NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 401

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 2,4-DIAMINOPHENOL DIHYDROCHLORIDE

(CAS NO. 137-09-7)

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

FOREWORD

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

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

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

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

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NTP TECHNICAL REPORT

ON THE

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NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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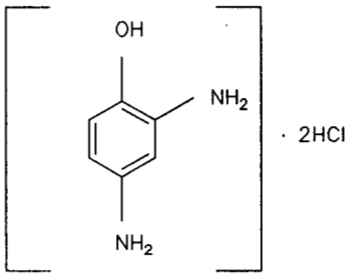
ABSTRACT



2,4-DIAMINOPHENOL DIHYDROCHLORIDE

CAS No. 137-09-7

Chemical Formula: $C_6H_8N_2O$ • 2HCl Molecular Weight: 197.06

Synonyms: Acrol, amidol, dianol

2,4-Diaminophenol dihydrochloride is used in the manufacture of dyes and as a color accelerator in photographic developers. Toxicology and carcinogenesis studies were conducted by administering 2,4-diaminophenol dihydrochloride (greater than 97% pure) in corn oil by gavage to F344/N rats and B6C3F$_1$ mice for 16 days, 13 weeks, and 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse lymphoma cells, *Drosophila melanogaster*, and Chinese hamster ovary cells.

16-Day Studies: Groups of five rats of each sex received doses of 0, 6, 13, 25, 50, or 100 mg/kg and groups of five mice of each sex received doses of 0, 13, 25, 50, 100, or 200 mg/kg of 2,4-diaminophenol dihydrochloride in corn oil by gavage. There were no deaths among rats during the 16-day studies and chemical exposure had no effect on final mean body weights. Organ weight differences were unrelated to chemical exposure. Renal tubule necrosis was present in male and female rats in the 25, 50, and 100 mg/kg dose groups. All male and four female mice that received 200 mg/kg, all males and three females that received 100 mg/kg, and two female mice that received 50 mg/kg died before the end of the studies. Final mean body weights of surviving dosed mice were similar to controls. Absolute liver weights were increased in female mice that received 50 and 100 mg/kg and relative liver weights were increased in all female dose groups. Renal tubule necrosis was present in the 100 mg/kg male and female dose groups.

13-Week Studies: Groups of ten male and female rats received doses of 0, 12, 25, 50, 100, or 200 mg/kg and groups of ten male and female mice received doses of 0, 5, 9, 19, 38, or 75 mg/kg of 2,4-diaminophenol dihydrochloride in corn oil by gavage. All female and nine male rats that received 200 mg/kg and four males and one female in the 100 mg/kg rat groups died before the end of the studies. Final mean body weights of male rats that received 50 or 100 mg/kg were significantly lower than controls. Relative kidney weights were significantly increased in all male dose groups; absolute and relative kidney and liver weights were significantly increased in females that received 50 and 100 mg/kg. Lesions in rats associated with chemical exposure included renal tubule necrosis in males that received 25 mg/kg and above and in females that received 100 or 200 mg/kg. Forestomach ulcers with acanthosis and hyperkeratosis were present at 50 mg/kg and above in both sexes. Pigment, presumably 2,4-diaminophenol dihydrochloride or a metabolite, was present in the duodenum and within

the renal tubule epithelium of all dose groups. Splenic lymphoid depletion was present in both sexes and bone marrow hyperplasia was present in groups of males that received 100 or 200 mg/kg. Hemosiderin was present in Kupffer cells of males that received 100 or 200 mg/kg. The severity of splenic extramedullary hematopoiesis increased with dose in males.

There were no deaths among mice attributed to chemical exposure. Final mean body weight of male mice that received 75 mg/kg was 8% lower than for the controls. Absolute and relative liver weights were increased in males that received 9 mg/kg or above and in all female dose groups. Absolute and relative kidney weights of 38 and 75 mg/kg male mice and all dosed female mice were significantly increased. Absolute heart weights were increased in the 19, 38, and 75 mg/kg female groups. Lesions in 75 mg/kg mice included increased incidences of renal tubule regeneration; forestomach acanthosis and hyperkeratosis occurred in 38 and 75 mg/kg groups. Hemosiderin was present in the spleen of mice from all dose groups and in hepatic Kupffer cells of female mice that received 38 or 75 mg/kg. Pigment was present in the duodenum of males and females that received 9 mg/kg and above and in the renal tubule epithelium of both sexes that received 75 mg/kg.

2-Year Studies: The 2-year studies were conducted by administering 2,4-diaminophenol dihydrochloride in corn oil by gavage to groups of 60 male and 60 female F344/N rats and $B6C3F_1$ mice. Ten animals from each dose group were evaluated after 15 months. Rats received doses of 0, 12.5, or 25 mg/kg; mice received doses of 0, 19, or 38 mg/kg.

Body Weight and Survival in the 2-Year Studies: Mean body weights of high-dose male and female rats and of high-dose male mice were lower than those of the respective controls. Survival of dosed rats and mice was similar to controls throughout the 2-year studies.

Neoplastic and Nonneoplastic Effects in the 2-Year Studies: The severity of nephropathy increased in high-dose male rats. The incidence of renal tubule cell hyperplasia was increased in rats that received 2,4-diaminophenol dihydrochloride; however, there were no renal tubule cell neoplasms attributed to chemical exposure. Renal tubule cell hyperplasia was present in three high-dose male mice and a renal tubule adenoma was present in one of the high-dose males with hyperplasia; two additional high-dose males also had renal tubule adenomas. These are uncommon neoplasms in male mice and were considered related to chemical exposure. In a supplemental review of step-sectioned kidneys, six additional hyperplasias were seen in high-dose male mice and adenomas in three other high-dose males. A tubule cell carcinoma was present in one low-dose female mouse. The incidences of several nonneoplastic kidney lesions, including necrosis and renal tubule regeneration, were also increased in male and female mice.

Pigment was observed in the lamina propria of the duodenum, the submucosa of the forestomach, and in pancreatic and mesenteric lymph nodes in dosed rats. Hemosiderin was present in the renal tubule epithelial cells of low- and high-dose rats. The incidence of forestomach acanthosis was increased in dosed male mice and pigment was present in liver Kupffer cells, in the lamina propria of the duodenum, and in the mesenteric lymph nodes of male and female mice. Pigment and hemosiderin were also present in the renal tubule epithelium of dosed mice.

Genetic Toxicology: 2,4-Diaminophenol dihydrochloride was mutagenic in the *Salmonella typhimurium* strain TA98 in the presence of exogenous metabolic activation (S9); it was not mutagenic in strain TA98 in the absence of S9, nor was it mutagenic in strains TA100, TA1535, or TA1537 with or without S9. 2,4-Diaminophenol dihydrochloride was positive in the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y cells without S9; it was not tested with S9. No induction of sister chromatid exchanges or chromosomal aberrations was observed in Chinese hamster ovary cells treated with 2,4-diaminophenol dihydrochloride with and without S9. In the *Drosophila melanogaster* sex-linked recessive lethal assay, 2,4-diaminophenol dihydrochloride gave equivocal results when administered in the feed and negative results when administered by injection.

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of 2,4-diaminophenol dihydrochloride in male or female F344/N rats that received 12.5 or 25 mg/kg. There was *some evidence of carcinogenic activity* of 2,4-diaminophenol dihydrochloride in male $B6C3F_1$ mice based on increased incidences of renal

tubule adenomas; there was *no evidence of carcinogenic activity* of 2,4-diaminophenol dihydrochloride in female B6C3F$_1$ mice that received 19 or 38 mg/kg.

Administration of 2,4-diaminophenol dihydrochloride to rats was associated with increased severity of nephropathy in males and females, increased incidence of nephropathy in females, and focal renal tubule hyperplasia in males and females. In mice, chemical exposure was associated with renal tubule necrosis and regeneration in males and females and forestomach acanthosis in males.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appears on page 10.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of 2,4-Diaminophenol Dihydrochloride

Variable	Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses	0, 12.5, or 25 mg/kg by corn oil gavage	0, 12.5, or 25 mg/kg by corn oil gavage	0, 19, or 38 mg/kg by corn oil gavage	0, 19, or 38 mg/kg by corn oil gavage
Body weights	High-dose lower than controls	High-dose lower than controls	High-dose lower than controls	Dosed similar to controls
2-Year survival rates	24/50; 21/50; 16/50	30/50; 32/50; 31/50	30/50; 33/50; 36/50	34/50; 31/50; 28/50
Nonneoplastic effects	Kidney: focal renal tubule hyperplasia (0/50, 2/49, 6/50); increased severity of nephropathy	Kidney: focal renal tubule hyperplasia (1/50, 1/50, 5/50); increased severity of nephropathy	Kidney: necrosis (0/50, 12/48, 30/50); renal tubule regeneration (34/50, 34/48, 48/50); Forestomach: acanthosis (4/50, 10/23, 13/50)	Kidney: necrosis (2/50, 5/39, 8/50); renal tubule regeneration (18/50, 24/39, 42/50)
Neoplastic effects[a]	None	None	Kidney: renal tubule adenoma 0/50; 0/48; 3/50	None
Level of evidence of carcinogenic activity	No evidence	No evidence	Some evidence	No evidence

Genetic toxicology

Salmonella typhimurium (gene mutation):	Positive with S9 in strain TA98; negative with and without S9 in strains TA100, TA1535, or TA1537
Mouse lymphoma cells (gene mutation):	Positive without S9
Sister chromatid exchanges	
Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Chromosomal aberrations	
Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Sex-linked recessive lethal mutations	
Drosophila melanogaster:	Equivocal when administered in the feed; negative when administered by injection

[a] Number with lesion/total evaluated

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the NTP draft Technical Report on 2,4-diaminophenol dihydrochloride on March 11, 1991 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 in reviewing NTP studies:

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

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SUMMARY OF PEER REVIEW COMMENTS

On March 11, 1991, the draft Technical Report on the toxicology and carcinogenesis studies of 2,4-diaminophenol dihydrochloride received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Committee and associated Peer Review Panel. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.D. Irwin, NIEHS, introduced the toxicology and carcinogenesis studies of 2,4-diaminophenol dihydrochloride by discussing the uses and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related neoplasms and nonneoplastic lesions in mice and rats. The conclusions were *no evidence of carcinogenic activity* in male or female F344/N rats, *some evidence of carcinogenic activity* in male $B6C3F_1$ mice, and *no evidence of carcinogenic activity* in female $B6C3F_1$ mice.

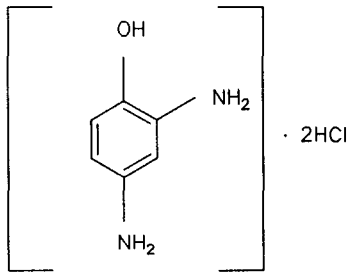
Mr. Beliczky, a principal reviewer, agreed in principle with the conclusions. By that, he meant that the predominant or overall conclusion for the studies should be *some evidence of carcinogenic activity.* His rationale was to apply a single conclusion for a Material Safety Data Sheet.

Dr. Carlson, the second principal reviewer, did not agree with the conclusion in male mice. He argued for changing the conclusion to *equivocal evidence of carcinogenic activity* because the increased incidence of renal tubule adenomas was only slightly greater than the previous maximum incidence observed in control mice, was not significantly different from concurrent controls, and not dose-related. Further, he said that treated male mice had a significantly increased survival, and the first tumors were observed at 688 days. Dr. Irwin stated that these tumors are very uncommon in mice, and a parallel increase in hyperplasias along with additional adenomas found on step sectioning bolstered the proposed conclusion in male mice. Dr. Carlson asked why the water soluble hydrochloride salt was administered in corn oil. Dr. Irwin said a suspension in corn oil was the most stable dose formulation.

Dr. Garman, the third principal reviewer, agreed with the conclusions. He said the special stains used to identify the pigment found in lesions in 15-month interim evaluation animals should be characterized. Dr. C.C. Shackelford, NIEHS, commented that a special stain was used to identify iron.

Mr. Beliczky moved that *some evidence of carcinogenic activity* be made the predominant conclusion for the Technical Report on 2,4-diaminophenol dihydrochloride. The motion was tabled for lack of a second. Mr. Beliczky then moved that the Technical Report be accepted with the revisions discussed and the conclusions as written, *no evidence of carcinogenic activity* for male and female rats and female mice, and *some evidence of carcinogenic activity* for male mice. Dr. Garman seconded the motion, which was accepted by nine votes to one (Dr. Carlson).

INTRODUCTION



2,4-DIAMINOPHENOL DIHYDROCHLORIDE

CAS No. 137-09-7

Chemical Formula: $C_6H_8N_2O$ • 2HCl Molecular Weight: 197.06

Synonyms: Acrol, amidol, dianol

PHYSICAL AND CHEMICAL PROPERTIES, PRODUCTION, USE, AND EXPOSURE

2,4-Diaminophenol dihydrochloride is a gray-brown microcrystalline powder which decomposes at 195° C. It is soluble in water but only slightly soluble in alcohol, ether, and other organic solvents. The major use of 2,4-diaminophenol dihydrochloride is as a color accelerator in photographic developers and in photographic bleaching baths. It is also used as an intermediate in the manufacture of certain dyes for animal fur (*Kirk-Othmer*, 1978).

The usual method of preparation involves reduction of 2,4-dinitrophenol with tin hydrochloride or phosphorus iodide in water. It can also be prepared by electrolytic reduction-hydroxylation of dinitrobenzene. The dihydrochloride salt is prepared from the free-base form (*Kirk-Othmer*, 1978).

From a survey conducted from 1981-1983, the National Institute of Occupational Safety and Health (NIOSH) has estimated that 6,638 workers (4,211 females) are potentially exposed to 2,4-diaminophenol dihydrochloride. All of these workers were in the personal service (laundry, barber shops, shoe repair, etc.) industry (NIOSH, 1991).

CARCINOGENICITY OF RELATED COMPOUNDS

There are no published reports dealing with the metabolism, toxicity, or carcinogenicity of 2,4-diaminophenol dihydrochloride or of the free-base form. However, several structurally similar compounds, including three aminophenols, have been evaluated for carcinogenicity in NCI/NTP 2-year studies.

4-Amino-2-nitrophenol was administered in the diet to F344/N rats and $B6C3F_1$ mice at concentrations of 1,250 and 2,500 ppm (NCI, 1978a). Survival and mean body weights of rats and mice were not affected by chemical exposure. The incidence of transitional cell carcinomas of the urinary bladder was significantly increased in high-dose male rats (11/39) compared to low-dose male rats (0/46) and controls (0/15). No neoplasms attributable to chemical exposure occurred in mice.

In the 2-year studies of 2-amino-4-nitrophenol, rats and mice received doses of 125 or 250 mg/kg in corn oil by gavage (NTP, 1988a). The severity of nephropathy increased in dosed male rats and may have contributed to the reduced survival of high-dose male rats after week 89 of the study. The

incidences of renal tubule hyperplasia, and renal cortical adenomas increased with dose in male rats and were considered to be due to chemical exposure. No neoplasms related to chemical administration were present in female rats or in mice.

2-Amino-5-nitrophenol was administered by gavage at doses of 100 or 200 mg/kg in corn oil to rats and 400 or 800 mg/kg to mice. The only carcinogenic response attributed to chemical exposure in these studies was an increased incidence of pancreatic acinar cell adenomas in low-dose male rats. The incidence of these neoplasms was not increased in high-dose male rats; however, the low incidence in the high-dose group may have been influenced by the reduced survival of the group (NTP, 1988b).

Two 2,4-diamino compounds have also been examined in 2-year studies. 2,4-Diaminoanisole sulfate was administered in the diet at concentrations of 0.12% or 0.5% to F344/N rats and 0.12% or 0.24% to B6C3F$_1$ mice. After a 78-week period of chemical exposure, the animals were maintained another 29 weeks on control diets prior to necropsy. In rats, chemical exposure caused increased incidences of malignant neoplasms of the skin (squamous cell and basal cell carcinomas and sebaceous adenomas and adenocarcinomas), the preputial gland in males, the clitoral gland in females, and the Zymbal's gland and the thyroid gland in both males and females. Chemical exposure was associated with an increased incidence of thyroid tumors in mice (NCI, 1978b).

2,4-Diaminotoluene administered in the diet to F344/N rats at concentrations of 125 or 250 ppm caused severe weight gain depression during the first 40 weeks of the studies. As a result, the concentrations were reduced to 50 and 100 ppm starting at week 41; by week 44 all high-dose rats had been killed in a moribund condition. Survival of low-dose rats (those that received 125 ppm for 40 weeks and then 50 ppm beginning in week 41) was somewhat reduced near the end of the studies, but was near 50% for both males and females. Survival of mice that received 100 or 200 ppm in the diet was similar to controls (NCI, 1979).

The incidences of hepatocellular carcinomas and neoplastic nodules of the liver were significantly increased in male and female rats exposed to 2,4-diaminotoluene. In addition, the incidences of mammary gland carcinomas in female rats and subcutaneous fibromas in male rats were increased. Significantly increased incidences of hepatocellular carcinomas occurred in dosed female mice, but no compound-related neoplasms were found in male mice (NCI, 1979).

GENETIC TOXICITY

There are no published reports on the genetic toxicity of 2,4-diaminophenol dihydrochloride other than the NTP studies described in this report. These data show that the compound is positive for gene mutation induction in the *Salmonella typhimurium* strain TA98 with S9 activation (Haworth *et al.*, 1983; Table E1), positive at toxic doses for induction of trifluorothymidine resistance in L5178Y mouse lymphoma cells without S9 (McGregor *et al.*, 1987; Table E2), equivocal for induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* (Zimmering *et al.*, 1985; Table E5), and negative in the *in vitro* Chinese hamster ovary cell cytogenetic assays for induction of sister chromatid exchanges and chromosomal aberrations (Galloway *et al.*, 1985, 1987; Tables E3 and E4). The free-base analogue, 2,4-diaminophenol, tested positive for gene mutation induction in the *S. typhimurium* frameshift strain TA1538 in the presence of S9 activation (Dybing and Thorgeirsson, 1977).

2-Aminophenol was positive for growth inhibition due to DNA damage in *Escherichia coli* (Nishioka, 1976; De Flora *et al.*, 1984a), but was uniformly negative for induction of gene mutations in *S. typhimurium* (Lahitova *et al.*, 1982; De Flora *et al.*, 1984a,b; Matula *et al.*, 1984) and *D. melanogaster* (Yoon *et al.*, 1985). The 4-aminophenol analogue was also negative for gene mutation induction in *S. typhimurium* (De Flora *et al.*, 1984a,b; Matula *et al.*, 1984; Zeiger *et al.*, 1988). Both of these monosubstituted derivatives induced sister chromatid exchanges (Wild *et al.*, 1981; Wilmer *et al.*, 1981) and inhibited DNA synthesis (Wild *et al.*, 1981; Holme *et al.*, 1988) in mammalian cells *in vitro*. 4-Aminophenol was also reported to induce DNA strand breaks in cultured mammalian cells (Garberg *et al.*, 1988). Both 2- and 4-aminophenol induced sperm-head abnormalities and bone marrow cell micronuclei in mice exposed by intraperitoneal injection *in vivo* (Wild *et al.*, 1981); 4-aminophenol was negative, however, for induction of bone marrow cell micronuclei in rats

dosed orally with the chemical (Hossack and Richardson, 1977).

3-Aminophenol was much less active than the 2- and 4-derivatives. It was negative for induction of gene mutations in *E. coli* and *S. typhimurium* (Yoshikawa *et al.*, 1976; Lavoie *et al.*, 1979; Thompson *et al.*, 1983; Zeiger *et al.*, 1988), aneuploidy in the yeast *Neurospora crassa* (Griffiths, 1981), and sister chromatid exchanges in cultured hamster cells (Wild *et al.*, 1981). It was positive for inhibition of DNA synthesis in hamster cells without S9 (Holme *et al.*, 1988). 3-Aminophenol was negative for unscheduled DNA synthesis in rat cells (Thompson *et al.*, 1983), and for induction of sperm-head abnormalities and micronuclei in mice and rats *in vivo* (Hossack and Richardson, 1977; Wild *et al.*, 1981).

Study Rationale

2,4-Diaminophenol dihydrochloride is one of a series of aminophenols and substituted anilines which are used in the manufacture of dyes and other colored compounds and have the potential for broad human exposure. Because several members of this chemical class were shown to be mutagenic in bacteria, a number of representative compounds were nominated for evaluation of carcinogenic potential by the National Toxicology Program.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION

2,4-Diaminophenol dihydrochloride was obtained from Eastern Chemical Division, Guardian Chemical Corporation, in one lot which was used throughout the studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute, Kansas City, MO (Appendix H). The study chemical, a gray-brown microcrystalline powder, was identified as 2,4-diaminophenol dihydrochloride by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy.

The lot was greater than 97% pure, as determined by Karl Fischer water analysis, weight loss on drying, high-performance liquid chromatography, titration, and elemental analysis. High-performance liquid chromatography indicated the presence of 2.7% 2-amino-4-nitrophenol as an impurity. Stability studies performed by high-performance liquid chromatography indicated that 2,4-diaminophenol dihydrochloride was stable as a bulk chemical for at least 2 weeks at temperatures to 60° C when protected from light. Based on the stability study results, the bulk chemical was stored in the dark at 0° ± 5° C at the testing laboratory throughout the study period. The stability of the bulk chemical was monitored periodically by high-performance liquid chromatography and titration during all phases of the studies. No change in the study material was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing appropriate amounts of 2,4-diaminophenol dihydrochloride and corn oil (Table H1). Studies were conducted by the analytical chemistry laboratory to determine the homogeneity and stability of 50 mg/mL 2,4-diaminophenol dihydrochloride in corn oil. Homogeneity was confirmed by spectroscopy, and high-performance liquid chromatography was used to confirm stability of the dose formulations for at least 14 days when stored in the dark at temperatures to 25° C. During the studies, the dose formulations were stored in sealed amber serum vials at 0° ± 5° C for no longer than 2 weeks.

The study laboratory conducted periodic analyses of the 2,4-diaminophenol dihydrochloride dose formulations using spectroscopy as described in Appendix H. During the 2-year studies, the dose formulations were analyzed at approximately 8-week intervals and 97% (29/30) of the dose formulations for rats and 93% (28/30) of the dose formulations for mice were within 10% of the target concentrations (Table H4). Results of periodic referee analyses of the dose formulations performed by the analytical chemistry laboratory were in agreement with the results from the study laboratory (Table H5).

16-DAY STUDIES

The experimental design of the 16-day studies is described in Table 1. Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Portage, MI) and observed for 14 days (rats) or 20 days (mice) before the studies began. Rats were approximately 7 weeks old and mice were approximately 9 weeks old when the studies began. Groups of five male and five female rats received 0, 6, 13, 25, 50, or 100 mg/kg of 2,4-diaminophenol dihydrochloride in corn oil by gavage. Groups of five male and five female mice received 0, 13, 25, 50, 100, or 200 mg/kg of 2,4-diaminophenol dihydrochloride in corn oil by gavage (Table 1). All groups received the doses for 12 days (days 1 through 5, 8 through 12, and at least two consecutive dosing days before the terminal sacrifice). Animals were housed five per cage, and water and feed were available *ad libitum*. Clinical observations were conducted twice daily and recorded daily. Animals were weighed at the start of the study, on day 8, and on day 16. Complete necropsies were performed on all animals. The brain, heart, liver, lung, right kidney, right testis, and thymus of survivors were weighed at necropsy. Histopathology of the kidney was performed on all animals. Further details are presented in Table 1.

13-WEEK STUDIES

The 13-week studies were conducted to determine the cumulative toxic effects of repeated exposure to 2,4-diaminophenol dihydrochloride and to determine appropriate chemical concentrations to be used in the 2-year studies. The experimental design of the 13-week studies is summarized in Table 1.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD) and were observed for 13 to 14 days before the studies began. Male rats were approximately 10 weeks old, female rats were 7 weeks old, and mice were 7 to 8 weeks old at the beginning of the studies. Groups of 10 rats received 0, 12, 25, 50, 100, or 200 mg/kg of 2,4-diaminophenol dihydrochloride and groups of 10 mice received 0, 5, 9, 19, 38, or 75 mg/kg 2,4-diaminophenol dihydrochloride in corn oil by gavage 5 days per week for 13 weeks. Animals were housed five per cage; water and feed were available *ad libitum*. Animals were observed twice each day and clinical observations were recorded weekly. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix J). Animals were weighed at the start of the study and weekly thereafter. Further experimental details are presented in Table 1.

Surviving animals were killed at the end of the 13-week studies. Necropsies were performed on all study animals. The brain, heart, right kidney, liver, lung, right testis, and thymus of survivors were weighed at necropsy. Complete histopathology was performed on all animals that died or were killed prior to study termination, all control animals, 100 mg/kg rats, and 75 mg/kg mice. Tissues examined for rats in the 12, 25, and 50 mg/kg groups and for mice in the 5, 9, 19, and 38 mg/kg groups are listed in Table 1.

2-YEAR STUDIES

Study Design

Groups of 60 rats and mice of each sex were administered 2,4-diaminophenol dihydrochloride in corn oil by gavage 5 days per week for up to 103 weeks. Rats received doses of 0, 12.5, or 25 mg/kg, and mice received 0, 19, or 38 mg/kg. After 15 months of chemical administration 10 male and 10 female rats and mice from each group were evaluated.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility for use in the 2-year studies. The rats were 5 to 6 weeks old when received, and the mice were 6 weeks old. Rats were quarantined 15 to 20 days and mice were quarantined 16 to 19 days. Five rats and mice per sex were randomly selected and killed for parasite evaluation and gross observation of disease. Serology samples were collected for viral screens. Rats and mice were 8 to 9 weeks old at study initiation. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix J).

Animal Maintenance

Rats and mice were housed five per cage. Feed and water were available *ad libitum*. Cages were rotated every 2 weeks during the studies. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix I.

Clinical Examinations and Pathology

All animals were observed twice daily and clinical findings were recorded weekly for 13 weeks, then monthly or as necessary. Animals were weighed at study initiation, weekly for 13 weeks, and monthly thereafter.

Ten rats or mice from each group were evaluated after 15 months of 2,4-diaminophenol dihydrochloride administration. Blood was drawn from the tails of rats and mice to measure the following hematology parameters: total leukocyte count, leukocyte differential count, erythrocyte count, hemoglobin, hematocrit, mean cell hemoglobin concentration, mean cell volume, and mean cell hemoglobin. Blood collected from the jugular vein of anesthetized rats and mice was analyzed for concentrations of blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and sorbitol dehydrogenase. The brain, liver, and right kidney of each animal were weighed at necropsy. Further details of the interim evaluations are presented in Table 1.

Animals found moribund, selected for the 15-month interim evaluations, or surviving to the end of the 2-year studies were killed. Necropsies were performed on all animals. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin for microscopic examination. Histopathology examinations were performed on control and high-dose animals in the 15-month interim evaluations; selected tissues were examined from low-dose animals in the 15-month interim evaluations. Complete histopathology examinations were performed on all grossly visible lesions in all dose groups and on all animals dying or killed moribund between 15 and 21 months on study. Histopathology of selected tissues was performed on all control and high-dose animals that died or were killed moribund after 21 months on study or were killed at study termination. Those tissues examined are listed in Table 1.

Upon completion of the microscopic evaluation by the laboratory pathologist, 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 pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slide and tissue counts were verified, and histotechnique was evaluated. All tissues with a diagnosis of neoplasia and all tissues from a randomly selected 10% of the control and high-dose rats and mice were reevaluated microscopically by a quality assessment pathologist.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the aforementioned tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of lesions from the duodenum, forestomach, kidney, and mesenteric and pancreatic lymph nodes of rats and mice, adrenal gland of male rats, thyroid gland of female rats, liver of mice, testis and bone of male mice, and lesions of general interest were selected by the chair for review by the PWG. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without knowledge of dose groups or previously rendered diagnoses. When the consensus opinion of the PWG differed from that of the laboratory pathologist, the diagnosis was changed. Thus, the final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for 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 to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

Tables A1, B1, C1, and D1 in the appendixes to this report present the incidence of neoplasms in male and female rats and mice. Tables A4, B4, C5, and D4 summarize the incidence of nonneoplastic lesions in male and female rats and mice. The incidence of neoplasms 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 gland tumors) prior to histologic sampling, or when lesions had multiple potential sites of occurrence (e.g., mononuclear cell leukemia), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence

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

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

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

Historical Control Data

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

Analysis of Continuous Variables

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

QUALITY ASSURANCE METHODS

The 13-week and 2-year studies were conducted in compliance with FDA Good Laboratory Practice Regulations (21 CFR Part 58). In addition, as study records were submitted to the NTP Archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of the NTP Technical Report were conducted. Audit procedures and findings are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by NTP staff so that all had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICITY

The genetic toxicity of 2,4-diaminophenol dihydrochloride was assessed by testing the ability of the chemical to induce mutations in *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, sex-linked recessive lethal mutations in

Drosophila melanogaster, and trifluorothymidine resistance in mouse L5178Y lymphoma cells. The protocols for these studies and tabular presentations of their findings are in Appendix E.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of 2,4-Diaminophenol Dihydrochloride

16-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)	EG&G Mason Research Institute (Worcester, MA)
Strain and Species		
Rats: F344/N Mice: B6C3F$_1$	Rats: F344/N Mice: B6C3F$_1$	Rats: F344/N Mice: B6C3F$_1$
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Frederick Cancer Research Facility (Frederick, MD)	Frederick Cancer Research Facility (Frederick, MD)
Date of Birth		
Rats: 21-28 April 1981 Mice: 14-21 April 1981	Male rats: 12 August 1981; Female rats: 8 September 1981 Mice: 15-16 September 1981	Rats: 4 August 1982 Male mice: 24 August 1982 Female mice: 25 August 1982
Time Held Before Study		
Rats: 14 days Mice: 20 days	Rats: 14 days Male mice: 14 days Female mice: 13 days	Male rats: 15 days Female rats: 20 days Male mice: 16 days Female mice: 19 days
Average Age When Studies Began		
Rats: 7 weeks Mice: 9 weeks	Male rats: 10 weeks Female rats: 7 weeks Mice: 7-8 weeks	Rats: 8-9 weeks Mice: 8-9 weeks
Date of First Dose		
Rats: 9 June 1981 Mice: 15 June 1981	Male rats: 21 October 1981 Female rats: 28 October 1981 Male mice: 4 November 1981 Female mice: 11 November 1981	Male rats: 23 September 1982 Female rats: 5 October 1982 Male mice: 15 October 1982; Female mice: 25 October 1982
Duration of Dosing		
Days 1-5, 8-12, 15, 16	13 weeks (5 days/week)	104 weeks (5 days/week)
Necropsy Dates		
Rats: 25-26 June 1981 Mice: 1-2 July 1981	Male rats: 20-21 January 1982 Female rats: 27 January 1982 Male mice: 3 February 1982 Female mice: 10 February 1982	15-month interim – Male rats: 20-22 December 1983; Female rats: 28-30 December 1983; Male mice: 18 January 1984; Female mice: 20 January 1984 2-year studies – Male rats: 20-28 September 1984; Female rats: 2-9 October 1984; Male mice: 12-22 October 1984; Female mice: 22-26 October 1984

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Average Age at Necropsy		
Rats: 9 weeks Mice: 11 weeks	Male rats: 23 weeks Female rats: 20 weeks Male mice: 20 weeks Female mice: 21 weeks	Rats: 112 weeks Mice: 112-114 weeks
Size of Study Groups		
5 males and 5 females	10 males and 10 females	60 males and 60 females
Method of Animal Distribution		
Animals randomized into dosed and control groups by weight so that cage weights are equal (± 2 g)	Same as 16-day studies	Animals grouped by weight intervals. Animals assigned to cages, then cages assigned to treatment groups using appropriate table of random numbers.
Animals per Cage		
5	5	5
Method of Animal Identification		
Ear punch	Ear punch	Ear punch
Diet		
NIH-07 Rat and Mouse Ration, Open formula, pellets (Zeigler Bros., Inc., Gardners, PA); available *ad libitum*	Same as 16-day studies	Same as 16-day studies
Feeders		
Stainless steel gang style food hoppers (Scientific Cages, Inc., Bryan, TX); changed once weekly	Same as 16-day studies	Same as 16-day studies
Water		
Tap water (City of Worcester Public Water Supply) via outside-the-cage automatic watering system (Edstrom Industries, Inc., Waterford, WI); available *ad libitum*	Same as 16-day studies	Same as 16-day studies
Cages		
Solid-bottom polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as 16-day studies	Same as 16-day studies
Bedding		
Aspen Bed (American Excelsior Co., Baltimore, MD) or BetaChips (Northeastern Products Corp., Warrensburg, NY); changed twice weekly	Same as 16-day studies	Same as 16-day studies
Cage Filters		
Non-woven fiber filters (Snow Filtration, Cincinnati, OH)	Non-woven fiber filters (Snow Filtration, Cincinnati, OH) or (Lab Products, Rochelle Park, NJ)	Same as 13-week studies

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Animal Room Environment		
Temperature: 22.2°-26.1° C Relative humidity: 61%-78% Fluorescent light: 12 hours/day Room air changes: 10-12/hour	Temperature: 22.1°-24° C Relative humidity: 41.4%-49.2% Fluorescent light: 12 hours/day Room air changes: 10-12/hour	Rats – Average temperature: 22.7° C Relative humidity: 44.9% Mice – Average temperature: 23.1° C Relative humidity: 44.2% Fluorescent light: 12 hours/day Room air changes: 10-12/hour
Doses		
Rats: 0, 6, 13, 25, 50, or 100 mg of 2,4-diaminophenol dihydrochloride in 5 mL corn oil/kg body weight by gavage Mice: 0, 13, 25, 50, 100, or 200 mg of 2,4-diaminophenol dihydrochloride in 10 mL corn oil/kg body weight by gavage	Rats: 0, 12, 25, 50, 100, or 200 mg of 2,4-diaminophenol dihydrochloride in 5 mL corn oil/kg body weight by gavage Mice: 0, 5, 9, 19, 38, or 75 mg of 2,4-diaminophenol dihydrochloride in 10 mL corn oil/kg body weight by gavage	Rats: 0, 12.5, or 25 mg of 2,4-diaminophenol dihydrochloride in 5 mL of corn oil/kg body weight by gavage Mice: 0, 19, or 38 mg of 2,4-diaminophenol dihydrochloride in 10 mL of corn oil/kg body weight by gavage
Storage Conditions for Dosing Solutions		
In serum vials in the dark at 0° ± 5° C	Same as 16-day studies	Same as 16-day studies
Maximum Storage Time for Dosing Solutions		
14 days	14 days	14 days
Type and Frequency of Observation		
Observed twice/day; body weight initially, once/week, and final body weight; clinical observations recorded daily	Observed twice/day; body weight initially and once/week; clinical observations recorded once/week	Observed twice/day; body weight initially, once/week for 13 weeks, once/month thereafter; clinical observations recorded once/week for 13 weeks, once/month thereafter
Clinical Pathology		
None	None	Hematology and clinical chemistry tests run on blood collected from 10 rats and mice of each sex from each dose group at 15 months. Parameters measured included: hematocrit, hemoglobin, erythrocyte count, leukocyte count and differential, mean cell volume, mean cell hemoglobin concentration, mean cell hemoglobin, sorbitol dehydrogenase, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and blood urea nitrogen.
Necropsy Examinations		
Necropsy performed on all animals. The following organs were weighed: brain, heart, liver, lung, right kidney, right testis, and thymus.	Necropsy performed on all animals. The following organs were weighed: brain, heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on all animals. The following organs were weighed at 15-months evaluation: brain, liver and right kidney.

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Histopathologic Examinations		
Histopathology of the kidneys performed on all animals.	Complete histopathology on all animals that died or were killed moribund during the study, all controls, 100 mg/kg rats, and 75 mg/kg mice. Tissues examined included: (rats) brain, clitoral or preputial gland, colon, epididymis, jejunum, ovary, pancreas, rectum, testis, thyroid gland, uterus; (mice) salivary gland, skin; (rats and mice) adrenal gland, bone and marrow (sternum), duodenum, heart, kidney, liver, lung with mainstem bronchi, lymph nodes (mesenteric), nasal cavity and turbinates, spleen, stomach, thymus, urinary bladder, and gross lesions. Tissues examined from rats in the 12, 25, and 50 mg/kg dose groups included: bone marrow (sternum), duodenum, kidney, liver (males), spleen, stomach, and gross lesions. Tissues examined from mice in the 5, 9, 19, and 38 mg/kg dose groups included: duodenum, kidney, liver, spleen, stomach, urinary bladder, and gross lesions.	Histopathology performed on control and high-dose animals from 15-month interim evaluations: (rats) adrenal gland, clitoral or preputial gland, lung, mandibular lymph nodes, pancreas (control), pituitary gland, prostate gland, testes; (mice) bone and marrow (sternum), epididymis (control), gallbladder (mice), ileum, jejunum, ovary, parathyroid gland, salivary gland, skin, spleen, thymus (38 mg/kg); (rats and mice) duodenum (25 mg/kg rats), heart (38 mg/kg mice), kidney, large intestine, liver, mesenteric lymph nodes (25 mg/kg rats), nasal cavity and turbinates, stomach (25 mg/kg rats), thyroid gland (25 mg/kg rats), urinary bladder, uterus, and gross lesions. Tissues for low-dose rats and mice from 15-month interim evaluations: duodenum, kidney (female rats, mice), liver (female rats, mice), lymph nodes (mesenteric, pancreatic), pancreas, and gross lesions. Complete histopathology on all animals that died or were killed moribund between 15 and 21 months. Tissues examined: adrenal gland, bone (except 19 mg/kg male mice) and marrow (sternum), brain, cecum, clitoral or preputial gland (rats), colon, duodenum, epididymis, esophagus, gallbladder (mice), heart, ileum, jejunum, kidney, liver, lungs with mainstem bronchi, lymph nodes (mesenteric), mammary gland (except 19 mg/kg male mice), nasal cavity and turbinates, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, rectum, salivary gland, seminal vesicle, skin, spleen, stomach, testis, thymus, thyroid gland, trachea, urinary bladder, uterus, and gross lesions. Essential histopathology on all control and high-dose animals that died or were killed moribund after 21 months on study, or at study termination. Tissues examined: (mice) bone and marrow (sternum), cecum, colon, gallbladder, heart, ileum, jejunum, mammary gland, nasal cavity, rectum, salivary gland, skin, thymus;

(continued on next page)

TABLE 1
Experimental Design and Materials and Methods in the Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Histopathologic Examinations (continued)		(continued) (rats and mice) adrenal gland, brain, duodenum, epididymis, esophagus, kidney, liver, lung, lymph node, ovary, pancreas, parathyroid gland, pituitary gland, prostate gland, seminal vesicle, spleen, stomach, testis, thyroid gland, trachea, urinary bladder, uterus, and gross lesions and tissue masses. Tissues examined in the low-dose animals that died or were killed moribund after 21 months or were killed at terminal sacrifice were: (rats) adrenal gland (males), lymph node, pituitary gland, testis, urinary bladder; (mice) liver; (rats and mice) duodenum, kidney (male mice), and gross lesions.

RESULTS

RATS

16-Day Studies

All rats survived to the end of the studies (Table 2); final mean body weights of rats administered 2,4-diaminophenol dihydrochloride were similar to final mean body weights of controls. No chemical-related clinical findings were observed during the studies and no gross lesions related to compound exposure were found at necropsy.

Reduced absolute heart and lung weights of males that received 100 mg/kg and the increased relative brain weights in females that received 100 mg/kg were not chemical related (Table F1).

Compound-related renal tubule necrosis of minimal to moderate severity was present in four males and all females that received 100 mg/kg. Renal tubule necrosis of minimal to moderate severity also occurred in three males and one female that received 50 mg/kg and in three males and all females that received 25 mg/kg.

TABLE 2
Survival and Mean Body Weights of Rats in the 16-Day Gavage Studies of 2,4-Diaminophenol Dihydrochloride

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b]			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	122 ± 4	198 ± 5	75 ± 2	
6	5/5	123 ± 3	201 ± 5	78 ± 3	102
13	5/5	122 ± 4	199 ± 8	77 ± 5	101
25	5/5	122 ± 3	202 ± 3	79 ± 2	102
50	5/5	123 ± 4	208 ± 4	85 ± 1	105
100	5/5	122 ± 4	198 ± 6	76 ± 4	100
Female					
0	5/5	102 ± 3	141 ± 4	40 ± 2	
6	5/5	101 ± 3	134 ± 4	33 ± 3	95
13	5/5	102 ± 3	132 ± 2	30 ± 2*	93
25	5/5	102 ± 3	140 ± 2	39 ± 3	99
50	5/5	102 ± 3	144 ± 4	41 ± 2	102
100	5/5	101 ± 3	139 ± 4	38 ± 3	99

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
[a] Number surviving/number initially in group
[b] Weights and weight changes given as mean ± standard error

13-Week Studies

All female rats and nine males that received 200 mg/kg died before the end of the studies; of these, four males and nine females died during the first week of dosing (Table 3). One female and four males that received 100 mg/kg died before the end of the studies. Final mean body weights of male rats that received 50 or 100 mg/kg were significantly lower than controls (11% and 21%). Final mean body weight of female rats that received 100 mg/kg was 4% lower than controls. Diarrhea and lethargy were noted among male and female rats that received 100 or 200 mg/kg.

Significant treatment-related increases in relative kidney weights occurred in all male dose groups (Table F2). Absolute and relative kidney and liver weights of females that received 50 or 100 mg/kg were significantly increased. Changes in the absolute and relative weights of other organs were considered secondary to decreased body weights of dosed rats.

