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid	+	+	–	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	33
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Ovary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Teratoma, benign																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lipoma			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	*49
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	*49
Malignant lymphoma, mixed type								X	X					X				X		X			X			11

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	125 mg/kg	250 mg/kg
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/49 (0%)	(b) 2/18 (11%)	3/49 (6%)
Adjusted Rates (c)	0.0%		10.0%
Terminal Rates (d)	0/28 (0%)		3/30 (10%)
Week of First Observation			105
Life Table Test (e)			P=0.132
Incidental Tumor Test (e)			P=0.132
Fisher Exact Test (e)			P=0.121
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	2/49 (4%)	(b) 2/18 (11%)	4/49 (8%)
Adjusted Rates (c)	7.1%		13.3%
Terminal Rates (d)	2/28 (7%)		4/30 (13%)
Week of First Observation	105		105
Life Table Test (e)			P=0.367
Incidental Tumor Test (e)			P=0.367
Fisher Exact Test (e)			P=0.339
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	8/49 (16%)	(b,f) 8/50 (16%)	15/49 (31%)
Adjusted Rates (c)	24.4%		42.4%
Terminal Rates (d)	4/28 (14%)		10/30 (33%)
Week of First Observation	95		73
Life Table Test (e)			P=0.103
Incidental Tumor Test (e)			P=0.045
Fisher Exact Test (e)			P=0.076
Hematopoietic System: All Lymphomas			
Overall Rates (a)	9/49 (18%)	(b,f) 9/50 (18%)	15/49 (31%)
Adjusted Rates (c)	26.3%		42.4%
Terminal Rates (d)	4/28 (14%)		10/30 (33%)
Week of First Observation	90		73
Life Table Test (e)			P=0.153
Incidental Tumor Test (e)			P=0.057
Fisher Exact Test (e)			P=0.120
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	9/49 (18%)	(b,f) 11/50 (22%)	15/49 (31%)
Adjusted Rates (c)	26.3%		42.4%
Terminal Rates (d)	4/28 (14%)		10/30 (33%)
Week of First Observation	90		73
Life Table Test (e)			P=0.153
Incidental Tumor Test (e)			P=0.057
Fisher Exact Test (e)			P=0.120
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	0/49 (0%)	(b,f) 3/50 (6%)	1/49 (2%)
Adjusted Rates (c)	0.0%		3.3%
Terminal Rates (d)	0/28 (0%)		1/30 (3%)
Week of First Observation			105
Life Table Test (e)			P=0.514
Incidental Tumor Test (e)			P=0.514
Fisher Exact Test (e)			P=0.500
Liver: Hepatocellular Adenoma			
Overall Rates (a)	1/49 (2%)	2/50 (4%)	3/49 (6%)
Adjusted Rates (c)	3.6%	6.5%	10.0%
Terminal Rates (d)	1/28 (4%)	2/31 (6%)	3/30 (10%)
Week of First Observation	105	105	105
Life Table Tests (e)	P=0.238	P=0.536	P=0.329
Incidental Tumor Tests (e)	P=0.238	P=0.536	P=0.329
Cochran-Armitage Trend Test (e)	P=0.221		
Fisher Exact Test (e)		P=0.508	P=0.309

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	125 mg/kg	250 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	2/49 (4%)	2/50 (4%)	4/49 (8%)
Adjusted Rates (c)	5.9%	6.5%	13.3%
Terminal Rates (d)	1/28 (4%)	2/31 (6%)	4/30 (13%)
Week of First Observation	75	105	105
Life Table Tests (e)	P=0.265	P=0.652N	P=0.354
Incidental Tumor Tests (e)	P=0.277	P=0.616	P=0.364
Cochran-Armitage Trend Test (e)	P=0.251		
Fisher Exact Test (e)		P=0.684N	P=0.339
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	20/49 (41%)	(b) 10/22 (45%)	13/49 (27%)
Adjusted Rates (c)	64.3%		40.5%
Terminal Rates (d)	17/28 (61%)		11/30 (37%)
Week of First Observation	98		95
Life Table Test (e)			P=0.059N
Incidental Tumor Test (e)			P=0.071N
Fisher Exact Test (e)			P=0.100N
Anterior Pituitary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	21/49 (43%)	(b) 10/22 (45%)	13/49 (27%)
Adjusted Rates (c)	65.4%		40.5%
Terminal Rates (d)	17/28 (61%)		11/30 (37%)
Week of First Observation	98		95
Life Table Test (e)			P=0.040N
Incidental Tumor Test (e)			P=0.048N
Fisher Exact Test (e)			P=0.068N
All Sites: Benign Tumors			
Overall Rates (a)	22/49 (45%)	14/50 (28%)	19/49 (39%)
Adjusted Rates (c)	70.8%	40.6%	57.0%
Terminal Rates (d)	19/28 (68%)	11/31 (35%)	16/30 (53%)
Week of First Observation	98	88	10
Life Table Tests (e)	P=0.217N	P=0.025N	P=0.237N
Incidental Tumor Tests (e)	P=0.246N	P=0.020N	P=0.255N
Cochran-Armitage Trend Test (e)	P=0.301N		
Fisher Exact Test (e)		P=0.062N	P=0.341N
All Sites: Malignant Tumors			
Overall Rates (a)	14/49 (29%)	16/50 (32%)	19/49 (39%)
Adjusted Rates (c)	36.4%	36.2%	52.5%
Terminal Rates (d)	5/28 (18%)	5/31 (16%)	13/30 (43%)
Week of First Observation	68	82	73
Life Table Tests (e)	P=0.203	P=0.569	P=0.238
Incidental Tumor Tests (e)	P=0.039	P=0.578N	P=0.078
Cochran-Armitage Trend Test (e)	P=0.167		
Fisher Exact Test (e)		P=0.440	P=0.196
All Sites: All Tumors			
Overall Rates (a)	32/49 (65%)	27/50 (54%)	29/49 (59%)
Adjusted Rates (c)	81.8%	60.8%	78.1%
Terminal Rates (d)	21/28 (75%)	14/31 (45%)	22/30 (73%)
Week of First Observation	68	82	10
Life Table Tests (e)	P=0.275N	P=0.111N	P=0.281N
Incidental Tumor Tests (e)	P=0.471N	P=0.048N	P=0.426N
Cochran-Armitage Trend Test (e)	P=0.303N		
Fisher Exact Test (e)		P=0.174N	P=0.339N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Incomplete sampling of tissues
(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) Only 21 spleens were examined microscopically.

TABLE D4. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Physiological Research Laboratories			
2-Amino-5-nitrophenol	13/49	0/49	13/49
4-Hexylresorcinol	12/49	1/49	13/49
2-Mercaptobenzothiazole	20/49	1/49	21/49
TOTAL	45/147 (30.6%)	2/147 (1.4%)	47/147 (32.0%)
SD (b)	8.90%	1.18%	9.43%
Range (c)			
High	20/49	1/49	21/49
Low	12/49	0/49	13/49
Overall Historical Incidence			
TOTAL	(d) 308/1,562 (19.7%)	(e) 21/1,562 (1.3%)	(d,e) 329/1,562 (21.1%)
SD (b)	9.47%	2.46%	9.84%
Range (c)			
High	20/49	5/47	21/49
Low	2/44	0/49	2/44

(a) Data as of August 7, 1986, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes 38 chromophobe adenomas and 1 acidophil adenoma
(e) Includes five adenocarcinomas, NOS, and one acidophil carcinoma

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL

	Vehicle Control	Low Dose	High Dose
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	49
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(49)
Inflammation, chronic			1 (2%)
*Subcutaneous tissue	(49)	(50)	(49)
Multiple cysts	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(49)	(50)	(49)
Hemorrhage	3 (6%)	1 (2%)	2 (4%)
Lymphocytic inflammatory infiltrate	4 (8%)	1 (2%)	11 (22%)
Inflammation, acute	5 (10%)		
#Trachea	(47)	(10)	(46)
Hemorrhage			1 (2%)
#Lung	(49)	(18)	(49)
Mineralization			1 (2%)
Congestion, NOS	1 (2%)	2 (11%)	10 (20%)
Hemorrhage	9 (18%)		9 (18%)
Lymphocytic inflammatory infiltrate	3 (6%)		7 (14%)
Bronchopneumonia, acute	1 (2%)		
Inflammation, active chronic	1 (2%)		
Pneumonia, interstitial chronic		1 (6%)	
Bronchopneumonia, chronic	4 (8%)	3 (17%)	1 (2%)
Cholesterol deposit		1 (6%)	
Hyperplasia, alveolar epithelium	3 (6%)	3 (17%)	
Histiocytosis	6 (12%)	5 (28%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(10)	(48)
Fibrosis	8 (16%)	2 (20%)	12 (25%)
Hyperplasia, cystic			1 (2%)
Myelofibrosis	4 (8%)		1 (2%)
Hyperplasia, granulocytic	39 (80%)	6 (60%)	22 (46%)
#Spleen	(49)	(21)	(49)
Pigmentation, NOS	41 (84%)	11 (52%)	42 (86%)
Hyperplasia, lymphoid	20 (41%)	5 (24%)	17 (35%)
Hematopoiesis	45 (92%)	15 (71%)	43 (88%)
#Mandibular lymph node	(49)	(16)	(49)
Inflammation, acute	1 (2%)		
Histiocytosis	1 (2%)		
Plasmacytosis	1 (2%)		
Hyperplasia, lymphoid	2 (4%)		3 (6%)
#Mesenteric lymph node	(49)	(16)	(49)
Hyperplasia, lymphoid	2 (4%)		
*Bone	(49)	(50)	(49)
Hyperplasia, granulocytic	1 (2%)		
#Liver	(49)	(50)	(49)
Hematopoiesis	30 (61%)	10 (20%)	17 (35%)
#Adrenal cortex	(48)	(10)	(49)
Hematopoiesis	1 (2%)		
#Thymus	(46)	(11)	(47)
Cyst, NOS	1 (2%)		1 (2%)
Multiple cysts		1 (9%)	
Necrosis, NOS	1 (2%)		
Hyperplasia, lymphoid		1 (9%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM			
#Heart	(49)	(11)	(49)
Mineralization	1 (2%)	1 (9%)	1 (2%)
*Artery	(49)	(50)	(49)