TABLE 3
Survival and Mean Body Weights of Rats in the 13-Week Gavage Studies of 2,4-Diaminophenol Dihydrochloride

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b]			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	118 ± 3	369 ± 6	251 ± 5	
12	10/10	119 ± 3	361 ± 5	242 ± 5	98
25	10/10	119 ± 3	358 ± 6	239 ± 6	97
50	10/10	119 ± 3	328 ± 6**	209 ± 5**	89
100	6/10[c]	120 ± 3	293 ± 7**	169 ± 8**	79
200	1/10[d]	120 ± 3	-	-	-
Female					
0	10/10	110 ± 2	205 ± 5	95 ± 4	
12	10/10	110 ± 2	209 ± 5	99 ± 3	102
25	10/10	109 ± 2	201 ± 2	92 ± 3	98
50	10/10	110 ± 2	204 ± 4	95 ± 4	100
100	9/10[e]	110 ± 2	197 ± 3	88 ± 2	96
200	0/10[f]	110 ± 2	-	-	-

** Significantly different (P≤0.01) from the control group by Williams' or Dunnett's test
[a] Number surviving/number initially in group
[b] Weights and weight changes given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. No data were calculated in groups with high mortality.
[c] Week of death: 10, 10, 10, 10
[d] Week of death: 1, 1, 1, 1, 2, 2, 4, 9, 9.
[e] Week of death: 1
[f] Week of death: 1, 1, 1, 1, 1, 1, 1, 1, 1, 4

Histopathologic lesions associated with 2,4-diaminophenol dihydrochloride administration were present in the kidney, forestomach, duodenum, and spleen of both male and female rats and in the liver and bone marrow of male rats (Table 4). In the kidney, the incidence of cortical tubule necrosis increased with dose in male rats that received 25 to 200 mg/kg and in female rats that received 100 and 200 mg/kg. Severe necrosis of the proximal convoluted tubules was observed in the two highest dose groups and minimal multifocal tubule cell necrosis with minimal tubule cell regeneration was observed in males that received 25 mg/kg. In the lower dose groups, the necrosis was associated with regenerative tubule epithelium. A dose-related increase in finely granular brown pigment, which did not stain positive for iron (presumably the parent compound or a metabolite), was present in the cytoplasm of renal cortical tubule cells of 50, 100, and 200 mg/kg male rats and all female rats administered 2,4-diaminophenol dihydrochloride.

Treatment-related lesions were also present in the forestomach (Table 4). Foci of spongiosis (intercellular edema) were present in the stratum spinosum or between the stratum spinosum and the keratin layer in a few rats of each sex. These foci consisted of cystic spaces filled with an amorphous eosinophilic fluid. Forestomach ulcers, which were usually associated with severe acute inflammation, occurred in the 50, 100, and 200 mg/kg male groups and in the 100 and 200 mg/kg female groups. The ulcers ranged in size from shallow microscopic ulcers with a base of neutrophils to visible transmural ulcers with a base containing granulation tissue, neutrophils, necrotic debris, and bacterial colonies. Occasionally, the epithelium surrounding the ulcers formed papillary projections (hyperplasia) into the stomach lumens. The hyperplasia occurred in the 25 to 200 mg/kg groups and was considered to be a secondary response to the presence of forestomach ulcers. Mildly to moderately severe multifocally thickened forestomach epithelium (acanthosis) and keratin (hyperkeratosis) were observed in all dose groups. Mildly severe lesions, especially at the squamoglandular junction, were observed in the 50 mg/kg dose group animals that did not have ulcers.

A black-brown granular pigment, which did not stain positive for iron (presumably the parent compound or a metabolite), was extracellular or located within the cytoplasm of macrophages in the lamina propria of the duodenum in all rats administered 2,4-diaminophenol dihydrochloride (Table 4).

Swollen Kupffer cells containing golden brown, iron-positive pigment (hemosiderin) and phagocytized erythrocytes were observed in the 100 and 200 mg/kg male groups; bone marrow hyperplasia was seen in these same groups (Table 4). The severity of splenic extramedullary hematopoiesis in males and hemosiderosis in females increased with dose. The incidences of lymphoid depletion in the spleen of 100 and 200 mg/kg rats were significantly increased compared to controls. The hepatic, splenic, and bone marrow lesions collectively suggest the presence of a hemolytic process.

Dose selection rationale: The results of the 13-week studies indicated an obvious dose-related increase in toxicity for both sexes of rats administered 2,4-diaminophenol dihydrochloride. The combination of reduced survival among groups of rats that received 100 or 200 mg/kg, increased kidney weights among groups that received 50 mg/kg and above, reduced final mean body weights, and the presence of renal tubule necrosis and pigmentation among male rats that received 50 mg/kg and above indicated that the 50 mg/kg dose level was too high to be used in the 2-year rat studies. Although administration of 25 mg/kg was associated with hemosiderosis of the spleen in female rats, as well as hyperkeratosis of the forestomach and pigmentation of the duodenum in males and females, these lesions were not considered life threatening for the 2-year studies. Therefore, 25 mg/kg was selected as the high dose for the 2-year studies in rats and 12.5 mg/kg was selected as the low dose.

TABLE 4
Selected Lesions in Rats in the 13-Week Gavage Studies of 2,4-Diaminophenol Dihydrochloride[a]

	Vehicle Control	12 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg
Male						
n	10	10	10	10	10	10
Bone marrow						
Hyperplasia	0	0	0	0	7**	3
Duodenum						
Pigmentation	0	10**	10**	10**	10**	3
Forestomach						
Acanthosis	0	4*	4*	4*	6**	3
Hyperkeratosis	0	3	5*	3	10**	5*
Hyperplasia	0	0	1	1	5*	1
Spongiosis	0	0	2	0	2	4*
Ulcer	0	0	0	1	6**	5*
Kidney						
Tubule necrosis	0	0	1	1	3	9**
Tubule pigmentation (compound-derived)	0	0	0	4*	5*	2
Liver (Kupffer cell)						
Pigmentation (hemosiderin)	0	0	0	0	2	4*
Spleen						
Lymphoid depletion	0	0	0	0	4*	7**
Extramedullary hematopoiesis	10 (1.0)[b]	10 (1.4)	10 (1.7)	10 (1.0)	10 (2.3)	10 (2.4)
Female						
n	10	10	10	10	10	10
Duodenum						
Pigmentation (compound-derived)	0	10**	10**	10**	8**	1
Forestomach						
Acanthosis	0	4*	2	1	8**	2
Hyperkeratosis	0	4*	4*	1	9**	2
Hyperplasia	0	0	2	2	6**	1
Spongiosis	0	0	2	0	2	0
Ulcer	0	0	0	0	6**	5*
Kidney						
Tubule necrosis	0	0	0	0	1	9**
Tubule pigmentation (compound-derived)	0	10**	10**	10**	10**	1
Spleen						
Lymphoid depletion	0	0	0	0	7**	9**
Hemosiderin	10 (1.5)	10 (2.4)	10 (2.4)	10 (2.5)	10 (3.0)	10 (3.0)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Data for this table were taken from the Quality Assurance report.
[b] Values in parentheses are average severity grades for affected animals. Severity of 1 = minimal, 2 = mild, 3 = moderate.

2-Year Studies

Survival

Survival values and Kaplan-Meier survival curves for rats are shown in Table 5 and Figure 1. Survival of exposed groups was similar to that of the controls; however, the overall mean survival of each female group was higher than that of each male group.

Clinical Chemistry and Hematology

No treatment-related effects were observed in the hematology or the clinical chemistry parameters at the 15-month interim evaluation (Table G1).

Body Weights and Clinical Findings

Mean body weights of 25 mg/kg males were 7% to 16% lower than those of controls after 25 weeks (Table 6 and Figure 2). Mean body weights of 25 mg/kg females were up to 11% lower than those of controls after 37 weeks (Table 7 and Figure 2). Mean body weights of 12.5 mg/kg males were slightly lower than controls but were generally within 5% of controls, while those of 12.5 mg/kg females were similar to controls. Relative kidney and liver weights were significantly increased in 25 mg/kg females; however, these increases were considered to be the result of reduced body weights (Table F3). There were no clinical findings related to administration of 2,4-diaminophenol dihydrochloride.

TABLE 5
Survival of Rats in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	12.5 mg/kg	25 mg/kg
Male			
Animals initially in study	60	60	60
15-Month interim evaluation[a]	9	10	10
Natural deaths[b]	12	16	15
Moribund kills	15	11	19
Accidental deaths[a]	0	2	0
Animals surviving until study termination	24[c]	21	16
Percent survival at end of studies[d]	48	45	32
Mean survival (days)[e]	626	588	595
Survival analysis[f]	P=0.120	P=0.667	P=0.125
Female			
Animals initially in study	60	60	60
15-Month interim evaluation[a]	10	10	10
Natural deaths[b]	7	6	2
Moribund kills	13	12	16
Accidental deaths[a]	0	0	1
Animals surviving until study termination	30	32	31
Percent survival at end of studies[d]	61	65	64
Mean survival (days)[e]	626	637	642
Survival analysis[f]	P=0.772N	P=0.871N	P=0.843N

[a] Censored from survival analyses
[b] Individual animal records suggest that one control, three low-dose, and three high-dose males listed as dying of natural causes may have died from gavage trauma. Further, one control and one high-dose female listed as natural death may have died from gavage trauma.
[c] Includes one animal that died during the last week of study
[d] Kaplan-Meier determinations. Survival rates adjusted for accidental deaths and interim evaluations.
[e] Mean of all deaths (uncensored, censored, terminal sacrifice).
[f] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.

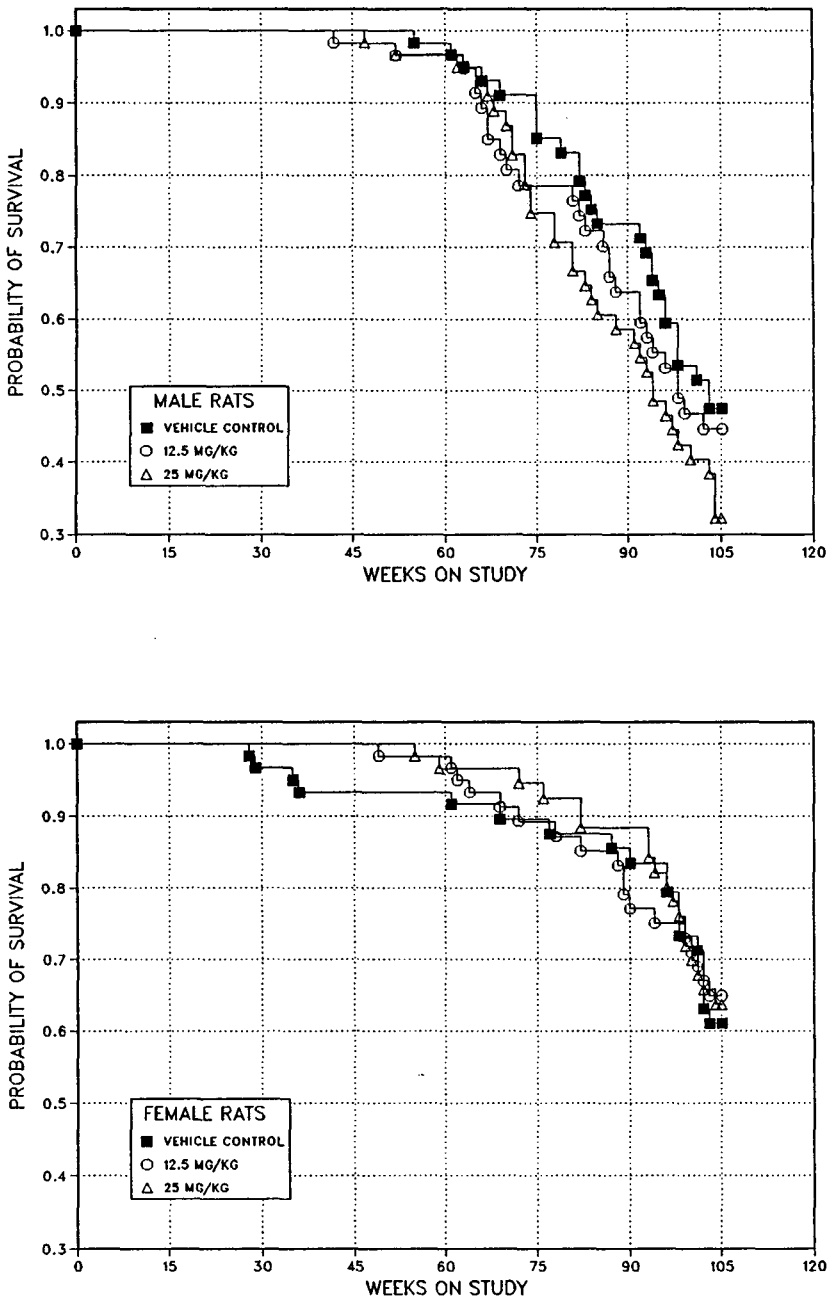


FIGURE 1
Kaplan-Meier Survival Curves for Rats Administered 2,4-Diaminophenol Dihydrochloride by Gavage for 2 Years

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

Weeks on Study	Vehicle Control		12.5 mg/kg			25 mg/kg		
	Av.Wt. (g)	Number of Survivors	Av.Wt. (g)	Wt. (% of controls)	Number of Survivors	Av.Wt. (g)	Wt. (% of controls)	Number of Survivors
2	166	60	169	102	60	171	103	60
3	198	60	201	102	60	203	103	60
4	223	60	228	102	60	228	102	60
5	245	60	250	102	60	248	101	60
6	261	60	267	102	60	264	101	60
7	278	60	284	102	60	278	100	60
8	296	60	300	101	60	292	99	60
9	307	60	310	101	60	303	99	60
10	317	60	313	99	60	308	97	60
11	330	60	332	101	60	318	97	60
12	342	60	343	100	60	328	96	60
13	358	60	359	100	60	344	96	60
17	373	60	378	101	60	360	97	60
21	396	60	392	99	60	374	95	60
25	417	60	408	98	59	386	93	60
29	437	60	426	98	59	406	93	60
33	453	60	438	97	59	415	92	60
37	457	60	447	98	59	425	93	60
41	465	60	454	98	59	430	92	60
45	475	60	459	97	57	437	92	60
49	482	60	469	97	57	447	93	59
53	494	60	479	97	56	450	91	58
57	498	59	482	97	56	456	92	58
61	499	59	484	97	56	455	91	58
65	504	57	484	96	55	448	89	57
69[a]	504	47	481	95	40	445	88	44
73	504	46	482	96	37	441	88	41
77	498	43	476	96	37	431	86	37
81	500	42	469	94	37	427	85	35
85	488	38	465	95	34	427	88	31
89	494	37	460	93	30	423	86	29
93	478	36	446	93	28	403	84	27
97	465	30	441	95	25	399	86	23
101	451	27	426	94	22	390	87	20
104	443	24	405	91	21	380	86	19
Terminal sacrifice		24			21			16
Mean for weeks								
1-13	277		280	101		274	99	
14-52	439		430	98		409	93	
53-104	487		463	95		427	88	

[a] Interim evaluation occurred.

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

Weeks on Study	Vehicle Control		12.5 mg/kg			25 mg/kg		
	Av.Wt. (g)	Number of Survivors	Av.Wt. (g)	Wt. (% of controls)	Number of Survivors	Av.Wt. (g)	Wt. (% of controls)	Number of Survivors
1	127	60	127	100	60	126	99	60
2	135	60	140	104	60	140	104	60
3	143	60	146	102	60	147	102	60
4	159	60	161	101	60	161	101	60
5	165	60	168	102	60	166	100	60
6	170	60	173	102	60	166	98	60
7	175	60	181	103	60	180	103	60
8	182	60	186	102	60	182	100	60
9	186	60	189	101	60	183	98	60
10	192	60	194	102	60	190	99	60
11	197	60	197	100	60	194	99	60
12	200	60	200	100	60	199	100	60
13	196	60	200	103	60	199	102	60
14	201	60	203	101	60	201	100	60
17	204	60	204	100	60	201	98	60
21	220	60	217	99	60	212	97	60
25	228	60	227	99	60	222	97	60
29	239	59	239	100	60	233	98	60
33	246	58	244	99	60	237	96	60
37	254	56	253	100	60	242	95	60
41	261	56	259	99	60	249	96	60
45	267	56	266	99	60	252	94	59
49	275	56	272	99	60	260	94	59
53	287	56	281	98	59	267	93	59
57	293	56	294	100	59	277	95	58
61	301	55	298	99	59	281	93	57
65	317	55	307	97	56	288	91	57
69[a]	324	45	319	98	46	301	93	47
73	326	44	319	98	44	301	92	46
77	328	44	322	98	44	308	94	45
81	309	43	309	100	43	303	98	45
85	330	43	327	99	42	307	93	43
89	339	42	336	99	40	311	92	43
93	343	41	339	99	38	310	91	43
97	343	39	340	99	37	312	91	39
101	341	36	337	99	35	310	91	34
104	343	30	338	99	32	305	89	32
Terminal sacrifice		30			32			31
Mean for weeks								
1-13	171		174	102		172	101	
14-52	240		238	99		231	96	
53-104	323		319	99		299	93	

[a] Interim evaluation occurred.

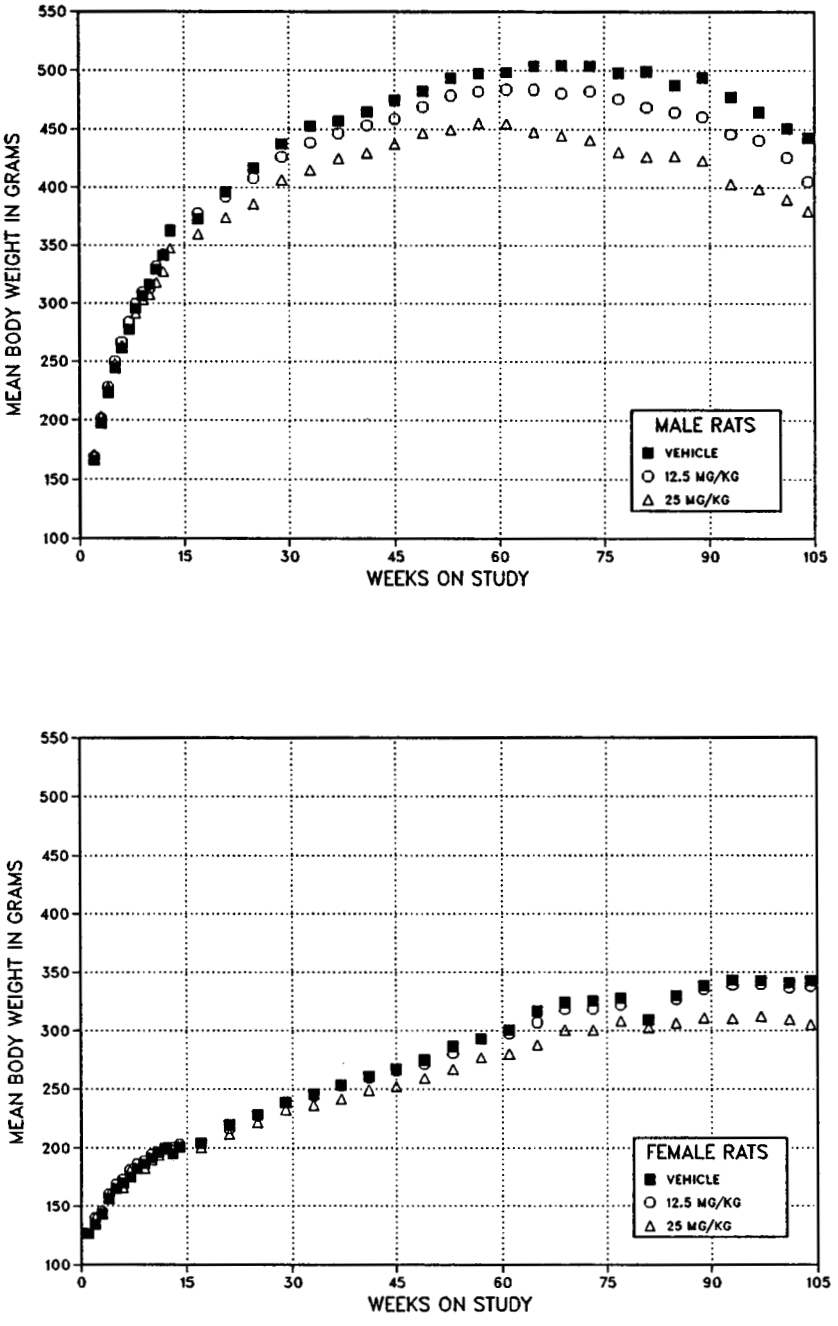


FIGURE 2
Growth Curves for Rats Administered 2,4-Diaminophenol Dihydrochloride by Gavage for 2 Years

Pathology and Statistical Analysis of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the kidney, duodenum, forestomach, and lymph nodes. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one rat group are presented in Appendixes A and B for male and female rats.

Kidney: The incidences of focal renal tubule hyperplasia were increased in high-dose males and females. A renal tubule adenoma was observed in one high-dose male, and a renal tubule carcinoma was observed in one control male rat. No renal tubule neoplasms were seen in female rats. Because of the low but significantly increased incidences of renal tubule hyperplasia observed in high-dose rats, additional step sections of residual formalin-fixed kidneys from all control and high-dose male and female rats were prepared and examined microscopically. Four additional high-dose males, eight high-dose females, three control males, and one control female were found to have hyperplasia (Table 8). Also, one high-dose female evaluated at 15 months had renal tubule hyperplasia. One high-dose female and two additional high-dose males were found to have renal tubule adenomas. Therefore, the incidence data from the evaluation of the single sections and the step sections support the findings of a chemical-related increase in renal tubule hyperplasia in dosed rats.

Renal tubule hyperplasia consisted of one to a few dilated tubules with the lumen partially (Plate 1) or completely (Plate 2) filled with tubule epithelial cells. The cells were small with scant basophilic or amphophilic cytoplasm and round vesicular nuclei with an occasional small solitary nucleolus. In one animal, the cells were large with abundant, pale cytoplasm.

TABLE 8
Selected Kidney Lesions in Rats in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride[a]

	Vehicle Control	12.5 mg/kg	25 mg/kg
Male			
Original Sections			
Renal Tubule: Focal Hyperplasia			
Overall rates[a]	0/50 (0%)	2/49 (4%)	6/50 (12%)
Logistic regression tests[b]	P=0.005	P=0.208	P=0.015
Renal Tubule: Adenoma			
Overall rates	0/50 (0%)	0/49 (0%)	1/50 (2%)
Renal Tubule: Carcinoma			
Overall rates	1/50 (2%)	0/49 (0%)	0/50 (0%)
Step Sections			
Renal Tubule: Focal Hyperplasia			
Overall rates	3/50 (6%)	-[c]	5/50 (10%)[d]
Logistic regression tests		-	P=0.221
Renal Tubule: Adenoma			
Overall rates	0/50 (0%)	-	2/50 (4%)
Logistic regression tests		-	P=0.183

TABLE 8
Selected Kidney Lesions in Rats in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Male (continued)			
Original and Step Sections Combined			
Renal Tubule: Focal Hyperplasia			
Overall rates	3/50 (6%)	-	10/50 (20%)
Logistic regression tests		-	P=0.018
Renal Tubule: Adenoma			
Overall rates	0/50 (0%)	-	3/50 (6%)
Logistic regression tests		-	P=0.076
Renal Tubule: Carcinoma			
Overall rates	1/50 (2%)	-	0/50 (0%)
Female			
Original Sections			
Renal Tubule: Focal Hyperplasia			
Overall rates	1/50 (2%)	1/50 (2%)	5/50 (10%)
Logistic regression tests	P=0.051	P=0.760	P=0.108
Step Sections			
Renal Tubule: Focal Hyperplasia			
Overall rates	1/50 (2%)	-	9/50 (18%)[d]
Logistic regression tests		-	P=0.010
Renal Tubule: Adenoma			
Overall rates	0/50 (0%)	-	1/50 (2%)
Original and Step Sections Combined			
Renal Tubule: Focal Hyperplasia			
Overall rates	2/50 (4%)	-	13/50 (26%)
Logistic regression tests		-	P=0.003
Renal Tubule: Adenoma			
Overall rates	0/50 (0%)	-	1/50 (2%)

[a] Number of lesion-bearing animals/number of animals examined at site
[b] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard lesions in animals dying prior to terminal kill as nonfatal.
[c] Step sections were not evaluated in the 12.5 mg/kg dose groups.
[d] Includes one animal that already had a diagnosis of hyperplasia

Nephropathy occurred more frequently in dosed female rats than in controls. The severity of nephropathy was significantly increased in high-dose males and females (Table 9). An independent reevaluation of the nephropathy severity grades confirmed the original findings. The incidence of nephropathy in high-dose males was 100%.

A golden brown, iron-positive pigment (hemosiderin) was present in the cytoplasm of the proximal renal tubule epithelial cells and occasionally in the lumen of the tubules of low- and high-dose male and female rats (Tables A4 and B4).

Pigmentation: Pigment was present in the duodenum, forestomach, and pancreatic and mesenteric lymph nodes of all dosed rat groups (Tables A4 and B4). Special staining procedures were performed to identify the pigment in lesions found in the 15-month interim evaluation animals. These pigmented lesions were similar to the lesions found in the 2-year study rats. Based on the pigment staining results in 15-month interim evaluation lesions, those similarly pigmented lesions found in rats from the 2-year studies were presumed to contain similar types of pigment. The dark brown, granular pigment located within macrophages and lacteals in the lamina propria of the duodenum and within macrophages in the submucosa of the forestomach was determined to be the parent compound or a metabolite.

Forestomach: Ulceration and acanthosis of the forestomach were present primarily in the high-dose rats and may have been related to the presence of pigment (Plate 3). The descriptions of these forestomach lesions are the same as those in the 13-week rat studies. The pale to golden yellow or occasionally brown, granular pigment present in the pancreatic and mesenteric lymph nodes was found within macrophages and determined to be a combination of hemosiderin and the parent compound or a metabolite. These large macrophages were usually arranged in clusters within the cortex and medullary cords of the lymph nodes.

TABLE 9
Incidences and Severity of Nephropathy in Rats in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride[a]

	Vehicle Control	12.5 mg/kg	25 mg/kg
Male			
Number examined	50	49	50
Absent (grade 0)	3	3	0
Minimal (grade 1)	7	4	0
Mild (grade 2)	8	15	13
Moderate (grade 3)	12	12	10
Marked (grade 4)	20	15	27
Average severity grade (mean ± standard error)	2.78 ± 0.18	2.65 ± 0.17	3.28 ± 0.12*
Female			
Number examined	50	49	50
Absent (grade 0)	19	11	8
Minimal (grade 1)	9	22	10
Mild (grade 2)	16	14	13
Moderate (grade 3)	3	1	13
Marked (grade 4)	3	2	6
Average severity grade (mean ± standard error)	1.24 ± 0.17	1.22 ± 0.13	1.98 ± 0.18**

* Significantly different ($P \leq 0.05$) from the control group by the Mann-Whitney U test
** $P \leq 0.01$

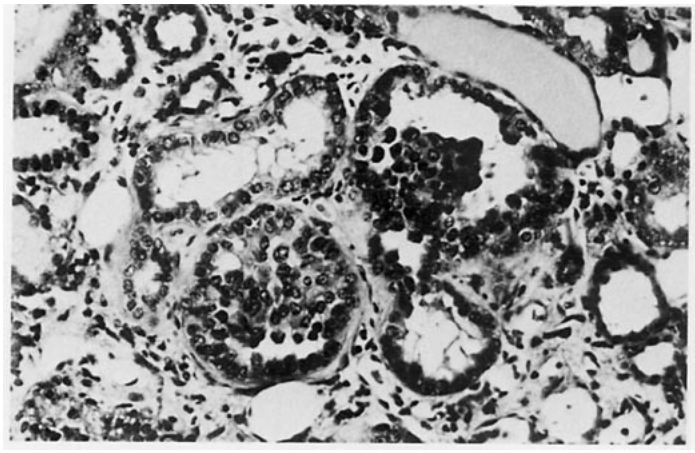


Plate 1
Mild renal tubular hyperplasia in the kidney of a male F344/N rat administered 25 mg/kg 2,4-diaminophenol dihydrochloride by corn oil gavage for 2 years. Two tubules are lined by enlarged epithelial cells with slight nuclear crowding and stratification. Magnification 66x

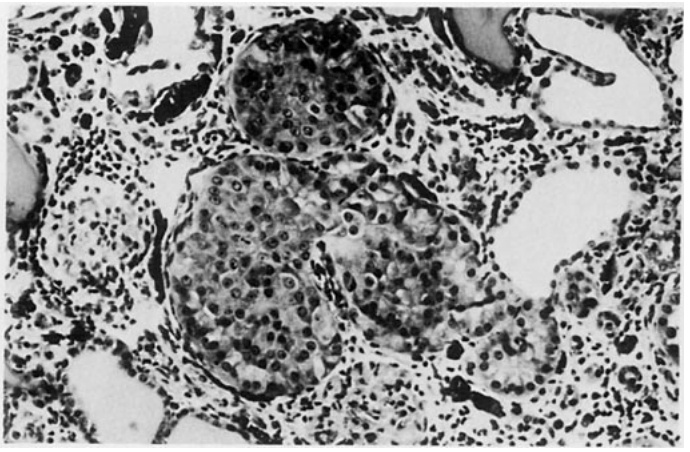


Plate 2
Marked renal tubular hyperplasia in the kidney of a male F344/N rat administered 25 mg/kg 2,4-diaminophenol dihydrochloride by corn oil gavage for 2 years. Enlarged and stratified epithelial cells obliterate tubular lumina. Magnification 50x

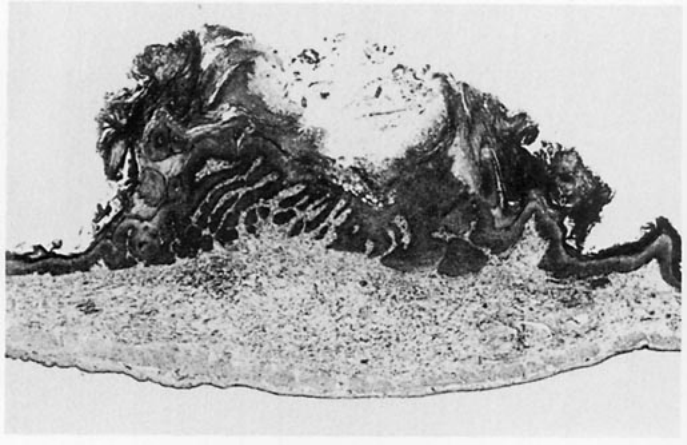


Plate 3
Acanthosis, hyperkeratosis, and chronic active inflammation in the forestomach of a female F344/N rat administered 25 mg/kg 2,4-diaminophenol dihydrochloride by corn oil gavage for 2 years. Note the thickened and folded keratinized epithelium and fibrosis and inflammatory cell infiltration in the submucosa. Magnification 8x

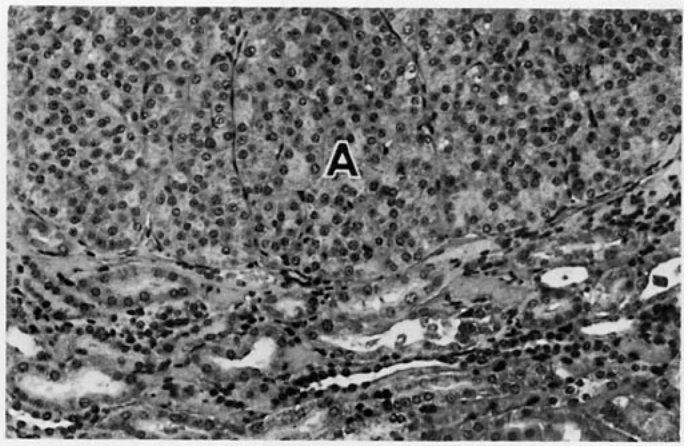


Plate 4
Renal tubular adenoma (A) in the kidney of a male $B6C3F_1$ mouse administered 38 mg/kg 2,4-diaminophenol dihydrochloride by corn oil gavage for 2 years. Magnification 50x

MICE

16-Day Studies

All male and four female mice that received 200 mg/kg, all males and three females that received 100 mg/kg, and two females that received 50 mg/kg died before the end of the studies (Table 10). The final mean body weights of dosed mice that survived to the end of the studies were similar to those of controls. No clinical findings associated with 2,4-diaminophenol dihydrochloride administration were observed during the studies.

Relative liver weights in all female dose groups and absolute liver weights of females that received 50 or 100 mg/kg were significantly increased over controls (Table F4).

Renal tubule necrosis occurred in four males and all females that received 100 mg/kg and was the only compound-related histopathologic lesion observed in mice.

TABLE 10
Survival and Mean Body Weights of Mice in the 16-Day Gavage Studies of 2,4-Diaminophenol Dihydrochloride

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b]			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	23.6 ± 0.6	25.3 ± 0.7	1.7 ± 0.2	
13	5/5	23.7 ± 0.6	24.7 ± 0.8	1.0 ± 0.4	98
25	5/5	23.6 ± 0.6	26.0 ± 0.6	2.4 ± 0.3	103
50	5/5	23.7 ± 0.4	25.6 ± 0.5	1.9 ± 0.3	101
100	0/5[c]	–	–	–	–
200	0/5[d]	–	–	–	–
Female					
0	5/5	19.6 ± 0.5	20.8 ± 0.4	1.2 ± 0.2	
13	5/5	19.7 ± 0.5	21.3 ± 0.7	1.6 ± 0.2	102
25	5/5	19.5 ± 0.6	20.5 ± 0.6	1.0 ± 0.1	98
50	3/5[e]	19.2 ± 0.9	20.0 ± 1.2	0.8 ± 0.5	96
100	2/5[f]	19.2 ± 0.9	20.7 ± 1.0	1.5 ± 0.1	99
200	1/5[g]	–	–	–	–

[a] Number surviving/number initially in group
[b] Weights and weight changes given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. Differences from the control group are not significant by Williams' or Dunnett's test. No data were calculated in groups with high mortality.
[c] Day of death: 3, 4, 5, 5, 5
[d] Day of death: 3, 4, 4, 5, 5
[e] Day of death: 12, 14
[f] Day of death: 3, 3, 3
[g] Day of death: 3, 3, 4, 6

13-Week Studies

One control male, two males from the 5 mg/kg group, one male from the 19 mg/kg group, and one male from the 75 mg/kg group died before the end of the study (Table 11). There were no deaths among the female mice. Final mean body weights of male mice that received 75 mg/kg were 8% lower than controls. Final mean body weights of other male and all female dose groups were similar to controls. No clinical findings were attributed to 2,4-diaminophenol dihydrochloride administration.

Absolute and relative liver and kidney weights were increased in females at all dose levels; males that received 19, 38, or 75 mg/kg had increased relative kidney and liver weights. Absolute heart weights were increased in the 19, 38, and 75 mg/kg female dose groups (Table F5).

TABLE 11
Survival and Mean Body Weights of Mice in the 13-Week Gavage Studies of 2,4-Diaminophenol Dihydrochloride

Dose (mg/kg)	Survival[a]	Mean Body Weight (g)[b]			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	9/10[c]	22.4 ± 0.3	33.4 ± 0.8	10.9 ± 0.6	
5	8/10[d]	22.7 ± 0.3	33.2 ± 0.8	10.4 ± 0.6	99
9	10/10	22.5 ± 0.3	33.5 ± 0.8	11.1 ± 0.7	101
19	9/10[e]	22.8 ± 0.4	32.0 ± 0.8	9.4 ± 0.8	96
38	10/10	22.6 ± 0.2	33.9 ± 0.4	11.4 ± 0.4	102
75	9/10[f]	22.5 ± 0.3	30.8 ± 1.0	8.3 ± 1.2	92
Female					
0	10/10	17.9 ± 0.4	25.4 ± 0.4	7.5 ± 0.5	
5	10/10	18.0 ± 0.3	25.1 ± 0.9	7.1 ± 0.7	99
9	10/10	17.8 ± 0.4	26.3 ± 0.5	8.6 ± 0.6	104
19	10/10	18.2 ± 0.4	25.8 ± 0.8	7.6 ± 0.5	102
38	10/10	17.8 ± 0.4	25.7 ± 0.6	7.9 ± 0.3	101
75	10/10	18.2 ± 0.4	25.2 ± 0.6	7.0 ± 0.3	99

[a] Number surviving/number initially in group
[b] Weights and weight changes given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies. Differences from the control group are not significant by Williams' or Dunnett's test.
[c] Week of death: 3
[d] Week of death: 1, 12
[e] Week of death: 12
[f] Week of death: 1

Lesions associated with 2,4-diaminophenol dihydrochloride administration were present in the kidney, forestomach, duodenum, and spleen of males and females and in the liver in females (Table 12). Kidney lesions included multifocal or diffuse renal cortical tubule regeneration in 75 mg/kg mice of each sex; these lesions were somewhat more severe in females than in males. In all control and lower dose groups, there were widely scattered foci of minimal cortical tubule regeneration; these changes were considered to be unrelated to 2,4-diaminophenol dihydrochloride administration. Finely granular, brown pigment was present in the cytoplasm of renal cortical tubule cells in the 75 mg/kg dose groups.

Forestomach lesions were present in male and female mice that received 38 or 75 mg/kg (Table 12). These minimally to mildly severe lesions included multifocally thickened epithelium (acanthosis) and keratin (hyperkeratosis). Black-brown granular pigment (presumably the parent compound or a metabolite) was seen in macrophages in the lamina propria of the duodenum in male and female mice that received 9, 19, 38, or 75 mg/kg. The incidence of splenic hemosiderosis was increased in all dose groups. Swollen Kupffer cells containing golden brown pigment were seen in the liver of 38 and 75 mg/kg females.

TABLE 12
Selected Lesions in Mice in the 13-Week Gavage Studies of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	5 mg/kg	9 mg/kg	19 mg/kg	38 mg/kg	75 mg/kg
Male						
n	10	10	10	10	10	10
Duodenum						
Pigmentation	0	0	5*	6**	9**	9**
Forestomach						
Acanthosis	0	0	0	0	0	1
Hyperkeratosis	0	0	0	0	1	2
Kidney						
Tubule pigmentation	0	0	0	0	0	2
Tubule regeneration	4 (1.0)[a]	1 (2.0)	1 (1.0)	1 (1.0)	5 (1.2)	9* (1.3)
Spleen						
Hemosiderosis	0 (0.0)	8** (1.6)	6** (2.0)	8** (1.3)	10** (2.4)	8** (1.3)
Female						
n	10	10	10	10	10	10
Duodenum						
Pigmentation	0	0	6**	9**	9**	9**
Forestomach						
Acanthosis	0	0	0	0	0	1
Hyperkeratosis	0	0	0	0	0	1
Kidney						
Tubule pigmentation	0	0	0	0	0	8**
Tubule regeneration	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)	3 (2.3)	10** (2.4)
Liver (Kupffer cell)						
Pigmentation	0	0	0	0	1	9**
Spleen						
Hemosiderosis	5 (1.0)	10* (2.2)	10* (1.7)	10* (2.2)	10* (2.0)	10* (1.8)

* Significantly different ($P \leq 0.05$) from the control group by the Fisher exact test
** $P \leq 0.01$
[a] Values in parentheses are average severity grades for affected animals. Severity of 1 = minimal, 2 = mild, and 3 = moderate.

Dose selection rationale: Because no compound-related deaths occurred during the 13-week studies and final mean body weights were somewhat variable, doses were selected primarily on the basis of the kidney lesions, which were increased in both incidence and severity in mice that received 75 mg/kg. In mice that received 9, 19, or 38 mg/kg, the lesions were of minimal to mild severity and were not considered the type to become life threatening in 2-year studies. Therefore, 38 mg/kg was selected as the high dose and 19 mg/kg as the low dose.

2-Year Studies

Survival

Survival of control male mice was slightly lower than that of dosed males, and survival of high-dose females was slightly lower than controls or low-dose females (Table 13 and Figure 3). However, overall survival of all groups of mice ranged from approximately 60% to 70%, and there were no significant differences between the survival of dosed and control mice.

TABLE 13
Survival of Mice in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	19 mg/kg	38 mg/kg
Male[a]			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Natural deaths	6	6	2
Moribund kills	14	11	12
Animals surviving until study termination	30	33	36
Percent survival at end of studies[b]	61	67	73
Mean survival (days)[c]	599	623	643
Survival values[d]	P=0.199N	P=0.610N	P=0.231N
Female[a]			
Animals initially in study	60	60	60
15-Month interim evaluation)	10	10	10
Natural deaths	5	7	2
Moribund kills	11	12	20
Animals surviving until study termination	34	31	28
Percent survival at end of studies[b]	69	63	58
Mean survival (days)[c]	638	620	598
Survival values[d]	P=0.174	P=0.603	P=0.208

[a] First day of terminal sacrifice: male, 729; female, 729
[b] Kaplan-Meier determinations. Survival rates adjusted for interim evaluations.
[c] Mean of all deaths (uncensored, censored, terminal sacrifice).
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A negative trend or a lower mortality in a dose group is indicated by N.

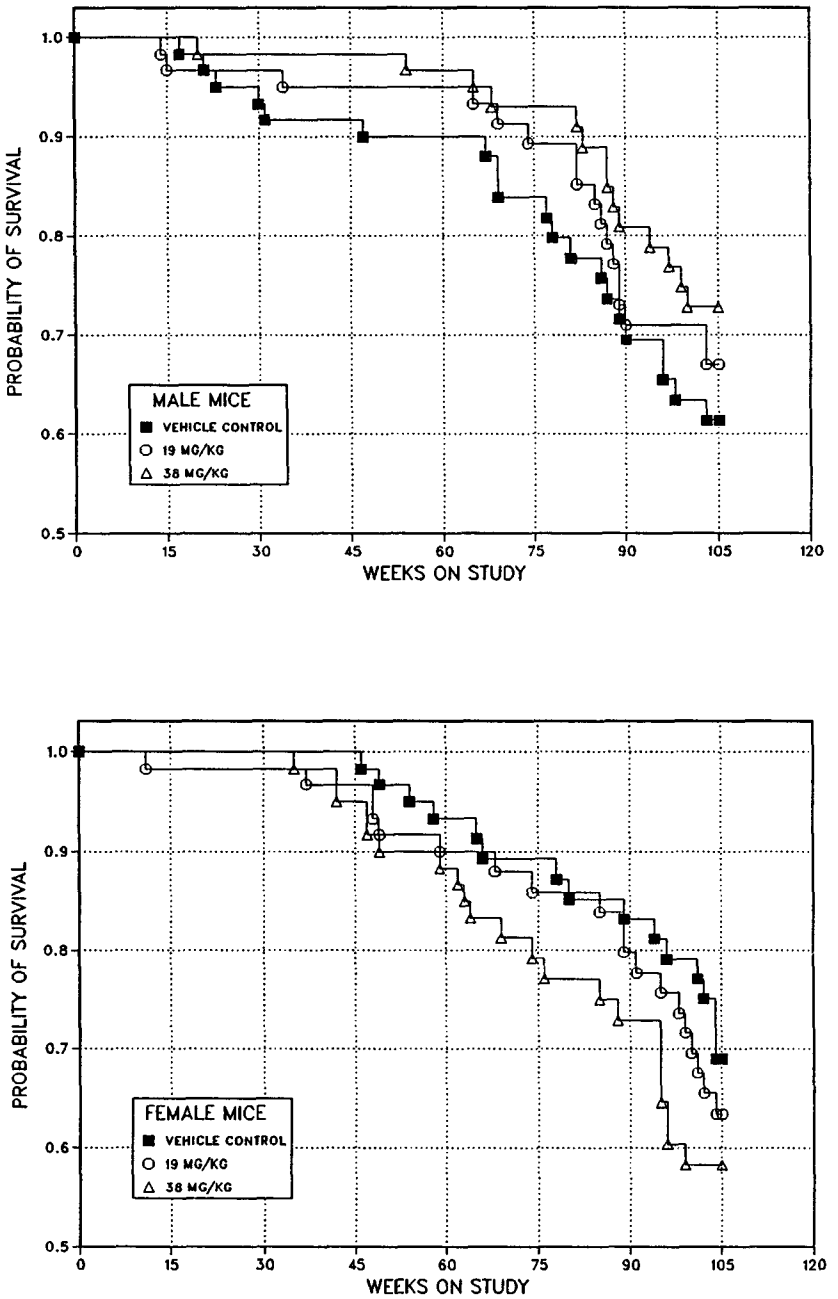


FIGURE 3
Kaplan-Meier Survival Curves for Mice Administered 2,4-Diaminophenol Dihydrochloride by Gavage for 2 Years

Clinical Chemistry and Hematology

Hematocrit, hemoglobin, and erythrocyte counts were significantly decreased, and leukocyte and segmented neutrophil counts were significantly increased in high-dose males and females at the 15-month interim evaluation (Table G2). These results are consistent with an anemia in the high-dose mice accompanied by a decrease in mean cell volume. In combination with leukocytosis, which is compatible with chronic inflammation, these results suggest that the anemia is possibly associated with the inflammation. No biologically significant changes in clinical chemistry parameters were observed in male or female dose groups.