Mineralization			1 (2%)
*Aorta	(49)	(50)	(49)
Mineralization			1 (2%)
*Pulmonary artery	(49)	(50)	(49)
Mineralization	1 (2%)		1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(12)	(49)
Lymphocytic inflammatory infiltrate		1 (8%)	
Inflammation, chronic		1 (8%)	
#Liver	(49)	(50)	(49)
Cyst, NOS		1 (2%)	
Congestion, NOS		2 (4%)	
Lymphocytic inflammatory infiltrate		27 (54%)	1 (2%)
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, active chronic	1 (2%)		
Necrosis, coagulative		1 (2%)	1 (2%)
Metamorphosis, fatty	1 (2%)	1 (2%)	2 (4%)
Cytoplasmic vacuolization	2 (4%)		1 (2%)
Focal cellular change	3 (6%)	1 (2%)	2 (4%)
Hepatocytomegaly	3 (6%)	2 (4%)	
#Liver/centrilobular	(49)	(50)	(49)
Metamorphosis, fatty	1 (2%)		
#Liver/periportal	(49)	(50)	(49)
Inflammation, acute	1 (2%)		
Inflammation, active chronic			3 (6%)
Inflammation, chronic		4 (8%)	
Degeneration, hydropic	1 (2%)		
Metamorphosis, fatty	2 (4%)	1 (2%)	
*Gallbladder	(49)	(50)	(49)
Cyst, NOS	2 (4%)		1 (2%)
Multiple cysts			1 (2%)
#Bile duct	(49)	(50)	(49)
Cyst, NOS			1 (2%)
#Pancreas	(49)	(50)	(49)
Cystic ducts	1 (2%)	1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate		23 (46%)	1 (2%)
Focal cellular change		1 (2%)	
#Pancreatic duct	(49)	(50)	(49)
Calculus, microscopic examination		1 (2%)	
#Pancreatic acinus	(49)	(50)	(49)
Necrosis, NOS			1 (2%)
Cytoplasmic vacuolization	1 (2%)		
Focal cellular change		1 (2%)	
Atrophy, NOS	2 (4%)	5 (10%)	2 (4%)
Hyperplasia, NOS		2 (4%)	
#Esophagus	(47)	(12)	(47)
Hemorrhage	1 (2%)		
Necrosis, NOS	1 (2%)		
#Gastric fundal gland	(49)	(10)	(49)
Dilatation, NOS	5 (10%)		4 (8%)
#Glandular stomach	(49)	(10)	(49)
Mineralization	1 (2%)		3 (6%)
Metaplasia, squamous			1 (2%)
#Forestomach	(49)	(10)	(49)
Inflammation, acute			1 (2%)
Inflammation, active chronic		1 (10%)	
Inflammation, chronic	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
*Rectum	(49)	(50)	(49)
Inflammation, active chronic			1 (2%)
URINARY SYSTEM			
#Kidney	(49)	(12)	(49)
Hemorrhage			1 (2%)
Lymphocytic inflammatory infiltrate	2 (4%)	1 (8%)	2 (4%)
Inflammation, chronic	1 (2%)	2 (17%)	1 (2%)
Nephrosis, NOS	2 (4%)		
Hyperplasia, tubular cell	7 (14%)	2 (17%)	10 (20%)
#Kidney/cortex	(49)	(12)	(49)
Metaplasia, osseous	1 (2%)		
#Kidney/tubule	(49)	(12)	(49)
Mineralization	8 (16%)		7 (14%)
Dilatation, NOS	6 (12%)	1 (8%)	5 (10%)
Necrosis, NOS	1 (2%)		1 (2%)
Cytoplasmic vacuolization	6 (12%)	8 (67%)	2 (4%)
Regeneration, NOS	1 (2%)		1 (2%)
#Urinary bladder	(45)	(11)	(47)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, chronic		1 (9%)	
Metaplasia, squamous		1 (9%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(22)	(49)
Cyst, NOS	1 (2%)	1 (5%)	4 (8%)
Multiple cysts		1 (5%)	
Hyperplasia, NOS	5 (10%)	3 (14%)	8 (16%)