Body Weights and Clinical Findings

Mean body weights of male mice that received 38 mg/kg were slightly decreased but were generally within 6% of control values. Mean body weights of both female dose groups and of low-dose males were similar to those of controls (Tables 14 and 15 and Figure 4). Absolute and relative liver and kidney weights were significantly increased in high-dose females at the 15-month interim evaluation (Table F6). There were no clinical findings associated with 2,4-diaminophenol dihydrochloride administration.

Pathology and Statistical Analysis of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the kidney, liver, duodenum, mesenteric lymph nodes, and forestomach. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one mouse group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice.

Kidney: The principal lesions associated with the administration of 2,4-diaminophenol dihydrochloride in mice occurred in the kidney. Initially, single sections of the left and right kidneys were examined microscopically. Renal tubule adenomas were identified in only three high-dose males, and a carcinoma was found in a low-dose female (Table 16). Focal renal tubule hyperplasia was also present in three high-dose male mice. Renal tubule adenomas occur infrequently in NTP corn oil gavage historical control male B6C3F$_1$ mice (1/598, mean 0.2%, range 0% to 2%) (Table C4). Because of the low, but increased, number of renal tubule adenomas and hyperplasias observed in the high-dose male mice, additional step sections of residual formalin-fixed kidneys from all control and high-dose male and female mice were prepared and examined microscopically. In these sections, adenomas were found in three additional high-dose males and in one high-dose female; hyperplasias were found in six additional high-dose males and two high-dose females. No adenomas or hyperplasias were found in control mice.

The adenomas were characterized by solid collections of epithelial cells that varied from small, more basophilic cells to larger, more eosinophilic, vacuolated cells (Plate 4). Adjacent renal structures were compressed; one adenoma extended into the subcapsular region with cells and nuclei becoming larger and more pleomorphic. Renal tubule hyperplasias were foci of dilated tubules lined with layers of proliferating, vacuolated epithelial cells with pleomorphic nuclei. The cells were somewhat hypertrophied and appeared to be degenerating in some areas.

Necrosis was observed with a dose-related increase in incidence and severity (Table 16). The necrosis was generally characterized by individual, small, wedge-shaped areas beneath the capsule which contained remnants of degenerative tubules; these lesions were interpreted as post-necrotic scars. Renal tubule regeneration, characterized by focal clusters of basophilic tubule epithelium in the cortex, also occurred with a dose-related increase in male and female mice. Renal tubule dilatation also increased in incidence among low-and high-dose male mice, but not in females.

There was a dose-related increase in accumulation of golden brown, granular pigment (hemosiderin) in the cytoplasm of the proximal renal tubule epithelial cells among dosed mice of each sex.

TABLE 14
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

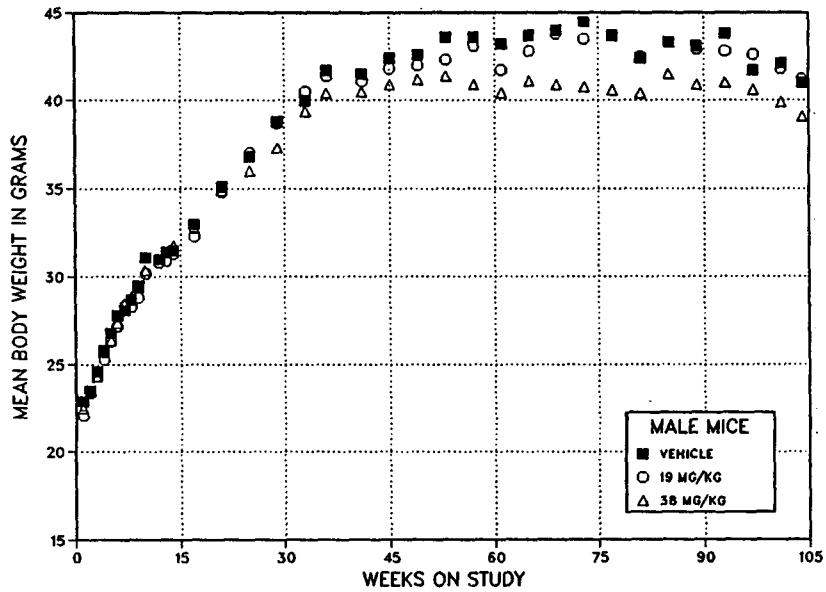
Weeks on Study	Vehicle Control		19 mg/kg			38 mg/kg		
	Av.Wt. (g)	Number of Survivors	Av.Wt. (g)	Wt. (% of controls)	Number of Survivors	Av.Wt. (g)	Wt. (% of controls)	Number of Survivors
1	22.9	60	22.1	97	60	22.5	98	60
2	23.5	60	23.4	100	60	23.5	100	60
3	24.6	60	24.3	99	60	24.3	99	60
4	25.8	60	25.3	98	60	25.7	100	60
5	26.8	60	26.3	98	60	26.4	99	60
6	27.8	60	27.2	98	60	27.4	99	60
7	28.1	60	28.3	101	60	28.5	101	60
8	28.8	60	28.3	98	60	28.9	100	60
9	29.5	60	28.8	98	60	29.4	100	60
10	30.6	60	29.9	98	60	30.3	99	60
12	31.0	60	30.8	99	60	31.0	100	60
13	31.4	60	30.9	98	60	31.4	100	60
14	31.5	60	31.3	99	60	31.8	101	60
17	33.0	59	32.3	98	58	32.8	99	60
21	35.1	59	34.8	99	58	34.9	99	59
25	36.8	57	37.0	101	58	36.0	98	59
29	38.8	57	38.7	100	58	37.3	96	59
33	40.0	55	40.5	101	58	39.4	99	59
36	41.7	55	41.4	99	57	40.4	97	59
41	41.5	55	41.1	99	57	40.5	98	59
45	42.4	55	41.8	99	57	40.9	97	59
49	42.6	54	42.0	99	57	41.2	97	59
53	43.6	54	42.3	97	57	41.4	95	59
57	43.6	54	43.1	99	57	40.9	94	58
61	43.2	54	41.7	97	57	40.4	94	58
65	43.7	54	42.8	98	57	41.1	94	58
69[a]	44.0	43	43.8	100	46	40.9	93	46
73	44.5	41	43.5	98	45	40.8	92	46
77	43.7	41	43.7	100	44	40.6	93	46
81	42.4	39	42.5	100	44	40.4	95	46
85	43.3	38	43.3	100	42	41.5	96	44
89	43.1	36	42.9	100	38	40.9	95	41
93	43.8	34	42.8	98	35	41.0	94	40
97	41.7	32	42.6	102	35	40.6	97	39
101	42.1	31	41.8	99	35	39.9	95	36
104	41.0	30	41.2	101	33	39.1	95	36
Terminal sacrifice		30			33			36
Mean for weeks								
1-13	27.6		27.1	98		27.4	99	
14-52	38.3		38.1	99		37.5	98	
53-104	43.1		42.7	99		40.7	94	

[a] Interim evaluation occurred.

TABLE 15
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

Weeks on Study	Vehicle Control		19 mg/kg			38 mg/kg		
	Av.Wt. (g)	Number of Survivors	Av.Wt. (g)	Wt. (% of controls)	Number of Survivors	Av.Wt. (g)	Wt. (% of controls)	Number of Survivors
1	17.9	60	18.1	101	60	18.0	101	60
2	18.4	60	18.3	100	60	18.4	100	60
3	19.4	60	19.4	100	60	19.4	100	60
4	20.3	60	20.5	101	60	20.3	100	60
5	20.9	60	20.9	100	60	20.7	99	60
6	21.6	60	21.8	101	60	21.3	99	60
7	21.4	60	22.2	104	60	21.7	101	60
8	22.2	60	23.2	105	60	22.5	101	60
9	22.7	60	23.5	104	60	23.2	102	60
10	22.6	60	23.2	103	60	23.2	103	60
11	23.4	60	23.8	102	59	23.7	101	60
12	23.7	60	24.1	102	59	23.7	100	60
13	24.4	60	24.2	99	59	23.8	98	60
14	24.6	60	25.0	102	59	24.7	100	60
17	26.0	60	26.6	102	59	25.5	98	60
21	28.0	60	28.7	103	59	27.3	98	60
25	29.4	60	30.0	102	59	28.8	98	60
29	30.6	60	31.8	104	59	29.4	96	60
33	31.8	60	33.2	104	59	30.7	97	60
37	32.0	60	33.7	105	59	31.4	98	59
41	33.5	60	34.4	103	58	32.2	96	59
45	33.6	60	35.6	106	58	33.1	99	57
49	35.6	59	36.5	103	56	34.8	98	55
53	34.7	58	35.6	103	55	32.4	93	54
57	35.5	57	36.8	104	55	34.4	97	54
61	36.0	56	37.7	105	54	34.6	96	53
65	35.5	56	37.2	105	54	35.0	99	50
69[a]	36.1	44	38.9	108	43	35.7	99	40
73	37.3	44	40.3	108	43	36.3	97	39
77	35.8	44	38.6	108	42	35.9	100	37
81	36.7	42	38.3	104	42	36.3	99	37
85	36.5	42	38.3	105	42	36.5	100	37
89	36.9	42	38.5	104	41	36.7	100	35
93	36.7	41	37.3	102	38	35.9	98	35
97	36.8	39	37.8	103	37	38.7	105	29
101	33.7	39	36.6	109	34	36.7	109	28
104	34.4	37	35.7	104	32	36.7	107	28
Terminal sacrifice		34			31			28
Mean for weeks								
1-13	21.5		21.8	101		21.5	100	
14-52	30.5		31.6	104		29.8	98	
53-104	35.9		37.7	105		35.8	100	

[a] Interim evaluation occurred.



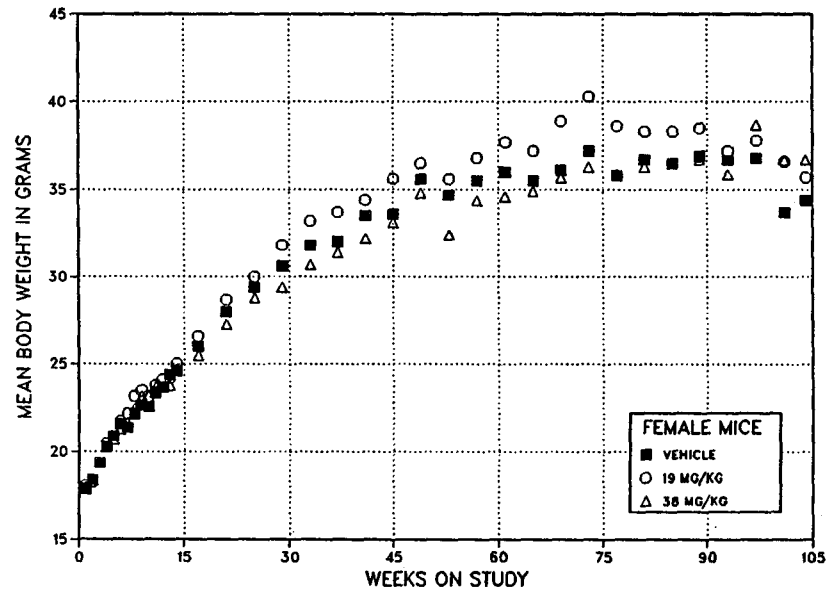


FIGURE 4
Growth Curves for Mice Administered 2,4-Diaminophenol Dihydrochloride by Gavage for 2 Years

TABLE 16
Kidney Lesions in Mice in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	19 mg/kg	38 mg/kg
Male			
Number examined	50	48	50
Necrosis	0 (0.0)[a]	12** (0.4)	30** (1.0)
Renal Tubule: Regeneration	34 (0.8)	34 (1.0)	48** (1.9)
Renal Tubule: Dilatation	1 (0.0)	15** (0.3)	46** (1.8)
Original Sections			
Renal Tubule: Hyperplasia			
Overall rates[b]	0/50 (0%)	0/48 (0%)	3/50 (6%)
Logistic regression tests[c]	P=0.050	–[d]	P=0.155
Renal Tubule: Adenoma[e]			
Overall rates	0/50 (0%)	0/50 (0%)	3/50 (6%)
Logistic regression tests	P=0.045	–[d]	P=0.146
Step Sections			
Renal Tubule: Hyperplasia			
Overall rates	0/50 (0%)	–[f]	7/50 (14%)[g]
Logistic regression tests		–	P=0.014
Renal Tubule: Adenoma			
Overall rates	0/50 (0%)	–	3/50 (6%)
Logistic regression tests			P=0.155
Original and Step Sections Combined			
Renal Tubule: Hyperplasia			
Overall rates	0/50 (0%)	–	9/50 (18%)
Logistic regression tests		–	P=0.005
Renal Tubule: Adenoma			
Overall rates	0/50 (0%)	–	6/50 (12%)
Logistic regression tests		–	P=0.027

TABLE 16
Kidney Lesions in Mice in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Female			
Number examined	50	39	50
Necrosis	2 (0.1)	5 (0.2)	8* (0.4)
Renal Tubule: Regeneration	18 (0.6)	24** (0.7)	42** (1.3)
Renal Tubule: Dilatation	0 (0.0)	1 (0.0)	1 (0.0)
Original Sections			
Renal Tubule: Hyperplasia			
Overall rates	0/50 (0%)	0/39 (0%)	1/50 (2%)
Renal Tubule: Adenoma			
Overall rates	0/50 (0%)	0/39 (0%)	0/50 (0%)
Renal Tubule: Carcinoma			
Overall rates	0/50 (0%)	1/39 (3%)	0/50 (0%)
Step Sections			
Renal Tubule: Hyperplasia			
Overall rates	0/50 (0%)	-	2/50 (4%)
Renal Tubule: Adenoma			
Overall rates	0/50 (0%)	-	1/50 (2%)
Original and Step Sections Combined			
Renal Tubule: Hyperplasia			
Overall rates	0/50 (0%)	-	3/50 (6%)
Renal Tubule: Adenoma			
Overall rates	0/50 (0%)	-	1/50 (2%)

* Significantly different ($P \leq 0.05$) from the control group by the logistic regression tests
** $P \leq 0.01$
[a] Values in parentheses are average severity grades for all animals. Severity of 1 = minimal, 2 = mild.
[b] Number of lesion-bearing animals/number of animals examined microscopically for this lesion type
[c] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression tests regard lesions in animals dying prior to terminal kill as nonfatal.
[d] Not applicable; no lesions in animal group
[e] Historical incidence in 2-year NTP corn oil gavage studies of vehicle control groups (mean ± standard deviation): 1/598 (0.2% ± 0.6%), range 0%–2%
[f] Step sections were not evaluated in the 19 mg/kg dose group
[g] Includes one animal that already had a diagnosis of hyperplasia

Pigmentation: Pigment was present in liver, duodenum, and mesenteric lymph nodes of all mice exposed to 2,4-diaminophenol dihydrochloride (Tables C5 and D4). Special staining procedures were performed to identify the pigment in lesions found in the 15-month interim evaluation animals. These pigmented lesions were similar to the lesions found in the 2-year study mice. Based on the pigment staining results in 15-month interim evaluation lesions, those similarly pigmented lesions found in mice from the 2-year studies were presumed to contain similar type of pigment. The golden brown pigment in the Kupffer cells of the liver, lamina propria of the duodenum, and macrophages of mesenteric lymph nodes did not react with the special stains for hemosiderin and was presumed to be the parent compound (2,4-diaminophenol dihydrochloride) or a metabolite.

Forestomach: Dose-related increases in ulceration and acanthosis of the forestomach were seen in male mice (ulcers: control 0/50, low-dose 2/23, high-dose 5/50; acanthosis: 4/50, 10/23, 13/50) (Table C5). Forestomach ulcers were characteristically mild to marked with peripherally thickened epithelium (acanthosis). Mild acanthosis was also observed in male mice that did not have ulcers. These lesions may have been related to the presence of pigment.

GENETIC TOXICITY

2,4-Diaminophenol dihydrochloride was mutagenic in *Salmonella typhimurium* strain TA98 when tested in a preincubation protocol with Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; it was not mutagenic in the absence of S9 activation, nor was it active in strains TA100, TA1535, or TA1537 (Haworth *et al.*, 1983; Table E1). The chemical was highly toxic, limiting the concentrations tested to a maximum of 10 μg/plate. In the mouse lymphoma assay, 2,4-diaminophenol dihydrochloride was positive for induction of trifluorothymidine resistance in L5178Y cells at concentrations of 2, 3, and 4 μg/mL without S9 activation; it was not tested with S9 (McGregor *et al.*, 1987; Table E2). In this assay, Trial 1 was judged inconclusive because the highest nonlethal dose tested yielded a nonsignificant increase in resistant colonies and the relative total growth indicated higher concentrations could have been tested. Trials 2 and 3 were judged positive. The 2 μg/mL dose in Trial 3 produced a positive response without toxicity.

2,4-Diaminophenol dihydrochloride was negative in cytogenetic tests for induction of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells, with or without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Galloway *et al.*, 1985, 1987; Tables E3 and E4). The toxicity of 2,4-diaminophenol dihydrochloride limited the doses in the sister chromatid exchange test to 0.9 μg/mL without S9 and 9.0 μg/mL with S9; in the chromosomal aberration test, 2.7 μg/mL 2,4-diaminophenol dihydrochloride was tested without S9 and 9.0 μg/mL was the highest dose tested with S9. 2,4-Diaminophenol dihydrochloride was tested for induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* (Zimmering *et al.*, 1985; Table E5). The chemical was administered in feed (3,500 ppm) and by abdominal injection (125 ppm). The results of the feeding experiment were judged to be equivocal ($P=0.0453$; frequency of recessive lethals=0.13%) and the results of the injection experiment were negative ($P=0.935$). Overall, 2,4-diaminophenol dihydrochloride was equivocal for the induction of sex-linked recessive lethal mutations in *D. melanogaster*.

DISCUSSION AND CONCLUSIONS

2,4-Diaminophenol dihydrochloride is one member of a broad class of monocyclic aromatic amino and nitro compounds that have been evaluated for carcinogenic potential by the NTP. The majority of these chemicals are used in the manufacture of dyes or in photographic processing and may therefore pose a risk for both occupational and consumer exposure. 2,4-Diaminophenol dihydrochloride is used primarily as a color accelerator in photographic developers and bleaching baths, and therefore the greatest exposure potential is occupational.

During the 16-day studies, there were no early deaths among rats that received doses up to 100 mg/kg, and only a mild toxic response was observed in rats at the high dose. Thus, a high dose of 200 mg/kg was selected for the 13-week studies. A low dose of 12 mg/kg allowed evaluation over a 17-fold range of doses which also overlapped the dose range evaluated in the 16-day studies.

All male and four female mice that received 200 mg/kg, all males and three females that received 100 mg/kg, and two females that received 50 mg/kg died before the end of the 16-day studies. Because of this apparent species difference in toxic response, 75 mg/kg was selected as the high dose for the 13-week studies of mice. This dose was intermediate between 50 and 100 mg/kg, and would verify the results observed in the 16-day studies. The remaining dose levels down to 5 mg/kg provided for evaluation over a 15-fold range.

During the 13-week studies, administration of 2,4-diaminophenol dihydrochloride to rats was associated with reduced survival at doses of 100 or 200 mg/kg, lower mean body weights at doses of 50 mg/kg and above in males, increases in absolute and relative mean kidney weights in males at all dose levels, and increased absolute and relative kidney and liver weights in 50, 100, and 200 mg/kg females. Renal tubule necrosis occurred in rats that received 100 or 200 mg/kg in both the 16-day and 13-week studies. Because of the compound-related effects which occurred at 50 mg/kg in the 13-week studies, and the obviously dose-related increase in the severity of toxic response above 50 mg/kg, the high dose for the 2-year studies in rats was selected to be 25 mg/kg and 12.5 mg/kg was selected as the low dose.

No deaths occurred among groups of female mice during the 13-week studies and the pattern of mortality among groups of male mice was not indicative of an association with chemical exposure. A review of the study records revealed no obvious evidence of problems associated with gavage technique (perforated esophagus or oil in the thoracic cavity or lungs). The major toxic end point used for setting doses for the 2-year studies of mice was the significantly increased incidence of compound-related renal tubule regeneration in the 75 mg/kg dose male and female mice. Because of the lower incidence and minimal severity of this lesion in lower dose groups, 38 mg/kg was selected as the high dose and 19 mg/kg as the low dose for the 2-year mouse studies.

During the 2-year studies, survival of rats exposed to 2,4-diaminophenol dihydrochloride was similar to survival of controls. However, overall survival of dosed and control females was considerably higher than overall survival of dosed and control male groups.

From approximately week 69 to the end of the studies, mean body weights of male rats that received 12.5 mg/kg were less than those of controls, and from approximately week 21, the mean body weights of the 25 mg/kg dose group were lower than mean body weights of both the control and the 12.5 mg/kg dose groups. The mean body weights of female rats that received 12.5 mg/kg were similar to those of controls throughout the studies; mean body weights of the 25 mg/kg dose group were less than either the control or 12.5 dose mg/kg group from week 37 to the end of the studies. Feed consumption by groups of dosed rats was similar to feed consumption by controls, indicating that the lower body weights represent a toxic effect of the chemical. Therefore, 12.5 and 25 mg/kg were considered adequate for evaluation of the carcinogenic potential of 2,4-diaminophenol dihydrochloride in rats.

Kidney lesions occurred in rats administered 2,4-diaminophenol dihydrochloride. The severity of nephropathy in male and female rats and the incidence of nephropathy in female rats increased with dose. The incidence of renal tubule cell hyperplasia increased in male and female rats. These kidney lesions appeared distinct from similar lesions normally associated with nephropathy in aging F344/N rats and were considered to be associated with chemical exposure. However, the incidence of renal tubule cell neoplasms was not increased in male or female rats.

Exposure to 2,4-diaminophenol dihydrochloride had no effect on survival of male or female B6C3F$_1$ mice. Mean body weights of male mice that received 38 mg/kg were lower than mean body weights of controls and of the low-dose group from approximately week 53 to the end of the studies. Because feed consumption by all groups of dosed mice was similar to feed consumption by controls, the reduced body weights appeared to be a toxic effect of the chemical.

Nonneoplastic lesions associated with exposure to 2,4-diaminophenol dihydrochloride occurred with significantly increased incidences in the kidneys of male and female mice. The incidences of tubule dilatation in males, kidney necrosis in males and females, and tubule regeneration in females increased with dose.

Renal tubule adenomas and renal tubule hyperplasias were present with increased incidences in high-dose male mice. The hyperplasias were not typical regenerative lesions and were considered potentially preneoplastic. Renal tubule adenomas are uncommon tumors in male B6C3F$_1$ mice and have been observed in only 1/658 (0.2%; range 0%-2%) NTP historical control male mice in 2-year corn oil gavage studies. Evidence that these lesions were associated with chemical exposure was enhanced by supplemental analysis of step sections of remaining kidney tissue; additional adenomas and hyperplasia were seen in high-dose males but not in controls. Altogether this response was considered some evidence of carcinogenic activity, the response was too strong to classify as equivocal evidence. However, in the absence of a more significant increase in numbers of tumors or evidence of progression to malignancy, the response was considered too weak to be classified as clear evidence of carcinogenic activity.

Kidney tumors considered to be related to chemical exposure have occurred in male and/or female mice in association with three chemicals: bromodichloromethane (NTP, 1987), nitrilotriacetic acid (NCI, 1977), and tris(2,3-dibromopropyl) phosphate (NCI, 1978c). There is little structural similarity among this group of compounds, nor are they structurally similar to 2,4-diaminophenol dihydrochloride. In other NTP studies, exposure to several structural analogues of 2,4-diaminophenol dihydrochloride, including 4-amino-2-nitrophenol (NCI, 1978a), 2-amino-4-nitrophenol (NTP, 1988a), 2,4-diaminoanisole sulfate (NCI, 1978b), and 2,4-diaminotoluene (NCI, 1979) failed to induce kidney tumors in mice. Administration of 2-amino-4-nitrophenol in corn oil by gavage was associated with increased severity of nephropathy, increased incidence of renal tubule hyperplasia, and a marginally increased incidence in renal tubule adenomas in male rats. Moreover, 2-amino-4-nitrophenol was toxic to rat proximal tubule epithelial cells in 13-week studies, but mice were not affected. 4-Amino-2-nitrophenol administered in the feed caused transitional cell carcinomas of the bladder in rats, and four high-dose male rats had renal tubule hyperplasia; however, none of the other structural analogues affected the kidney or bladder of either rats or mice.

Pigment, presumed to be the parent compound or a metabolite, was present in the lamina propria of the duodenum and the mesenteric lymph nodes of all groups of rats and mice, in the submucosa of the forestomach and pancreatic lymph nodes of male and female rats, and in Kupffer cells of the liver in male and female mice that received 2,4-diaminophenol dihydrochloride; no pigment was observed in the duodenum, Kupffer cells, lymph nodes, or forestomach of controls. The incidence of acanthosis of the forestomach was increased in high-dose female rats and high-dose male mice but was not increased in male rats or female mice; therefore, it is uncertain whether the increased incidences were related to chemical exposure. Similar pigmentation of the forestomach and duodenum has been observed in 2-year studies of other aminophenols including 2-amino-4-nitrophenol (NTP, 1988a), 2-amino-5-nitrophenol (NTP, 1988b), and 4-amino-2-nitrophenol (NCI, 1978a). Although occasionally associated with nonneoplastic lesions such as ulceration and acanthosis, no neoplasms of the gastrointestinal tract have been associated with the presence of pigmentation in any of these studies.

Hemosiderin, as well as a golden brown pigment presumed to be the parent compound or a metabolite, was present in renal tubules of treated animals, and was particularly evident in the high-dose groups. However, the presence of pigment did not appear to be a contributing factor in the tubule cell lesions which occurred in male rats and mice.

Conclusions

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of 2,4-diaminophenol dihydrochloride in male or female F344/N rats that received 12.5 or 25 mg/kg. There was *some evidence of carcinogenic activity* of 2,4-diaminophenol dihydrochloride in male B6C3F$_1$ mice based on increased incidences of renal tubule adenomas; there was *no evidence of carcinogenic activity* of 2,4-diaminophenol dihydrochloride in female B6C3F$_1$ mice that received 19 or 38 mg/kg.

Administration of 2,4-diaminophenol dihydrochloride to rats was associated with increased severity of nephropathy in males and females, increased incidence of nephropathy in females, and focal renal tubule hyperplasia in males and females. In mice, chemical exposure was associated with renal tubule necrosis and regeneration in males and females and acanthosis of the forestomach in males.

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of peer review comments and the public discussion on this Technical Report appears on page 10.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF 2,4-DIAMINOPHENOL DIHYDROCHLORIDE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	12.5 mg/kg	25 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	9	10	10
Early deaths			
Natural death[a]	12	16	15
Moribund	15	11	19
Accidental death[a]		2	
Survivors			
Died last week of study	1		
Terminal sacrifice	23	21	16
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, rectum	(11)	(19)	(21)
Serosa, sarcoma, metastatic			1 (5%)
Intestine small, duodenum	(47)	(50)	(50)
Liver	(50)	(31)	(50)
Sarcoma, metastatic, uncertain primary site			1 (2%)
Mesentery	(7)	(8)	(4)
Pancreas	(50)	(22)	(50)
Sarcoma, metastatic, uncertain primary site			1 (2%)
Acinus, adenoma	1 (2%)		3 (6%)
Acinus, adenoma, multiple		1 (5%)	
Stomach, forestomach	(49)	(23)	(50)
Stomach, glandular	(49)	(23)	(50)
Tongue			(1)
Papilloma squamous			1 (100%)
Cardiovascular System			
Heart	(50)	(22)	(50)
Endocrine System			
Adrenal gland	(50)	(50)	(50)
Pheochromocytoma benign		1 (2%)	
Adrenal gland, cortex	(50)	(50)	(50)
Adrenal gland, medulla	(49)	(50)	(50)
Pheochromocytoma malignant	7 (14%)	2 (4%)	3 (6%)
Pheochromocytoma benign	8 (16%)	6 (12%)	7 (14%)
Bilateral, pheochromocytoma benign	2 (4%)	1 (2%)	
Islets, pancreatic	(50)	(22)	(50)
Adenoma	3 (6%)	3 (14%)	2 (4%)
Carcinoma	1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Endocrine System (continued)			
Pituitary gland	(50)	(50)	(49)
Pars distalis, adenoma	23 (46%)	17 (34%)	14 (29%)
Pars distalis, carcinoma	1 (2%)		1 (2%)
Thyroid gland	(50)	(20)	(50)
Bilateral, C-cell, carcinoma	1 (2%)		
C-cell, adenoma	4 (8%)	4 (20%)	2 (4%)
C-cell, adenoma, mild			1 (2%)
C-cell, carcinoma	1 (2%)		2 (4%)
General Body System			
None			
Genital System			
Epididymis	(50)	(20)	(50)
Serosa, sarcoma, metastatic, uncertain primary site			1 (2%)
Preputial gland	(17)	(24)	(26)
Adenoma	1 (6%)	2 (8%)	2 (8%)
Carcinoma	2 (12%)	3 (13%)	2 (8%)
Sarcoma, metastatic, uncertain primary site			1 (4%)
Prostate	(49)	(19)	(50)
Adenoma	2 (4%)		1 (2%)
Seminal vesicle	(50)	(25)	(50)
Testes	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	25 (50%)	25 (50%)	35 (70%)
Interstitial cell, adenoma	17 (34%)	17 (34%)	11 (22%)
Hematopoietic System			
Bone marrow	(11)	(20)	(21)
Sarcoma, metastatic, uncertain primary site			1 (5%)
Lymph node	(50)	(50)	(50)
Lymph node, mandibular	(49)	(14)	(47)
Lymph node, mesenteric	(49)	(49)	(50)
Spleen	(50)	(29)	(50)
Hemangiosarcoma		1 (3%)	
Sarcoma	1 (2%)	2 (7%)	1 (2%)
Sarcoma, metastatic, uncertain primary site			1 (2%)
Sarcoma, poorly differentiated	1 (2%)		
Thymus	(17)	(17)	(24)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Integumentary System			
Mammary gland	(9)	(10)	(12)
Fibroadenoma	4 (44%)		
Skin	(20)	(26)	(28)
Basal cell adenoma	1 (5%)	1 (4%)	1 (4%)
Keratoacanthoma	2 (10%)		3 (11%)
Keratoacanthoma, multiple			1 (4%)
Papilloma squamous		1 (4%)	1 (4%)
Squamous cell carcinoma	1 (5%)		1 (4%)
Trichoepithelioma		1 (4%)	
Sebaceous gland, carcinoma	1 (5%)		
Subcutaneous tissue, fibroma	1 (5%)		1 (4%)
Subcutaneous tissue, fibrosarcoma	1 (5%)	1 (4%)	1 (4%)
Subcutaneous tissue, sarcoma	1 (5%)		
Subcutaneous tissue, sarcoma, metastatic, uncertain primary site			1 (4%)
Subcutaneous tissue, schwannoma malignant			1 (4%)
Musculoskeletal System			
Skeletal muscle			(2)
Abdominal, sarcoma			1 (50%)
Hindlimb, sarcoma, metastatic, uncertain primary site			1 (50%)
Nervous System			
Brain	(50)	(20)	(50)
Astrocytoma malignant			1 (2%)
Glioma NOS		1 (5%)	
Granular cell tumor benign			1 (2%)
Squamous cell carcinoma, early invasion, metastatic, Zymbal's gland		1 (5%)	
Respiratory System			
Lung	(50)	(30)	(50)
Alveolar/bronchiolar adenoma	2 (4%)		3 (6%)
Carcinoma, metastatic, Zymbal's gland			1 (2%)
Pheochromocytoma malignant, metastatic, adrenal gland		1 (3%)	
Sarcoma, metastatic, uncertain primary site			1 (2%)
Nose	(12)	(21)	(21)
Sarcoma, metastatic, uncertain primary site			1 (5%)
Nares, papilloma squamous		1 (5%)	
Special Senses System			
Zymbal's gland	(1)	(1)	(2)
Carcinoma	1 (100%)	1 (100%)	1 (50%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Urinary System			
Kidney	(50)	(49)	(50)
Sarcoma, metastatic			1 (2%)
Renal tubule, adenoma			1 (2%)
Renal tubule, carcinoma	1 (2%)		
Transitional epithelium, carcinoma			1 (2%)
Urinary bladder	(50)	(48)	(50)
Transitional epithelium, carcinoma		1 (2%)	
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Leukemia mononuclear	7 (14%)	4 (8%)	5 (10%)
Mesothelioma malignant	2 (4%)	3 (6%)	
Tumor Summary			
Total animals with primary neoplasms[c]	49	46	49
Total primary neoplasms	126	100	112
Total animals with benign neoplasms	47	45	48
Total benign neoplasms	96	81	91
Total animals with malignant neoplasms	24	16	18
Total malignant neoplasms	30	18	21
Total animals with secondary neoplasms[d]		2	2
Total secondary neoplasms		2	13
Total animals with malignant neoplasms of uncertain primary site			1
Total animals with neoplasms uncertain-benign or malignant		1	
Total uncertain neoplasms		1	

[a] One control, three low-dose, and three high-dose males listed as natural death may have died from gavage trauma.
[b] Number of animals with any tissue examined microscopically
[c] Primary tumors: all tumors except metastatic tumors
[d] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control

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

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 2 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 6 4	0 7 1	0 2 1	0 2 2	0 3 1	0 3 2	0 3 4	0 5 1	0 4 1	0 4 2	0 4 3	0 6 2	0 6 3	0 7 2	1 2 1	0 5 2	0 6 1	0 8 1	0 8 2	0 8 3	0 9 1	0 9 2	1 0 1	1 0 2	1 2 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large																										13
Intestine large, cecum																										11
Intestine large, colon																										11
Intestine large, rectum																										11
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum																										10
Intestine small, jejunum																										10
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+	+	+											+										7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma								X																		1
Salivary glands	+	+	+	+			+	+		+	+	+	+	+		+	+	+		+	+				+	40
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth							+																			1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant			X			X	X												X					X		7
Pheochromocytoma benign				X			X							X				X					X			8
Bilateral, pheochromocytoma benign						X															X					2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															3
Carcinoma								X																		1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X		X			X		X	X	X			X			X	X						X	23
Pars distalis, carcinoma																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 2 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 6 4	0 7 1	0 2 1	0 2 2	0 3 1	0 3 2	0 3 4	0 5 1	0 4 1	0 4 2	0 4 3	0 6 2	0 6 3	0 7 2	0 7 2 1	1 2 1	0 5 2	0 6 1	0 8 1	0 8 2	0 8 3	0 9 1	0 9 2	1 0 1	1 0 2	1 2 2	**Total Tissues/ Tumors**
Endocrine System (continued)																											
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, carcinoma														X													1
C-cell, adenoma																			X	X							4
C-cell, carcinoma								X																			1
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland		A	+									+															17
Adenoma												X															1
Carcinoma																											2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma														X								X					2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X	X	X	X	X	X		X		X	X	X		X	X	X	X	X		X		X			25
Interstitial cell, adenoma		X							X		X				X						X		X		X		17
Hematopoietic System																											
Bone marrow																											11
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																							X				1
Sarcoma, poorly differentiated																											1
Thymus																					+				+		17
Integumentary System																											
Mammary gland															+	+								+			9
Fibroadenoma															X	X											4

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	3	4	4	4	5	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7				
	8	2	4	8	2	2	2	4	6	7	7	8	9	4	4	5	5	5	7	7	8	8	8	0	2		
	0	6	0	1	2	4	5	9	9	0	6	7	1	2	7	3	8	9	1	2	1	5	6	2	0		
Carcass ID Number	0	0	0	0	1	0	1	0	0	1	0	0	1	0	0	0	0	1	0	0	0	1	1	0	0		
	1	4	5	5	1	5	1	8	2	1	9	2	1	9	1	4	9	2	8	3	6	0	2	7	1		
	2	5	5	4	4	3	3	5	4	2	5	3	1	4	3	4	3	4	4	3	5	3	3	3	1		
Integumentary System (continued)																											
Skin	+	+	+	+	+	+	M	+	+	+	+	+	+			+											
Basal cell adenoma																											
Keratoacanthoma					X																						
Squamous cell carcinoma																											
Sebaceous gland, carcinoma										X																	
Subcutaneous tissue, fibroma																											
Subcutaneous tissue, fibrosarcoma																											
Subcutaneous tissue, sarcoma								X																			
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+														
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Alveolar/bronchiolar adenoma																											
Nose	+	+	+	+	+	+	+	A	+	+	+	+	+														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Special Senses System																											
Eye			+	+					+			+												+			
Harderian gland			+						+																		
Zymbal's gland															+												
Carcinoma															X												
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Renal tubule, carcinoma																											
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Leukemia mononuclear					X						X									X							
Mesothelioma malignant																											

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 2 1	7 3 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 6 4	0 7 1	0 2 1	0 2 2	0 3 1	0 3 2	0 3 4	0 5 1	0 4 1	0 4 2	0 4 3	0 6 2	0 6 3	0 7 2	1 2 1	0 5 2	0 6 1	0 8 1	0 8 2	0 8 3	0 9 1	0 9 2	1 0 1	1 0 2	1 2 2	**Total Tissues/ Tumors**
Integumentary System (continued)																										
Skin	+			+		+					+								+				+	+		20
Basal cell adenoma																								X		1
Keratoacanthoma							X																			2
Squamous cell carcinoma																							X			1
Sebaceous gland, carcinoma																										1
Subcutaneous tissue, fibroma											X															1
Subcutaneous tissue, fibrosarcoma					X																					1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone																										13
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X							X						2
Nose																										12
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										5
Harderian gland																										2
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma														X												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X	X					X											X						7
Mesothelioma malignant				X			X																			2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg (continued)

Number of Days on Study	6 8 1	6 8 1	6 8 1	7 0 1	7 2 1	7 2 1	7 2 1	7 2 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	2 1 2	2 0 3	1 9 3	2 3 2	1 3 2	1 4 1	1 4 3	1 5 1	1 5 2	1 6 1	1 6 2	1 7 1	1 7 2	1 7 3	1 7 4	1 8 1	1 9 1	1 9 2	2 0 1	2 0 2	2 1 1	2 3 1	2 4 1	2 4 2	2 4 3	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										18
Intestine large						+																				20
Intestine large, cecum																										18
Intestine large, colon						+																				19
Intestine large, rectum																										19
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum																										18
Intestine small, jejunum																										18
Liver			+	+	+	+	+		+					+						+	+					31
Mesentery												+			+			+	+							8
Pancreas							+						+								+					22
Acinus, adenoma, multiple													X													1
Salivary glands																										20
Stomach					+																					23
Stomach, forestomach					+																					23
Stomach, glandular					+																					23
Cardiovascular System																										
Heart																+										22
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																			X		X					2
Pheochromocytoma benign			X			X			X					X					X			X		X		7
Bilateral, pheochromocytoma benign											X															1
Islets, pancreatic						+														+						22
Adenoma						X														X						3
Parathyroid gland																										12
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X	X	X		X	X						X				X				X	X	X		17
Thyroid gland																			+							20
C-cell, adenoma																			X							4
General Body System																										
None																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg (continued)

Number of Days on Study	1 4 7	2 8 6	2 9 1	3 6 0	4 3 5	4 5 0	4 5 4	4 6 1	4 6 3	4 6 7	4 8 2	4 8 8	5 0 3	5 6 1	5 6 8	5 8 1	5 9 7	6 0 4	6 0 8	6 1 1	6 3 9	6 3 9	6 4 8	6 5 3	6 7 2
Carcass ID Number	1 4 2	1 3 1	2 2 5	1 8 5	1 6 5	2 3 5	2 0 5	1 3 3	1 5 5	2 1 3	1 8 4	1 8 3	2 4 5	2 2 3	1 6 3	2 2 1	1 5 4	2 4 4	2 4 4	1 3 3	1 4 4	1 9 4	2 0 4	2 4 3	1 8 2
Genital System																									
Epididymis	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+	
Adenoma												X										X			
Carcinoma																X								X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+					
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma												X		X		X			X		X	X	X		X
Interstitial cell, adenoma						X	X	X			X		X		X			X		X				X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	M	M	M	+	+	+	+	+	M	+	+	M	+	+	M	M	+	+				
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		
Hemangiosarcoma																									
Sarcoma																					X				
Thymus	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+					
Integumentary System																									
Mammary gland	+	+	M	M	+	M	M	+	M	+	+	+	M		M		M	M	+	M					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Basal cell adenoma																									
Papilloma squamous																									
Trichoepithelioma																									
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Glioma NOS														X											
Squamous cell carcinoma, early invasion, metastatic, Zymbal's gland							X																		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg (continued)

Number of Days on Study	6 8 1	6 8 6	6 8 7	7 0 8	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 1 2	2 0 3	1 9 3	2 3 2	1 3 2	1 4 1	1 4 3	1 5 1	1 5 2	1 6 1	1 6 2	1 7 1	1 7 2	1 7 3	1 7 4	1 8 1	1 9 1	1 9 2	2 0 1	2 0 2	2 1 1	2 3 1	2 4 1	2 4 2	2 4 3	**Total Tissues/ Tumors**
Genital System																										
Epididymis																										20
Preputial gland										+	+															24
Adenoma																										2
Carcinoma											X															3
Prostate																										19
Seminal vesicle			+														+						+			25
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X					X		X		X	X	X	X	X	X	X	X	X	X		X	X	X		X	25
Interstitial cell, adenoma		X	X	X	X		X		X											X				X		17
Hematopoietic System																										
Bone marrow																										20
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular																										14
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+						+		+	+	+								+			+				29
Hemangiosarcoma							X																			1
Sarcoma											X															2
Thymus																										17
Integumentary System																										
Mammary gland						+		+																		10
Skin		+												+			+	+				+			+	26
Basal cell adenoma																						X				1
Papilloma squamous																									X	1
Trichoepithelioma		X																								1
Subcutaneous tissue, fibrosarcoma																	X									1
Musculoskeletal System																										
Bone																										19
Nervous System																										
Brain																										20
Glioma NOS																										1
Squamous cell carcinoma, early invasion, metastatic, Zymbal's gland																										1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg (continued)

Number of Days on Study	1 4 7	2 8 6	2 9 1	3 6 0	4 3 5	4 5 0	4 5 4	4 6 1	4 6 3	4 6 7	4 8 2	4 8 8	5 0 3	5 6 1	5 6 8	5 8 1	5 9 7	6 0 4	6 0 8	6 1 1	6 3 9	6 3 9	6 4 8	6 5 3	6 7 2
Carcass ID Number	1 4 2	1 3 1	2 2 5	1 8 5	1 6 5	2 3 5	2 0 5	1 3 3	1 5 5	2 1 3	1 8 4	1 8 3	2 4 5	2 2 3	1 6 3	2 2 1	1 5 4	2 4 4	2 3 4	1 5 3	1 4 4	1 9 4	2 0 4	2 3 3	1 8 2
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+		+
Pheochromocytoma malignant, metastatic, adrenal gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			
Nares, papilloma squamous																						X			
Trachea	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					
Special Senses System																									
Eye						+																+			+
Harderian gland						+																			
Zymbal's gland							+																		
Carcinoma							X																		
Urinary System																									
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma				X																					
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X														X		
Mesothelioma malignant														X								X			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg (continued)

Number of Days on Study	6 8 1	6 8 6	6 8 7	7 0 8	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	2 1 2	2 0 3	1 9 3	2 3 2	1 3 2	1 4 1	1 4 3	1 5 1	1 5 2	1 6 1	1 6 2	1 7 1	1 7 2	1 7 3	1 7 4	1 8 1	1 9 1	1 9 2	2 0 1	2 0 2	2 1 1	2 3 1	2 4 1	2 4 2	2 4 3	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+		+							+					+				+	+		+		30
Pheochromocytoma malignant, metastatic, adrenal gland																					X					1
Nose																										21
Nares, papilloma squamous																										1
Trachea																										19
Special Senses System																										
Eye																+	+									5
Harderian gland																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional epithelium, carcinoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear							X		X																	4
Mesothelioma malignant																		X								3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg

Number of Days on Study	3 2 7	3 6 0	4 3 3	4 6 2	4 6 8	4 7 5	4 8 9	4 9 2	4 9 2	5 0 6	5 1 0	5 1 2	5 1 2	5 4 1	5 4 6	5 6 1	5 6 2	5 7 5	5 8 8	5 9 5	6 1 0	6 3 2	6 4 4	6 4 8	6 5 3
Carcass ID Number	3 3 5	3 3 4	3 2 5	3 6 4	2 9 4	3 3 3	3 3 2	2 5 5	3 6 3	3 6 2	2 5 4	3 1 5	3 6 1	3 8 4	3 0 4	3 2 4	2 5 3	3 5 4	2 9 3	2 7 5	3 1 2	2 8 3	3 1 4	2 9 2	2 6 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+			
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+			
Serosa, sarcoma, metastatic																		X							
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+		+	+	+	+	+	+	+	+		+	+	+	+	+	+			
Intestine small, jejunum	+	+	+	+	+	+		+	+	+	+	+	+	+	+		+	+	+	+	+	+			
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																		X							
Mesentery																					+				+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, uncertain primary site																		X							
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Papilloma squamous																									
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																							X		
Pheochromocytoma benign					X																				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	6 5 3	6 6 7	6 7 7	6 8 0	6 9 4	7 1 5	7 2 5	7 2 5	7 2 8	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 4 3	3 4 2	3 0 3	3 4 1	3 2 3	2 7 4	2 6 3	3 5 3	3 0 2	2 5 1	2 5 2	2 6 2	2 7 2	2 7 3	2 8 1	2 8 2	2 9 1	3 1 3	3 2 2	3 3 1	3 5 1	3 5 2	3 0 1	3 1 1	3 2 1	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large		+																								23
Intestine large, cecum																										22
Intestine large, colon		+																								22
Intestine large, rectum																										21
Serosa, sarcoma, metastatic																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum																	+									20
Intestine small, jejunum																										20
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site																										1
Mesentery													+		+											4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, uncertain primary site																										1
Acinus, adenoma																					X	X		X		3
Salivary glands		+				+		+	+	+		+		+	+	+	+				+		+	+		37
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue													+													1
Papilloma squamous													X													1
Tooth									+																	1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																X				X						3
Pheochromocytoma benign			X				X							X		X	X				X					7
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma												X											X			2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	44

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	3	3	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	6	6	6	6	6
	2	6	3	6	6	7	8	9	9	0	1	1	1	4	4	6	6	7	8	9	1	3	4	4	5
	7	0	3	2	8	5	9	2	2	6	0	2	2	1	6	1	2	5	8	5	0	2	4	8	3
Carcass ID Number	3	3	3	3	2	3	3	2	3	3	2	3	3	2	3	3	2	3	2	2	3	2	3	2	2
	3	3	2	6	9	3	3	5	6	6	5	1	6	8	0	2	5	5	9	7	1	8	1	9	6
	5	4	5	4	4	3	2	5	3	2	4	5	1	4	4	4	3	4	3	5	2	3	4	2	4
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pars distalis, adenoma													X	X			X							X	X
Pars distalis, carcinoma															X										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																					X				
C-cell, adenoma, mild																									
C-cell, carcinoma					X																				
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, sarcoma, metastatic, uncertain primary site																		X							
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			
Adenoma																									
Carcinoma																						X			
Sarcoma, metastatic, uncertain primary site																		X							
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X			X	X	X				X	X			X		X	X		X	X	X		X
Interstitial cell, adenoma				X	X				X	X	X				X		X			X				X	
Hematopoietic System																									
Bone marrow	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Sarcoma, metastatic, uncertain primary site																		X							
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Sarcoma, metastatic, uncertain primary site																		X							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	6 5 3	6 6 7	6 7 7	6 8 0	6 9 4	7 1 5	7 2 5	7 2 5	7 2 8	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 4 3	3 4 2	3 0 3	3 4 1	3 2 3	2 7 4	2 6 3	3 5 3	3 0 2	2 5 1	2 5 2	2 6 2	2 7 2	2 7 3	2 8 1	2 8 2	2 9 1	3 1 3	3 2 2	3 3 1	3 5 1	5 5 2	0 1 1	1 2 1	2 1 1	**Total Tissues/ Tumors**
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X					X				X					X	X	X	X		X				X		14
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																	X									2
C-cell, adenoma, mild			X																							1
C-cell, carcinoma				X																						2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Serosa, sarcoma, metastatic, uncertain primary site																										1
Preputial gland	+					+				+						+		+								26
Adenoma	X									X																2
Carcinoma						X																				2
Sarcoma, metastatic, uncertain primary site																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X																			1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	35
Interstitial cell, adenoma									X											X						11
Hematopoietic System																										
Bone marrow																										21
Sarcoma, metastatic, uncertain primary site																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																		X								1
Sarcoma, metastatic, uncertain primary site																										1
Thymus							+	+																		24

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	3 2 7	3 6 0	4 3 3	4 6 2	4 6 8	4 7 5	4 8 9	4 9 2	4 9 2	5 0 6	5 1 0	5 1 2	5 1 2	5 4 1	5 4 6	5 6 1	5 6 2	5 7 5	5 8 8	5 9 5	6 1 0	6 3 2	6 4 4	6 4 8	6 5 3
Carcass ID Number	3 3 5	3 3 4	3 2 5	3 6 4	2 9 4	3 3 3	3 3 2	2 5 5	3 6 3	3 6 2	2 5 4	3 1 5	3 6 1	2 8 4	3 0 4	3 2 4	3 5 3	2 5 4	3 9 3	2 7 5	2 1 2	3 8 3	2 1 4	3 9 2	2 6 4
Integumentary System																									
Mammary gland	+	M	M	+	+	M	M	M	M	+	+	M	M	M	+	M	+		+	+	+	+			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+
Basal cell adenoma																									
Keratoacanthoma																X									X
Keratoacanthoma, multiple																									
Papilloma squamous														X											
Squamous cell carcinoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, sarcoma, metastatic, uncertain primary site																		X							
Subcutaneous tissue, schwannoma malignant																			X						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+				
Skeletal muscle	+																	+							
Abdominal, sarcoma	X																								
Hindlimb, sarcoma, metastatic, uncertain primary site																		X							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																								X	
Granular cell tumor benign																									
Spinal cord	+																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Carcinoma, metastatic, Zymbal's gland																									
Sarcoma, metastatic, uncertain primary site																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M			
Sarcoma, metastatic, uncertain primary site																		X							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	6 5 3	6 6 7	6 7 7	6 8 0	6 9 4	7 1 5	7 2 5	7 2 5	7 2 8	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 4 3	3 4 2	3 0 3	3 4 1	3 2 3	2 7 4	2 6 3	3 5 3	3 0 2	2 5 1	2 5 2	2 6 2	2 7 2	2 7 3	2 8 1	2 8 2	2 9 1	3 1 3	3 2 2	3 3 1	3 5 1	3 5 2	3 0 1	3 1 1	3 2 1	**Total Tissues/ Tumors**
Integumentary System																										
Mammary gland	+																									12
Skin				+					+						+					+			+			28
Basal cell adenoma																							X			1
Keratoacanthoma															X											3
Keratoacanthoma, multiple																				X						1
Papilloma squamous																										1
Squamous cell carcinoma																							X			1
Subcutaneous tissue, fibroma																							X			1
Subcutaneous tissue, fibrosarcoma									X																	1
Subcutaneous tissue, sarcoma, metastatic, uncertain primary site																										1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone																										20
Skeletal muscle																										2
Abdominal, sarcoma																										1
Hindlimb, sarcoma, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Granular cell tumor benign																	X									1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X								X											3
Carcinoma, metastatic, Zymbal's gland									X																	1
Sarcoma, metastatic, uncertain primary site																										1
Nose																										21
Sarcoma, metastatic, uncertain primary site																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	3 2 7	3 6 0	4 3 3	4 6 2	4 6 8	4 7 5	4 8 9	4 9 2	4 9 2	5 0 6	5 1 0	5 1 2	5 1 2	5 4 1	5 4 6	5 6 1	5 6 2	5 7 5	5 8 8	5 9 5	6 1 0	6 3 2	6 4 4	6 4 8	6 5 3
Carcass ID Number	3 3 5	3 3 4	3 2 5	3 6 4	2 9 4	3 3 3	3 3 2	2 5 5	3 6 3	3 6 2	2 5 4	3 1 5	3 6 1	3 8 4	3 0 4	3 2 4	2 5 3	3 5 4	2 9 3	2 7 5	3 1 2	2 8 3	3 1 4	2 9 2	2 6 4
Special Senses System																									
Ear																								+	
Eye																						M			+
Zymbal's gland																								+	
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic																		X							
Renal tubule, adenoma																									
Transitional epithelium, carcinoma										X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																				X		X		X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	6 5 3	6 6 7	6 7 7	6 8 0	6 9 4	7 1 5	7 2 5	7 2 5	7 2 8	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	
Carcass ID Number	3 4 3	3 4 2	3 4 3	3 4 1	3 2 3	2 7 4	2 7 6	3 5 3	3 0 2	2 5 1	2 5 2	2 6 2	2 7 2	2 7 3	2 8 1	2 8 2	2 9 1	3 1 3	3 2 2	3 3 1	3 5 1	3 5 2	3 0 1	3 1 1	3 2 1	**Total Tissues/ Tumors**
Special Senses System																										
Ear																										1
Eye			+				+																			3
Zymbal's gland									+																	2
Carcinoma									X																	1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic																										1
Renal tubule, adenoma														X												1
Transitional epithelium, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X					X																		5

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	12.5 mg/kg	25 mg/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	10/49 (20%)	7/50 (14%)	7/50 (14%)
Adjusted rates[b]	35.2%	31.7%	33.5%
Terminal rates[c]	7/24 (29%)	6/21 (29%)	4/16 (25%)
First incidence (days)	570	687	468
Life table tests[d]	P=0.532N	P=0.417N	P=0.596N
Logistic regression tests[d]	P=0.409N	P=0.441N	P=0.442N
Cochran-Armitage test[d]	P=0.233N		
Fisher exact test[d]		P=0.282N	P=0.282N
Adrenal Medulla: Malignant Pheochromocytoma			
Overall rates	7/49 (14%)	2/50 (4%)	3/50 (6%)
Adjusted rates	24.8%	9.5%	15.6%
Terminal rates	5/24 (21%)	2/21 (10%)	2/16 (13%)
First incidence (days)	525	729 (T)	644
Life table tests	P=0.217N	P=0.120N	P=0.336N
Logistic regression tests	P=0.155N	P=0.117N	P=0.229N
Cochran-Armitage test	P=0.093N		
Fisher exact test		P=0.075N	P=0.151N
Adrenal Medulla: Benign or Malignant Pheochromocytoma			
Overall rates	15/49 (31%)	8/50 (16%)	9/50 (18%)
Adjusted rates	49.4%	36.2%	41.2%
Terminal rates	10/24 (42%)	7/21 (33%)	5/16 (31%)
First incidence (days)	525	687	468
Life table tests	P=0.325N	P=0.147N	P=0.413N
Logistic regression tests	P=0.189N	P=0.146N	P=0.219N
Cochran-Armitage test	P=0.081N		
Fisher exact test		P=0.069N	P=0.109N
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	2/50 (4%)	0/30 (0%)	3/50 (6%)
Adjusted rates	8.3%	0.0%	14.2%
Terminal rates	2/24 (8%)	0/5 (0%)	1/16 (6%)
First incidence (days)	729 (T)	–[e]	632
Life table tests	P=0.270	P=0.616N	P=0.350
Logistic regression tests	P=0.303	P=0.616N	P=0.391
Cochran-Armitage test	P=0.397		
Fisher exact test		P=0.388N	P=0.500
Mammary Gland: Fibroadenoma			
Overall rates	4/50 (8%)	0/50 (0%)	0/50 (0%)
Adjusted rates	14.4%	0.0%	0.0%
Terminal rates	2/24 (8%)	0/21 (0%)	0/16 (0%)
First incidence (days)	653	–	–
Life table tests	P=0.030N	P=0.092N	P=0.120N
Logistic regression tests	P=0.024N	P=0.085N	P=0.094N
Cochran-Armitage test	P=0.015N		
Fisher exact test		P=0.059N	P=0.059N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Pancreas: Adenoma			
Overall rates	1/50 (2%)	1/22 (5%)[f]	3/50 (6%)
Adjusted rates	4.2%		18.8%
Terminal rates	1/24 (4%)		3/16 (19%)
First incidence (days)	729 (T)		729 (T)
Life table tests			P=0.170
Logistic regression tests			P=0.170
Fisher exact test			P=0.309
Pancreatic Islets: Adenoma			
Overall rates	3/50 (6%)	3/22 (14%)[f]	2/50 (4%)
Adjusted rates	10.1%		12.5%
Terminal rates	1/24 (4%)		2/16 (13%)
First incidence (days)	570		729 (T)
Life table tests			P=0.655N
Logistic regression tests			P=0.588N
Fisher exact test			P=0.500N
Pancreatic Islets: Adenoma or Carcinoma			
Overall rates	4/50 (8%)	3/22 (14%)[f]	2/50 (4%)
Adjusted rates	14.0%		12.5%
Terminal rates	2/24 (8%)		2/16 (13%)
First incidence (days)	570		729 (T)
Life table tests			P=0.511N
Logistic regression tests			P=0.436N
Fisher exact test			P=0.339N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	23/50 (46%)	17/50 (34%)	14/49 (29%)
Adjusted rates	60.3%	54.2%	56.3%
Terminal rates	10/24 (42%)	8/21 (38%)	7/16 (44%)
First incidence (days)	426	463	512
Life table tests	P=0.286N	P=0.366N	P=0.337N
Logistic regression tests	P=0.080N	P=0.223N	P=0.094N
Cochran-Armitage test	P=0.044N		
Fisher exact test		P=0.154N	P=0.056N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rates	24/50 (48%)	17/50 (34%)	15/49 (31%)
Adjusted rates	61.6%	54.2%	57.5%
Terminal rates	10/24 (42%)	8/21 (38%)	7/16 (44%)
First incidence (days)	426	463	512
Life table tests	P=0.301N	P=0.311N	P=0.360N
Logistic regression tests	P=0.081N	P=0.170N	P=0.094N
Cochran-Armitage test	P=0.046N		
Fisher exact test		P=0.111N	P=0.059N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Preputial Gland: Carcinoma			
Overall rates	2/17 (12%)	3/24 (13%)	2/26 (8%)
Adjusted rates	4.8%	53.2%	8.3%
Terminal rates	0/2 (0%)	1/2 (50%)	0/3 (0%)
First incidence (days)	525	581	632
Life table tests	P=0.531	P=0.445	P=0.611
Logistic regression tests	P=0.446N	P=0.549	P=0.570N
Cochran-Armitage test	P=0.412N		
Fisher exact test		P=0.665	P=0.521N
Preputial Gland: Adenoma or Carcinoma			
Overall rates	3/17 (18%)	5/24 (21%)	4/26 (15%)
Adjusted rates	52.4%	56.0%	41.3%
Terminal rates	1/2 (50%)	1/2 (50%)	1/3 (33%)
First incidence (days)	525	488	632
Life table tests	P=0.391	P=0.287	P=0.470
Logistic regression tests	P=0.542N	P=0.397	P=0.674N
Cochran-Armitage test	P=0.482N		
Fisher exact test		P=0.563	P=0.581N
Skin: Keratoacanthoma			
Overall rates	2/50 (4%)	0/50 (0%)	4/50 (8%)
Adjusted rates	6.2%	0.0%	18.3%
Terminal rates	1/24 (4%)	0/21 (0%)	2/16 (13%)
First incidence (days)	522	-	561
Life table tests	P=0.140	P=0.279N	P=0.207
Logistic regression tests	P=0.203	P=0.224N	P=0.315
Cochran-Armitage test	P=0.222		
Fisher exact test		P=0.247N	P=0.339
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma			
Overall rates	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rates	10.5%	4.8%	11.8%
Terminal rates	2/24 (8%)	1/21 (5%)	1/16 (6%)
First incidence (days)	549	729 (T)	728
Life table tests	P=0.543N	P=0.356N	P=0.657N
Logistic regression tests	P=0.482N	P=0.350N	P=0.583N
Cochran-Armitage test	P=0.399N		
Fisher exact test		P=0.309N	P=0.500N
Testes: Adenoma			
Overall rates	42/50 (84%)	42/50 (84%)	46/50 (92%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	24/24 (100%)	21/21 (100%)	16/16 (100%)
First incidence (days)	481	450	433
Life table tests	P=0.008	P=0.193	P=0.010
Logistic regression tests	P=0.010	P=0.083	P=0.023
Cochran-Armitage test	P=0.152		
Fisher exact test		P=0.607N	P=0.178

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Thyroid Gland (C-cell): Adenoma			
Overall rates	4/50 (8%)	4/20 (20%)[f]	3/50 (6%)
Adjusted rates	13.8%		13.3%
Terminal rates	2/24 (8%)		1/16 (6%)
First incidence (days)	647		610
Life table tests			P=0.632
Logistic regression tests			P=0.584N
Fisher exact test			P=0.500N
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rates	6/50 (12%)	4/20 (20%)[f]	5/50 (10%)
Adjusted rates	21.6%		19.1%
Terminal rates	4/24 (17%)		1/16 (6%)
First incidence (days)	647		468
Life table tests			P=0.538
Logistic regression tests			P=0.577N
Fisher exact test			P=0.500N
All Organs: Mononuclear Cell Leukemia			
Overall rates	7/50 (14%)	4/50 (8%)	5/50 (10%)
Adjusted rates	23.1%	14.8%	18.5%
Terminal rates	4/24 (17%)	2/21 (10%)	0/16 (0%)
First incidence (days)	522	463	595
Life table tests	P=0.504N	P=0.357N	P=0.588N
Logistic regression tests	P=0.359N	P=0.297N	P=0.433N
Cochran-Armitage test	P=0.314N		
Fisher exact test		P=0.262N	P=0.380N
All Organs: Malignant Mesothelioma			
Overall rates	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted rates	8.3%	10.4%	0.0%
Terminal rates	2/24 (8%)	1/21 (5%)	0/16 (0%)
First incidence (days)	729 (T)	561	-
Life table tests	P=0.298N	P=0.434	P=0.330N
Logistic regression tests	P=0.238N	P=0.449	P=0.330N
Cochran-Armitage test	P=0.202N		
Fisher exact test		P=0.500	P=0.247N
All Organs: Benign Tumors			
Overall rates	47/50 (94%)	45/50 (90%)	48/50 (96%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	24/24 (100%)	21/21 (100%)	16/16 (100%)
First incidence (days)	426	450	433
Life table tests	P=0.028	P=0.282	P=0.030
Logistic regression tests	P=0.087	P=0.272	P=0.160
Cochran-Armitage test	P=0.421		
Fisher exact test		P=0.357N	P=0.500

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
All Organs: Malignant Tumors			
Overall rates	24/50 (48%)	16/50 (32%)	19/50 (38%)
Adjusted rates	65.7%	49.0%	57.0%
Terminal rates	13/24 (54%)	7/21 (33%)	4/16 (25%)
First incidence (days)	440	360	327
Life table tests	P=0.497	P=0.234N	P=0.490
Logistic regression tests	P=0.209N	P=0.097N	P=0.236N
Cochran-Armitage test	P=0.178N		
Fisher exact test		P=0.076N	P=0.210N
All Organs: Benign or Malignant Tumors			
Overall rates	49/50 (98%)	46/50 (92%)	49/50 (98%)
Adjusted rates	100.0%	100.0%	100.0%
Terminal rates	24/24 (100%)	21/21 (100%)	16/16 (100%)
First incidence (days)	426	360	327
Life table tests	P=0.041	P=0.330	P=0.044
Logistic regression tests	P=0.331	P=0.741	P=0.520
Cochran-Armitage test	P=0.601		
Fisher exact test		P=0.181N	P=0.753N

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

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	12.5 mg/kg	25 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	9	10	10
Early deaths			
Natural death[a]	12	16	15
Moribund	15	11	19
Accidental death[a]		2	
Survivors			
Died last week of study	1		
Terminal sacrifice	23	21	16
Animals examined microscopically	50	50	50
Alimentary System			
Esophagus	(50)	(18)	(50)
Periesophageal tissue, inflammation, suppurative		1 (6%)	
Intestine large, cecum	(11)	(18)	(22)
Parasite metazoan	1 (9%)		
Colon, parasite metazoan			1 (5%)
Intestine large, colon	(11)	(19)	(22)
Parasite metazoan	4 (36%)	2 (11%)	2 (9%)
Intestine large, rectum	(11)	(19)	(21)
Parasite metazoan	1 (9%)	1 (5%)	
Intestine small, duodenum	(47)	(50)	(50)
Lamina propria, pigmentation		50 (100%)	50 (100%)
Liver	(50)	(31)	(50)
Basophilic focus	21 (42%)	5 (16%)	17 (34%)
Clear cell focus	10 (20%)		7 (14%)
Congestion	2 (4%)	2 (6%)	4 (8%)
Fatty change	26 (52%)	18 (58%)	17 (34%)
Fibrosis, focal	1 (2%)		
Hematopoietic cell proliferation		1 (3%)	
Hepatodiaphragmatic nodule	4 (8%)	5 (16%)	1 (2%)
Inflammation, acute, focal			1 (2%)
Inflammation, chronic	1 (2%)		
Necrosis			1 (2%)
Bile duct, hyperplasia	40 (80%)	20 (65%)	41 (82%)
Centrilobular, degeneration			1 (2%)
Mesentery	(7)	(8)	(4)
Artery, inflammation, acute			1 (25%)
Artery, inflammation, chronic		1 (13%)	
Fat, necrosis, focal	5 (71%)	5 (63%)	4 (100%)
Pancreas	(50)	(22)	(50)
Inflammation, chronic	1 (2%)		1 (2%)
Acinus, atrophy	8 (16%)	3 (14%)	3 (6%)
Acinus, hyperplasia	5 (10%)		2 (4%)
Acinus, hyperplasia, focal	3 (6%)		4 (8%)
Acinus, vacuolization cytoplasmic	1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Alimentary System (continued)			
Pancreas (continued)			
Artery, hypertrophy	2 (4%)		1 (2%)
Artery, inflammation, chronic	1 (2%)	1 (5%)	1 (2%)
Artery, thrombus	1 (2%)		
Artery, media, hyperplasia		1 (5%)	
Duct, ectasia, multifocal		1 (5%)	
Serosa, inflammation, chronic	1 (2%)		
Stomach	(49)	(23)	(50)
Serosa, inflammation, acute	1 (2%)		
Stomach, forestomach	(49)	(23)	(50)
Acanthosis	4 (8%)	1 (4%)	4 (8%)
Pigmentation		2 (9%)	6 (12%)
Pigmentation, focal		1 (4%)	
Ulcer	2 (4%)	3 (13%)	6 (12%)
Stomach, glandular	(49)	(23)	(50)
Mineralization	1 (2%)		1 (2%)
Necrosis	1 (2%)		1 (2%)
Muscularis, inflammation, chronic		1 (4%)	
Serosa, inflammation, chronic		1 (4%)	
Cardiovascular System			
Heart	(50)	(22)	(50)
Cardiomyopathy	40 (80%)	10 (45%)	30 (60%)
Fibrosis	1 (2%)		
Inflammation, chronic		2 (9%)	
Artery, myocardium, inflammation, chronic		1 (5%)	
Endocrine System			
Adrenal gland, cortex	(50)	(50)	(50)
Cyst	1 (2%)		
Degeneration		1 (2%)	
Hyperplasia, focal		5 (10%)	5 (10%)
Hypertrophy		4 (8%)	1 (2%)
Hypertrophy, focal		1 (2%)	1 (2%)
Metaplasia, osseous			1 (2%)
Vacuolization cytoplasmic	7 (14%)	12 (24%)	12 (24%)
Vacuolization cytoplasmic, diffuse	2 (4%)	1 (2%)	
Vacuolization cytoplasmic, focal		1 (2%)	2 (4%)
Adrenal gland, medulla	(49)	(50)	(50)
Hyperplasia, focal	2 (4%)	2 (4%)	5 (10%)
Islets, pancreatic	(50)	(22)	(50)
Hyperplasia	1 (2%)		2 (4%)
Parathyroid gland	(48)	(12)	(44)
Hyperplasia			1 (2%)
Pituitary gland	(50)	(50)	(49)
Pars distalis, angiectasis, focal	1 (2%)	1 (2%)	
Pars distalis, cyst	2 (4%)		1 (2%)
Pars distalis, hyperplasia, focal	3 (6%)	10 (20%)	8 (16%)
Thyroid gland	(50)	(20)	(50)
C-cell, hyperplasia	4 (8%)	1 (5%)	1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
General Body System			
None			
Genital System			
Preputial gland	(17)	(24)	(26)
Inflammation, chronic	10 (59%)	4 (17%)	4 (15%)
Inflammation, suppurative		1 (4%)	
Duct, cyst	1 (6%)		1 (4%)
Prostate	(49)	(19)	(50)
Hyperplasia, focal	1 (2%)		
Inflammation, chronic		1 (5%)	
Inflammation, subacute			1 (2%)
Inflammation, suppurative	19 (39%)	5 (26%)	11 (22%)
Seminal vesicle	(50)	(25)	(50)
Dilatation	1 (2%)		
Testes	(50)	(50)	(50)
Interstitial cell, hyperplasia	2 (4%)	4 (8%)	
Seminiferous tubule, degeneration	7 (14%)	3 (6%)	2 (4%)
Hematopoietic System			
Lymph node	(50)	(50)	(50)
Lumbar, hyperplasia, lymphoid		1 (2%)	
Mediastinal, congestion	5 (10%)	2 (4%)	3 (6%)
Mediastinal, cyst			1 (2%)
Mediastinal, hyperplasia, lymphoid			1 (2%)
Mediastinal, pigmentation	1 (2%)	3 (6%)	1 (2%)
Pancreatic, cyst			1 (2%)
Pancreatic, pigmentation		22 (44%)	21 (42%)
Renal, congestion			1 (2%)
Renal, pigmentation		1 (2%)	
Lymph node, mandibular	(49)	(14)	(47)
Hyperplasia, plasma cell	3 (6%)	1 (7%)	4 (9%)
Lymph node, mesenteric	(49)	(49)	(50)
Congestion			1 (2%)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	
Necrosis, focal			1 (2%)
Pigmentation	20 (41%)	22 (45%)	42 (84%)
Pigmentation, hemosiderin	1 (2%)		
Spleen	(50)	(29)	(50)
Congestion		2 (7%)	
Cyst			1 (2%)
Ectopic tissue		1 (3%)	
Fibrosis	1 (2%)		1 (2%)
Hematopoietic cell proliferation		1 (3%)	
Hyperplasia, nodular			1 (2%)
Hyperplasia, re cell		1 (3%)	
Pigmentation, hemosiderin	2 (4%)	1 (3%)	1 (2%)
Endothelium, hyperplasia	2 (4%)		1 (2%)
Red pulp, atrophy	1 (2%)		

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Integumentary System			
Mammary gland	(9)	(10)	(12)
Hyperplasia	1 (11%)		1 (8%)
Hyperplasia, cystic	1 (11%)	1 (10%)	
Inflammation, granulomatous, focal		1 (10%)	
Duct, cyst		1 (10%)	
Duct, hemorrhage, chronic		1 (10%)	
Skin	(20)	(26)	(28)
Cyst epithelial inclusion	1 (5%)	1 (4%)	
Hyperkeratosis	1 (5%)		1 (4%)
Head, inflammation, acute		1 (4%)	
Subcutaneous tissue, hemorrhage	1 (5%)	1 (4%)	
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(20)	(50)
Lateral ventricle, hemorrhage	1 (2%)		
Pons, hemorrhage		1 (5%)	
Respiratory System			
Lung	(50)	(30)	(50)
Adenomatosis			1 (2%)
Congestion	12 (24%)	22 (73%)	16 (32%)
Hemorrhage		1 (3%)	1 (2%)
Inflammation, chronic	1 (2%)		
Inflammation, granulomatous	11 (22%)	1 (3%)	1 (2%)
Alveolar epithelium, hyperplasia, focal	1 (2%)		
Alveolar epithelium, pigmentation			1 (2%)
Alveolus, inflammation, acute		1 (3%)	
Interstitium, inflammation, chronic	1 (2%)		
Perivascular, inflammation, chronic		1 (3%)	1 (2%)
Nose	(12)	(21)	(21)
Nasolacrimal duct, inflammation, chronic	4 (33%)	4 (19%)	1 (5%)
Sinus, inflammation, chronic		2 (10%)	
Trachea	(50)	(19)	(50)
Mucosa, pigmentation			2 (4%)
Special Senses System			
Eye	(5)	(5)	(3)
Cataract	2 (40%)		1 (33%)
Anterior chamber, inflammation, suppurative			1 (33%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Urinary System			
Kidney	(50)	(49)	(50)
Congestion	4 (8%)		
Cyst			1 (2%)
Necrosis, focal	1 (2%)		
Nephropathy	47 (94%)	46 (94%)	50 (100%)
Artery, pelvis, inflammation, chronic		1 (2%)	
Capsule, developmental malformation	1 (2%)		
Renal tubule, hyperplasia, focal		2 (4%)	6 (12%)
Renal tubule, pigmentation, hemosiderin	1 (2%)	27 (55%)	42 (84%)
Urinary bladder	(50)	(48)	(50)
Concretion		1 (2%)	1 (2%)
Mucosa, hyperplasia, focal			1 (2%)
Wall, inflammation, suppurative	1 (2%)		

[a] One control, three low-dose, and three high-dose males may have died from gavage trauma.

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF 2,4-DIAMINOPHENOL DIHYDROCHLORIDE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	12.5 mg/kg	25 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Natural death[a]	7	6	2
Moribund	13	12	16
Accidental death			1
Survivors			
Terminal sacrifice	30	32	31
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, colon	(9)	(14)	(9)
Adenocarcinoma	1 (11%)		
Intestine large, rectum	(8)	(11)	(7)
Liver	(50)	(30)	(50)
Mesentery	(6)	(5)	(4)
Hemangiosarcoma	1 (17%)		
Pancreas	(49)	(13)	(50)
Acinus, adenoma		1 (8%)	
Stomach, forestomach	(50)	(14)	(50)
Stomach, glandular	(48)	(13)	(49)
Cardiovascular System			
Heart	(50)	(13)	(49)
Endocrine System			
Adrenal gland	(50)	(15)	(50)
Adrenal gland, cortex	(50)	(15)	(50)
Adenoma	1 (2%)		
Medulla, osteosarcoma, metastatic, uncertain primary site	1 (2%)		
Adrenal gland, medulla	(47)	(15)	(48)
Pheochromocytoma benign	2 (4%)	1 (7%)	3 (6%)
Islets, pancreatic	(49)	(14)	(50)
Adenoma		1 (7%)	
Carcinoma		1 (7%)	
Pituitary gland	(50)	(50)	(50)
Pars distalis, adenoma	22 (44%)	26 (52%)	25 (50%)
Pars distalis, carcinoma	2 (4%)		3 (6%)
Thyroid gland	(50)	(12)	(50)
Bilateral, C-cell, adenoma			1 (2%)
C-cell, adenoma	7 (14%)		6 (12%)
C-cell, carcinoma	2 (4%)	1 (8%)	3 (6%)
Follicular cell, adenoma			2 (4%)
Follicular cell, carcinoma			1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
General Body System			
None			
Genital System			
Clitoral gland	(12)	(17)	(9)
Adenoma	1 (8%)	1 (6%)	1 (11%)
Adenoma, moderate	1 (8%)		
Carcinoma	1 (8%)	5 (29%)	1 (11%)
Ovary	(49)	(15)	(49)
Osteosarcoma, metastatic, uncertain primary site	1 (2%)		
Uterus	(50)	(15)	(50)
Polyp stromal	12 (24%)	4 (27%)	9 (18%)
Hematopoietic System			
Lymph node	(49)	(49)	(50)
Deep cervical, carcinoma, metastatic, thyroid gland	1 (2%)		
Lymph node, mandibular	(44)	(10)	(46)
Lymph node, mesenteric	(49)	(49)	(50)
Spleen	(50)	(20)	(50)
Osteosarcoma, metastatic, uncertain primary site	1 (2%)		
Thymus	(7)	(11)	(8)
Integumentary System			
Mammary gland	(27)	(29)	(19)
Carcinoma	3 (11%)		
Fibroadenoma	12 (44%)	16 (55%)	11 (58%)
Fibroadenoma, multiple	5 (19%)	5 (17%)	2 (11%)
Skin	(12)	(13)	(9)
Basal cell adenoma			1 (11%)
Sebaceous gland, adenoma			1 (11%)
Subcutaneous tissue, fibroma	1 (8%)	1 (8%)	
Subcutaneous tissue, fibrosarcoma	3 (25%)		
Subcutaneous tissue, sarcoma, multiple		1 (8%)	
Musculoskeletal System			
Skeletal muscle			(1)
Abdominal, sarcoma			1 (100%)
Nervous System			
Brain	(50)	(11)	(50)
Carcinoma, metastatic			2 (4%)
Cerebrum, carcinoma, deep invasion, metastatic, pituitary gland	1 (2%)		
Pons, glioma NOS		1 (9%)	
Spinal cord		(1)	

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Respiratory System			
Lung	(50)	(17)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (6%)	
Carcinoma, metastatic, thyroid gland		1 (6%)	
Special Senses System			
None			
Urinary System			
Kidney	(50)	(50)	(50)
Urinary bladder	(49)	(49)	(50)
Papilloma		1 (2%)	
Systemic Lesions			
Multiple organs[b]	(50)	(50)	(50)
Leukemia mononuclear	13 (26%)	7 (14%)	11 (22%)
Mesothelioma malignant			1 (2%)
Tumor Summary			
Total animals with primary neoplasms[c]	40	41	47
Total primary neoplasms	91	74	83
Total animals with benign neoplasms	32	38	39
Total benign neoplasms	65	58	62
Total animals with malignant neoplasms	22	13	19
Total malignant neoplasms	26	15	21
Total animals with secondary neoplasms[d]	3	1	2
Total secondary neoplasms	5	1	2
Total animals with malignant neoplasms of uncertain primary site	1		
Total animals with neoplasms uncertain-benign or malignant		1	
Total uncertain neoplasms		1	

[a] One control and one 25 mg/kg female listed as natural death may have died from gavage trauma.
[b] Number of animals with any tissue examined microscopically
[c] Primary tumors: all tumors except metastatic tumors
[d] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control

Number of Days on Study	1 9 3	1 9 9	2 4 5	2 4 6	4 2 1	4 8 1	5 3 6	6 0 4	6 2 7	6 6 7	6 6 8	6 8 0	6 8 0	6 8 2	7 0 4	7 0 8	7 0 9	7 0 9	7 1 1	7 1 7	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	4 0 5	4 7 1	4 5 5	4 8 3	3 8 3	4 6 2	4 2 5	4 1 5	3 8 5	4 4 5	3 9 4	3 9 2	4 4 2	4 6 5	3 8 1	4 6 4	4 2 2	4 6 1	3 9 5	3 7 1	3 7 2	3 7 4	3 8 4	3 9 3	4 1 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	A	+	+	+	+	+	+																
Intestine large, cecum	+	+	A	+	+	+	+	+	+																
Intestine large, colon	+	+	A	+	+	+	+	+	+																
Adenocarcinoma																									
Intestine large, rectum	+	+	A	+	+	+	+	+	+																
Intestine small	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	A	+	+	+	+	+	+																
Intestine small, jejunum	+	+	A	+	+	+	+	+	+																
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+			+																					
Hemangiosarcoma	X																								
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+		+		+					+		+	+				
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Medulla, osteosarcoma, metastatic, uncertain primary site				^																					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	M	+	+	+	+	+	M	+	M	M	+	+	+	+	M	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X			X			X					X				X		X	X	X
Pars distalis, carcinoma							X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma						X																			
C-cell, carcinoma														X											

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 1 2	4 1 4	4 2 1	4 2 4	4 3 5	3 7 5	3 9 1	4 0 2	4 0 3	4 1 3	4 3 1	4 3 2	4 3 4	4 4 3	4 4 4	4 5 1	4 5 2	4 5 3	4 5 4	4 6 3	4 7 2	4 7 3	4 7 5	4 8 1	4 8 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large																					+					9
Intestine large, cecum																										8
Intestine large, colon																					+					9
Adenocarcinoma																					X					1
Intestine large, rectum																										8
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum																										8
Intestine small, jejunum																										8
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+		+						+											+					6
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands		+					+				+			+	+					+			+			21
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Medulla, osteosarcoma, metastatic, uncertain primary site																								X		1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	47
Pheochromocytoma benign																X			X							2
Islets, pancreatic	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X		X	X		X	X		X		X	X				X		X	X	X		X		X	22
Pars distalis, carcinoma									X																	2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X											X							X		X	X			X	7
C-cell, carcinoma																	X									2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	1 9 3	1 9 9	2 4 5	2 4 6	4 2 1	4 8 1	5 3 6	6 0 4	6 2 7	6 6 7	6 6 8	6 8 0	6 8 0	6 8 2	7 0 4	7 0 8	7 0 9	7 0 9	7 1 1	7 1 7	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	4 0 5	4 7 1	4 5 5	4 8 3	3 8 3	4 6 2	4 2 5	4 1 5	3 8 5	4 4 5	3 9 4	3 9 2	4 4 2	4 6 5	3 8 1	4 6 4	4 2 2	4 6 1	3 9 5	3 7 1	3 7 2	3 8 4	3 9 4	3 8 3	4 9 1
General Body System																									
Tissue NOS			+																						
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+																+
Adenoma																									
Adenoma, moderate																									
Carcinoma																									X
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site																									
Oviduct					+	+	+																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal												X	X			X		X						X	
Vagina																								+	
Hematopoietic System																									
Bone marrow	+	+	A	+	+	+	+	+	+																
Lymph node	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Deep cervical, carcinoma, metastatic, thyroid gland														X											
Lymph node, mandibular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mesenteric	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site																									
Thymus	+	+	A	+	+	+	+	M	+																
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+			+	+		+	+	+			+	+			+	+	+
Carcinoma		X			X																				
Fibroadenoma													X		X	X	X			X				X	X
Fibroadenoma, multiple												X									X				
Skin	+	+	+	+	+	+	+	+	+									+							
Subcutaneous tissue, fibroma																		X							
Subcutaneous tissue, fibrosarcoma								X																	
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+																