#Adrenal/capsule	(48)	(10)	(49)
Pigmentation, NOS		1 (10%)	
Hyperplasia, NOS	48 (100%)	10 (100%)	48 (98%)
Hyperplasia, cystic			1 (2%)
#Adrenal cortex	(48)	(10)	(49)
Cyst, NOS			1 (2%)
Hemorrhagic cyst			1 (2%)
Degeneration, lipoid	1 (2%)		
Metamorphosis, fatty	2 (4%)		
Pigmentation, NOS	38 (79%)	5 (50%)	38 (78%)
Cytomegaly	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Adrenal medulla	(48)	(10)	(49)
Hyperplasia, NOS		1 (10%)	1 (2%)
Hyperplasia, focal			2 (4%)
#Thyroid	(47)	(10)	(46)
Cystic follicles	23 (49%)	4 (40%)	13 (28%)
Inflammation, acute	1 (2%)		
Hyperplasia, follicular cell	6 (13%)		3 (7%)
#Thyroid follicle	(47)	(10)	(46)
Atrophy, NOS	4 (9%)	1 (10%)	2 (4%)
#Parathyroid	(40)	(8)	(33)
Cyst, NOS	1 (3%)		
Multiple cysts	1 (3%)		
#Pancreatic islets	(49)	(50)	(49)
Hyperplasia, NOS	10 (20%)	4 (8%)	1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(49)
Hyperplasia, cystic	18 (37%)	2 (4%)	10 (20%)
#Uterus	(49)	(48)	(49)
Hydrometra	5 (10%)	1 (2%)	4 (8%)
Inflammation, suppurative	1 (2%)		
Inflammation, acute	6 (12%)	3 (6%)	6 (12%)
#Uterus/endometrium	(49)	(48)	(49)
Inflammation, acute		3 (6%)	
Inflammation, active chronic		1 (2%)	
Hyperplasia, cystic	44 (90%)	48 (100%)	42 (86%)
Metaplasia, squamous	1 (2%)		1 (2%)
#Ovary	(47)	(21)	(44)
Mineralization	1 (2%)		
Follicular cyst, NOS	4 (9%)	1 (5%)	
Parovarian cyst	8 (17%)	9 (43%)	7 (16%)
Hemorrhagic cyst	1 (2%)	1 (5%)	
Abscess, NOS	1 (2%)		
#Ovary/follicle	(47)	(21)	(44)
Inflammation, acute	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(49)	(15)	(49)
Lymphocytic inflammatory infiltrate		1 (7%)	
Inflammation, active chronic			1 (2%)
#Fourth ventricle	(49)	(15)	(49)
Hemorrhage	1 (2%)		
*Choroid plexus	(49)	(50)	(49)
Granuloma, NOS	1 (2%)		
Cholesterol deposit	1 (2%)		
Metaplasia, squamous	1 (2%)		
#Brain	(49)	(15)	(49)
Compression, NOS	1 (2%)	3 (20%)	1 (2%)
Mineralization	21 (43%)	7 (47%)	13 (27%)
Congestion, NOS			1 (2%)
Hemorrhage	1 (2%)		
SPECIAL SENSE ORGANS			
*Nasolacrimal duct	(49)	(50)	(49)
Hemorrhage	3 (6%)	1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate			2 (4%)
*Middle ear	(49)	(50)	(49)
Inflammation, suppurative	2 (4%)		
MUSCULOSKELETAL SYSTEM			
*Bone	(49)	(50)	(49)
Fibrosis	3 (6%)		
BODY CAVITIES			
*Pleura	(49)	(50)	(49)
Inflammation, active chronic	1 (2%)		
Infection, bacterial	1 (2%)		
*Mesentery	(49)	(50)	(49)
Cyst, NOS	1 (2%)	2 (4%)	
Steatitis		3 (6%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 2-AMINO-4-NITROPHENOL (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(49)
Lymphocytic inflammatory infiltrate	44 (90%)	7 (14%)	36 (73%)
Calcification, metastatic	1 (2%)		
Panniculus adiposus			
Atrophy, NOS		1	
SPECIAL MORPHOLOGY SUMMARY			
Autolysis/no necropsy	1		1