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 1 2	4 1 4	4 2 1	4 2 4	4 3 5	3 7 5	3 9 1	4 0 2	4 0 3	4 1 3	4 3 1	4 3 2	4 3 4	4 4 3	4 4 4	4 5 1	4 5 2	4 5 3	4 6 4	4 6 3	4 7 2	4 7 3	4 7 5	4 8 1	4 8 5	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Genital System																										
Clitoral gland								+													+					12
Adenoma								X																		1
Adenoma, moderate																					X					1
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma, metastatic, uncertain primary site																								X		1
Oviduct																										3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X					X		X			X	X			X					X				12
Vagina																										1
Hematopoietic System																										
Bone marrow																										8
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Deep cervical, carcinoma, metastatic, thyroid gland																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	M	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, metastatic, uncertain primary site																								X		1
Thymus																										7
Integumentary System																										
Mammary gland		+					+	+		+				+			+							+		27
Carcinoma																								X		3
Fibroadenoma		X					X			X				X			X									12
Fibroadenoma, multiple								X												X				X		5
Skin	+									+																12
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, fibrosarcoma	X									X																3
Musculoskeletal System																										
Bone																										9

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	1 9 3	1 9 9	2 4 5	2 4 6	4 2 1	4 8 1	5 3 6	6 0 4	6 2 7	6 6 7	6 6 8	6 6 0	6 8 0	6 8 0	7 0 2	7 0 4	7 0 8	7 0 9	7 1 9	7 1 1	7 1 7	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	4 0 5	4 7 1	4 5 5	4 8 3	3 8 3	4 6 2	4 2 5	4 1 5	3 8 5	4 4 5	3 9 4	3 9 2	4 4 2	4 6 5	3 8 1	4 6 4	4 2 2	4 6 1	3 9 5	3 7 1	3 7 2	3 7 4	3 8 4	3 9 3	4 1 1
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebrum, carcinoma, deep invasion, metastatic, pituitary gland							X																		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear							+																		
Eye																									
Harderian gland																									
Lacrimal gland																									
Zymbal's gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra			+																						
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X										X					X	X			X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	4 1 2	4 1 4	4 2 1	4 2 4	4 3 5	3 7 5	3 9 1	4 0 2	4 0 3	4 1 3	4 3 1	4 3 2	4 3 4	4 4 3	4 4 4	4 5 1	4 5 2	4 5 3	4 5 4	4 6 3	4 7 2	4 7 3	4 7 5	4 8 1	4 8 5	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cerebrum, carcinoma, deep invasion, metastatic, pituitary gland																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X																		1
Nose																										9
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear									+																	2
Eye									+																	1
Harderian gland									+																	1
Lacrimal gland								+																		1
Zymbal's gland								+	+																	2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X								X				X	X		X			X	X		X				13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	5 0 4	5 1 1	5 1 2	5 3 1	5 3 2	5 4 1	5 4 2	5 4 3	5 5 1	5 5 2	5 6 1	5 6 2	5 6 3	5 6 4	5 7 1	5 8 1	5 8 2	5 8 3	5 8 4	5 9 1	5 9 2	5 9 3	5 9 4	6 0 1	6 0 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										11
Intestine large									+							+	+	+								16
Intestine large, cecum																										11
Intestine large, colon									+							+	+	+								14
Intestine large, rectum																										11
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum																										10
Intestine small, jejunum																										11
Liver		+	+		+				+			+		+					+	+	+		+	+	+	30
Mesentery		+					+	+											+	+						5
Pancreas																				+						13
Acinus, adenoma																				X						1
Salivary glands																										12
Stomach																										14
Stomach, forestomach																										14
Stomach, glandular																										13
Cardiovascular System																										
Heart			+																							13
Endocrine System																										
Adrenal gland																							+			15
Adrenal gland, cortex																							+			15
Adrenal gland, medulla																							+			15
Pheochromocytoma benign																							X			1
Islets, pancreatic						+																				14
Adenoma						X																				1
Carcinoma																										1
Parathyroid gland																										11
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X			X		X	X	X		X	X		X		X		X	X			X		X	26
Thyroid gland																										12
C-cell, carcinoma																										1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg (continued)

Number of Days on Study	3 4 2 2	4 2 2 4	4 3 4 3	4 4 8 0	4 9 8 8	5 4 0 8	5 6 8 0	6 1 7 0	6 1 7 0	6 2 0 5	6 2 5 3	6 5 9 0	6 9 9 4	7 0 1 4	7 1 1 4	7 1 3 6	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1	7 3 3 1
Carcass ID Number	5 7 5 5	5 1 9 5	5 9 3 5	5 3 2 5	5 2 0 5	6 0 2 4	5 2 5 3	5 4 9 5	4 5 9 3	5 6 7 4	6 0 0 3	6 1 3 3	5 8 2 5	5 2 2 3	5 3 3 2	5 7 9 1	4 9 9 2	4 9 9 3	4 9 9 4	5 0 1 1	5 0 0 2	5 0 0 3
Genital System																						
Clitoral gland	M	+	M	M	+	+	+	+	+	+	+	+	+									
Adenoma																						
Carcinoma							X					X										
Ovary	+	+	+	+	+	+	+	+	+	+	+										+	
Oviduct	+	+	+	+	+	+	+															
Uterus	+	+	+	+	+	+	+	+	+	+	+						+			+		
Polyp stromal										X		X								X		
Hematopoietic System																						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+											
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	M	+	+	M	+	M	+	+											
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+					
Thymus	+	+	M	+	M	+	+	+	+	+	+					+						
Integumentary System																						
Mammary gland	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+				+	+
Fibroadenoma				X		X							X	X	X						X	X
Fibroadenoma, multiple																X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+								+		
Subcutaneous tissue, fibroma																				X		
Subcutaneous tissue, sarcoma, multiple										X												
Musculoskeletal System																						
Bone	+	+	+	+	+	+	+	+	+	+	+	+										
Nervous System																						
Brain	+	+	+	+	+	+	+	+	+	+	M	+										
Pons, glioma NOS					X																	
Spinal cord												+										
Respiratory System																						
Lung	+	+	+	+	+	+	+	+	+	+	+	+			+	+				+		
Alveolar/bronchiolar adenoma												X										
Carcinoma, metastatic, thyroid gland								X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	5 0 4	5 1 1	5 1 2	5 3 1	5 3 2	5 4 1	5 4 2	5 4 3	5 5 1	5 5 2	5 6 1	5 6 2	5 6 3	5 6 4	5 7 1	5 8 1	5 8 2	5 8 3	5 8 4	5 9 1	5 9 2	5 9 3	5 9 4	6 0 1	6 0 2	**Total Tissues/ Tumors**
Genital System																										
Clitoral gland						+		+		+									+	+			+	+		17
Adenoma								X																		1
Carcinoma						X													X					X		5
Ovary							+	+																		15
Oviduct																										7
Uterus			+																							15
Polyp stromal			X																							4
Hematopoietic System																										
Bone marrow																										12
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular																							+			10
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Spleen									+										+					+		20
Thymus																										11
Integumentary System																										
Mammary gland		+	+	+	+	+	+	+	+	+				+	+		+	+		+						29
Fibroadenoma		X		X	X		X	X						X	X		X	X								16
Fibroadenoma, multiple			X			X			X	X																5
Skin																										13
Subcutaneous tissue, fibroma																										1
Subcutaneous tissue, sarcoma, multiple																										1
Musculoskeletal System																										
Bone																										12
Nervous System																										
Brain																										11
Pons, glioma NOS																										1
Spinal cord																										1
Respiratory System																										
Lung						+																+				17
Alveolar/bronchiolar adenoma																										1
Carcinoma, metastatic, thyroid gland																										1
Nose																										12
Trachea																										12

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg (continued)

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 12.5 mg/kg (continued)

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	5 0 4	5 1 1	5 1 2	5 3 1	5 3 2	5 4 1	5 4 2	5 4 3	5 5 1	5 5 2	5 6 1	5 6 2	5 6 3	5 6 4	5 7 1	5 8 1	5 8 2	5 8 3	5 8 4	5 9 1	5 9 2	5 9 3	5 9 4	6 0 1	6 0 2	**Total Tissues/ Tumors**
Special Senses System																										
Eye												+						+	+							7
Harderian gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma	X																									1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X																	7

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	6 3 1	6 3 2	6 3 3	6 3 4	6 4 1	6 4 2	6 4 3	6 4 5	6 5 1	6 5 2	6 6 1	6 6 2	6 7 1	6 7 2	6 8 1	6 8 2	6 8 3	6 9 1	7 0 1	7 0 2	7 1 1	7 1 2	7 1 3	7 2 1	7 2 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large		+					+																			10
Intestine large, cecum		+																								8
Intestine large, colon		+					+																			9
Intestine large, rectum		+																								7
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum																										7
Intestine small, jejunum																M										7
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																					+					4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+			+		+	+				+		+					+	+	+	+	28
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																						X				3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X				X	X	X		X	X	X	X	X		X	X			X	X	X		25
Pars distalis, carcinoma																	X									3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																										1
C-cell, adenoma					X						X		X	X		X						X				6
C-cell, carcinoma												X														3
Follicular cell, adenoma													X													2
Follicular cell, carcinoma																										1
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	2 8 2	3 7 9	4 1 1	4 9 8	5 2 6	5 7 0	5 7 1	6 4 5	6 4 5	6 5 3	6 6 9	6 7 6	6 8 1	6 8 7	6 8 8	6 9 5	7 0 3	7 1 1	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0
Carcass ID Number	6 8 5	6 2 4	6 5 5	7 2 4	7 2 3	6 5 3	6 1 5	6 1 4	7 0 5	6 4 4	6 9 3	7 0 4	6 9 2	6 6 3	6 0 3	7 7 4	6 7 3	6 3 5	7 1 4	6 1 1	6 1 2	6 1 3	6 2 2	6 2 3	6 2 1
Genital System																									
Clitoral gland	+	+	+	+	+	+						+													
Adenoma																									
Carcinoma												X													
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct			+	+	+																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X										X									X	X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+																		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+																	
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+									+	+	+				+		+	
Fibroadenoma																X	X	X						X	
Fibroadenoma, multiple																						X			
Skin	+	+	+	+	+	+	+																		
Basal cell adenoma																									
Sebaceous gland, adenoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+																			
Skeletal muscle		+																							
Abdominal, sarcoma		X																							
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic														X											
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	M	+																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	6 3 1	6 3 2	6 3 3	6 3 4	6 4 1	6 4 2	6 4 3	6 4 5	6 5 1	6 5 2	6 6 1	6 6 2	6 7 1	6 7 2	6 8 1	6 8 2	6 8 3	6 9 1	7 0 1	7 0 2	7 1 1	7 1 2	7 1 3	7 2 1	7 2 2	**Total Tissues/ Tumors**
Genital System																										
Clitoral gland					+													+								9
Adenoma																		X								1
Carcinoma																										1
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Oviduct																										3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal						X			X		X			X											X	9
Hematopoietic System																										
Bone marrow																										7
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+		+	M	+	+	+	+	+		+	+	+	+	46
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus																										8
Integumentary System																										
Mammary gland			+	+		+	+												+	+		+		+		19
Fibroadenoma			X	X		X	X												X			X		X		11
Fibroadenoma, multiple																				X						2
Skin					+												+									9
Basal cell adenoma					X																					1
Sebaceous gland, adenoma																	X									1
Musculoskeletal System																										
Bone																										6
Skeletal muscle																										1
Abdominal, sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic																	X									2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose																										6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	2 8 2	3 7 9	4 1 1	4 9 8	5 2 6	5 7 0	5 7 1	6 4 5	6 4 5	6 5 3	6 6 9	6 7 6	6 8 1	6 8 7	6 8 8	6 9 5	7 0 3	7 1 1	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0
Carcass ID Number	6 8 5	6 2 4	6 5 5	7 2 4	7 2 3	6 5 3	6 1 5	6 1 4	7 0 5	6 4 4	6 9 3	7 0 4	6 9 2	6 6 3	7 0 3	6 7 4	6 7 3	6 3 5	7 1 4	6 1 1	6 1 2	6 1 3	6 2 2	6 2 3	6 2 1
Special Senses System																									
Ear													+												
Eye								+																	
Harderian gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X	X	X		X			X		X				X				X		
Mesothelioma malignant						X																			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 25 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	6 3 1	6 3 2	6 3 3	6 3 4	6 4 1	6 4 2	6 4 3	6 4 5	6 5 1	6 5 2	6 6 1	6 6 2	6 7 1	6 7 2	6 8 1	6 8 2	6 8 3	6 9 1	7 0 1	7 0 2	7 1 1	7 1 2	7 1 3	7 2 1	7 2 2	**Total Tissues/ Tumors**
Special Senses System																										
Ear												+														2
Eye												+												+		3
Harderian gland																								+		1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X					X															11
Mesothelioma malignant																										1

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	12.5 mg/kg	25 mg/kg
Adrenal Medulla: Benign Pheochromocytoma			
Overall rates[a]	2/48 (4%)	1/15 (7%)[e]	3/48 (6%)
Adjusted rates[b]	6.9%		8.4%
Terminal rates[c]	2/29 (7%)		1/31 (3%)
First incidence (days)	729 (T)		645
Life table tests[d]			P=0.528
Logistic regression tests[d]			P=0.514
Fisher exact test[d]			P=0.500
Clitoral Gland: Carcinoma			
Overall rates	1/12 (8%)	5/17 (29%)	1/9 (11%)
Adjusted rates	33.3%	45.6%	2.6%
Terminal rates	1/3 (33%)	3/7 (43%)	0/2 (0%)
First incidence (days)	729 (T)	540	676
Life table tests	P=0.539	P=0.244	P=0.716
Logistic regression tests	P=0.546	P=0.378	P=0.732
Cochran-Armitage test[d]	P=0.488		
Fisher exact test		P=0.182	P=0.686
Clitoral Gland: Adenoma or Carcinoma			
Overall rates	3/12 (25%)	6/17 (35%)	2/9 (22%)
Adjusted rates	100.0%	59.2%	51.3%
Terminal rates	3/3 (100%)	4/7 (57%)	1/2 (50%)
First incidence (days)	729 (T)	540	676
Life table tests	P=0.536N	P=0.651	P=0.716N
Logistic regression tests	P=0.518N	P=0.557N	P=0.708N
Cochran-Armitage test	P=0.571N		
Fisher exact test		P=0.432	P=0.647N
Mammary Gland: Carcinoma			
Overall rates	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rates	7.4%	0.0%	0.0%
Terminal rates	1/30 (3%)	0/32 (0%)	0/31 (0%)
First incidence (days)	199	-[f]	-
Life table tests	P=0.036N	P=0.115N	P=0.120N
Logistic regression tests	P=0.077N	P=0.202N	P=0.201N
Cochran-Armitage test	P=0.037N		
Fisher exact test		P=0.121N	P=0.121N
Mammary Gland: Fibroadenoma			
Overall rates	17/50 (34%)	21/50 (42%)	13/50 (26%)
Adjusted rates	46.7%	56.0%	38.1%
Terminal rates	11/30 (37%)	16/32 (50%)	10/31 (32%)
First incidence (days)	680	443	695
Life table tests	P=0.216N	P=0.338	P=0.251N
Logistic regression tests	P=0.198N	P=0.264	P=0.236N
Cochran-Armitage test	P=0.230N		
Fisher exact test		P=0.268	P=0.257N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Mammary Gland: Fibroadenoma or Carcinoma			
Overall rates	19/50 (38%)	21/50 (42%)	13/50 (26%)
Adjusted rates	48.9%	56.0%	38.1%
Terminal rates	11/30 (37%)	16/32 (50%)	10/31 (32%)
First incidence (days)	199	443	695
Life table tests	P=0.122N	P=0.492	P=0.147N
Logistic regression tests	P=0.103N	P=0.438	P=0.122N
Cochran-Armitage test	P=0.125N		
Fisher exact test		P=0.419	P=0.142N
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	22/50 (44%)	26/50 (52%)	25/50 (50%)
Adjusted rates	63.9%	64.8%	67.0%
Terminal rates	18/30 (60%)	18/32 (56%)	19/31 (61%)
First incidence (days)	481	540	498
Life table tests	P=0.360	P=0.362	P=0.395
Logistic regression tests	P=0.347	P=0.262	P=0.387
Cochran-Armitage test	P=0.308		
Fisher exact test		P=0.274	P=0.344
Pituitary Gland (Pars Distalis): Carcinoma			
Overall rates	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted rates	5.5%	0.0%	8.2%
Terminal rates	1/30 (3%)	0/32 (0%)	1/31 (3%)
First incidence (days)	536	-	669
Life table tests	P=0.402	P=0.233N	P=0.513
Logistic regression tests	P=0.389	P=0.245N	P=0.500
Cochran-Armitage test	P=0.390		
Fisher exact test		P=0.247N	P=0.500
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma			
Overall rates	24/50 (48%)	26/50 (52%)	28/50 (56%)
Adjusted rates	67.7%	64.8%	71.3%
Terminal rates	19/30 (63%)	18/32 (56%)	20/31 (65%)
First incidence (days)	481	540	498
Life table tests	P=0.299	P=0.514	P=0.333
Logistic regression tests	P=0.280	P=0.427	P=0.319
Cochran-Armitage test	P=0.242		
Fisher exact test		P=0.421	P=0.274
Skin (Subcutaneous Tissue): Fibrosarcoma			
Overall rates	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rates	8.8%	0.0%	0.0%
Terminal rates	2/30 (7%)	0/32 (0%)	0/31 (0%)
First incidence (days)	536	-	-
Life table tests	P=0.036N	P=0.115N	P=0.118N
Logistic regression tests	P=0.037N	P=0.121N	P=0.121N
Cochran-Armitage test	P=0.037N		
Fisher exact test		P=0.121N	P=0.121N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma			
Overall rates	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted rates	11.5%	3.1%	0.0%
Terminal rates	2/30 (7%)	1/32 (3%)	0/31 (0%)
First incidence (days)	536	729 (T)	-
Life table tests	P=0.025N	P=0.172N	P=0.064N
Logistic regression tests	P=0.025N	P=0.176N	P=0.062N
Cochran-Armitage test	P=0.026N		
Fisher exact test		P=0.181N	P=0.059N
Skin (Subcutaneous Tissue): Fibrosarcoma or Sarcoma			
Overall rates	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rates	8.8%	2.4%	0.0%
Terminal rates	2/30 (7%)	0/32 (0%)	0/31 (0%)
First incidence (days)	536	617	-
Life table tests	P=0.059N	P=0.299N	P=0.118N
Logistic regression tests	P=0.063N	P=0.310N	P=0.121N
Cochran-Armitage test	P=0.060N		
Fisher exact test		P=0.309N	P=0.121N
Skin (Subcutaneous Tissue): Fibroma, Fibrosarcoma, or Sarcoma			
Overall rates	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted rates	11.5%	5.5%	0.0%
Terminal rates	2/30 (7%)	1/32 (3%)	0/31 (0%)
First incidence (days)	536	617	-
Life table tests	P=0.037N	P=0.328N	P=0.064N
Logistic regression tests	P=0.036N	P=0.334N	P=0.062N
Cochran-Armitage test	P=0.037N		
Fisher exact test		P=0.339N	P=0.059N
Thyroid Gland (C-cell): Adenoma			
Overall rates	7/50 (14%)	0/12 (0%)[e]	7/50 (14%)
Adjusted rates	21.8%		22.6%
Terminal rates	6/30 (20%)		7/31 (23%)
First incidence (days)	481		729 (T)
Life table tests			P=0.590N
Logistic regression tests			P=0.597N
Fisher exact test			P=0.613N
Thyroid Gland (C-cell): Carcinoma			
Overall rates	2/50 (4%)	1/12 (8%)[e]	3/50 (6%)
Adjusted rates	5.9%		7.9%
Terminal rates	1/30 (3%)		1/31 (3%)
First incidence (days)	682		645
Life table tests			P=0.510
Logistic regression tests			P=0.510
Fisher exact test			P=0.500

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Thyroid Gland (C-cell): Adenoma or Carcinoma			
Overall rates	9/50 (18%)	1/12 (8%)[e]	10/50 (20%)
Adjusted rates	27.1%		29.4%
Terminal rates	7/30 (23%)		8/31 (26%)
First incidence (days)	481		645
Life table tests			P=0.530
Logistic regression tests			P=0.525
Fisher exact test			P=0.500
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma			
Overall rates	0/50 (0%)	0/12 (0%)[e]	3/50 (6%)
Adjusted rates	0.0%		9.1%
Terminal rates	0/30 (0%)		2/31 (6%)
First incidence (days)	-		695
Life table tests			P=0.125
Logistic regression tests			P=0.122
Cochran-Armitage test			
Fisher exact test			P=0.121
Uterus: Stromal Polyp			
Overall rates	12/50 (24%)	4/50 (8%)	9/50 (18%)
Adjusted rates	34.4%	10.9%	26.2%
Terminal rates	8/30 (27%)	2/32 (6%)	7/31 (23%)
First incidence (days)	680	617	411
Life table tests	P=0.242N	P=0.029N	P=0.298N
Logistic regression tests	P=0.232N	P=0.027N	P=0.287N
Cochran-Armitage test	P=0.251N		
Fisher exact test		P=0.027N	P=0.312N
All Organs: Mononuclear Cell Leukemia			
Overall rates	13/50 (26%)	7/50 (14%)	11/50 (22%)
Adjusted rates	37.5%	18.1%	26.2%
Terminal rates	9/30 (30%)	1/32 (3%)	3/31 (10%)
First incidence (days)	246	620	526
Life table tests	P=0.344N	P=0.106N	P=0.383N
Logistic regression tests	P=0.351N	P=0.101N	P=0.404N
Cochran-Armitage test	P=0.356N		
Fisher exact test		P=0.105N	P=0.408N
All Organs: Benign Tumors			
Overall rates	32/50 (64%)	38/50 (76%)	39/50 (78%)
Adjusted rates	81.8%	84.4%	95.0%
Terminal rates	23/30 (77%)	25/32 (78%)	29/31 (94%)
First incidence (days)	481	443	411
Life table tests	P=0.154	P=0.268	P=0.162
Logistic regression tests	P=0.092	P=0.138	P=0.111
Cochran-Armitage test	P=0.072		
Fisher exact test		P=0.138	P=0.093

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
All Organs: Malignant Tumors			
Overall rates	23/50 (46%)	13/50 (26%)	19/50 (38%)
Adjusted rates	59.0%	31.1%	41.8%
Terminal rates	15/30 (50%)	4/32 (13%)	6/31 (19%)
First incidence (days)	193	540	379
Life table tests	P=0.239N	P=0.039N	P=0.269N
Logistic regression tests	P=0.268N	P=0.034N	P=0.312N
Cochran-Armitage test	P=0.234N		
Fisher exact test		P=0.030N	P=0.272N
All Organs: Benign or Malignant Tumors			
Overall rates	41/50 (82%)	41/50 (82%)	47/50 (94%)
Adjusted rates	89.0%	87.2%	95.9%
Terminal rates	25/30 (83%)	26/32 (81%)	29/31 (94%)
First incidence (days)	193	443	379
Life table tests	P=0.244	P=0.459N	P=0.270
Logistic regression tests	P=0.074	P=0.569N	P=0.073
Cochran-Armitage test	P=0.056		
Fisher exact test		P=0.602N	P=0.061

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

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	12.5 mg/kg	25 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Natural death[a]	7	6	2
Moribund	13	12	16
Accidental death			1
Survivors			
Terminal sacrifice	30	32	31
Animals examined microscopically	50	50	50
Alimentary System			
Intestine large, cecum	(8)	(11)	(8)
Mucosa, pigmentation		1 (9%)	
Intestine large, colon	(9)	(14)	(9)
Parasite metazoan			1 (11%)
Intestine large, rectum	(8)	(11)	(7)
Parasite metazoan		1 (9%)	
Intestine small, duodenum	(49)	(50)	(50)
Lamina propria, inflammation, acute			1 (2%)
Lamina propria, pigmentation		50 (100%)	50 (100%)
Liver	(50)	(30)	(50)
Angiectasis, focal	1 (2%)		
Basophilic focus	36 (72%)	19 (63%)	40 (80%)
Clear cell focus	3 (6%)		5 (10%)
Congestion		2 (7%)	
Eosinophilic focus	1 (2%)		
Fatty change	14 (28%)	12 (40%)	9 (18%)
Granuloma	1 (2%)		
Hematocyst			1 (2%)
Hematopoietic cell proliferation		1 (3%)	
Hemorrhage, multifocal		1 (3%)	
Hepatodiaphragmatic nodule	5 (10%)	3 (10%)	5 (10%)
Inflammation, chronic	3 (6%)		
Inflammation, granulomatous	4 (8%)	2 (7%)	10 (20%)
Mixed cell focus	1 (2%)	1 (3%)	1 (2%)
Necrosis, focal			1 (2%)
Necrosis, multifocal		1 (3%)	
Bile duct, hyperplasia	25 (50%)	10 (33%)	27 (54%)
Centrilobular, inflammation, acute	1 (2%)		
Centrilobular, necrosis	1 (2%)		
Midzonal, necrosis	1 (2%)		
Sinusoid, embolus bacterial	1 (2%)		
Mesentery	(6)	(5)	(4)
Inflammation, chronic	1 (17%)		1 (25%)
Fat, necrosis, focal	3 (50%)	5 (100%)	2 (50%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Alimentary System (continued)			
Pancreas	(49)	(13)	(50)
Inflammation, chronic, diffuse			1 (2%)
Acinus, atrophy	5 (10%)		4 (8%)
Acinus, hyperplasia, focal	1 (2%)		5 (10%)
Acinus, hypertrophy, focal			1 (2%)
Artery, inflammation, chronic active			1 (2%)
Duct, cyst			1 (2%)
Duct, hyperplasia			1 (2%)
Serosa, neovascularization, diffuse	1 (2%)		
Salivary glands	(21)	(12)	(28)
Embolus bacterial	1 (5%)		
Stomach, forestomach	(50)	(14)	(50)
Acanthosis			7 (14%)
Pigmentation		1 (7%)	9 (18%)
Ulcer	2 (4%)	3 (21%)	3 (6%)
Stomach, glandular	(48)	(13)	(49)
Edema			1 (2%)
Embolus bacterial	1 (2%)		
Erosion, focal			1 (2%)
Hyperplasia, focal			1 (2%)
Cardiovascular System			
Heart	(50)	(13)	(49)
Cardiomyopathy	16 (32%)	2 (15%)	17 (35%)
Inflammation, chronic			1 (2%)
Interstitium, embolus bacterial	1 (2%)		
Ventricle, fibrosis		1 (8%)	
Endocrine System			
Adrenal gland	(50)	(15)	(50)
Capsule, degeneration		1 (7%)	
Adrenal gland, cortex	(50)	(15)	(50)
Congestion		1 (7%)	1 (2%)
Degeneration	12 (24%)	2 (13%)	5 (10%)
Degeneration, focal			1 (2%)
Embolus bacterial	1 (2%)		
Hyperplasia	2 (4%)	1 (7%)	2 (4%)
Hyperplasia, focal	3 (6%)		1 (2%)
Hypertrophy			1 (2%)
Necrosis	1 (2%)		1 (2%)
Vacuolization cytoplasmic			1 (2%)
Adrenal gland, medulla	(47)	(15)	(48)
Congestion		1 (7%)	
Hyperplasia	4 (9%)		1 (2%)
Hyperplasia, focal	3 (6%)	1 (7%)	
Islets, pancreatic	(49)	(14)	(50)
Hyperplasia	2 (4%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Endocrine System (continued)			
Pituitary gland	(50)	(50)	(50)
Cyst	3 (6%)		1 (2%)
Pars distalis, angiectasis	2 (4%)	3 (6%)	2 (4%)
Pars distalis, cyst	3 (6%)	1 (2%)	2 (4%)
Pars distalis, embolus bacterial	1 (2%)		
Pars distalis, hemorrhage	2 (4%)		
Pars distalis, hyperplasia, focal	3 (6%)	7 (14%)	5 (10%)
Thyroid gland	(50)	(12)	(50)
Embolus bacterial	1 (2%)		
C-cell, hyperplasia	10 (20%)		2 (4%)
Follicular cell, hyperplasia			1 (2%)
General Body System			
Tissue NOS	(1)		
Necrosis	1 (100%)		
Genital System			
Clitoral gland	(12)	(17)	(9)
Inflammation, chronic		1 (6%)	
Inflammation, suppurative	1 (8%)	1 (6%)	1 (11%)
Duct, cyst	1 (8%)		
Ovary	(49)	(15)	(49)
Cyst	1 (2%)		
Follicle, cyst	1 (2%)	1 (7%)	
Uterus	(50)	(15)	(50)
Endometriosis			1 (2%)
Hydrometra		1 (7%)	1 (2%)
Cervix, hyperplasia, cystic	1 (2%)		
Endometrium, hyperplasia, cystic	2 (4%)		5 (10%)
Lumen, hemorrhage			1 (2%)
Wall, necrosis			1 (2%)
Vagina	(1)		
Inflammation, suppurative	1 (100%)		
Hematopoietic System			
Lymph node	(49)	(49)	(50)
Lumbar, cyst		1 (2%)	
Mediastinal, congestion	1 (2%)		1 (2%)
Mediastinal, pigmentation, hemosiderin	3 (6%)		2 (4%)
Pancreatic, pigmentation	2 (4%)	35 (71%)	33 (66%)
Renal, congestion			1 (2%)
Lymph node, mandibular	(44)	(10)	(46)
Congestion	1 (2%)		
Hyperplasia, plasma cell	1 (2%)		
Pigmentation			1 (2%)
Lymph node, mesenteric	(49)	(49)	(50)
Congestion	1 (2%)	1 (2%)	
Pigmentation	32 (65%)	26 (53%)	45 (90%)
Pigmentation, hemosiderin	2 (4%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Hematopoietic System (continued)			
Spleen	(50)	(20)	(50)
Embolus bacterial	1 (2%)		
Fibrosis	1 (2%)		
Hematopoietic cell proliferation	2 (4%)	4 (20%)	2 (4%)
Necrosis	1 (2%)		
Pigmentation, hemosiderin	2 (4%)		
Thrombus	1 (2%)		
Integumentary System			
Mammary gland	(27)	(29)	(19)
Hyperplasia	3 (11%)	1 (3%)	
Hyperplasia, cystic	4 (15%)	5 (17%)	1 (5%)
Skin	(12)	(13)	(9)
Face, abscess			1 (11%)
Musculoskeletal System			
None			
Nervous System			
Brain	(50)	(11)	(50)
Embolus bacterial	1 (2%)		
Cerebrum, perivascular, inflammation	1 (2%)		
Spinal cord		(1)	
Hemorrhage		1 (100%)	
Respiratory System			
Lung	(50)	(17)	(50)
Adenomatosis	2 (4%)		1 (2%)
Congestion	5 (10%)	7 (41%)	2 (4%)
Hemorrhage, focal		1 (6%)	
Inflammation, acute	1 (2%)		
Inflammation, chronic, focal	1 (2%)		
Inflammation, granulomatous	1 (2%)		
Alveolar epithelium, hyperplasia, focal	1 (2%)	1 (6%)	
Capillary, embolus bacterial	1 (2%)		
Interstitium, inflammation, chronic			1 (2%)
Nose	(9)	(12)	(6)
Nasolacrimal duct, inflammation, chronic	1 (11%)		1 (17%)
Special Senses System			
Eye	(1)	(7)	(3)
Lens, mineralization			2 (67%)
Harderian gland	(1)	(1)	(1)
Inflammation, chronic		1 (100%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	12.5 mg/kg	25 mg/kg
Urinary System			
Kidney	(50)	(50)	(50)
Congestion	1 (2%)		
Nephropathy	31 (62%)	39 (78%)	42 (84%)
Capillary, embolus bacterial	1 (2%)		
Cortex, cyst	2 (4%)		
Papilla, necrosis, diffuse		1 (2%)	
Renal tubule, hyperplasia, focal	1 (2%)	1 (2%)	5 (10%)
Renal tubule, pigmentation, hemosiderin	1 (2%)	48 (96%)	49 (98%)
Urinary bladder	(49)	(49)	(50)
Inflammation, chronic	1 (2%)		
Submucosa, inflammation, granulomatous		1 (2%)	

[a] One control and one 25 mg/kg female listed as natural death may have died from gavage trauma.

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF 2,4-DIAMINOPHENOL DIHYDROCHLORIDE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	19 mg/kg	38 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Natural death	6	6	2
Moribund	14	11	12
Survivors			
Terminal sacrifice	30	33	36
Animals examined microscopically	50	50	50
Alimentary System			
Gallbladder	(46)	(14)	(44)
Intestine small, duodenum	(47)	(49)	(48)
Histiocytic sarcoma	1 (2%)		
Intestine small, ileum	(45)	(13)	(48)
Intestine small, jejunum	(46)	(14)	(48)
Liver	(50)	(50)	(50)
Carcinoma, metastatic, harderian gland		1 (2%)	
Hemangioma		1 (2%)	
Hemangiosarcoma			1 (2%)
Hemangiosarcoma, metastatic	1 (2%)		
Hepatocellular carcinoma	5 (10%)	5 (10%)	3 (6%)
Hepatocellular carcinoma, multiple		1 (2%)	
Hepatocellular adenoma	11 (22%)	14 (28%)	5 (10%)
Histiocytic sarcoma	1 (2%)		
Mesentery	(3)	(3)	
Pancreas	(50)	(16)	(50)
Stomach, forestomach	(50)	(23)	(50)
Papilloma squamous	2 (4%)	1 (4%)	1 (2%)
Cardiovascular System			
None			
Endocrine System			
Adrenal gland, cortex	(49)	(15)	(50)
Carcinoma, metastatic, uncertain primary site			1 (2%)
Adrenal gland, medulla	(49)	(15)	(49)
Pheochromocytoma benign	2 (4%)		2 (4%)
Thyroid gland	(49)	(15)	(49)
Follicular cell, adenoma	1 (2%)		1 (2%)
Follicular cell, carcinoma	1 (2%)		1 (2%)
General Body System			
None			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Genital System			
Testes	(50)	(16)	(50)
Interstitial cell, adenoma			2 (4%)
Hematopoietic System			
Bone marrow	(49)	(15)	(50)
Hemangiosarcoma, metastatic		1 (7%)	
Lymph node	(44)	(36)	(49)
Mandibular, carcinoma, metastatic, harderian gland		1 (3%)	
Mediastinal, histiocytic sarcoma	1 (2%)		
Lymph node, mesenteric	(44)	(32)	(49)
Histiocytic sarcoma	1 (2%)		
Spleen	(50)	(19)	(50)
Hemangioma			1 (2%)
Hemangiosarcoma	2 (4%)	1 (5%)	
Histiocytic sarcoma	1 (2%)		
Thymus	(29)	(11)	(31)
Thymoma benign	1 (3%)		
Integumentary System			
Skin	(49)	(29)	(50)
Carcinoma, metastatic, uncertain primary site			1 (2%)
Fibrosarcoma	1 (2%)	3 (10%)	4 (8%)
Fibrosarcoma, multiple	1 (2%)		
Hemangiosarcoma	1 (2%)		
Papilloma squamous	1 (2%)		
Subcutaneous tissue, sarcoma, poorly differentiated	1 (2%)		
Musculoskeletal System			
Skeletal muscle		(1)	(1)
Hemangiosarcoma			1 (100%)
Nervous System			
None			
Respiratory System			
Lung	(50)	(19)	(50)
Alveolar/bronchiolar adenoma	2 (4%)	2 (11%)	7 (14%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (5%)	
Alveolar/bronchiolar carcinoma, multiple		1 (5%)	
Carcinoma, metastatic, harderian gland	1 (2%)	1 (5%)	
Carcinoma, metastatic, uncertain primary site			1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Special Senses System			
Ear			(1)
Schwannoma malignant			1 (100%)
Harderian gland	(2)	(1)	(1)
Adenoma	1 (50%)		1 (100%)
Carcinoma	1 (50%)	1 (100%)	
Urinary System			
Kidney	(50)	(48)	(50)
Fibrosarcoma, metastatic, skin			1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		
Osteosarcoma, metastatic, uncertain primary site	1 (2%)		
Renal tubule, adenoma			3 (6%)
Systemic Lesions			
Multiple organs[a]	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant lymphocytic	3 (6%)	2 (4%)	3 (6%)
Lymphoma malignant mixed	1 (2%)	1 (2%)	
Lymphoma malignant undifferentiated cell	1 (2%)	1 (2%)	2 (4%)
Tumor Summary			
Total animals with primary neoplasms[b]	30	27	31
Total primary neoplasms	41	35	39
Total animals with benign neoplasms	17	15	20
Total benign neoplasms	21	18	23
Total animals with malignant neoplasms	17	15	16
Total malignant neoplasms	20	17	16
Total animals with secondary neoplasms[c]	4	2	3
Total secondary neoplasms	5	4	5
Total animals with malignant neoplasms of uncertain primary site	1		1

[a] Number of animals with any tissue examined microscopically
[b] Primary tumors: all tumors except metastatic tumors
[c] Secondary tumors: metastatic tumors or tumors invasive to an adjacent organ

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control

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

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 9	7 3 9	7 3 9	7 3 9	7 3 9	
Carcass ID Number	0 3 1	0 3 2	0 4 2	0 4 3	0 5 1	0 5 3	0 6 1	0 6 3	0 6 4	0 7 1	0 7 2	0 8 1	1 0 1	1 0 2	1 0 3	1 0 4	1 1 1	1 2 2	1 2 3	1 2 4	0 4 4	0 5 4	0 8 2	0 8 3	1 1 4	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic																										1
Hepatocellular carcinoma								X																		5
Hepatocellular adenoma				X		X						X					X	X						X		11
Histiocytic sarcoma																										1
Mesentery				+																						3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																									X	2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																			+							1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Pheochromocytoma benign																		X								2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	M	M	M	+	M	+	M	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	33
Pituitary gland	M	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	I	41
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Follicular cell, adenoma										X																1
Follicular cell, carcinoma																						X				1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	1 1 1 2 2 3 4 4 4 5 5 5 6 6 6 6 6 6 7 7 7 7 7 7 1 4 5 0 1 2 6 8 8 3 4 6 0 0 2 3 6 7 8 1 3 3 3 3 3 3 7 7 4 4 8 9 3 3 7 3 3 2 7 1 0 9 0 5 9 6 6 6 6 6
Carcass ID Number	1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 4 9 9 6 1 7 1 7 1 2 9 1 8 7 2 3 3 9 5 1 2 2 2 2 5 1 5 4 5 3 5 5 4 4 5 3 2 4 3 5 4 5 1 2 1 1 2 3 4
General Body System	
None	
Genital System	
Epididymis	+ +
Penis	+
Preputial gland	+ + + + +
Prostate	+ +
Seminal vesicle	+ + M +
Testes	+ +
Hematopoietic System	
Bone marrow	+ +
Lymph node	+ + M M + + + + M + + + + + + M + + + + + + + +
Mediastinal, histiocytic sarcoma	X
Lymph node, mesenteric	+ + M M + + + + M + + + + + + M + + + + + + + +
Histiocytic sarcoma	X
Spleen	+ +
Hemangiosarcoma	
Histiocytic sarcoma	X
Thymus	M + M M + M M + + M M + + + M M + + + M + M + + +
Thymoma benign	X
Integumentary System	
Mammary gland	M M M M M M M M M M M M M M M M M M M + M M M M M
Skin	+ M + +
Fibrosarcoma	X
Fibrosarcoma, multiple	X
Hemangiosarcoma	X
Papilloma squamous	
Subcutaneous tissue, sarcoma, poorly differentiated	X
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 3 1	0 3 2	0 4 2	0 4 3	0 5 1	0 5 3	0 6 1	0 6 3	0 6 4	0 7 1	0 7 2	0 8 1	1 0 1	1 0 2	1 0 3	1 0 4	1 1 1	1 2 2	1 2 3	1 2 4	0 4 4	0 5 4	0 8 2	0 8 3	1 1 4	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland																										4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		49
Lymph node	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		44
Mediastinal, histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		44
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma			X	X																						2
Histiocytic sarcoma																										1
Thymus	M	+	M	+	+	+	+	M	M	+	M	+	M	+	M	+	M	M	+	+	M	+	+	+		29
Thymoma benign																										1
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																										1
Fibrosarcoma, multiple																										1
Hemangiosarcoma																										1
Papilloma squamous												X														1
Subcutaneous tissue, sarcoma, poorly differentiated																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	1 1 1 2 2 3 4 4 4 5 5 5 6 6 6 6 6 6 7 7 7 7 7 7 1 4 5 0 1 2 6 8 8 3 4 6 0 0 2 3 6 7 8 1 3 3 3 3 3 3 7 7 4 4 8 9 3 3 7 3 3 2 7 1 0 9 0 5 9 6 6 6 6 6
Carcass ID Number	1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 0 0 0 0 0 0 0 0 0 0 4 9 9 6 1 7 1 7 1 2 9 1 8 7 2 3 3 9 5 1 2 2 2 2 5 1 5 4 5 3 5 5 4 4 5 3 2 4 3 5 4 5 1 2 1 1 2 3 4
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	
Alveolar/bronchiolar carcinoma	
Carcinoma, metastatic, harderian gland	X
Hepatocellular carcinoma, metastatic, liver	X
Nose	+ + + M + + + + + M + M + + + + M + + + + + + + +
Trachea	+ +
Special Senses System	
Eye	
Harderian gland	+
Adenoma	
Carcinoma	X
Urinary System	
Kidney	+ +
Hepatocellular carcinoma, metastatic, liver	X
Osteosarcoma, metastatic, uncertain primary site	X
Urethra	+
Urinary bladder	+ + A + M +
Systemic Lesions	
Multiple organs	+ +
Histiocytic sarcoma	X
Lymphoma malignant lymphocytic	X X
Lymphoma malignant mixed	X
Lymphoma malignant undifferentiated cell type	X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 3 1	0 3 2	0 4 2	0 4 3	0 5 1	0 5 3	0 6 1	0 6 3	0 6 4	0 7 1	0 7 2	0 8 1	1 0 1	1 0 2	1 0 3	1 0 4	1 1 1	1 2 2	1 2 3	1 2 4	0 4 4	0 5 4	0 8 2	0 8 3	1 1 4	**Total Tissues/ Tumors**
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X	X														2
Alveolar/bronchiolar carcinoma									X																	1
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M	42
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye		+																								1
Harderian gland																						+				2
Adenoma																						X				1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Osteosarcoma, metastatic, uncertain primary site																										1
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic																							X			3
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	
Carcass ID Number	1 5 1	1 5 2	1 5 3	1 6 2	1 6 3	1 6 4	1 7 2	1 7 3	1 8 1	1 8 2	2 0 2	2 0 3	2 1 1	2 1 2	2 1 3	2 1 4	2 2 2	2 2 4	2 2 5	2 3 3	2 3 5	2 4 1	2 4 2	2 4 3	2 4 4	2 2 1	**Total Tissues/ Tumors**
Alimentary System																											
Esophagus																											14
Gallbladder																											14
Intestine large																											14
Intestine large, cecum																											12
Intestine large, colon																											14
Intestine large, rectum																											12
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum						+																					13
Intestine small, jejunum																											14
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																											1
Hemangioma																											1
Hepatocellular carcinoma					X																						5
Hepatocellular carcinoma, multiple										X																	1
Hepatocellular adenoma	X		X		X						X			X											X	X	14
Mesentery								+									+										3
Pancreas																									+		16
Salivary glands																											15
Stomach								+		+						+		+						+		+	23
Stomach, forestomach								+		+						+		+						+		+	23
Papilloma squamous																		X									1
Stomach, glandular								+		+								+						+		+	22
Cardiovascular System																											
Heart																											15
Endocrine System																											
Adrenal gland																											15
Adrenal gland, cortex																											15
Adrenal gland, medulla																											15
Islets, pancreatic																											15
Parathyroid gland																											8
Pituitary gland																											15
Thyroid gland																											15
General Body System																											
None																											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg (continued)