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

APPENDIX E

GENETIC TOXICOLOGY OF

2-AMINO-4-NITROPHENOL

TABLE E1. MUTAGENICITY OF 2-AMINO-4-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
Study Performed at SRI International							
TA100	0	139 ± 7.8	107 ± 4.0	163 ± 8.8	129 ± 6.9	112 ± 7.9	142 ± 4.3
	10	--	--	--	--	146 ± 3.2	121 ± 5.4
	33	135 ± 9.5	114 ± 4.7	156 ± 8.4	164 ± 10.3	162 ± 7.7	133 ± 4.9
	100	145 ± 8.4	117 ± 11.8	223 ± 11.0	210 ± 8.7	169 ± 10.2	132 ± 14.2
	333	142 ± 6.2	101 ± 7.4	247 ± 9.0	268 ± 2.9	191 ± 6.4	134 ± 10.0
	1,000	146 ± 10.3	97 ± 11.6	282 ± 5.9	289 ± 17.3	180 ± 3.5	122 ± 2.7
	3,333	(c) 86 ± 49.7	Toxic	(c) 0 ± 0.0	(c) 0 ± 0.0	--	--
	Trial summary	Negative	Negative	Weakly positive	Positive	Weakly positive	Negative
	Positive control (d)	434 ± 3.7	407 ± 18.7	1,796 ± 23.7	1,290 ± 45.3	551 ± 3.5	690 ± 15.4
TA1535	0	27 ± 0.9	--	42 ± 4.5	--	46 ± 3.8	--
	33	29 ± 3.7	--	41 ± 2.1	--	28 ± 1.7	--
	100	25 ± 3.5	--	36 ± 0.3	--	21 ± 1.8	--
	333	27 ± 3.0	--	37 ± 2.2	--	16 ± 1.2	--
	1,000	28 ± 5.2	--	32 ± 3.5	--	(c) 0 ± 0.0	--
	3,333	(c) 9 ± 3.1	--	(c) 0 ± 0.0	--	Toxic	--
	Trial summary	Negative	--	Negative	--	Negative	--
	Positive control (d)	427 ± 7.1	--	536 ± 12.8	--	277 ± 7.1	--
TA1537	0	5 ± 0.9	--	5 ± 0.6	--	10 ± 1.0	--
	33	6 ± 1.0	--	12 ± 2.8	--	7 ± 1.2	--
	100	6 ± 1.7	--	12 ± 4.0	--	7 ± 0.9	--
	333	6 ± 0.3	--	15 ± 1.3	--	11 ± 1.2	--
	1,000	10 ± 2.0	--	10 ± 2.0	--	12 ± 2.3	--
	3,333	5 ± 0.3	--	(c) 0 ± 0.0	--	9 ± 1.7	--
	Trial summary	Negative	--	Negative	--	Negative	--
	Positive control (d)	172 ± 4.7	--	500 ± 5.5	--	167 ± 14.8	--
TA98	0	29 ± 2.2	21 ± 2.0	37 ± 3.7	37 ● 4.3	37 ± 3.5	40 ± 1.7
	10	--	--	--	--	44 ± 1.3	27 ± 1.5
	33	52 ± 7.2	26 ± 3.1	50 ± 3.0	54 ± 3.2	53 ± 0.7	38 ± 4.2
	100	64 ± 4.6	30 ± 2.7	67 ± 3.6	62 ± 3.7	57 ± 1.9	50 ± 2.3
	333	64 ± 6.6	17 ± 2.3	94 ± 4.7	86 ± 0.3	75 ± 6.8	55 ± 3.5
	1,000	84 ± 7.1	17 ± 1.0	242 ± 19.6	113 ± 13.5	83 ± 1.2	56 ± 4.7
	3,333	(c) 0 ± 0.0	Toxic	Toxic	(c) 0 ± 0.0	--	--
	Trial summary	Positive	Negative	Positive	Positive	Positive	Negative
	Positive control (d)	724 ± 7.1	724 ± 34.0	1,514 ±107.5	1,027 ± 53.1	382 ± 27.0	425 ± 15.3

TABLE E1. MUTAGENICITY OF 2-AMINO-4-NITROPHENOL IN *SALMONELLA TYPHIMURIUM* (Continued)