Number of Days on Study	0 9 8	1 0 2	2 3 3	4 4 9	4 8 3	5 1 8	5 7 0	5 7 1	5 9 0	6 0 2	6 0 7	6 1 3	6 1 7	6 1 7	6 2 4	7 1 9	7 2 1	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5
Carcass ID Number	1 6 5	1 4 5	1 7 5	2 3 1	2 0 5	1 4 4	1 9 5	1 4 3	1 7 4	2 4 2	2 1 5	2 0 4	1 4 1	1 9 1	1 5 4	1 3 5	1 0 1	1 8 3	1 8 4	1 8 5	2 4 4	1 3 1	1 3 2	1 3 3	1 3 4
Genital System																									
Epididymis	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+										
Penis		+				+											+								
Preputial gland			+	M		+						+	+			+					+				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+							
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Hemangiosarcoma, metastatic							X																		
Lymph node	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+			
Mandibular, carcinoma, metastatic, harderian gland																X									
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+			+	+	+		+			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+								
Hemangiosarcoma							X																		
Thymus	M	+	M	M	+	M	+	+	+	+	+	+	+	+	+										
Integumentary System																									
Mammary gland	M	M	M	M	M	M									M										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+		+	
Fibrosarcoma				X																					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+		+			+	+	+					+					
Skeletal muscle			+																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+	
Alveolar/bronchiolar adenoma												X													
Alveolar/bronchiolar carcinoma																								X	
Alveolar/bronchiolar carcinoma, multiple																									
Carcinoma, metastatic, harderian gland																X									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	
Carcass ID Number	1 5 1	1 5 2	1 5 3	1 6 2	1 6 3	1 6 4	1 7 2	1 7 3	1 8 1	1 8 2	2 0 2	2 0 3	2 1 1	2 1 2	2 1 3	2 1 4	2 2 2	2 2 4	2 3 5	3 3 5	4 1 1	4 4 2	4 4 3	2 2 1		**Total Tissues/ Tumors**
Genital System																										
Epididymis								+																		15
Penis																										3
Preputial gland																			+					+		8
Prostate																										15
Seminal vesicle								+		+																19
Testes								+																		16
Hematopoietic System																										
Bone marrow																										15
Hemangiosarcoma, metastatic																										1
Lymph node	+	+		+		+	+	+	+	+	+	+	+	+			+				+			+	+	36
Mandibular, carcinoma, metastatic, harderian gland																										1
Lymph node, mesenteric	+	+		+		+	+	+		+	+	+	+	+			+				+				+	32
Spleen	+			+																			+			19
Hemangiosarcoma																										1
Thymus																										11
Integumentary System																										
Mammary gland																										
Skin		+						+	+	+	+		+	+				+	+	+		+			+	29
Fibrosarcoma								X													X					3
Musculoskeletal System																										
Bone		+			+							+	+		+						+					19
Skeletal muscle																										1
Nervous System																										
Brain																										15
Respiratory System																										
Lung			+				+																			19
Alveolar/bronchiolar adenoma			X																							2
Alveolar/bronchiolar carcinoma																										1
Alveolar/bronchiolar carcinoma, multiple							X																			1
Carcinoma, metastatic, harderian gland																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg (continued)

Number of Days on Study	0	1	2	4	4	5	5	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7		
	9	0	3	4	8	1	7	7	9	0	0	1	1	1	2	1	2	3	3	3	3	3	3	3	
	8	2	3	9	3	8	0	1	0	2	7	3	7	7	4	9	1	4	4	4	4	5	5	5	5
Carcass ID Number	1	1	1	2	2	1	1	1	1	1	2	2	1	1	1	1	2	1	1	1	2	1	1	1	1
	6	4	7	3	0	4	9	4	7	4	1	0	4	9	5	3	0	8	8	8	4	3	3	3	3
	5	5	5	1	5	4	5	3	4	2	5	4	1	1	4	5	1	3	4	5	4	1	2	3	4
Respiratory System (continued)																									
Nose	+	+	M	+	+	M	M	+	M	+	+	+	+	+	+										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Special Senses System																									
Eye																									+
Harderian gland																+									
Carcinoma																X									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic											X														
Lymphoma malignant mixed									X																
Lymphoma malignant undifferentiated cell type																	X								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg (continued)

Number of Days on Study	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6	
Carcass ID Number	1 5 1	1 5 2	1 5 3	1 6 2	1 6 3	1 6 4	1 7 2	1 7 3	1 8 1	1 8 2	2 0 2	2 0 3	2 1 1	2 1 2	2 1 3	2 1 4	2 2 2	2 2 4	2 2 5	2 3 3	2 3 5	2 4 1	2 4 2	2 4 3	2 4 1	2 2 1	**Total Tissues/ Tumors**
Respiratory System (continued)																											
Nose																											11
Trachea																											15
Special Senses System																											
Eye																											1
Harderian gland																											1
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+		48
Urinary bladder																											15
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant lymphocytic																								X			2
Lymphoma malignant mixed																											1
Lymphoma malignant undifferentiated cell type																											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg

Number of Days on Study	1 3 6	3 7 8	4 5 3	4 7 0	5 6 8	5 7 9	6 0 3	6 0 6	6 1 3	6 2 1	6 5 7	6 7 9	6 8 8	6 9 4	7 2 9	7 2 9	7 2 9	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	3 2 5	3 3 5	3 6 5	3 5 4	3 1 4	2 8 4	3 3 4	3 0 5	3 5 3	3 2 4	3 6 4	2 5 1	2 6 5	2 6 2	2 5 2	2 5 3	2 5 4	2 6 1	2 6 2	2 6 3	2 6 4	2 7 1	2 7 2	2 7 3	2 7 5
Alimentary System																								
Esophagus	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Gallbladder	M	+	+	+	+	+	+	+	+	M	A	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X													
Hepatocellular carcinoma													X											
Hepatocellular adenoma						X									X	X				X				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																								+
Cardiovascular System																								
Blood vessel		+																						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uncertain primary site														X										
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																								
Follicular cell, carcinoma																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 8 1	2 8 2	2 9 1	2 9 2	2 9 3	2 9 4	2 9 5	3 0 1	3 0 3	3 0 4	3 1 1	3 1 2	3 1 3	3 2 1	3 2 2	3 2 3	3 3 1	3 3 3	3 5 1	3 5 2	3 4 1	3 4 2	3 4 3	3 4 4	3 4 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	44
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma		X				X																				3
Hepatocellular adenoma											X															5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																						X				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth													+													2
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign			X	X																						2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	M	M	+	+	M	M	+	+	+	+	M	M	+	M	+	+	+	+	+	+	M	M	M	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma					X																					1
Follicular cell, carcinoma			X																							1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg (continued)

Number of Days on Study	1 3 4 4 5 5 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 3 7 5 7 6 7 0 0 1 2 5 7 8 9 2 2 2 3 3 3 3 3 3 3 6 8 3 0 8 9 3 6 3 1 7 9 8 4 9 9 9 3 3 3 3 3 3 3
Carcass ID Number	3 3 3 3 3 2 3 3 3 3 3 2 2 3 2 2 2 2 2 2 2 2 2 2 2 3 6 5 1 8 3 0 5 2 6 5 6 6 5 5 5 6 6 6 6 7 7 7 7 5 5 5 4 4 4 4 5 3 4 4 1 5 2 2 3 4 1 2 3 4 1 2 3 5
General Body System	
None	
Genital System	
Epididymis	+ +
Preputial gland	+
Prostate	+ + + + + + + + + + + + + + M + M + + + + M + +
Seminal vesicle	+ +
Testes	+ +
Interstitial cell, adenoma	
Hematopoietic System	
Blood	
Bone marrow	+ +
Lymph node	+ + + + + + + + + + + + + + + + + + + M + + + +
Lymph node, mesenteric	+ + + + + + + + + + + + + + + + + + + M + + + +
Spleen	+ +
Hemangioma	
Thymus	A M + + + + + + + + M M M M + M + + + + + + M + +
Integumentary System	
Mammary gland	M M M M M M + M M M M M M M M M M M M M M M M M
Skin	+ +
Carcinoma, metastatic, uncertain primary site	X
Fibrosarcoma	X X X X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Hemangiosarcoma	X
Nervous System	
Brain	+ +

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	
Carcass ID Number	2 8 1	2 8 2	2 9 1	2 9 2	2 9 3	2 9 4	2 9 5	3 0 1	3 0 3	3 0 4	3 1 1	3 1 2	3 1 3	3 2 1	3 2 2	3 2 3	3 3 1	3 3 3	3 5 1	3 5 2	4 4 1	4 4 2	4 4 3	4 4 4	4 4 5	**Total Tissues/ Tumors**
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland							+				+			+		+			+							6
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma									X												X					2
Hematopoietic System																										
Blood																			+						+	2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																							X			1
Thymus	+	M	+	+	+	+	+	M	+	+	M	+	M	M	+	M	M	M	M	+	+	+	M	M	+	31
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uncertain primary site																										1
Fibrosarcoma																										4
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Hemangiosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg (continued)

Number of Days on Study	1 3 4 4 5 5 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 3 7 5 7 6 7 0 0 1 2 5 7 8 9 2 2 2 3 3 3 3 3 3 3 3 6 8 3 0 8 9 3 6 3 1 7 9 8 4 9 9 9 3 3 3 3 3 3 3 3
Carcass ID Number	3 3 3 3 3 2 3 3 3 3 3 2 2 3 2 2 2 2 2 2 2 2 2 2 2 3 6 5 1 8 3 0 5 2 6 5 6 6 5 5 5 6 6 6 6 7 7 7 7 5 5 5 4 4 4 4 5 3 4 4 1 5 2 2 3 4 1 2 3 4 1 2 3 5
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X X
Carcinoma, metastatic, uncertain primary site	X
Hepatocellular carcinoma, metastatic, liver	X
Nose	I + + + M M + + M + + + M + + + M + + + + + + + +
Trachea	+ + + + + + + M + + + + + + + + + + + + + + + +
Special Senses System	
Ear	+
Schwannoma malignant	X
Eye	+
Harderian gland	+
Adenoma	X
Urinary System	
Kidney	+ +
Fibrosarcoma, metastatic, skin	X
Renal tubule, adenoma	X X
Urinary bladder	+ +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant lymphocytic	
Lymphoma malignant undifferentiated cell type	X

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg (continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	2 8 1	2 8 2	2 9 1	2 9 2	2 9 3	2 9 4	2 9 5	3 0 1	3 0 3	3 0 4	3 1 1	3 1 2	3 1 3	3 2 1	3 2 2	3 2 3	3 3 1	3 3 3	3 5 1	3 5 2	4 4 1	4 4 2	4 4 3	4 4 4	4 4 5	**Total Tissues/ Tumors**
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Alveolar/bronchiolar adenoma										X				X	X									X		7	
Carcinoma, metastatic, uncertain primary site																										1	
Hepatocellular carcinoma, metastatic, liver																										1	
Nose	M	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	39	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Special Senses System																											
Ear																										1	
Schwannoma malignant																										1	
Eye																										1	
Harderian gland																										1	
Adenoma																										1	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Fibrosarcoma, metastatic, skin																										1	
Renal tubule, adenoma										X																3	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lymphoma malignant lymphocytic							X					X									X					3	
Lymphoma malignant undifferentiated cell type																	X									2	

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	19 mg/kg	38 mg/kg
Kidney (Renal Tubule): Adenoma			
Overall rates[a]	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted rates[b]	0.0%	0.0%	8.0%
Terminal rates[c]	0/30 (0%)	0/33 (0%)	2/36 (6%)
First incidence (days)	–[e]	–	688
Life table tests[d]	P=0.050	–	P=0.158
Logistic regression tests[d]	P=0.045	–	P=0.146
Cochran-Armitage test[d]	P=0.037		
Fisher exact test[d]		–	P=0.121
Liver: Hepatocellular Adenoma			
Overall rates	11/50 (22%)	14/50 (28%)	5/50 (10%)
Adjusted rates	32.4%	37.9%	13.1%
Terminal rates	8/30 (27%)	11/33 (33%)	4/36 (11%)
First incidence (days)	483	483	579
Life table tests	P=0.038N	P=0.423	P=0.044N
Logistic regression tests	P=0.052N	P=0.380	P=0.056N
Cochran-Armitage test	P=0.085N		
Fisher exact test		P=0.322	P=0.086N
Liver: Hepatocellular Carcinoma			
Overall rates	5/50 (10%)	6/50 (12%)	3/50 (6%)
Adjusted rates	13.1%	15.7%	8.0%
Terminal rates	1/30 (3%)	3/33 (9%)	2/36 (6%)
First incidence (days)	469	590	688
Life table tests	P=0.230N	P=0.546	P=0.283N
Logistic regression tests	P=0.298N	P=0.500	P=0.358N
Cochran-Armitage test	P=0.303N		
Fisher exact test		P=0.500	P=0.357N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	15/50 (30%)	18/50 (36%)	8/50 (16%)
Adjusted rates	40.4%	46.3%	20.7%
Terminal rates	9/30 (30%)	13/33 (39%)	6/36 (17%)
First incidence (days)	469	483	579
Life table tests	P=0.031N	P=0.452	P=0.037N
Logistic regression tests	P=0.045N	P=0.388	P=0.051N
Cochran-Armitage test	P=0.072N		
Fisher exact test		P=0.335	P=0.077N
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	2/50 (4%)	2/50 (4%)	7/50 (14%)
Adjusted rates	6.7%	5.5%	18.7%
Terminal rates	2/30 (7%)	1/33 (3%)	6/36 (17%)
First incidence (days)	729 (T)	613	613
Life table tests	P=0.070	P=0.661N	P=0.130
Logistic regression tests	P=0.059	P=0.672N	P=0.117
Cochran-Armitage test	P=0.042		
Fisher exact test		P=0.691N	P=0.080

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	3/50 (6%)	4/50 (8%)	7/50 (14%)
Adjusted rates	10.0%	11.4%	18.7%
Terminal rates	3/30 (10%)	3/33 (9%)	6/36 (17%)
First incidence (days)	729 (T)	613	613
Life table tests	P=0.178	P=0.551	P=0.239
Logistic regression tests	P=0.159	P=0.543	P=0.221
Cochran-Armitage test	P=0.114		
Fisher exact test		P=0.500	P=0.159
Skin: Fibrosarcoma			
Overall rates	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted rates	5.7%	8.1%	8.8%
Terminal rates	0/30 (0%)	2/33 (6%)	0/36 (0%)
First incidence (days)	607	449	453
Life table tests	P=0.334	P=0.535	P=0.412
Logistic regression tests	P=0.218	P=0.498	P=0.271
Cochran-Armitage test	P=0.264		
Fisher exact test		P=0.500	P=0.339
All Organs: Hemangiosarcoma			
Overall rates	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rates	9.0%	2.3%	5.2%
Terminal rates	2/30 (7%)	0/33 (0%)	1/36 (3%)
First incidence (days)	543	570	657
Life table tests	P=0.336N	P=0.270N	P=0.424N
Logistic regression tests	P=0.393N	P=0.304N	P=0.473N
Cochran-Armitage test	P=0.399N		
Fisher exact test		P=0.309N	P=0.500N
All Organs: Hemangioma or Hemangiosarcoma			
Overall rates	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted rates	9.0%	4.5%	7.9%
Terminal rates	2/30 (7%)	0/33 (0%)	2/36 (6%)
First incidence (days)	543	570	657
Life table tests	P=0.508N	P=0.450N	P=0.580N
Logistic regression tests	P=0.585N	P=0.506N	P=0.628N
Cochran-Armitage test	P=0.588N		
Fisher exact test		P=0.500N	P=0.661N
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)			
Overall rates	5/50 (10%)	4/50 (8%)	5/50 (10%)
Adjusted rates	13.4%	10.4%	13.3%
Terminal rates	1/30 (3%)	1/33 (3%)	4/36 (11%)
First incidence (days)	469	590	621
Life table tests	P=0.470N	P=0.453N	P=0.530N
Logistic regression tests	P=0.554N	P=0.501N	P=0.614N
Cochran-Armitage test	P=0.568		
Fisher exact test		P=0.500N	P=0.630N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of 2,4 Diaminophenol Dihydrochloride (continued)

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

TABLE C4
Historical Incidence of Renal Tubule Tumors in Male B6C3F$_1$ Mice Receiving Corn Oil Vehicle by Gavage[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
2,4-Diaminophenol dihydrochloride	0/50	0/50	0/50
Bromoform	0/50	0/50	0/50
Phenylbutazone	0/49	0/49	0/49
Probenecid	0/49	0/49	0/49
Overall Historical Incidence			
Total	1/598 (0.2%)	0/598 (0.0%)	1/598 (0.5%)
Standard deviation	0.6%		0.6%
Range	0%–2%		0%–2%

[a] Data as of 17 September 1990

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	19 mg/kg	38 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Natural death	6	6	2
Moribund	14	11	12
Survivors			
Terminal sacrifice	30	33	36
Animals examined microscopically	50	50	50
Alimentary System			
Gallbladder	(46)	(14)	(44)
Serosa, inflammation, acute			1 (2%)
Intestine small, duodenum	(47)	(49)	(48)
Lamina propria, pigmentation		48 (98%)	47 (98%)
Intestine small, ileum	(45)	(13)	(48)
Hyperplasia, lymphoid			1 (2%)
Peyer's patch, hyperplasia, neutrophil		1 (8%)	
Liver	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)	
Cyst		1 (2%)	
Fatty change	2 (4%)		1 (2%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)	2 (4%)	3 (6%)
Mixed cell focus			1 (2%)
Necrosis	4 (8%)		3 (6%)
Kupffer cell, pigmentation		44 (88%)	47 (94%)
Mesentery	(3)	(3)	
Necrosis, multifocal		1 (33%)	
Fat, necrosis, focal	1 (33%)	1 (33%)	
Pancreas	(50)	(16)	(50)
Inflammation, chronic	3 (6%)	1 (6%)	2 (4%)
Acinus, atrophy	2 (4%)		2 (4%)
Acinus, hypertrophy, focal			1 (2%)
Salivary glands	(50)	(15)	(50)
Inflammation, chronic	26 (52%)	7 (47%)	31 (62%)
Inflammation, suppurative	1 (2%)		
Acinus, atrophy, focal			1 (2%)
Stomach, forestomach	(50)	(23)	(50)
Acanthosis	4 (8%)	10 (43%)	13 (26%)
Cyst		1 (4%)	
Inflammation, acute	1 (2%)		5 (10%)
Inflammation, chronic	1 (2%)	3 (13%)	1 (2%)
Inflammation, focal			1 (2%)
Mineralization			1 (2%)
Ulcer		2 (9%)	5 (10%)
Stomach, glandular	(50)	(22)	(50)
Pigmentation			1 (2%)
Tooth	(1)		(2)
Peridontal tissue, inflammation, chronic			1 (50%)
Peridontal tissue, inflammation, suppurative	1 (100%)		
Pulp, inflammation, necrotizing			1 (50%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Cardiovascular System			
Blood vessel			(1)
Artery, inflammation, chronic			1 (100%)
Heart	(50)	(15)	(50)
Coronary artery, inflammation, chronic			1 (2%)
Endocrine System			
Adrenal gland, cortex	(49)	(15)	(50)
Cyst	1 (2%)		
Hypertrophy	1 (2%)		
Adrenal gland, medulla	(49)	(15)	(49)
Hyperplasia	2 (4%)	1 (7%)	
Islets, pancreatic	(50)	(15)	(50)
Hyperplasia			3 (6%)
Parathyroid gland	(33)	(8)	(33)
Cyst, multiple			1 (3%)
Pituitary gland	(41)	(15)	(50)
Pars distalis, cyst	1 (2%)		
Pars intermedia, hyperplasia, focal			1 (2%)
Thyroid gland	(49)	(15)	(49)
Follicle, hyperplasia	1 (2%)		
Follicular cell, hyperplasia			3 (6%)
General Body System			
None			
Genital System			
Epididymis	(50)	(15)	(50)
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, granulomatous, focal		1 (7%)	
Penis	(1)	(3)	
Inflammation, chronic active		1 (33%)	
Inflammation, suppurative	1 (100%)	1 (33%)	
Necrosis		1 (33%)	
Preputial gland	(4)	(8)	(6)
Inflammation, chronic		1 (13%)	2 (33%)
Inflammation, suppurative		3 (38%)	2 (33%)
Duct, ectasia	2 (50%)	3 (38%)	2 (33%)
Prostate	(50)	(15)	(46)
Inflammation, acute	1 (2%)	1 (7%)	1 (2%)
Inflammation, chronic	1 (2%)		
Inflammation, suppurative	5 (10%)	2 (13%)	1 (2%)
Seminal vesicle	(49)	(19)	(50)
Inflammation, chronic	1 (2%)		
Testes	(50)	(16)	(50)
Inflammation, suppurative	1 (2%)		
Interstitial cell, hyperplasia	1 (2%)		
Interstitial tissue, inflammation, suppurative	1 (2%)		
Seminiferous tubule, degeneration	2 (4%)	1 (6%)	
Seminiferous tubule, mineralization	1 (2%)		

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Hematopoietic System			
Bone marrow	(49)	(15)	(50)
Myelofibrosis	1 (2%)		1 (2%)
Myeloid cell, hyperplasia		1 (7%)	
Lymph node	(44)	(36)	(49)
Lumbar, hyperplasia, plasma cell	2 (5%)	1 (3%)	
Mediastinal, hyperplasia, lymphoid		1 (3%)	
Pancreatic, pigmentation		1 (3%)	7 (14%)
Renal, hyperplasia, histiocyte			1 (2%)
Lymph node, mesenteric	(44)	(32)	(49)
Congestion	6 (14%)	18 (56%)	16 (33%)
Hematopoietic cell proliferation		2 (6%)	
Hyperplasia, lymphoid			1 (2%)
Pigmentation		5 (16%)	17 (35%)
Spleen	(50)	(19)	(50)
Angiectasis	1 (2%)		
Hematopoietic cell proliferation	3 (6%)	4 (21%)	5 (10%)
Hyperplasia, lymphoid	1 (2%)	1 (5%)	1 (2%)
Pigmentation			2 (4%)
Thymus	(29)	(11)	(31)
Necrosis	1 (3%)		
Integumentary System			
Skin	(49)	(29)	(50)
Inflammation, chronic	1 (2%)	1 (3%)	
Parakeratosis, multifocal		1 (3%)	
Ulcer, multiple		1 (3%)	1 (2%)
Dermis, fibrosis		1 (3%)	2 (4%)
Dermis, inflammation, chronic		1 (3%)	
Dermis, subcutaneous tissue, fibrosis	1 (2%)		
Prepuce, hyperkeratosis	1 (2%)		
Prepuce, inflammation, suppurative	2 (4%)	2 (7%)	
Prepuce, necrosis, focal	1 (2%)		
Subcutaneous tissue, inflammation, acute	1 (2%)		
Subcutaneous tissue, inflammation, chronic			1 (2%)
Subcutaneous tissue, inflammation, granulomatous		1 (3%)	
Musculoskeletal System			
Bone	(50)	(19)	(50)
Hyperostosis		1 (5%)	1 (2%)
Joint, tarsal, hyperostosis	7 (14%)	14 (74%)	12 (24%)
Nervous System			
None			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Respiratory System			
Lung	(50)	(19)	(50)
Congestion	2 (4%)	1 (5%)	1 (2%)
Hemorrhage	1 (2%)		
Alveolar epithelium, hyperplasia	2 (4%)		
Peribronchiolar, perivascular, inflammation, chronic			1 (2%)
Perivascular, inflammation, chronic		1 (5%)	
Nose	(42)	(11)	(39)
Mucosa, inflammation, suppurative	1 (2%)		
Nasolacrimal duct, hyperplasia, squamous			1 (3%)
Nasolacrimal duct, inflammation, chronic	2 (5%)	1 (9%)	
Special Senses System			
Eye	(1)	(1)	(1)
Cataract		1 (100%)	
Urinary System			
Kidney	(50)	(48)	(50)
Inflammation, chronic	26 (52%)	16 (33%)	38 (76%)
Metaplasia			1 (2%)
Metaplasia, osseous	1 (2%)		1 (2%)
Necrosis		12 (25%)	30 (60%)
Nephropathy	1 (2%)		
Cortex, inflammation, suppurative	1 (2%)		
Papilla, necrosis	1 (2%)		1 (2%)
Pelvis, inflammation, acute		1 (2%)	
Renal tubule, calculus micro observation only		1 (2%)	
Renal tubule, dilatation	1 (2%)	15 (31%)	46 (92%)
Renal tubule, hyperplasia			2 (4%)
Renal tubule, hyperplasia, focal			1 (2%)
Renal tubule, mineralization	2 (4%)		8 (16%)
Renal tubule, pigmentation		8 (17%)	47 (94%)
Renal tubule, regeneration	34 (68%)	34 (71%)	48 (96%)
Urethra	(1)		
Mucosa, lumen, inflammation, suppurative	1 (100%)		
Urinary bladder	(47)	(15)	(50)
Concretion			1 (2%)
Mucosa, inflammation, acute	1 (2%)		
Mucosa, inflammation, subacute		1 (7%)	
Mucosa, necrosis	1 (2%)	1 (7%)	
Serosa, inflammation			1 (2%)
Serosa, inflammation, acute	1 (2%)		
Submucosa, hemorrhage	1 (2%)		
Submucosa, inflammation, chronic	3 (6%)		6 (12%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF 2,4-DIAMINOPHENOL DIHYDROCHLORIDE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	19 mg/kg	38 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Natural death	5	7	2
Moribund	11	12	20
Survivors			
Terminal sacrifice	34	31	28
Animals examined microscopically	50	50	50
Alimentary System			
Gallbladder	(43)	(10)	(45)
Intestine large, cecum	(49)	(11)	(50)
Intestine small, ileum	(49)	(11)	(49)
Liver	(50)	(50)	(50)
Hemangioma		1 (2%)	
Hepatocellular carcinoma	1 (2%)	4 (8%)	
Hepatocellular adenoma	3 (6%)	3 (6%)	3 (6%)
Histiocytic sarcoma	1 (2%)		
Mesentery	(7)	(4)	(4)
Histiocytic sarcoma		1 (25%)	
Pancreas	(50)	(14)	(49)
Histiocytic sarcoma	1 (2%)		
Salivary glands	(49)	(11)	(49)
Histiocytic sarcoma	1 (2%)		
Stomach, forestomach	(49)	(20)	(50)
Papilloma squamous	1 (2%)	2 (10%)	3 (6%)
Squamous cell carcinoma	1 (2%)		
Stomach, glandular	(49)	(15)	(50)
Squamous cell carcinoma, deep invasion	1 (2%)		
Cardiovascular System			
Heart	(50)	(12)	(50)
Endocrine System			
Adrenal gland	(49)	(14)	(50)
Adrenal gland, medulla	(46)	(12)	(44)
Pheochromocytoma benign		1 (8%)	
Pituitary gland	(46)	(13)	(44)
Pars distalis, adenoma	7 (15%)	3 (23%)	4 (9%)
Thyroid gland	(50)	(13)	(50)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
General Body System			
Tissue NOS	(1)	(1)	
Fibrosarcoma		1 (100%)	
Genital System			
Ovary	(48)	(25)	(44)
Cystadenoma, papillary	1 (2%)		
Histiocytic sarcoma	1 (2%)		
Luteoma		1 (4%)	1 (2%)
Teratoma		1 (4%)	
Uterus	(50)	(26)	(49)
Hemangioma			1 (2%)
Histiocytic sarcoma	1 (2%)		
Endometrium, polyp stromal			1 (2%)
Hematopoietic System			
Bone marrow	(49)	(12)	(50)
Lymph node	(47)	(27)	(49)
Axillary, histiocytic sarcoma	1 (2%)		
Inguinal, histiocytic sarcoma	1 (2%)		
Lumbar, histiocytic sarcoma	1 (2%)	1 (4%)	
Mandibular, histiocytic sarcoma	1 (2%)		
Mediastinal, histiocytic sarcoma	1 (2%)		
Renal, histiocytic sarcoma	1 (2%)	1 (4%)	
Lymph node, mesenteric	(46)	(23)	(46)
Histiocytic sarcoma	1 (2%)	1 (4%)	
Spleen	(50)	(24)	(50)
Hemangiosarcoma		1 (4%)	
Histiocytic sarcoma	1 (2%)		
Thymus	(33)	(10)	(39)
Integumentary System			
Mammary gland	(36)	(10)	(37)
Carcinoma	1 (3%)	2 (20%)	
Skin	(50)	(31)	(49)
Fibrosarcoma		1 (3%)	1 (2%)
Fibrosarcoma, multiple		1 (3%)	
Subcutaneous tissue, sarcoma		1 (3%)	
Vulva, squamous cell carcinoma, noninvasive		1 (3%)	
Musculoskeletal System			
Skeletal muscle	(3)	(1)	
Head, sarcoma	1 (33%)		
Hindlimb, rhabdomyoma	1 (33%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Nervous System			
None			
Respiratory System			
Lung	(50)	(20)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (5%)	3 (6%)
Alveolar/bronchiolar carcinoma	1 (2%)	4 (20%)	
Histiocytic sarcoma	1 (2%)		
Mediastinum, hemangioma			1 (2%)
Nose	(45)	(11)	(46)
Histiocytic sarcoma	1 (2%)		
Special Senses System			
Harderian gland	(2)	(1)	(1)
Adenoma	1 (50%)	1 (100%)	1 (100%)
Urinary System			
Kidney	(50)	(39)	(50)
Histiocytic sarcoma	1 (2%)		
Renal tubule, carcinoma		1 (3%)	
Urinary bladder	(47)	(10)	(47)
Systemic Lesions			
Multiple organs[a]	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)	1 (2%)	
Lymphoma malignant histiocytic		3 (6%)	
Lymphoma malignant lymphocytic	5 (10%)	2 (4%)	1 (2%)
Lymphoma malignant mixed	4 (8%)	4 (8%)	5 (10%)
Lymphoma malignant undifferentiated cell	3 (6%)		1 (2%)
Tumor Summary			
Total animals with primary neoplasms[b]	24	29	17
Total primary neoplasms	34	41	26
Total animals with benign neoplasms	14	12	13
Total benign neoplasms	15	14	18
Total animals with malignant neoplasms	15	21	8
Total malignant neoplasms	19	27	8

[a] Number of animals with any tissue examined microscopically
[b] Primary tumors: all tumors except metastatic tumors

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control

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

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 9 4	3 8 1	3 8 2	3 9 1	4 0 1	4 0 2	4 1 1	4 1 3	4 1 4	4 4 5	4 5 1	4 5 2	4 6 1	4 6 2	4 8 3	4 3 1	4 3 2	4 3 4	4 4 1	4 4 2	4 7 1	4 7 2	4 7 3	4 7 5	4 8 2	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	43
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Intestine large, rectum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma																		X								3
Histiocytic sarcoma																										1
Mesentery												+														7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																										1
Squamous cell carcinoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, deep invasion																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	46
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	M	+	M	M	M	M	+	+	+	M	+	+	+	+	+	30
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma			X										X		X											7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	3 2 1	3 4 0	3 7 6	4 0 0	4 0 4	4 5 8	5 4 2	5 5 8	6 2 1	6 5 6	6 7 0	7 0 5	7 1 0	7 2 2	7 2 2	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	4 2 1	3 7 4	4 2 5	4 2 3	4 8 5	4 2 2	3 7 5	4 8 4	4 6 4	3 8 3	4 5 5	4 8 1	4 0 5	3 9 5	4 3 5	4 5 4	3 7 3	4 0 3	4 0 4	4 1 5	4 6 5	3 7 1	3 7 2	3 8 4	3 8 5
General Body System																									
Tissue NOS					+																				
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, papillary									X																
Histiocytic sarcoma															X										
Oviduct			+		+																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Hematopoietic System																									
Bone marrow	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Axillary, histiocytic sarcoma															X										
Inguinal, histiocytic sarcoma															X										
Lumbar, histiocytic sarcoma															X										
Mandibular, histiocytic sarcoma															X										
Mediastinal, histiocytic sarcoma															X										
Renal, histiocytic sarcoma															X										
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+
Histiocytic sarcoma															X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma															X										
Thymus	M	+	M	+	+	+	+	+	M	M	+	M	+	M	M	M	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	+	+	+	+	+	M	+	+	M	+	+	M	+	+	M	M	M	+	+	+	+	+	M
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+						+			+														
Head, sarcoma								X																	
Hindlimb, rhabdomyoma		X																							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 9 4	3 8 1	3 8 2	3 9 1	4 0 1	4 0 2	4 1 1	4 1 3	4 1 4	4 4 5	4 5 1	4 5 2	4 6 1	4 6 2	4 8 3	4 3 1	4 3 2	4 3 4	4 4 1	4 4 2	4 7 1	4 7 2	4 7 3	4 7 5	4 8 2	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Genital System																										
Ovary	I	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma, papillary																										1
Histiocytic sarcoma																										1
Oviduct																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Axillary, histiocytic sarcoma																										1
Inguinal, histiocytic sarcoma																										1
Lumbar, histiocytic sarcoma																										1
Mandibular, histiocytic sarcoma																										1
Mediastinal, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	M	+	M	+	+	+	+	M	+	M	+	+	+	+	M	M	M	M	+	M	33
Integumentary System																										
Mammary gland	+	+	+	M	+	M	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	M	+	36
Carcinoma															X											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										3
Head, sarcoma																										1
Hindlimb, rhabdomyoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 9 4	3 8 1	3 8 2	3 9 1	4 0 1	4 0 2	4 1 1	4 1 3	4 1 4	4 4 5	4 5 1	4 5 2	4 6 1	4 6 2	4 8 3	4 3 1	4 3 2	4 3 4	4 4 1	4 4 2	4 7 1	4 7 2	4 7 3	4 7 5	4 8 2	**Total Tissues/ Tumors**
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																1
Alveolar/bronchiolar carcinoma																										1
Histiocytic sarcoma																										1
Nose	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear								+																		1
Eye																										1
Harderian gland															+											2
Adenoma															X											1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic																					X					5
Lymphoma malignant mixed																X							X			4
Lymphoma malignant undifferentiated cell type											X			X												3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg (continued)

Number of Days on Study	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	51 14	51 15	52 14	51 11	51 13	52 13	53 11	53 12	54 12	54 13	54 14	55 13	55 14	56 11	56 13	57 12	58 12	58 13	58 14	59 11	59 13	59 14	59 15	60 11	60 12	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus																										12
Gallbladder																										10
Intestine large																										11
Intestine large, cecum																										11
Intestine large, colon																										11
Intestine large, rectum																										10
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum																										11
Intestine small, jejunum																										11
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																							X			1
Hepatocellular carcinoma															X											4
Hepatocellular adenoma								X																		3
Mesentery																										4
Histiocytic sarcoma																										1
Pancreas	+															+										14
Salivary glands																										11
Stomach					+		+						+		+	+										20
Stomach, forestomach					+		+						+		+	+										20
Papilloma squamous							X								X											2
Stomach, glandular					+											+										15
Cardiovascular System																										
Heart																										12
Endocrine System																										
Adrenal gland										+																14
Adrenal gland, cortex																										13
Adrenal gland, medulla										+																12
Pheochromocytoma benign										X																1
Islets, pancreatic																										12
Parathyroid gland																										9
Pituitary gland																						+				13
Pars distalis, adenoma																						X				3
Thyroid gland																										13

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg (continued)

Number of Days on Study	0 7 1	2 5 6	3 3 0	3 3 0	3 3 7	4 1 0	4 7 1	5 1 6	5 9 2	6 1 9	6 2 0	6 3 1	6 6 0	6 8 3	6 9 2	7 0 0	7 0 4	7 1 3	7 2 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	5 0 3	5 5 2	5 7 4	5 9 2	5 7 5	6 0 5	5 7 3	5 2 1	5 0 5	5 6 5	6 0 4	5 8 5	5 5 1	5 3 3	5 3 5	5 6 4	5 4 1	5 9 4	4 2 5	4 9 1	4 9 2	4 9 3	5 0 1	5 0 2	5 0 4
General Body System																									
Tissue NOS													+												
Fibrosarcoma													X												
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+		+		+		+			+	+	+		
Luteoma								X																	
Teratoma		X																							
Oviduct			+	+	+	+	+	+																	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+				+				+					+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+													
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+		+	+		+		+	
Lumbar, histiocytic sarcoma														X											
Renal, histiocytic sarcoma														X											
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+		+		+	+		+	+		+			
Histiocytic sarcoma														X											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+			+					
Hemangiosarcoma												X													
Thymus	+	M	+	+	+	+	M	+	+	M	+	+													
Integumentary System																									
Mammary gland	M	+	M	M	+	+	M	+	+	+	+	+								+					
Carcinoma																				X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Fibrosarcoma												X													
Fibrosarcoma, multiple													X												
Subcutaneous tissue, sarcoma																									
Vulva, squamous cell carcinoma, noninvasive					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+													
Skeletal muscle							+																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+													

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 1 4	5 1 5	5 2 4	5 1 1	5 1 3	5 2 3	5 3 1	5 3 2	5 4 2	5 4 3	5 4 4	5 5 3	5 5 4	5 6 1	5 6 3	5 7 2	5 8 2	5 8 3	5 8 4	5 9 1	5 9 3	5 9 4	5 9 5	6 0 1	6 0 2	**Total Tissues/ Tumors**
General Body System																										
Tissue NOS																										1
Fibrosarcoma																										1
Genital System																										
Ovary	+		+		+					+		+										+		+		25
Luteoma																										1
Teratoma																										1
Oviduct																										6
Uterus		+	+		+				+					+		+	+	+	+	+	+					26
Hematopoietic System																										
Bone marrow																										12
Lymph node			+							+			+			+	+	+			+				+	27
Lumbar, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mesenteric										+						+	+	+			+				+	23
Histiocytic sarcoma																										1
Spleen											+		+		+	+	+				+		+		+	24
Hemangiosarcoma																										1
Thymus													+													10
Integumentary System																										
Mammary gland																			+							10
Carcinoma																			X							2
Skin			+	+			+	+			M					+				+	M	+	+	+		31
Fibrosarcoma																										1
Fibrosarcoma, multiple																										1
Subcutaneous tissue, sarcoma							X																			1
Vulva, squamous cell carcinoma, noninvasive																										1
Musculoskeletal System																										
Bone																										12
Skeletal muscle																										1
Nervous System																										
Brain																										12

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg (continued)

Number of Days on Study	0	2	3	3	3	4	4	5	5	6	6	6	6	6	7	7	7	7	7	7	7	7	7				
	7	5	3	3	3	1	7	1	9	1	2	3	6	8	9	0	0	1	2	3	3	3	3	3	3		
	1	6	0	0	7	0	1	6	2	9	0	1	0	3	2	0	4	3	6	0	0	0	0	0	0		
Carcass ID Number	5	5	5	5	5	6	5	5	5	5	6	5	5	5	5	5	5	4	5	4	4	4	5	5	5		
	0	5	7	9	7	0	7	2	0	6	0	8	5	3	3	6	4	9	2	9	9	9	0	0	0		
	3	2	4	2	5	5	3	1	5	5	4	5	1	3	5	4	1	4	5	1	2	3	1	2	4		
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+				+			+	+							
Alveolar/bronchiolar adenoma																											
Alveolar/bronchiolar carcinoma																			X	X							
Nose	M	+	+	+	+	+	+	+	+	+	+	+															
Trachea	+	+	+	+	+	+	+	+	+	+	+	+															
Special Senses System																											
Eye																											
Harderian gland																											
Adenoma																											
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+			+	+	+	+	+	+		
Renal tubule, carcinoma																									X		
Urinary bladder	+	+	+	+	M	+	+	+	+	M	+	+															
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Histiocytic sarcoma														X													
Lymphoma malignant histiocytic																											
Lymphoma malignant lymphocytic																											
Lymphoma malignant mixed																	X			X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 19 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	5 1 4	5 1 5	5 2 4	5 1 1	5 1 3	5 2 3	5 3 1	5 3 2	5 4 2	5 4 3	5 4 4	5 5 3	5 5 4	5 6 1	5 6 3	5 7 2	5 8 2	5 8 3	5 8 4	5 9 1	5 9 3	5 9 4	5 9 5	6 0 1	6 0 2	**Total Tissues/ Tumors**
Respiratory System																										
Lung												+				+						+	+		+	20
Alveolar/bronchiolar adenoma																									X	1
Alveolar/bronchiolar carcinoma																X						X				4
Nose																										11
Trachea																										12
Special Senses System																										
Eye																		+								1
Harderian gland																							+			1
Adenoma																							X			1
Urinary System																										
Kidney	+	+		+		+	+	+	+	+		+	+	+	+				+	+		+	+	+	+	39
Renal tubule, carcinoma																										1
Urinary bladder																										10
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic																X						X			X	3
Lymphoma malignant lymphocytic											X												X			2
Lymphoma malignant mixed													X				X									4

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 1 5	6 2 1	6 2 2	6 2 3	6 3 4	6 4 1	6 5 1	6 5 3	6 5 5	6 6 1	6 6 5	6 7 1	6 7 3	6 8 1	6 8 4	6 9 4	7 0 2	7 0 3	7 1 1	7 1 2	7 1 3	7 1 4	7 2 2	7 2 3	7 2 5	**Total Tissues/ Tumors**
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X									X							X			3
Mesentery											+															4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																	X						X			3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	44
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	M	M	M	+	M	+	M	+	+	+	+	M	+	M	+	+	+	M	M	+	+	M	+	30
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	I	+	M	+	+	+	44
Pars distalis, adenoma							X			X			X											X		4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg (continued)

Number of Days on Study	2 4 5	2 8 8	2 8 8	3 2 7	3 2 7	3 4 0	4 1 0	4 3 0	4 4 1	4 4 3	4 4 9	5 1 6	5 3 1	5 9 2	6 1 4	6 5 9	6 6 1	6 6 2	6 6 2	6 6 7	6 6 7	6 8 8	7 3 0	7 3 0
Carcass ID Number	6 4 5	6 6 2	6 9 3	6 6 3	6 6 4	6 3 1	6 5 4	7 0 1	7 1 5	6 3 2	6 8 5	6 4 3	6 2 5	6 4 2	6 7 5	7 7 2	6 0 4	7 7 4	6 8 2	7 0 5	7 2 4	6 9 2	6 1 1	6 1 3
Genital System																								
Ovary	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Luteoma																								
Oviduct				+	+	+	+	+	+	+	+									+				
Uterus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								
Endometrium, polyp stromal											X													
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	A	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																		X						
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Mediastinum, hemangioma																								
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye																				+				
Harderian gland																				+				
Adenoma																				X				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 1 5	6 2 1	6 2 2	6 2 3	6 3 4	6 4 1	6 5 1	6 5 3	6 5 5	6 6 1	6 6 5	6 7 1	6 7 3	6 8 1	6 8 4	6 9 4	7 0 2	7 0 3	7 1 1	7 1 2	7 1 3	7 1 4	7 2 2	7 2 3	7 2 5	**Total Tissues/ Tumors**
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	44
Luteoma	X																									1
Oviduct																										9
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma	X																									1
Endometrium, polyp stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	39
Integumentary System																										
Mammary gland	+	M	M	M	+	M	M	M	M	M	M	+	+	+	+	+	M	+	+	+	+	M	+	M	M	37
Skin	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X	X						X				3
Mediastinum, hemangioma																							X			1
Nose	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland																										1
Adenoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg (continued)

Number of Days on Study	2	2	2	3	3	3	4	4	4	4	4	5	5	5	6	6	6	6	6	6	6	6	7	7	7
	4	8	8	2	2	4	1	3	4	4	7	1	3	9	1	5	6	6	6	6	6	8	3	3	3
	5	8	8	7	7	0	0	0	1	3	9	6	1	2	4	9	1	2	2	7	7	8	0	0	0
Carcass ID Number	6	6	6	6	6	6	6	7	7	6	6	6	6	6	6	6	7	6	6	7	7	6	6	6	6
	4	6	9	6	6	3	5	0	1	3	8	4	2	4	7	7	0	7	8	0	2	9	1	1	1
	5	2	3	3	4	1	4	1	5	2	5	3	5	2	5	2	4	4	2	5	4	2	1	2	3
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urethra	+																								
Urinary bladder	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed																				X			X		
Lymphoma malignant undifferentiated cell type							X																		

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride: 38 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 1 5	6 1 2	6 2 2	6 2 3	6 3 4	6 4 1	6 5 1	6 5 3	6 5 5	6 6 1	6 6 5	6 7 1	6 7 3	6 8 1	6 8 4	6 9 4	7 0 2	7 0 3	7 1 1	7 1 2	7 1 3	7 1 4	7 2 2	7 2 3	7 2 5	**Total Tissues/ Tumors**
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urethra																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic							X																			1
Lymphoma malignant mixed			X			X											X									5
Lymphoma malignant undifferentiated cell type																										1

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	19 mg/kg	38 mg/kg
Liver: Hepatocellular Adenoma			
Overall rates[a]	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted rates[b]	8.8%	8.8%	10.7%
Terminal rates[c]	3/34 (9%)	1/31 (3%)	3/28 (11%)
First incidence (days)	729 (T)	700	729 (T)
Life table tests[d]	P=0.475	P=0.615	P=0.571
Logistic regression tests[d]	P=0.466	P=0.632	P=0.571
Cochran-Armitage test[d]	P=0.583		
Fisher exact test[d]		P=0.661N	P=0.661N
Liver: Hepatocellular Carcinoma			
Overall rates	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted rates	2.6%	10.7%	0.0%
Terminal rates	0/34 (0%)	1/31 (3%)	0/28 (0%)
First incidence (days)	710	619	–[e]
Life table tests	P=0.484N	P=0.163	P=0.561N
Logistic regression tests	P=0.422N	P=0.171	P=0.534N
Cochran-Armitage test	P=0.390N		
Fisher exact test		P=0.181	P=0.500N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall rates	4/50 (8%)	7/50 (14%)	3/50 (6%)
Adjusted rates	11.2%	18.7%	10.7%
Terminal rates	3/34 (9%)	2/31 (6%)	3/28 (11%)
First incidence (days)	710	619	729 (T)
Life table tests	P=0.557	P=0.223	P=0.614N
Logistic regression tests	P=0.537N	P=0.235	P=0.640N
Cochran-Armitage test	P=0.432N		
Fisher exact test		P=0.262	P=0.500N
Lung: Alveolar/bronchiolar Adenoma			
Overall rates	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rates	2.9%	3.2%	10.7%
Terminal rates	1/34 (3%)	1/31 (3%)	3/28 (11%)
First incidence (days)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.153	P=0.741	P=0.237
Logistic regression tests	P=0.153	P=0.741	P=0.237
Cochran-Armitage test	P=0.202		
Fisher exact test		P=0.753N	P=0.309
Lung: Alveolar/bronchiolar Carcinoma			
Overall rates	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted rates	2.6%	12.5%	0.0%
Terminal rates	0/34 (0%)	3/31 (10%)	0/28 (0%)
First incidence (days)	705	726	–
Life table tests	P=0.473N	P=0.153	P=0.566N
Logistic regression tests	P=0.474N	P=0.155	P=0.530N
Cochran-Armitage test	P=0.390N		
Fisher exact test		P=0.181	P=0.500N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Lung: Alveolar/bronchiolar Adenoma or Carcinoma			
Overall rates	2/50 (4%)	5/50 (10%)	3/50 (6%)
Adjusted rates	5.4%	15.6%	10.7%
Terminal rates	1/34 (3%)	4/31 (13%)	3/28 (11%)
First incidence (days)	705	726	729 (T)
Life table tests	P=0.315	P=0.181	P=0.400
Logistic regression tests	P=0.290	P=0.181	P=0.391
Cochran-Armitage test	P=0.421		
Fisher exact test		P=0.218	P=0.500
Pituitary Gland (Pars Distalis): Adenoma			
Overall rates	7/46 (15%)	3/50 (6%)	4/44 (9%)
Adjusted rates	19.0%	8.0%	16.7%
Terminal rates	5/34 (15%)	1/31 (3%)	4/24 (17%)
First incidence (days)	670	516	729 (T)
Life table tests	P=0.356N	P=0.203N	P=0.484N
Logistic regression tests	P=0.299N	P=0.143N	P=0.485N
Cochran-Armitage test	P=0.209N		
Fisher exact test		P=0.127N	P=0.287N
Stomach (Forestomach): Squamous Papilloma			
Overall rates	1/49 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rates	2.9%	6.5%	10.7%
Terminal rates	1/34 (3%)	2/31 (6%)	3/28 (11%)
First incidence (days)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.165	P=0.468	P=0.237
Logistic regression tests	P=0.165	P=0.468	P=0.237
Cochran-Armitage test	P=0.228		
Fisher exact test		P=0.508	P=0.316
Stomach (Forestomach): Squamous Papilloma or Squamous Cell Carcinoma			
Overall rates	2/49 (4%)	2/50 (4%)	3/50 (6%)
Adjusted rates	5.9%	6.5%	10.7%
Terminal rates	2/34 (6%)	2/31 (6%)	3/28 (11%)
First incidence (days)	729 (T)	729 (T)	729 (T)
Life table tests	P=0.324	P=0.662	P=0.411
Logistic regression tests	P=0.324	P=0.662	P=0.411
Cochran-Armitage test	P=0.415		
Fisher exact test		P=0.684N	P=0.510
All Organs: Malignant Lymphoma (Histiocytic, Lymphocytic, Mixed, or Undifferentiated Cell Type)			
Overall rates	11/50 (22%)	9/50 (18%)	7/50 (14%)
Adjusted rates	27.5%	28.0%	22.3%
Terminal rates	6/34 (18%)	8/31 (26%)	5/28 (18%)
First incidence (days)	558	704	410
Life table tests	P=0.336N	P=0.496N	P=0.385N
Logistic regression tests	P=0.270N	P=0.449N	P=0.290N
Cochran-Armitage test	P=0.181N		
Fisher exact test		P=0.402N	P=0.218N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

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

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride

	Vehicle Control	19 mg/kg	38 mg/kg
Disposition Summary			
Animals initially in study	60	60	60
15-Month interim evaluation	10	10	10
Early deaths			
Natural death	5	7	2
Moribund	11	12	20
Survivors			
Terminal sacrifice	34	31	28
Animals examined microscopically	50	50	50
Alimentary System			
Gallbladder	(43)	(10)	(45)
Serosa, inflammation, suppurative	3 (7%)	1 (10%)	
Intestine small, duodenum	(48)	(48)	(48)
Lamina propria, congestion, diffuse			1 (2%)
Lamina propria, pigmentation		44 (92%)	47 (98%)
Intestine small, jejunum	(50)	(11)	(50)
Lamina propria, congestion, diffuse			1 (2%)
Liver	(50)	(50)	(50)
Abscess, single			1 (2%)
Angiectasis	1 (2%)		1 (2%)
Basophilic focus	1 (2%)	3 (6%)	
Clear cell focus	1 (2%)		1 (2%)
Eosinophilic focus	1 (2%)		
Fatty change	1 (2%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	4 (8%)	5 (10%)	5 (10%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Inflammation, chronic	9 (18%)	2 (4%)	8 (16%)
Necrosis	1 (2%)		1 (2%)
Kupffer cell, pigmentation		31 (62%)	50 (100%)
Serosa, inflammation, suppurative	2 (4%)	1 (2%)	
Serosa, inflammation, membranous	1 (2%)		
Mesentery	(7)	(4)	(4)
Inflammation, acute	1 (14%)		
Inflammation, chronic	3 (43%)		1 (25%)
Inflammation, chronic active			1 (25%)
Inflammation, suppurative		2 (50%)	1 (25%)
Fat, necrosis	1 (14%)	1 (25%)	1 (25%)
Mesothelium, inflammation, membranous	1 (14%)		
Pancreas	(50)	(14)	(49)
Atrophy		1 (7%)	
Hyperplasia, lymphoid	1 (2%)		
Inflammation, chronic	4 (8%)	2 (14%)	6 (12%)
Inflammation, suppurative	1 (2%)		
Acinus, atrophy			1 (2%)
Duct, cyst			1 (2%)
Duct, interlobular, ectasia		1 (7%)	
Interlobular, inflammation, acute			1 (2%)
Serosa, inflammation, suppurative	1 (2%)		
Serosa, interlobular, inflammation, suppurative			1 (2%)
Salivary glands	(49)	(11)	(49)
Inflammation, chronic	23 (47%)	7 (64%)	18 (37%)
Artery, inflammation, necrotizing, chronic			1 (2%)

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Alimentary System (continued)			
Stomach	(49)	(20)	(50)
Serosa, inflammation, suppurative	1 (2%)		
Stomach, forestomach	(49)	(20)	(50)
Acanthosis	10 (20%)	9 (45%)	12 (24%)
Inflammation, acute, focal	2 (4%)	1 (5%)	2 (4%)
Inflammation, chronic	1 (2%)		3 (6%)
Ulcer	2 (4%)	5 (25%)	3 (6%)
Stomach, glandular	(49)	(15)	(50)
Inflammation, chronic	1 (2%)		
Pigmentation	2 (4%)		
Cardiovascular System			
Heart	(50)	(12)	(50)
Hyperplasia, lymphoid	1 (2%)		
Artery, inflammation, chronic			1 (2%)
Coronary artery, inflammation, acute	1 (2%)		
Myocardium, inflammation, acute			1 (2%)
Pericardium, inflammation, suppurative			1 (2%)
Endocrine System			
Adrenal gland	(49)	(14)	(50)
Capsule, inflammation, suppurative		1 (7%)	
Capsule, inflammation, membranous	1 (2%)		
Adrenal gland, cortex	(49)	(13)	(50)
Congestion			1 (2%)
Hematopoietic cell proliferation	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
Capsule, inflammation		1 (8%)	
Parathyroid gland	(30)	(9)	(30)
Cyst	1 (3%)		
Pituitary gland	(46)	(13)	(44)
Pars distalis, hyperplasia	3 (7%)		1 (2%)
Pars distalis, hyperplasia, focal	2 (4%)		1 (2%)
Thyroid gland	(50)	(13)	(50)
Inflammation, chronic	2 (4%)		
Follicular cell, hyperplasia	2 (4%)	1 (8%)	4 (8%)
General Body System			
Tissue NOS	(1)	(1)	
Necrosis	1 (100%)		

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Genital System			
Ovary	(48)	(25)	(44)
Cyst	14 (29%)	8 (32%)	6 (14%)
Cyst, multiple	1 (2%)		
Hyperplasia, cystic, papillary	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
Inflammation, chronic			1 (2%)
Inflammation, suppurative	6 (13%)	6 (24%)	5 (11%)
Bilateral, inflammation, suppurative	2 (4%)		2 (5%)
Follicle, cyst	5 (10%)		1 (2%)
Periovarian tissue, inflammation, chronic	2 (4%)	1 (4%)	3 (7%)
Periovarian tissue, inflammation, suppurative			1 (2%)
Periovarian tissue, necrosis			1 (2%)
Oviduct	(2)	(6)	(9)
Inflammation, suppurative		1 (17%)	1 (11%)
Uterus	(50)	(26)	(49)
Hydrometra		1 (4%)	3 (6%)
Endometrium, hemorrhage		1 (4%)	
Endometrium, hyperplasia, cystic	30 (60%)	15 (58%)	23 (47%)
Endometrium, inflammation, suppurative	8 (16%)	1 (4%)	9 (18%)
Muscularis, inflammation, suppurative			1 (2%)
Hematopoietic System			
Bone marrow	(49)	(12)	(50)
Hyperplasia	1 (2%)		
Myelofibrosis	1 (2%)		4 (8%)
Myeloid cell, hyperplasia	1 (2%)	1 (8%)	3 (6%)
Lymph node	(47)	(27)	(49)
Lumbar, hematopoietic cell proliferation		1 (4%)	
Lumbar, hyperplasia, lymphoid		1 (4%)	
Lumbar, hyperplasia, plasma cell	2 (4%)		2 (4%)
Mandibular, hyperplasia, plasma cell		1 (4%)	2 (4%)
Mediastinal, hematopoietic cell proliferation		1 (4%)	
Mediastinal, hyperplasia, plasma cell	2 (4%)	1 (4%)	1 (2%)
Mediastinal, inflammation, acute	2 (4%)		
Pancreatic, hyperplasia, lymphoid	1 (2%)		
Pancreatic, pigmentation			5 (10%)
Renal, hyperplasia, lymphoid	1 (2%)	2 (7%)	1 (2%)
Renal, hyperplasia, plasma cell	2 (4%)	2 (7%)	1 (2%)
Lymph node, mesenteric	(46)	(23)	(46)
Congestion			2 (4%)
Hyperplasia, lymphoid			1 (2%)
Hyperplasia, plasma cell	1 (2%)	1 (4%)	
Inflammation, suppurative		1 (4%)	
Pigmentation	1 (2%)	4 (17%)	8 (17%)
Serosa, inflammation, membranous	1 (2%)		
Spleen	(50)	(24)	(50)
Hematopoietic cell proliferation	8 (16%)	9 (38%)	13 (26%)
Hyperplasia, lymphoid	4 (8%)	1 (4%)	3 (6%)
Metaplasia			1 (2%)
Pigmentation	1 (2%)		1 (2%)
Subcapsular, inflammation, acute	1 (2%)		
Thymus	(33)	(10)	(39)
Inflammation		1 (10%)	
Thymocyte, necrosis		1 (10%)	

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Integumentary System			
Mammary gland	(36)	(10)	(37)
Hyperplasia		1 (10%)	
Hyperplasia, cystic	3 (8%)		
Hyperplasia, lymphoid	1 (3%)		
Inflammation, chronic	1 (3%)		
Musculoskeletal System			
Bone	(50)	(12)	(50)
Joint, tarsal, hyperostosis			1 (2%)
Skeletal muscle	(3)	(1)	
Abdominal, inflammation, suppurative		1 (100%)	
Nervous System			
Brain	(50)	(12)	(50)
Cerebellum, abscess, multiple			1 (2%)
Meninges, inflammation, acute			1 (2%)
Meninges, inflammation, chronic	1 (2%)		1 (2%)
Respiratory System			
Lung	(50)	(20)	(50)
Congestion		1 (5%)	1 (2%)
Edema		1 (5%)	
Hyperplasia, lymphoid	1 (2%)		
Inflammation, acute, focal		1 (5%)	
Inflammation, chronic	1 (2%)	1 (5%)	1 (2%)
Alveolar epithelium, hyperplasia, focal	1 (2%)	1 (5%)	
Alveolus, hyperplasia, macrophage	1 (2%)		
Lymphatic, perivascular, inflammation, acute	1 (2%)		
Mediastinum, inflammation, suppurative			1 (2%)
Peribronchiolar, inflammation, chronic	2 (4%)		
Peribronchiolar, perivascular, inflammation, chronic	2 (4%)		
Perivascular, inflammation, acute	1 (2%)		
Perivascular, inflammation, chronic	1 (2%)		
Pleura, inflammation, chronic			1 (2%)
Pleura, inflammation, suppurative		1 (5%)	1 (2%)
Nose	(45)	(11)	(46)
Inflammation, suppurative		2 (18%)	1 (2%)
Mucosa, inflammation, chronic		1 (9%)	2 (4%)
Mucosa, inflammation, suppurative			5 (11%)
Nasolacrimal duct, inflammation, chronic			1 (2%)
Turbinate, inflammation, chronic		1 (9%)	1 (2%)
Turbinate, inflammation, suppurative	1 (9%)	1 (2%)	
Special Senses System			
None			

TABLE D4
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of 2,4-Diaminophenol Dihydrochloride (continued)

	Vehicle Control	19 mg/kg	38 mg/kg
Urinary System			
Kidney	(50)	(39)	(50)
Amyloid deposition			1 (2%)
Hyperplasia, lymphoid	1 (2%)		
Inflammation, acute	1 (2%)		1 (2%)
Inflammation, chronic	27 (54%)	10 (26%)	35 (70%)
Metaplasia		3 (8%)	1 (2%)
Necrosis	2 (4%)	5 (13%)	8 (16%)
Cortex, abscess, single			1 (2%)
Fat, inflammation, chronic		1 (3%)	
Papilla, mineralization			3 (6%)
Papilla, necrosis	1 (2%)		
Renal tubule, dilatation		1 (3%)	1 (2%)
Renal tubule, hyperplasia			1 (2%)
Renal tubule, mineralization	1 (2%)		1 (2%)
Renal tubule, necrosis			1 (2%)
Renal tubule, pigmentation		4 (10%)	50 (100%)
Renal tubule, regeneration	18 (36%)	24 (62%)	42 (84%)
Urinary bladder	(47)	(10)	(47)
Artery, serosa, inflammation, chronic			1 (2%)
Serosa, inflammation, suppurative	1 (2%)		
Submucosa, inflammation, chronic	14 (30%)	1 (10%)	15 (32%)
Submucosa, ulcer, chronic	1 (2%)		

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). 2,4-Diaminophenol dihydrochloride was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strain (TA98, TA100, TA1535, or TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C prior to the addition of soft agar supplemented with *l*-histidine and *d*-biotin, and subsequent plating on minimal glucose agar plates. Incubation continued for an additional 48 hours.

Each trial consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of test chemical. The high dose was limited by toxicity. Tests were repeated for all negative assays, and all positive assays were retested under the conditions that elicited the positive response.

A positive response in this assay is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which was not dose-related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A response was considered negative when no increase in revertant colonies was observed after chemical treatment.

MOUSE LYMPHOMA PROTOCOL

The experimental protocol is presented in detail by McGregor *et al.* (1987) and follows the basic format of Clive *et al.* (1979). 2,4-Diaminophenol dihydrochloride was supplied as a coded aliquot by Radian Corporation (Austin, TX). The highest dose of the study compound was determined by toxicity. Mouse lymphoma L5178Y cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM *l*-glutamine, 110 μg/mL sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (TFT) resistant cells, subcultures were exposed once to medium containing THMG (thymidine, hypoxanthine, methotrexate, glycine) for 1 day, to THG for 1 day, and to normal medium for 3 to 5 days. For cloning, horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6 x 10^6 cells in 10 mL of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with study chemical continued for 4 hours, at which time the medium plus chemical was removed and the cells were resuspended in 20 mL of fresh medium and incubated for an additional 2 days to allow expression of the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3 x 10^6 cells were plated in medium and soft agar supplemented with trifluorothimidine for selection of TFT-resistant cells ($TK^{-/-}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO_2 for 10 to 12 days. All data were evaluated statistically for both trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for a chemical to be considered "positive," i.e., capable of inducing TFT-resistance; a single significant response led to a "questionable" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr *et al.* (1985). This assay was initially performed without S9; because a clearly positive response was obtained, the experiment was not repeated with induced S9.

Chinese Hamster Ovary Cell Cytogenetics Assays

Testing was performed as reported by Galloway *et al.* (1985, 1987) and is briefly described as follows. 2,4-Diaminophenol dihydrochloride was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) and chromosomal aberrations (Abs) both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, *l*-glutamine (2mM), and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing the study chemical was removed and replaced with fresh medium containing BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the study chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no study chemical, and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

In the Abs test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 12 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 12 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the the same manner as for the treatment without S9.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were scored for frequency of SCE per cell from each dose; 100 first-division metaphase cells were scored at each dose for the Abs test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on the slopes of the dose-response curves and on the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Abs data are presented as percentages of cells with aberrations. For Abs data, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P \leq 0.05$) difference for one dose point was considered weak evidence for a positive response (+w); significant differences for two or more doses indicated the trial was positive (+) (Galloway *et al.*, 1987).

DROSOPHILA Protocol

The assay for induction of mutations was performed as described in Zimmering *et al.* (1985). 2,4-Diaminophenol dihydrochloride was supplied as a coded aliquot from Radian Corporation (Austin, TX). Initially, the study chemical was assayed in the sex-linked recessive lethal (SLRL) test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. If no clearly positive response was obtained, the chemical was retested by injection into adult males. Because no positive response was obtained by either route of administration, the chemical was not assayed for induction of reciprocal translocations.

To administer a chemical by injection, a glass Pasteur pipette was drawn out in a flame to a microfine filament and the tip was broken off to allow delivery of the test solution. Injection was performed either manually, by attaching a rubber bulb to the other end of the pipette and forcing through sufficient solution (0.2 to 0.3 μL) to slightly distend the abdomen of the fly, or by attaching the pipette to a microinjector which automatically delivered a calibrated volume. Flies were anesthetized with ether and immobilized on a strip of double stick tape; the chemical was injected into the thorax under the wing with the aid of a dissecting microscope.

Toxicity tests were performed to set concentrations of study chemical at a level which would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. For the SLRL test, oral exposure was achieved by allowing Canton-S males (10 to 20 flies/vial) to feed for 72 hours on a solution of the study chemical in 5% sucrose. In the injection experiments, 24- to 72-hour-old Canton-S males were treated with a solution of the chemical dissolved in 0.7% saline and were allowed to recover for 24 hours. Exposed males were mated to three *Basc* females for 3 days and were given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days; sample sperm from successive matings were treated at successively earlier post-meiotic stages. F_1 heterozygous females were allowed to mate with their siblings and were then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event, and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution). If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as occurring in vials containing no wild-type males after 17 days; these were retested. The two experiments, utilizing feed and injection, resulted in the testing of more than 5,000 treated and 5,000 control chromosomes.

Recessive lethal data were analyzed by the normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered to be positive if the P value was less than 0.01 and the mutation frequency in the tested group was greater that 0.10%, or if the P value was less than 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if (a) the P value was between 0.01 and 0.05 but the frequency in the treatment group was between 0.10% and 0.15%, or (b) the P value was between 0.05 and 0.10 but the frequency in the treatment group was greater than 0.10%. A result was considered to be negative if the P value was greater than 0.10 or if the frequency in the treatment group was less than 0.10%.

RESULTS

2,4-Diaminophenol dihydrochloride was mutagenic in *Salmonella typhimurium* strain TA98 when tested in a preincubation protocol with Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9; it was not mutagenic in the absence of S9 activation, nor was it active in the other three tester strains (TA100, TA1535, and TA1537) employed in this test (Table E1; Haworth *et al.*, 1983). The high toxicity of the chemical limited the concentrations tested to a maximum of 10 μg/plate. In the mouse lymphoma assay for induction of trifluorothymidine resistance in L5178Y cells, 2,4-diaminophenol dihydrochloride gave positive results at concentrations of 2, 3, and 4 μg/mL without S9 activation; it was

not tested with S9 (Table E2; McGregor *et al.*, 1987). In this test, Trial 1 was judged inconclusive because the highest nonlethal dose tested yielded a slight, but not significant, increase in resistant colonies and the relative total growth indicated that higher concentrations could have been tested. Trials 2 and 3 were judged positive. The 2 μg/mL dose in Trial 3 was the only concentration that produced a positive response in the absence of extreme toxicity. 2,4-Diaminophenol dihydrochloride was negative in cytogenetic tests for induction of SCE and Abs in CHO cells, with or without Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Tables E3 and E4; Galloway *et al.*, 1987). The toxicity of 2,4-diaminophenol dihydrochloride limited the doses in the SCE test to 0.9 μg/mL without S9 and 9.0 μg/mL with S9; in the Abs test, 2.7 μg/mL 2,4-diaminophenol dihydrochloride was tested without S9 and 9.0 μg/mL was the highest dose tested in the presence of S9. 2,4-Diaminophenol dihydrochloride was tested for induction of sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* (Table E5; Zimmering *et al.*, 1985). The chemical was administered in feed (3,500 ppm) and by abdominal injection (125 ppm). The results of the feeding experiment were judged to be equivocal (P=0.045, with a 0.13% frequency of recessive lethal mutations) and the injection experiment was negative (P=0.935); overall, 2,4-diaminophenol dihydrochloride was concluded to be equivocal for induction of sex-linked recessive lethal mutations in *D. melanogaster*.

TABLE E1
Mutagenicity of 2,4-Diaminophenol Dihydrochloride in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/Plate[b]		
		-S9	+10% S9 (hamster)	+10% S9 (rat)
TA100	0.00	116 ± 7.2	107 ± 11.6	111 ± 6.4
	0.10	106 ± 5.1	94 ± 6.9	124 ± 0.9
	0.33	90 ± 3.3	99 ± 11.1	129 ± 4.5
	1.00	111 ± 5.2	111 ± 11.3	128 ± 3.7
	3.30	95 ± 6.2	110 ± 7.0	109 ± 12.1
	10.00	79 ± 3.8[c]	117 ± 11.4	117 ± 13.3
Trial summary		Negative	Negative	Negative
Positive control[d]		2,181 ± 19.4	2,118 ± 75.9	1,172 ± 163.2
TA1535	0.00	13 ± 1.7	8 ± 2.5	8 ± 0.9
	0.10	17 ± 1.2	11 ± 2.0	8 ± 2.3
	0.33	15 ± 3.2	9 ± 0.7	9 ± 0.6
	1.00	15 ± 1.3	12 ± 1.2	9 ± 0.7
	3.30	7 ± 0.3	10 ± 1.2	9 ± 0.9
	10.00	4 ± 2.3[c]	11 ± 1.0	7 ± 1.7
Trial summary		Negative	Negative	Negative
Positive control		1,102 ± 30.3	193 ± 13.7	121 ± 8.9
TA1537	0.0	5 ± 0.6	6 ± 1.5	6 ± 1.7
	0.10	6 ± 0.6	10 ± 1.5	8 ± 0.9
	0.33	6 ± 0.9	6 ± 1.2	5 ± 1.9
	1.00	9 ± 1.9	6 ± 1.2	5 ± 0.6
	3.30	9 ± 1.8	11 ± 0.9	5 ± 1.5
	10.00	4 ± 1.2	7 ± 1.2	6 ± 1.9
Trial summary		Negative	Negative	Negative
Positive control		645 ± 73.5	312 ± 11.9	58 ± 6.4

		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA98	0.00	15 ± 1.2	15 ± 3.5	20 ± 1.2	13 ± 1.2	15 ± 1.7	14 ± 2.7
	0.10	14 ± 1.2	12 ± 4.2	20 ± 4.0	21 ± 3.4	20 ± 1.5	14 ± 2.5
	0.33	15 ± 0.6	18 ± 2.5	24 ± 6.5	28 ± 5.2	19 ± 1.9	21 ± 4.0
	1.00	16 ± 4.1	17 ± 3.4	27 ± 1.5	35 ± 1.9	16 ± 3.5	31 ± 1.7
	3.30	3 ± 2.4[c]	–[e]	68 ± 7.3	78 ± 12.6	33 ± 3.8	42 ± 8.1
	10.00	3 ± 0.3[c]	–[e]	27 ± 2.2	57 ± 17.7	59 ± 4.5	83 ± 13.9
Trial summary		Negative	Negative	Equivocal	Positive	Positive	Positive
Positive control		1,571 ± 28.5	1,774 ± 100.0	2,076 ± 134.0	1,387 ± 6.9	1,328 ± 60.5	1,013 ± 25.2

[a] Study performed at EG&G Mason Research Corp. The detailed protocol and these data are presented in Haworth *et al.* (1983). Cells and 2,4-diaminophenol dihydrochloride or solvent (distilled water) 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. 0 μg/plate dose is the solvent control.

[b] Revertants are presented as mean ± standard error from three plates.

[c] Slight toxicity

[d] 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537.

[e] Toxic

TABLE E2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by 2,4-Diaminophenol Dihydrochloride[a]

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction[c]
-S9						
Trial 1						
Distilled water						
		66	84	144	73	
		69	77	140	67	
		80	140	129	54	64
Ethylmethanesulfonate						
		53	41	513	324	
	250.00	45	36	500	373	348*
2,4-Diaminophenol dihydrochloride						
	0.25	56	64	95	56	
		73	89	107	49	53
	0.50	69	86	158	76	
		76	61	153	68	72
	1.00	63	64	125	66	
		72	78	122	57	62
	2.00	70	50	176	84	
		77	52	157	68	76
	4.00	Lethal				
		Lethal				
Trial 2						
Distilled water						
		87	105	85	33	
		87	64	77	30	
		117	139	109	31	
		82	91	72	29	31
Ethylmethanesulfonate						
		66	49	553	280	
	250.00	59	53	582	328	304*
2,4-Diaminophenol dihydrochloride						
	0.25	79	96	89	38	
		73	86	100	46	42
	0.50	102	99	106	35	
		80	85	101	42	38
	1.00	80	101	84	35	
		91	96	121	44	40
	2.00	87	56	95	36	
		75	49	105	47	42
	4.00	39	4	180	153	
		65	6	293	151	152*
	8.00	Lethal				
		Lethal				

TABLE E2
Induction of Trifluorothymidine Resistance in Mouse L5178Y Lymphoma Cells by 2,4-Diaminophenol Dihydrochloride (continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9						
Trial 3						
Distilled water						
		88	116	137	52	
		83	76	150	60	
		88	98	154	58	
		97	110	185	64	59
Ethylmethanesulfonate						
		62	61	581	313	
	250.0	79	67	606	257	285*
2,4-Diaminophenol dihydrochloride						
	0.5	64	92	141	73	
		83	93	149	60	
		86	98	174	68	67
	1.0	68	91	179	88	
		76	70	166	73	
		75	75	157	70	77
	2.0	83	53	271	109	
		70	45	224	107	
		66	56	221	112	109*
	3.0	47	8	644	457	
		39	7	628	537	
		42	7	542	427	473*
	4.0	Lethal				
		Lethal				
		Lethal				

* Significant positive response ($P \leq 0.05$)
[a] Study performed at Inveresk Research International. These data and the experimental protocol are presented in detail by McGregor *et al.* (1987); protocol follows the basic format of Clive *et al.* (1979). The highest dose of 2,4-diaminophenol dihydrochloride was limited by toxicity. All doses are tested more than once; the average of the three tests is presented in the table. Cells (6×10^5/mL) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
[b] Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF/1 x 10^6 cells treated).
[c] Mean from three replicate plates of approximately 10^6 cells each

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by 2,4-Diaminophenol Dihydrochloride[a]

Compound	Dose (μg/mL)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosomes	SCEs/ Cell	Hrs in BrdU	Relative SCEs/Chromosome (%)[b]
-S9[c]								
Trial 1								
Summary: Negative								
Distilled water		50	1,049	490	0.46	9.8	26.0	
Mitomycin-C	0.005	25	524	600	1.14	24.0	26.0	145.13
2,4-Diaminophenol dihydrochloride								
	0.090	50	1,047	431	0.41	8.6	26.0	-11.87
	0.270	50	1,049	359	0.34	7.2	26.0	-26.74
	0.900	50	1,049	427	0.40	8.5	26.0	-12.86
								P=0.997[d]
+S9[e]								
Trial 1								
Summary: Negative								
Distilled water		50	1,048	431	0.41	8.6	26.0	
Mitomycin-C	1.0	25	522	586	1.12	23.4	26.0	172.97
2,4-Diaminophenol dihydrochloride								
	0.9	50	1,046	430	0.41	8.6	26.0	-0.04
	2.7	50	1,050	435	0.41	8.7	26.0	0.74
	9.0	50	1,047	493	0.47	9.9	26.0	14.49
								P=0.021

[a] Study performed at Columbia University. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol and these data are presented by Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with 2,4-diaminophenol dihydrochloride or solvent (distilled water) as described in [c] and [d] 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] Percent increase in SCEs/chromosome of culture exposed to 2,4-diaminophenol dihydrochloride relative to those of culture exposed to solvent.

[c] In the absence of S9, cells were incubated with 2,4-diaminophenol dihydrochloride 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 hours.

[d] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

[e] In the presence of S9, cells were incubated with 2,4-diaminophenol dihydrochloride or solvent for 2 hours at 37° C. The cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with Colcemid present for the final 2 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE E4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by 2,4-Diaminophenol Dihydrochloride[a]

-S9[b]					+S9[c]				
Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (μg/mL)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Trial 1 – Harvest time: 14.0 hours Summary: Negative					**Trial 1** – Harvest time: 14.0 hours Summary: Negative				
Distilled water					Distilled water				
	100	4	0.04	3.0		100	4	0.04	4.0
Mitomycin-C					Cyclophosphamide				
0.15	100	30	0.30	25.0	15.0	100	29	0.29	26.0
2,4-Diaminophenol dihydrochloride					2,4-Diaminophenol dihydrochloride				
0.27	100	4	0.04	4.0	0.9	100	4	0.04	4.0
0.90	100	7	0.07	7.0	2.7	100	7	0.07	7.0
2.70	100	7	0.07	6.0	9.0	100	6	0.06	6.0
				P=0.107[d]					P=0.187

[a] Study performed at Columbia University. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations and these data are found in Galloway *et al.* (1987). Briefly, Chinese hamster ovary cells were incubated with 2,4-diaminophenol dihydrochloride or solvent (distilled water) as described in [b] and [c]. Cells were arrested in first metaphase by addition of Colcemid and harvested by mitotic shake off, fixed, and stained in 6% Giemsa.

[b] In the absence of S9, cells were incubated with 2,4-diaminophenol dihydrochloride or solvent for 12 hours at 37° C. Cells were then washed and fresh medium containing Colcemid was added for an additional 2 hours followed by harvest.

[c] In the presence of S9, cells were incubated with 2,4-diaminophenol dihydrochloride or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 12 hours. Colcemid was added for the last 2 hours of incubation before harvest. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

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

TABLE E5
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by 2,4-Diaminophenol Dihydrochloride[a]

Route of Exposure	Dose (ppm)	Incidence of Deaths (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested			
				Mating 1	Mating 2	Mating 3	Total[b]
Feeding[c]	3,500	69	13	3/3,054	4/1,668	1/1,513	8/6,235 (0.13%)
	0			1/2,338	2/2,327	0/2,290	3/6,955 (0.04%)
Injection	125	29	32	3/3,148	0/2,255	0/2,548	3/7,951 (0.04%)
	0			2/2,308	1/2,240	4/2,270	7/6,818 (0.10%)

[a] Study performed at Bowling Green State University. A detailed protocol of the sex-linked recessive lethal assay and these data are presented in Zimmering *et al.* (1985). In the feed exposure experiments, 24-hour-old Canton-S males were allowed to feed for 3 days on a solution of the 2,4-diaminophenol dihydrochloride dissolved in 5% sucrose. In the injection experiments, 24-hour-old Canton-S males were treated with a solution of the chemical dissolved in 0.7% saline and allowed to recover for 24 hours. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days; sample sperm from successive matings were treated as spermatozoa (mating 1), spermatids (mating 2), and spermatocytes (mating 3). F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters; clusters were removed in the injection experiment. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested.

[b] Combined total number of lethal mutations/number of X chromosomes tested for three mating trials.

[c] Results of the feeding experiment were considered to be equivocal by normal approximation to the binomial test (Margolin *et al.*, 1983).