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
Studies Performed at Case Western Reserve University							
TA100	0	165 ± 16.2	61 ± 6.4	238 ± 13.5	93 ± 5.2	220 ± 7.3	80 ± 7.2
	33	188 ± 7.8	59 ± 9.8	198 ± 11.7	85 ± 10.1	223 ± 6.9	66 ± 7.5
	100	200 ± 15.3	60 ± 2.8	245 ± 16.8	93 ± 6.7	197 ± 2.5	74 ± 3.8
	333	204 ± 2.8	59 ± 4.8	249 ± 10.4	93 ± 14.8	210 ± 8.3	70 ± 2.4
	1,000	179 ± 17.9	51 ± 2.7	246 ± 18.0	85 ± 8.1	203 ± 29.4	85 ± 8.7
	3,333	61 ± 4.4	27 ± 3.5	103 ± 5.8	42 ± 1.7	67 ± 7.9	28 ± 7.2
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	911 ± 35.7	1,610 ± 77.6	1,550 ± 95.5	2,524 ± 217.1	1,897 ± 81.2	1,430 ± 157.3
TA1537	0	7 ± 1.7	13 ± 1.2	25 ± 5.5	16 ± 1.5	15 ± 0.9	16 ± 1.8
	33	7 ± 1.5	16 ± 3.4	21 ± 2.3	21 ± 2.8	15 ± 0.0	12 ± 1.2
	100	12 ± 2.2	17 ± 4.2	14 ± 2.2	16 ± 0.7	15 ± 2.2	11 ± 1.7
	333	12 ± 1.5	16 ± 2.1	15 ± 5.2	17 ± 2.1	21 ± 3.1	12 ± 2.3
	1,000	14 ± 1.2	14 ± 0.6	16 ± 3.3	18 ± 0.9	19 ± 1.9	10 ± 1.7
	3,333	7 ± 0.6	6 ± 0.0	18 ± 1.3	11 ± 1.5	14 ± 1.9	7 ± 0.7
	Trial summary	Negative	Negative	Negative	Negative	Negative	Negative
	Positive control (d)	149 ± 41.9	303 ± 30.7	159 ± 2.6	338 ± 23.1	130 ± 4.5	167 ± 17.3
TA98	0	15 ± 2.7	12 ± 0.6	33 ± 0.7	18 ± 0.7	33 ± 5.6	19 ± 0.6
	33	18 ± 2.7	16 ± 3.2	29 ± 2.6	18 ± 1.5	31 ± 3.5	21 ± 2.3
	100	23 ± 6.7	25 ± 3.1	38 ± 5.2	20 ± 2.9	33 ± 3.2	17 ± 0.9
	333	21 ± 1.2	19 ± 0.7	41 ± 3.8	39 ± 6.9	33 ± 3.8	18 ± 2.6
	1,000	28 ± 1.9	22 ± 4.1	67 ± 5.5	49 ± 2.9	28 ± 3.5	18 ± 1.0
	3,333	25 ± 3.0	12 ± 1.5	90 ± 3.4	63 ± 6.7	31 ± 3.3	16 ± 3.7
	Trial summary	Equivocal	Equivocal	Positive	Positive	Negative	Negative
	Positive control (d)	195 ± 33.0	264 ± 15.6	1,114 ± 44.8	897 ± 67.9	1,076 ± 88.6	618 ± 134.3

Strain	Dose (µg/plate)	Revertants/plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (hamster) Trial 3	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA1535	0	14 ± 1.2	8 ± 1.2	11 ± 1.5	8 ± 1.3	8 ± 1.7	9 ± 1.9	13 ± 0.3
	33	9 ± 2.1	6 ± 0.3	14 ± 1.5	15 ± 1.5	11 ± 1.5	12 ± 0.9	11 ± 2.6
	100	14 ± 0.3	4 ± 1.7	19 ± 2.0	14 ± 2.6	5 ± 1.9	18 ± 1.2	14 ± 3.5
	333	15 ± 1.8	6 ± 1.5	25 ± 3.5	13 ± 0.7	14 ± 1.3	18 ± 3.6	6 ± 1.2
	1,000	16 ± 3.0	5 ± 0.3	30 ± 3.3	14 ± 0.5	9 ± 2.2	17 ± 2.0	5 ± 1.9
	3,333	10 ± 0.0	1 ± 0.7	18 ± 2.7	5 ± 1.2	0 ± 0.0	10 ± 2.6	0 ± 0.3
	Trial summary	Negative	Negative	Weakly positive	Negative	Negative	Negative	Negative
	Positive control (c)	414 ± 69.9	117 ± 8.4	191 ± 56.0	131 ± 29.6	46 ± 8.4	58 ± 13.5	43 ± 4.2

(a) The detailed protocol is presented by Haworth et al. (1983). Cells and study compound or solvent (SRI study: 95% ethanol; Case Western Reserve University study: 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) Slight toxicity
(d) 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-4-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 (d)		96.5 ± 8.6	99.8 ± 2.0	121.5 ± 10.3	42.5 ± 3.7
2-Amino-4-nitrophenol	25	61.0 ± 5.2	56.0 ± 3.0	180.3 ± 23.4	(e) 97.7 ± 8.6
	50	65.7 ± 3.3	52.3 ± 1.2	212.3 ± 11.6	(e) 108.0 ± 4.4
	100	55.7 ± 5.0	22.3 ± 2.3	321.7 ± 15.3	(e) 194.3 ± 8.0
	150	53.3 ± 4.9	6.0 ± 2.0	431.0 ± 38.1	(e) 271.0 ± 14.9
	(f) 200	49.0 ± 3.0	3.5 ± 0.5	399.5 ± 33.5	(e) 272.5 ± 5.5
	300	Lethal	--	--	--
Methyl methanesulfonate	5	69.0 ± 4.0	48.7 ± 11.3	536.3 ± 30.9	(e) 258.3 ± 0.9
Trial 2					
Dimethyl sulfoxide		104.3 ± 5.7	100.0 ± 8.5	90.3 ± 4.1	29.3 ± 2.8
2-Amino-4-nitrophenol	50	79.7 ± 7.1	45.3 ± 2.8	170.0 ± 15.1	(e) 71.7 ± 2.7
	75	88.7 ± 12.8	47.0 ± 5.1	193.3 ± 28.8	(e) 73.0 ± 1.5
	100	89.3 ± 1.5	30.7 ± 3.5	219.0 ± 12.0	(e) 82.0 ± 4.7
	150	82.0 ± 7.8	19.0 ± 1.0	291.7 ± 39.4	(e) 118.0 ± 6.8
	200	81.7 ± 7.0	11.3 ± 3.5	320.7 ± 21.3	(e) 133.3 ± 13.0
	300	81.0 ± 9.8	6.0 ± 1.0	344.0 ± 28.3	(e) 143.7 ± 6.4
Methyl methanesulfonate	5	63.3 ± 5.8	47.3 ± 8.1	622.3 ± 24.1	(e) 334.7 ± 35.6

(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 in the absence of exogenous metabolic activation. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

(b) Mean ± standard error of replicate trials 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 four 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 presented are the average of two tests; the dose in one test was lethal.

TABLE E3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 2-AMINO-4-NITROPHENOL (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)--Summary: Positive								
Dimethyl sulfoxide		50	1,029	600	0.58	12.0	25.5	--
2-Amino-4-nitrophenol	5	50	1,018	720	0.71	14.4	25.5	120.0
	16.7	50	1,012	1,048	1.04	21.0	(d) 34.3	175.0
	50	50	1,013	1,074	1.06	21.5	(d) 34.3	179.2
Mitomycin C	0.001	50	1,036	644	0.62	12.9	25.5	107.5
	0.010	5	103	259	2.51	51.8	25.5	431.7
+S9 (e)--Summary: Positive								
Dimethyl sulfoxide		50	1,036	424	0.41	8.5	25.5	--
2-Amino-4-nitrophenol	1,740	50	1,031	616	0.60	12.3	25.5	144.7
	2,180	50	1,015	744	0.73	14.9	(d) 34.0	175.3
	2,670	50	1,007	936	0.93	18.7	(d) 34.0	220.0
Cyclophosphamide	0.3	50	1,041	664	0.64	13.3	25.5	156.5
	2	5	104	146	1.40	29.2	25.5	343.5

(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-4-NITROPHENOL (a)

−S9 (b)					+S9 (c)				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time 20.8 h (d)					Harvest time 20.8 h (d)				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	2	0.02	2		100	2	0.02	2
	100	2	0.02	2		100	1	0.01	1
2-Amino-4-nitrophenol					2-Amino-4-nitrophenol				
150	100	12	0.12	3	2,460	100	14	0.14	5
199	100	7	0.07	6	2,760	100	103	1.03	28
249	100	12	0.12	11	2,990	50	74	1.48	34
300	0				3,520	0			
Summary: Weakly positive					Summary: Positive				
Mitomycin C					Cyclophosphamide				
0.062	50	18	0.36	26	10	50	10	0.20	18

(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 (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, 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) 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.
(d) Because of significant chemically induced cell cycle delay, incubation time before addition of colcemid was lengthened to provide sufficient metaphases at harvest.

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 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 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 (6,12,24 mo) MHV (6,12,24 mo)	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (18 mo)	MHV (mouse hepatitis virus) (18 mo)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6,12,24 mo)	RCV (rat coronavirus) Sendai (18 mo)	*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-4-NITROPHENOL (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	10/10	PVM
	10/10	RCV
	10/10	Sendai
12	9/10	RCV
18	10/10	Sendai
	7/10	RCV
	10/10	PVM
24	3/9	Sendai
	2/9	RCV
	9/9	PVM
MICE		
6	(b) 1/11	PVM
	(b) 5/11	Sendai
12	5/10	Sendai
	3/10	PVM
18	5/6	Sendai
24	2/10	PVM
	1/10	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) Includes a sample from a study animal that died

APPENDIX G

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

Pelleted Diet: December 1980 to January 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
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

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

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

TABLE G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.85 ± 0.78	22.7-25.3	24
Crude fat (percent by weight)	5.02 ± 0.44	4.2-5.7	24
Crude fiber (percent by weight)	3.31 ± 0.23	2.9-3.8	24
Ash (percent by weight)	6.44 ± 0.44	5.7-7.43	24
Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	10,917 ± 1,876	8,210-15,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm) (b)	16.8 ± 2.0	14.0-21.0	23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.25 ± 0.15	1.08-1.69	24
Phosphorus (percent)	0.98 ± 0.06	0.88-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) 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)	0.48 ± 0.17	<0.29-1.06	24
Cadmium (ppm) (a)	<0.10		24
Lead (ppm)	1.00 ± 0.74	0.42-3.37	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.29 ± 0.07	0.13-0.40	24
Aflatoxins (ppb) (a,b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	9.22 ± 3.62	3.8-17.0	24
Nitrite nitrogen (ppm) (c)	2.16 ± 1.53	0.4-6.9	24
BHA (ppm) (d)	6.68 ± 4.95	<0.4-17.0	24
BHT (ppm) (d)	3.45 ± 2.56	0.9-12.0	24
Aerobic plate count (CFU/g) (e)	40,557 ± 29,431	4,900-88,000	23
Aerobic plate count (CFU/g) (f)	77,617 ± 183,824	4,900-930,000	24
Coliform (MPN/g) (g)	16.6 ± 22.9	<3-93	22
Coliform (MPN/g) (h)	80.20 ± 236.3	<3-1,100	24
E. coli (MPN/g) (i)	<3		24
Total nitrosamines (ppb) (j,k)	4.63 ± 4.19	0.8-18.5	21
Total nitrosamines (ppb) (j,l)	27.15 ± 64.35	0.8-273.2	24
N-Nitrosodimethylamine (ppb) (j,k)	3.43 ± 3.96	0.8-16.5	21
N-Nitrosodimethylamine (ppb) (j,l)	25.71 ± 64.90	0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.05 ± 0.49	0.3-2.9	24
Pesticides (ppm)			
α-BHC (a,m)	<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 (n)	<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 (n)	<0.1	0.2; 4/27/81	24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (o)	0.10 ± 0.07	<0.05-0.27	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

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) Mean, standard deviation, and range exclude one very high value of 930,000 obtained for the batch produced on 12/22/82; CFU = colony-forming unit.
(f) Mean, standard deviation, and range include the high value listed in footnote (e).
(g) Mean, standard deviation, and range exclude one very high value of 1,100 obtained for the batch produced on 12/16/80 and one high value of 460 obtained in the batch produced on 9/23/82; MPN = most probable number.
(h) Mean, standard deviation, and range include the high values listed in footnote (g).
(i) All values were less than 3 MPN/g.
(j) All values were corrected for percent recovery.
(k) Mean, standard deviation, and range exclude three very high values in the range of 115-273.2 ppb obtained for batches produced on 1/26/81, 2/23/81, and 4/27/81.
(l) Mean, standard deviation, and range include the very high values given in footnote (k).
(m) BHC = hexachlorocyclohexane or benzene hexachloride.
(n) There was one observation above the detection limit; the value and date it was obtained are given under the range.
(o) Thirteen batches contained more than 0.05 ppm.

APPENDIX H

AUDIT SUMMARY

APPENDIX H. AUDIT SUMMARY

The experimental data, documents, and pathology materials for the 2-year toxicology and carcinogenesis studies of 2-amino-4-nitrophenol in rats and mice were audited for accuracy, consistency, completeness, and compliance with Good Laboratory Practice (GLP) regulations of the Food and Drug Administration (fully implemented by the NTP beginning October 1, 1981). The laboratory experiments were conducted for the NTP by Physiological Research Laboratories, Minneapolis, Minnesota, under a subcontract with Tracor Jitco, Inc., until February 28, 1983, and then under contract with the NIEHS. The first gavage administration was on January 8, 1981, for rats and on January 22, 1981, for mice. The retrospective audit was conducted at the NTP Archives in March 1986 by Argus Research Laboratories, Inc., Paul A. Wennerberg, D.V.M., M.S., 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 3 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, date of death, and disposition with necropsy records.
(4) All chemistry records, including chromatograms, Midwest Research Institute reports, receipt reports, chemical use and dose preparation 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) Blocks and slides of tissues from a random 20% sample of the study animals to examine for proper match and inventory.

For the audit of the inlife portion of the studies, all necessary study records were present except for the standard operating procedures referred to in the protocol and information on the disposition of extra animals and on the randomization procedure. The audit revealed the following points that may be considered in the evaluation of these studies: Four rats and eight mice had a reference to a mass inlife but no corresponding observation on their individual animal data record.

All analytical chemistry study records necessary for the audit were available except for the analytical laboratory microfiche and the chemical repository receipt. There were no additional points requiring further evaluation.

For the audit of the pathology portion of the studies, all necessary records and specimens were present. The audit revealed the following: Ears (part of identification) or feet were not present for many animals, so identity could not be directly verified in all cases. Eight untrimmed potential lesions were noted in two mice, and eight gross observations did not have a corresponding microscopic diagnosis in rats. However, review of residual lesions in wet tissues indicated correspondence with necropsy records and gave no indication that animals had been transposed. Because these few findings were scattered among tissue sites and dose groups, they were considered unlikely to affect study interpretation and were not pursued further.

In conclusion, the documents and materials at the NTP Archives support the data and results presented in this Technical Report.

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
PUBLISHED AS OF APRIL 1988

TR No.	CHEMICAL
200	2,6-Toluenediamine Dihydrochloride
201	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dermal)
202	1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin and 1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (Dermal)
203	Phenol
204	Benzoin
205	4,4'-Oxydianiline
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
273	Trichloroethylene (Four strains of rats)
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
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol

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