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

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Studies of 2,4-Diaminophenol Dihydrochloride[a]

Organ	Vehicle Control	6 mg/kg	13 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Male						
n	5	5	5	5	5	5
Necropsy body wt	210 ± 4	216 ± 6	206 ± 8	209 ± 3	211 ± 5	192 ± 8
Brain						
Absolute	1.80 ± 0.04	1.80 ± 0.04	1.77 ± 0.05	1.78 ± 0.04	1.69 ± 0.14	1.34 ± 0.33
Relative	8.57 ± 0.10	8.32 ± 0.10	8.63 ± 0.19	8.55 ± 0.17	8.02 ± 0.66	7.01 ± 1.66
Heart						
Absolute	0.76 ± 0.03	0.77 ± 0.01	0.70 ± 0.03	0.68 ± 0.02	0.71 ± 0.03	0.67 ± 0.02*
Relative	3.63 ± 0.11	3.55 ± 0.05	3.43 ± 0.09	3.27 ± 0.06*	3.38 ± 0.08	3.51 ± 0.13
R. Kidney						
Absolute	0.93 ± 0.02	0.94 ± 0.03	0.92 ± 0.05	0.94 ± 0.02	1.04 ± 0.04	0.86 ± 0.08
Relative	4.41 ± 0.10	4.33 ± 0.06	4.48 ± 0.12	4.50 ± 0.07	4.92 ± 0.13	4.51 ± 0.45
Liver						
Absolute	9.99 ± 0.33	11.41 ± 0.68	10.43 ± 0.82	9.50 ± 0.52	10.13 ± 0.47	9.34 ± 0.72
Relative	47.6 ± 1.1	52.6 ± 1.8	50.5 ± 2.3	45.5 ± 2.3	48.0 ± 1.5	48.4 ± 2.4
Lungs						
Absolute	1.53 ± 0.20[b]	1.23 ± 0.07	1.49 ± 0.10	1.65 ± 0.08	1.54 ± 0.08	0.91 ± 0.14**
Relative	7.35 ± 0.90[b]	5.68 ± 0.37	7.28 ± 0.44	7.94 ± 0.46	7.30 ± 0.33	4.82 ± 0.76*
R. Testis						
Absolute	1.36 ± 0.15	1.24 ± 0.03	1.18 ± 0.02	1.32 ± 0.12	1.22 ± 0.03	1.04 ± 0.11
Relative	6.52 ± 0.81	5.74 ± 0.09	5.74 ± 0.17	6.33 ± 0.60	5.81 ± 0.04	5.49 ± 0.63
Thymus						
Absolute	0.45 ± 0.03[b]	0.46 ± 0.03	0.46 ± 0.06	0.40 ± 0.06	0.46 ± 0.03	0.51 ± 0.11
Relative	2.15 ± 0.13[b]	2.14 ± 0.14	2.22 ± 0.23	1.93 ± 0.30	2.21 ± 0.16	2.63 ± 0.48

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

Organ	Vehicle Control	6 mg/kg	13 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg
Female						
n	5	5	5	5	5	5
Necropsy body wt	145 ± 4	142 ± 5	139 ± 2	138 ± 2	144 ± 4	134 ± 3*
Brain						
Absolute	1.67 ± 0.02	1.61 ± 0.03	1.66 ± 0.01	1.67 ± 0.04	1.72 ± 0.02	1.71 ± 0.03
Relative	11.5 ± 0.3	11.4 ± 0.3	12.0 ± 0.2	12.1 ± 0.3	12.0 ± 0.4	12.8 ± 0.1**
Heart						
Absolute	0.57 ± 0.02	0.53 ± 0.03	0.52 ± 0.01	0.53 ± 0.02	0.52 ± 0.01	0.52 ± 0.02
Relative	3.92 ± 0.11	3.71 ± 0.14	3.73 ± 0.10	3.82 ± 0.09	3.64 ± 0.15	3.88 ± 0.08
R. Kidney						
Absolute	0.68 ± 0.02	0.64 ± 0.03	0.65 ± 0.02	0.67 ± 0.02	0.72 ± 0.04	0.61 ± 0.03
Relative	4.71 ± 0.05	4.52 ± 0.09	4.66 ± 0.17	4.83 ± 0.13	5.01 ± 0.18	4.55 ± 0.12
Liver						
Absolute	6.49 ± 0.28	7.24 ± 0.58	6.08 ± 0.22	5.84 ± 0.24	6.50 ± 0.42	6.22 ± 1.15[c]
Relative	44.7 ± 0.8	50.7 ± 2.8	43.9 ± 1.7	42.3 ± 1.4	45.2 ± 2.4	47.1 ± 7.3[c]
Lungs						
Absolute	1.05 ± 0.06	1.01 ± 0.07	1.12 ± 0.06	1.21 ± 0.13	1.09 ± 0.05	1.16 ± 0.16
Relative	7.23 ± 0.27	7.06 ± 0.38	8.08 ± 0.40	8.78 ± 0.94	7.67 ± 0.48	8.64 ± 1.10
Thymus						
Absolute	0.42 ± 0.02	0.36 ± 0.02	0.24 ± 0.07	0.35 ± 0.04	0.29 ± 0.06	0.35 ± 0.04
Relative	2.91 ± 0.11	2.50 ± 0.12	1.73 ± 0.45	2.56 ± 0.33	2.07 ± 0.48	2.57 ± 0.30

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=4
[c] n=3

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Studies of 2,4-Diaminophenol Dihydrochloride[a]

Organ	Vehicle Control	12 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg
Male						
n	10	10	10	10	6	1
Necropsy body wt	368 ± 6	358 ± 5	359 ± 6	331 ± 5**	296 ± 8**	–[b]
Brain						
Absolute	1.99 ± 0.02	2.02 ± 0.02	1.98 ± 0.04	1.98 ± 0.03	1.92 ± 0.03	–
Relative	5.44 ± 0.10	5.65 ± 0.11	5.51 ± 0.04	5.98 ± 0.10**	6.51 ± 0.11**	–
Heart						
Absolute	1.10 ± 0.02	1.08 ± 0.04	1.01 ± 0.02*	0.96 ± 0.03**	0.93 ± 0.03**	–
Relative	2.99 ± 0.04	3.01 ± 0.08	2.81 ± 0.05	2.90 ± 0.05	3.16 ± 0.09	–
R. Kidney						
Absolute	1.39 ± 0.03	1.50 ± 0.05	1.49 ± 0.04	1.48 ± 0.08[c]	1.52 ± 0.06	–
Relative	3.78 ± 0.05	4.20 ± 0.15*	4.16 ± 0.07*	4.47 ± 0.21**[c]	5.13 ± 0.07**	–
Liver						
Absolute	16.41 ± 0.47	16.34 ± 0.49[c]	15.81 ± 0.34	14.90 ± 0.41*[c]	13.30 ± 0.61**	–
Relative	44.6 ± 1.1	46.1 ± 1.3[c]	44.0 ± 0.6	44.9 ± 0.8[c]	44.9 ± 1.0	–
Lungs						
Absolute	2.05 ± 0.11	1.78 ± 0.08*[c]	1.84 ± 0.08*	1.77 ± 0.06*	1.74 ± 0.08*[d]	–
Relative	5.56 ± 0.25	4.97 ± 0.22[c]	5.12 ± 0.23	5.35 ± 0.20	5.79 ± 0.13[d]	–
R. Testis						
Absolute	1.54 ± 0.02[c]	1.50 ± 0.01	1.53 ± 0.03	1.48 ± 0.02[c]	1.49 ± 0.03	–
Relative	4.16 ± 0.05[c]	4.19 ± 0.07	4.26 ± 0.06	4.48 ± 0.05**[c]	5.06 ± 0.10**	–
Thymus						
Absolute	0.30 ± 0.01	0.32 ± 0.02	0.25 ± 0.01**	0.24 ± 0.01**	0.17 ± 0.02**	–
Relative	0.82 ± 0.04	0.89 ± 0.04	0.70 ± 0.02*	0.73 ± 0.03*	0.57 ± 0.04**	–

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

Organ	Vehicle Control	12 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg
Female						
n	10	10	10	10	9	0
Necropsy body wt	199 ± 5	205 ± 5	200 ± 2	201 ± 4	195 ± 3	–[b]
Brain						
Absolute	1.85 ± 0.03	1.82 ± 0.02	1.83 ± 0.03	1.79 ± 0.04	1.77 ± 0.02	–
Relative	9.36 ± 0.26	9.14 ± 0.18	9.19 ± 0.13	8.93 ± 0.25	9.10 ± 0.14	–
Heart						
Absolute	0.68 ± 0.01	0.68 ± 0.02	0.65 ± 0.01	0.69 ± 0.04	0.67 ± 0.02	–
Relative	3.45 ± 0.09	3.35 ± 0.07	3.24 ± 0.06	3.44 ± 0.21	3.44 ± 0.08	–
R. Kidney						
Absolute	0.77 ± 0.01	0.79 ± 0.03	0.76 ± 0.02	0.84 ± 0.03*	0.97 ± 0.02**	–
Relative	3.88 ± 0.07	3.84 ± 0.08	3.80 ± 0.09	4.17 ± 0.09*	4.95 ± 0.07**	–
Liver						
Absolute	6.83 ± 0.23	7.32 ± 0.15	7.13 ± 0.14	7.68 ± 0.26**	8.58 ± 0.11**	–
Relative	34.4 ± 1.1	35.8 ± 0.4	35.7 ± 0.8	38.1 ± 0.8**	44.1 ± 0.6**	–
Lungs						
Absolute	1.27 ± 0.08	1.30 ± 0.06	1.13 ± 0.04	1.20 ± 0.06	1.21 ± 0.05	–
Relative	6.41 ± 0.40	6.37 ± 0.30	5.68 ± 0.18	5.95 ± 0.31	6.18 ± 0.23	–
Thymus						
Absolute	0.28 ± 0.03	0.25 ± 0.01	0.25 ± 0.01	0.24 ± 0.01	0.22 ± 0.01**[e]	–
Relative	1.40 ± 0.08	1.22 ± 0.05	1.25 ± 0.05	1.21 ± 0.08	1.13 ± 0.07*[e]	–

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] No data were calculated due to high mortality.
[c] n=9
[d] n=5
[e] n=8

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride[a]

Organ	Vehicle Control	12.5 mg/kg	25 mg/kg
Male			
n	9	10	10
Necropsy body wt	482 ± 11	478 ± 10	448 ± 10*
Brain			
Absolute	2.17 ± 0.05	2.05 ± 0.05	2.10 ± 0.05
Relative	4.51 ± 0.13	4.29 ± 0.09	4.72 ± 0.17
R. Kidney			
Absolute	1.46 ± 0.06	1.40 ± 0.04	1.47 ± 0.06[b]
Relative	3.03 ± 0.14	2.94 ± 0.07	3.31 ± 0.15[b]
Liver			
Absolute	15.30 ± 0.84	15.56 ± 0.65	13.97 ± 0.51
Relative	31.7 ± 1.3	32.5 ± 1.0	31.2 ± 1.0
Female			
n	10	10	10
Necropsy body wt	301 ± 8	304 ± 7	280 ± 5*
Brain			
Absolute	1.86 ± 0.02	1.86 ± 0.01	1.83 ± 0.01
Relative	6.21 ± 0.12	6.16 ± 0.13	6.53 ± 0.13*
R. Kidney			
Absolute	0.77 ± 0.02	0.81 ± 0.02	0.78 ± 0.02
Relative	2.58 ± 0.05	2.66 ± 0.07	2.78 ± 0.08*
Liver			
Absolute	7.62 ± 0.29	8.04 ± 0.22	8.06 ± 0.17
Relative	25.3 ± 0.6	26.5 ± 0.7	28.8 ± 0.5**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Studies of 2,4-Diaminophenol Dihydrochloride[a]

Organ	Vehicle Control	13 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg
Male						
n	5	5	5	5	0	0
Necropsy body wt[b]	25.4 ± 0.6	24.9 ± 0.6	24.9 ± 0.6	24.8 ± 0.6	20.3 ± 0.7**	21.5 ± 0.3**
Brain						
Absolute	0.45 ± 0.01	0.44 ± 0.00	0.46 ± 0.01	0.45 ± 0.02	–[c]	–
Relative	17.6 ± 0.2	17.7 ± 0.4	18.6 ± 0.8	18.1 ± 0.9	–	–
Heart[d]						
Absolute	110.24 ± 4.92	121.34 ± 4.34	120.70 ± 3.16	115.90 ± 3.85	–	–
Relative	4.34 ± 0.20	4.87 ± 0.12	4.85 ± 0.15	4.67 ± 0.10	–	–
R. Kidney						
Absolute	0.23 ± 0.01	0.24 ± 0.01	0.22 ± 0.01	0.24 ± 0.00	–	–
Relative	9.08 ± 0.40	9.48 ± 0.24	8.91 ± 0.12	9.70 ± 0.30	–	–
Liver						
Absolute	1.34 ± 0.03	1.25 ± 0.04	1.26 ± 0.04	1.34 ± 0.04	–	–
Relative	52.9 ± 1.9	50.0 ± 1.0	50.4 ± 1.2	53.9 ± 1.0	–	–
Lungs						
Absolute	0.19 ± 0.01	0.19 ± 0.01	0.20 ± 0.01	0.21 ± 0.01	–	–
Relative	7.44 ± 0.44	7.47 ± 0.31	8.18 ± 0.47	8.31 ± 0.40	–	–
R. Testis[d]						
Absolute	101.16 ± 1.73	103.98 ± 3.73	97.40 ± 4.00	102.86 ± 3.16	–	–
Relative	3.98 ± 0.10	4.18 ± 0.16	3.90 ± 0.08	4.16 ± 0.18	–	–
Thymus[d]						
Absolute	41.30 ± 5.13	40.52 ± 2.94	50.26 ± 4.10	38.50 ± 4.96	–	–
Relative	1.63 ± 0.20	1.64 ± 0.15	2.03 ± 0.19	1.54 ± 0.17	–	–

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

Organ	Vehicle Control	13 mg/kg	25 mg/kg	50 mg/kg	100 mg/kg	200 mg/kg
Female						
n	5	5	4	3	2	1
Necropsy body wt[b]	20.1 ± 0.7	20.3 ± 0.8	20.0 ± 0.7	19.5 ± 1.0	19.7 ± 0.5	18.6 ± 0.9
Brain[b]						
Absolute	0.46 ± 0.01	0.47 ± 0.01	0.46 ± 0.01	0.47 ± 0.00	0.47 ± 0.02	–[c]
Relative	22.8 ± 0.6	23.4 ± 0.9	22.5 ± 0.7	24.8 ± 2.1	22.6 ± 0.2	–
Heart[d]						
Absolute	99.50 ± 2.50	102.36 ± 2.07	103.95 ± 2.49	100.63 ± 5.34	110.00 ± 6.50	–
Relative	4.96 ± 0.06	5.06 ± 0.12	5.10 ± 0.10	5.31 ± 0.17	5.31 ± 0.03	–
R. Kidney						
Absolute	0.16 ± 0.01	0.17 ± 0.01	0.17 ± 0.01	0.18 ± 0.01	0.18 ± 0.02	–
Relative	8.03 ± 0.21	8.16 ± 0.14	8.37 ± 0.11	9.81 ± 1.50	8.54 ± 0.29	–
Liver						
Absolute	0.91 ± 0.03	0.99 ± 0.05	1.03 ± 0.06	1.14 ± 0.09*	1.24 ± 0.04**	–
Relative	45.4 ± 0.8	48.9 ± 1.1*	50.2 ± 1.5*	59.9 ± 1.9**	59.9 ± 1.2**	–
Lungs						
Absolute	0.18 ± 0.01	0.17 ± 0.01	0.19 ± 0.01	0.17 ± 0.01	0.21 ± 0.00	–
Relative	9.06 ± 0.42	8.29 ± 0.46	9.40 ± 0.22	8.99 ± 0.44	10.07 ± 0.36	–
Thymus[d]						
Absolute	48.00 ± 5.72	50.32 ± 3.57	45.60 ± 7.91	35.93 ± 10.39	52.65 ± 7.75	–
Relative	2.37 ± 0.24	2.49 ± 0.18	2.24 ± 0.38	1.82 ± 0.43	2.53 ± 0.24	–

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams unless otherwise specified; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] Includes data from early deaths
[c] No data were calculated due to high mortality.
[d] Organ weights are given in milligrams.

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Studies of 2,4-Diaminophenol Dihydrochloride[a]

Organ	Vehicle Control	5 mg/kg	9 mg/kg	19 mg/kg	38 mg/kg	75 mg/kg
Male						
n	9	8	10	9	10	9
Necropsy body wt	31.3 ± 0.7	31.2 ± 0.7	32.0 ± 0.7	30.7 ± 0.7	32.2 ± 0.4	30.1 ± 1.0
Brain						
Absolute	0.49 ± 0.01	0.47 ± 0.01	0.49 ± 0.00	0.47 ± 0.02	0.48 ± 0.01	0.46 ± 0.01
Relative	15.6 ± 0.5	15.0 ± 0.3	15.5 ± 0.4	15.4 ± 0.7	15.0 ± 0.3	15.3 ± 0.4
Heart[b]						
Absolute	166.11 ± 4.67	165.14 ± 4.76	165.94 ± 4.56	173.42 ± 10.47	183.09 ± 6.00[c]	167.88 ± 8.78
Relative	5.31 ± 0.12	5.32 ± 0.21	5.21 ± 0.20	5.63 ± 0.29	5.68 ± 0.18[c]	5.57 ± 0.21
R. Kidney[b]						
Absolute	276.79 ± 7.95	284.00 ± 5.83	299.73 ± 7.49[c]	298.56 ± 12.57	325.95 ± 7.86**	324.72 ± 12.23**
Relative	8.85 ± 0.20	9.12 ± 0.17	9.47 ± 0.21[c]	9.69 ± 0.24*	10.15 ± 0.27**	10.80 ± 0.31**
Liver						
Absolute	1.54 ± 0.07	1.61 ± 0.06	1.80 ± 0.05*	1.79 ± 0.09*	1.92 ± 0.04**	2.00 ± 0.11**
Relative	49.3 ± 1.8	51.8 ± 1.9	56.2 ± 1.4**	58.1 ± 1.9**	59.8 ± 1.0**	66.1 ± 2.1**
Lungs						
Absolute	0.24 ± 0.01	0.26 ± 0.02	0.23 ± 0.01[c]	0.29 ± 0.03	0.28 ± 0.01	0.26 ± 0.02
Relative	7.58 ± 0.31	8.51 ± 0.60	7.23 ± 0.30[c]	9.53 ± 1.03	8.63 ± 0.43	8.67 ± 0.60
R. Testis[b]						
Absolute	124.75 ± 2.64[d]	116.88 ± 5.38[e]	121.53 ± 3.72[c]	113.64 ± 4.02[d]	116.08 ± 3.42	115.64 ± 3.61
Relative	3.99 ± 0.09[d]	3.78 ± 0.15[e]	3.79 ± 0.15[c]	3.73 ± 0.16[d]	3.62 ± 0.12	3.87 ± 0.17
Thymus[b]						
Absolute	39.17 ± 3.35	42.99 ± 4.91	43.86 ± 4.78	41.74 ± 2.93	44.61 ± 2.21	40.44 ± 5.33
Relative	1.26 ± 0.12	1.37 ± 0.14	1.37 ± 0.14[c]	1.38 ± 0.13	1.38 ± 0.06[c]	1.35 ± 0.19

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

Organ	Vehicle Control	5 mg/kg	9 mg/kg	19 mg/kg	38 mg/kg	75 mg/kg
Female						
n	10	10	10	10	10	10
Necropsy body wt	23.8 ± 0.5	24.5 ± 0.9	24.9 ± 0.4	25.2 ± 0.6	24.7 ± 0.5	24.8 ± 0.6
Brain						
Absolute	0.47 ± 0.00	0.48 ± 0.01	0.49 ± 0.01	0.50 ± 0.01	0.48 ± 0.01	0.48 ± 0.01
Relative	19.9 ± 0.4	20.0 ± 0.7	19.6 ± 0.4	19.6 ± 0.3	19.6 ± 0.3	19.2 ± 0.4
Heart[b]						
Absolute	113.06 ± 4.17	119.08 ± 2.82	118.74 ± 3.60	128.11 ± 3.08**	128.38 ± 2.77**	135.89 ± 5.35**
Relative	4.75 ± 0.14	4.90 ± 0.09	4.78 ± 0.18	5.10 ± 0.17	5.21 ± 0.16	5.47 ± 0.18**
R. Kidney[b]						
Absolute	162.31 ± 3.46[c]	179.66 ± 6.58*	180.56 ± 4.61*	184.33 ± 6.09*	190.10 ± 4.10**	226.53 ± 7.44**
Relative	6.78 ± 0.14[c]	7.36 ± 0.11*	7.27 ± 0.22*	7.31 ± 0.14*	7.69 ± 0.11**	9.12 ± 0.18**
Liver						
Absolute	1.02 ± 0.03	1.25 ± 0.07**	1.28 ± 0.04**	1.34 ± 0.04**	1.33 ± 0.04**	1.52 ± 0.04**
Relative	42.7 ± 0.7	51.0 ± 1.7**	51.2 ± 1.3**	53.3 ± 1.4**	53.7 ± 1.1**	61.6 ± 2.0**
Lungs						
Absolute	0.24 ± 0.02	0.24 ± 0.02	0.24 ± 0.01	0.27 ± 0.01	0.26 ± 0.02[c]	0.29 ± 0.02
Relative	10.1 ± 0.5	9.8 ± 0.6	9.6 ± 0.6	10.7 ± 0.6	10.4 ± 0.9[c]	11.4 ± 0.6
Thymus[b]						
Absolute	43.86 ± 2.29	53.99 ± 3.42	42.47 ± 3.55	47.99 ± 2.58	54.21 ± 4.36	49.39 ± 2.63
Relative	1.86 ± 0.11	2.21 ± 0.11	1.70 ± 0.12	1.90 ± 0.09	2.18 ± 0.16	2.00 ± 0.11

* Significantly different (P≤0.05) from the control group by Williams' or Dunnett's test
** P≤0.01
[a] Organ weights and body weights are given in grams unless otherwise specified; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] Organ weights are given in milligrams.
[c] n=9
[d] n=8
[e] n=5

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluations in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride[a]

Organ	Vehicle Control	19 mg/kg	38 mg/kg
Male			
n	10	10	10
Necropsy body wt	41.4 ± 1.9	37.6 ± 2.0	41.6 ± 1.9
Brain			
Absolute	0.46 ± 0.00	0.45 ± 0.00	0.45 ± 0.01
Relative	11.2 ± 0.5	12.2 ± 0.6	11.1 ± 0.5
R. Kidney			
Absolute	0.28 ± 0.01	0.30 ± 0.01	0.32 ± 0.01
Relative	6.97 ± 0.33	8.16 ± 0.42*	7.66 ± 0.13
Liver			
Absolute	1.57 ± 0.09	1.85 ± 0.29	1.79 ± 0.08
Relative	38.2 ± 2.0	47.7 ± 4.4	43.2 ± 0.9
Female			
n	10	10	10
Necropsy body wt	34.6 ± 1.5	33.9 ± 1.0	34.3 ± 1.1
Brain			
Absolute	0.48 ± 0.01	0.48 ± 0.00	0.48 ± 0.01
Relative	14.0 ± 0.8	14.2 ± 0.5	14.1 ± 0.4
R. Kidney			
Absolute	0.20 ± 0.01	0.20 ± 0.00	0.22 ± 0.01*
Relative	5.77 ± 0.26	5.81 ± 0.19	6.43 ± 0.14*
Liver			
Absolute	1.25 ± 0.05	1.33 ± 0.05	1.47 ± 0.05**
Relative	36.4 ± 1.1	39.3 ± 1.3	43.1 ± 0.9**

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE G1
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluations of the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride[a]

Analysis	Vehicle Control	12.5 mg/kg	25 mg/kg
Male			
n	10	10	10
Hematology			
Hematocrit (%)	43.2 ± 0.8	44.5 ± 1.1	45.0 ± 0.9
Hemoglobin (g/dL)	17.3 ± 0.2	17.4 ± 0.5	17.8 ± 0.2
Erythrocytes ($10^6/\mu L$)	9.49 ± 0.10	9.47 ± 0.24	9.49 ± 0.08
Mean cell volume (μ^3)	45.6 ± 0.8	47.1 ± 0.9	47.6 ± 1.0
Mean cell hemoglobin (pg)	18.2 ± 0.3	18.4 ± 0.1	18.8 ± 0.1**
Mean cell hemoglobin concentration (g/dL)	40.0 ± 0.6	39.2 ± 0.7	39.8 ± 0.9
Leukocytes ($10^3/\mu L$)	4.54 ± 0.27	4.54 ± 0.24	4.33 ± 0.17
Segmented neutrophils ($10^3/\mu L$)	1.76 ± 0.22	1.66 ± 0.12	1.73 ± 0.10
Lymphocytes ($10^3/\mu L$)	2.34 ± 0.18	2.45 ± 0.13	2.16 ± 0.13
Monocytes ($10^3/\mu L$)	0.32 ± 0.05	0.35 ± 0.05	0.25 ± 0.04
Eosinophils ($10^3/\mu L$)	0.12 ± 0.02	0.09 ± 0.02	0.17 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)	0.00 ± 0.00	0.05 ± 0.02*	0.05 ± 0.02*
Clinical Chemistry			
Blood urea nitrogen (mg/dL)	10.7 ± 0.4[b]	10.9 ± 0.4	13.1 ± 0.6**
Alkaline phosphatase (IU/L)	151 ± 7[b]	152 ± 4	141 ± 6
Alanine aminotransferase (IU/L)	57 ± 6[b]	50 ± 3	47 ± 6
Aspartate aminotransferase (IU/L)	110 ± 9[b]	106 ± 6	93 ± 10
Sorbitol dehydrogenase (SU/mL)	724 ± 53[b]	813 ± 43	611 ± 65
Female			
n	10	10	10
Hematology			
Hematocrit (%)	46.4 ± 1.2	44.8 ± 1.2	49.3 ± 1.0
Hemoglobin (g/dL)	16.3 ± 0.1	16.3 ± 0.1	16.8 ± 0.1*
Erythrocytes ($10^6/\mu L$)	8.43 ± 0.13	8.31 ± 0.15	8.86 ± 0.12*
Mean cell volume (μ^3)	55.0 ± 0.8	53.9 ± 0.8	55.8 ± 1.0
Mean cell hemoglobin (pg)	19.4 ± 0.3	19.7 ± 0.3	19.0 ± 0.2
Mean cell hemoglobin concentration (g/dL)	35.5 ± 1.0	36.7 ± 0.8	34.3 ± 0.6
Leukocytes ($10^3/\mu L$)	2.92 ± 0.14	3.21 ± 0.14	3.28 ± 0.25
Segmented neutrophils ($10^3/\mu L$)	0.91 ± 0.10	1.05 ± 0.14	1.09 ± 0.08
Lymphocytes ($10^3/\mu L$)	1.78 ± 0.11	1.89 ± 0.15	1.99 ± 0.20
Monocytes ($10^3/\mu L$)	0.15 ± 0.01	0.20 ± 0.02	0.14 ± 0.02
Eosinophils ($10^3/\mu L$)	0.08 ± 0.01	0.08 ± 0.02	0.06 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.05 ± 0.02	0.08 ± 0.01	0.05 ± 0.01
Clinical Chemistry			
Blood urea nitrogen (mg/dL)	13.6 ± 0.6	15.0 ± 0.9	11.9 ± 0.5
Alkaline phosphatase (IU/L)	174 ± 13	181 ± 10	155 ± 5
Alanine aminotransferase (IU/L)	38 ± 4	31 ± 4	36 ± 2
Aspartate aminotransferase (IU/L)	93 ± 9	75 ± 8	87 ± 7
Sorbitol dehydrogenase (SU/mL)	483 ± 56	506 ± 46	477 ± 29

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error.
[b] n=9

TABLE G2
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluations of the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride[a]

Analysis	Vehicle Control	19 mg/kg	38 mg/kg
Male			
n	10	10	10
Hematology			
Hematocrit (%)	42.8 ± 0.6	42.4 ± 1.8	36.9 ± 1.2**
Hemoglobin (g/dL)	15.0 ± 0.1	14.9 ± 0.5	13.5 ± 0.2**
Erythrocytes ($10^6/\mu L$)	9.83 ± 0.11	9.94 ± 0.44	8.97 ± 0.22**
Mean cell volume (μ^3)	43.5 ± 0.5	42.9 ± 0.4	41.0 ± 0.5**
Mean cell hemoglobin (pg)	15.3 ± 0.1	15.1 ± 0.3	15.2 ± 0.2
Mean cell hemoglobin concentration (g/dL)	35.2 ± 0.4	35.2 ± 0.5	37.0 ± 0.9
Leukocytes ($10^3/\mu L$)	2.56 ± 0.29	4.35 ± 0.85	7.52 ± 1.52**
Segmented neutrophils ($10^3/\mu L$)	0.81 ± 0.09	2.01 ± 0.59**	2.00 ± 0.40**
Lymphocytes ($10^3/\mu L$)	1.68 ± 0.24	2.20 ± 0.51	5.33 ± 1.12**
Monocytes ($10^3/\mu L$)	0.04 ± 0.02	0.08 ± 0.03	0.14 ± 0.07
Eosinophils ($10^3/\mu L$)	0.03 ± 0.01	0.05 ± 0.02	0.08 ± 0.03
Nucleated erythrocytes ($10^3/\mu L$)	0.03 ± 0.01	0.07 ± 0.02	0.04 ± 0.02
Clinical Chemistry			
Blood urea nitrogen (mg/dL)	16.9 ± 1.6	12.1 ± 0.6*	11.2 ± 0.7**
Alkaline phosphatase (IU/L)	38 ± 2	39 ± 2	43 ± 2
Alanine aminotransferase (IU/L)	20 ± 2	28 ± 4[b]	28 ± 4
Aspartate aminotransferase (IU/L)	79 ± 9	155 ± 35[c]	160 ± 30**
Sorbitol dehydrogenase (SU/mL)	1,617 ± 72[b]	1,267 ± 242[d]	1,633 ± 111[c]
Female			
n	10	10	10
Hematology			
Hematocrit (%)	44.3 ± 0.7	44.6 ± 0.8	37.5 ± 1.3**
Hemoglobin (g/dL)	16.1 ± 0.2	15.8 ± 0.1	14.1 ± 0.4**
Erythrocytes ($10^6/\mu L$)	9.77 ± 0.14	9.62 ± 0.12	8.61 ± 0.30**
Mean cell volume (μ^3)	45.5 ± 0.8	46.4 ± 0.6	44.0 ± 1.1
Mean cell hemoglobin (pg)	16.5 ± 0.2	16.5 ± 0.2	16.4 ± 0.3
Mean cell hemoglobin concentration (g/dL)	36.3 ± 0.6	35.6 ± 0.7	37.7 ± 0.5
Leukocytes ($10^3/\mu L$)	2.31 ± 0.33	3.73 ± 0.84	3.79 ± 0.59*
Segmented neutrophils ($10^3/\mu L$)	0.78 ± 0.11	1.56 ± 0.44	1.36 ± 0.25*
Lymphocytes ($10^3/\mu L$)	1.49 ± 0.25	2.10 ± 0.41	2.35 ± 0.37
Monocytes ($10^3/\mu L$)	0.03 ± 0.01	0.03 ± 0.01	0.05 ± 0.03
Eosinophils ($10^3/\mu L$)	0.02 ± 0.01	0.04 ± 0.02	0.04 ± 0.01
Nucleated erythrocytes ($10^3/\mu L$)	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01
Clinical Chemistry			
Blood urea nitrogen (mg/dL)	24.4 ± 4.8[c]	34.0 ± 9.6[b]	27.0 ± 8.7[d]
Alkaline phosphatase (IU/L)	106 ± 10	104 ± 7	93 ± 8[c]
Alanine aminotransferase (IU/L)	21 ± 2[c]	33 ± 7	77 ± 40[c]
Aspartate aminotransferase (IU/L)	95 ± 34[e]	173 ± 37[c]	215 ± 103[e]
Sorbitol dehydrogenase (SU/mL)	821 ± 46	893 ± 74	1,126 ± 107*

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error.
[b] n=8
[c] n=9
[d] n=7
[e] n=5

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION

2,4-Diaminophenol dihydrochloride was obtained from Eastern Chemical Division, Guardian Chemical Corporation, in one lot (055148), which was used throughout the studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute, (MRI), Kansas City, MO. MRI reports on analyses performed in support of the 2,4-diaminophenol dihydrochloride studies are on file at the National Institute of Environmental Health Sciences.

The study chemical, a gray-brown microcrystalline powder, was identified as 2,4-diaminophenol dihydrochloride by infrared, ultraviolet/visible, and nuclear magnetic resonance (NMR) spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra of 2,4-diaminophenol dihydrochloride, as shown in Figures H1 and H2 (*Sadtler Standard Spectra*; Kolodkin, 1975).

The purity was determined by elemental analysis, weight loss on drying, titration, and high-performance liquid chromatography (HPLC). Titration to neutralize the dihydrochloride salt was performed in deionized water with 0.05 N sodium hydroxide as the titrant. Titration was monitored potentiometrically with a combination mV/pH electrode. HPLC was performed with a μBondapak C_{18} column in a mixture of two solvents: A) 0.02 M heptane-sulfonic acid sodium salt in water, with pH adjusted to 2.13 with 10% (v/v) phosphoric acid, and B) 0.005 M heptane-sulfonic acid sodium salt, with an equal volume of phosphoric acid added as solvent A, with a ratio of 70:30 A:B, at a flow rate of 1 mL/minute. Ultraviolet detection was at 280 nm.

Elemental analyses for carbon, hydrogen, nitrogen, and chlorine were in agreement with theoretical values. Because 2,4-diaminophenol dihydrochloride reacted with the Karl Fischer titrant, weight loss on drying was used to estimate the water content. Less than 0.1% water was found. Neutralization of the dihydrochloride salt indicated a purity of 100.0 ± 0.4%. HPLC indicated six impurities with a combined area of 10.3% relative to the major peak. The area of the largest impurity increased from 8.6% to 22% relative to the major peak when a detection wavelength of 254 nm was used. A solvent ratio of 60:40 A:B indicated three additional impurities with a combined area of 0.49% relative to the major peak.

The identity of the major impurity in 2,4-diaminophenol dihydrochloride was determined by HPLC and mass spectrometry. Mass spectrometry indicated a spectrum consistent with that of an isomer of aminonitrophenol. HPLC was performed with a μBondapak C_{18} column in a mixture of two solvents: A) 0.005 M heptane-sulfonic acid sodium salt in water, with pH adjusted to 2.0 with concentrated phosphoric acid and B) 0.005 M heptane-sulfonic acid sodium salt in methanol, with an equal volume of concentrated phosphoric acid added as solvent A, with a ratio of 80:20 A:B, at a flow rate of 2 mL/minute. Ultraviolet detection was at 280 nm. HPLC indicated the presence of 2.7 ± 0.4% 2-amino-4-nitrophenol as an impurity. Thus, the concentration of the impurity, which had been estimated at 8.6% relative to the major peak in the HPLC analysis, was found to have been overestimated. The overall purity of 2,4-diaminophenol dihydrochloride was 97%.

Stability studies performed by HPLC with the system described for the impurity analysis but with a solvent system of 100% A and with acetanilide added as an internal standard indicated that 2,4-diaminophenol dihydrochloride, when stored protected from light, was stable as a bulk chemical for 2 weeks at temperatures up to 60° C. During the 2-year studies, the stability of the bulk chemical was monitored by the study laboratory using HPLC, with the system above but with a solvent system of: A) 0.005 M heptane-sulfonic acid sodium salt with 9.5% phosphoric acid, and B) 0.005 M heptane-

sulfonic acid sodium salt in methanol with 0.1% phosphoric acid, a solvent ratio of 75:25 A:B, and 4-hydroxyacetanilide as an internal standard; no degradation of the study material was seen throughout the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by mixing appropriate quantities of 2,4-diaminophenol dihydrochloride and corn oil to give the required concentrations (Table H1). The dose formulations, which were stored at 0 ± 5° C, were brought to room temperature and hand agitated before administration. Dose formulations were prepared weekly and discarded 2 weeks after the date of preparation.

Homogeneity and stability analyses of the corn oil suspensions were conducted by the analytical chemistry laboratory. For the homogeneity analyses, the formulations were extracted with methanol and centrifuged, then further diluted with methanol. The absorbance of the samples was measured versus methanol by ultraviolet spectroscopy at 242 nm. For the stability studies, a solvent of methanol containing 0.005 M heptane-sulfonic acid sodium salt and 3.5 mL of phosphoric acid per liter (to adjust the pH to 2) was used for extraction; the extract was injected into an HPLC system equipped with a μBondapak C_{18} column and a 254 nm detector. The mobile phase was a mixture of two solvents: A) water containing 0.005 M heptane-sulfonic acid sodium salt, with approximately 3.5 mL phosphoric acid per liter added to adjust the pH to 2, and B) methanol containing 0.005 M heptane-sulfonic acid sodium salt and the same amount of phosphoric acid added as solvent A, with a ratio of 60:40 A:B and a flow rate of 1 mL/minute. Visible detection was at 254 nm. Homogeneity of these formulations was confirmed; stability of the formulation was established for at least 2 weeks when stored in the dark at temperatures up to 25° C.

Periodic analyses of the dose formulations of 2,4-diaminophenol dihydrochloride were conducted at the study laboratory and at the analytical chemistry laboratory using spectroscopy at 500 nm. Dose formulations were analyzed once during the 16-day studies and twice during the 13-week studies. During the 16-day studies, 3/5 dose formulations were outside the acceptable range of ±10% of target concentrations (Table H2). These samples were stored for more than 6 weeks before analysis, and the discoloration and higher absorbance readings caused by prolonged storage may have resulted in the higher than theoretical values. During the 13-week studies, 9/10 dose formulations for rats and 8/10 dose formulations for mice were within 10% of the target concentrations (Table H3). During the 2-year studies, the dose formulations were analyzed at least once every 8 weeks; 29/30 dose formulations for rats and 28/30 dose formulations for mice were within 10% of the target concentrations. Results of the dose formulation analyses studies for the 2-year studies are presented in Table H4. Periodic analyses of the corn oil vehicle by the study laboratory demonstrated peroxide levels within the acceptable limit of 10 mEq/kg. Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratory (Table H5).

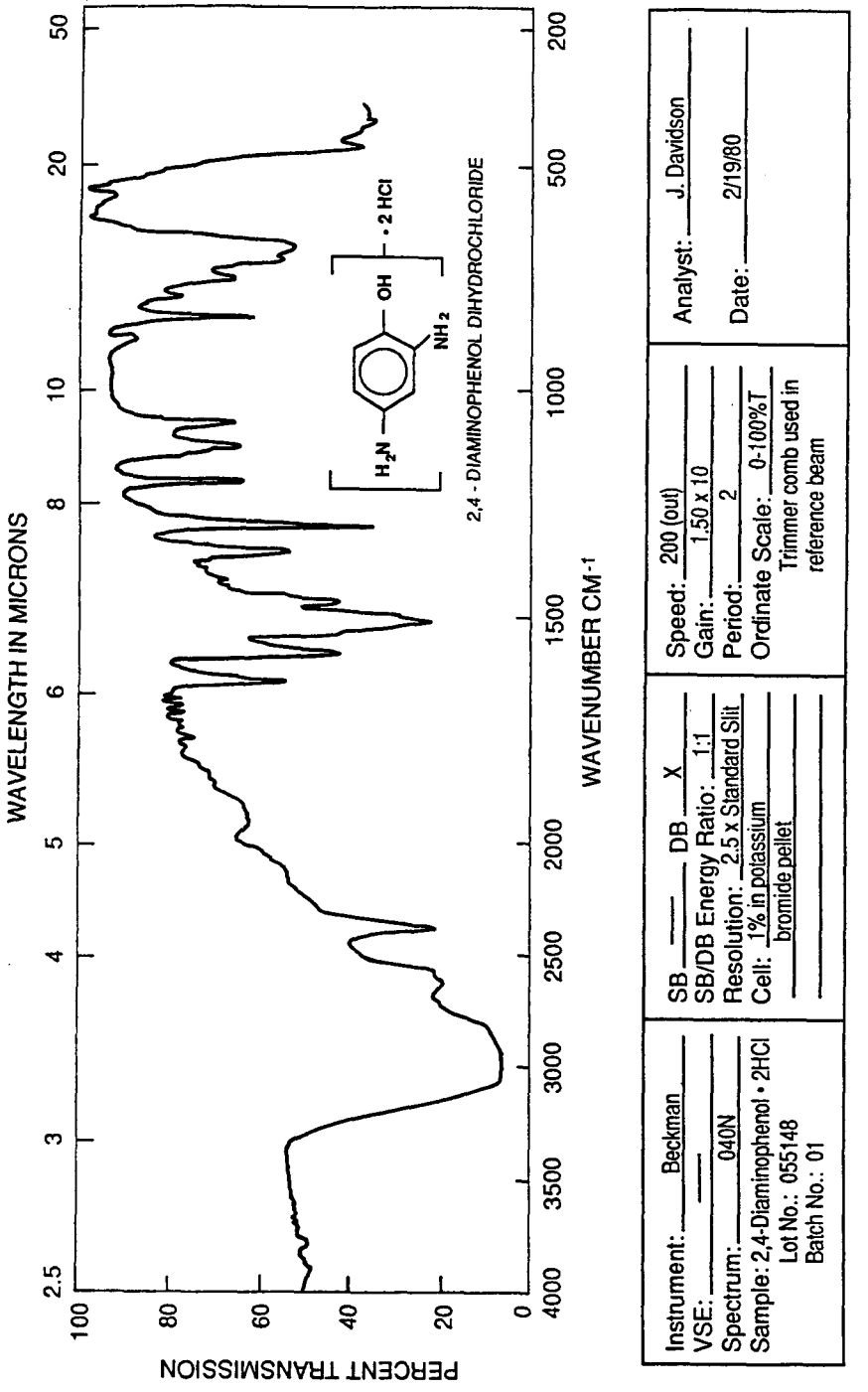

FIGURE H1
Infrared Absorption Spectrum of 2,4-Diaminophenol Dihydrochloride

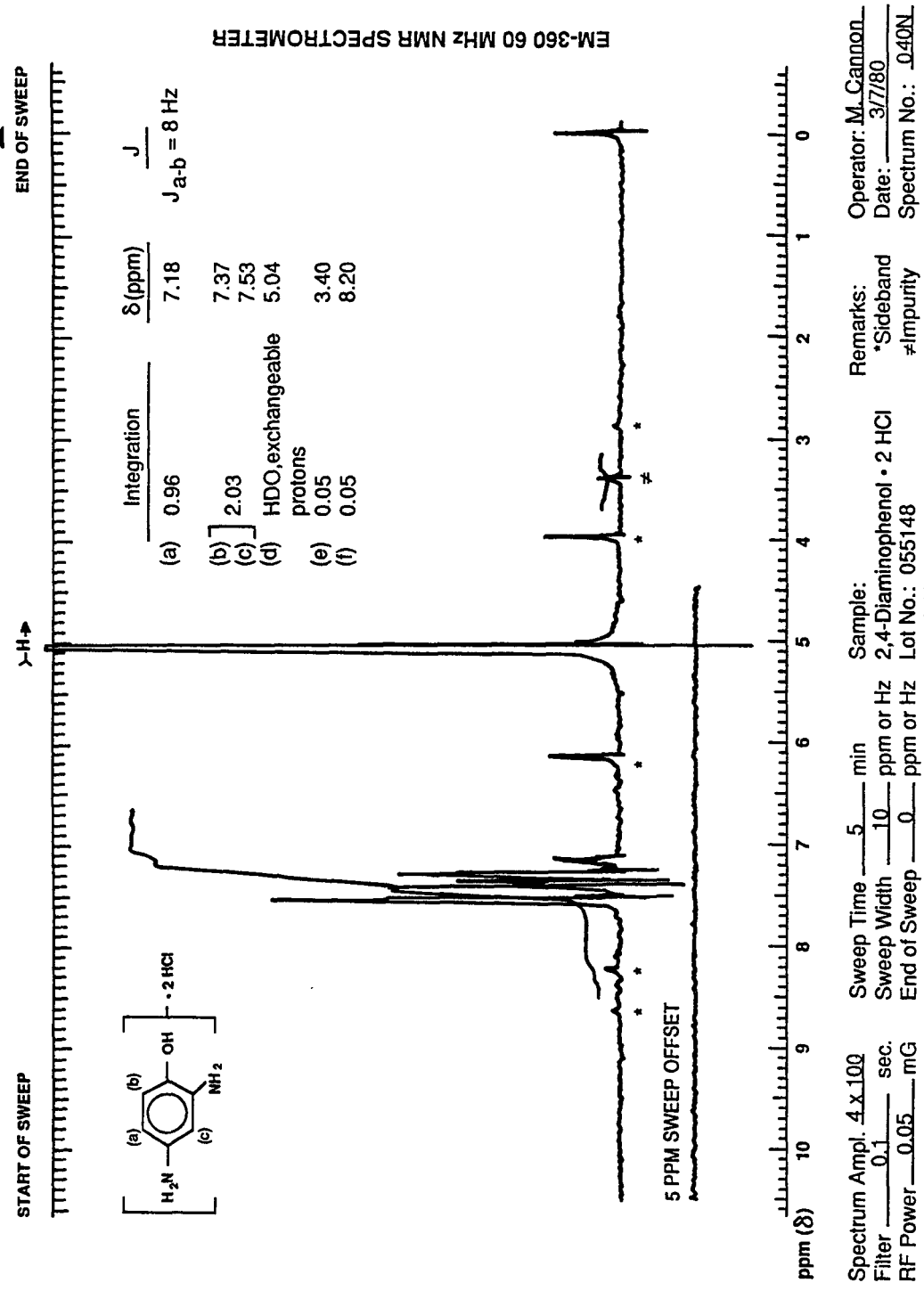

FIGURE H2
Nuclear Magnetic Resonance Spectrum of 2,4-Diaminophenol Dihydrochloride

TABLE H1
Preparation and Storage of Dose Formulations in the Gavage Studies of 2,4-Diaminophenol Dihydrochloride

16-Day Studies	13-Week Studies	2-Year Studies
Preparation		
2,4-Diaminophenol dihydrochloride was mixed with corn oil (w/v) in a centrifuge bottle with a Brinkmann Polytron® blender for 1 minute at high speed under a nitrogen atmosphere. The mixture was then degassed by being swirled briefly while a vacuum was drawn on the bottle.	2,4-Diaminophenol dihydrochloride was mixed with corn oil (w/v) in a centrifuge bottle with a Brinkmann Polytron® blender for 1 minute at medium speed under an argon atmosphere. The mixture was then degassed by being swirled briefly while a vacuum was drawn on the bottle.	2,4-Diaminophenol dihydrochloride was mixed with corn oil (w/v) in a centrifuge bottle with a Brinkmann Polytron® blender for 1 minute at medium speed under an argon atmosphere. The mixture was then degassed by being swirled briefly while a vacuum was drawn on the bottle. Formulations were allowed to equilibriate to room temperature and were hand agitated prior to administration. Magnetic stirring instituted on 30 September 1982.
Chemical Lot Number		
055148	055148	055148
Maximum Storage Time		
14 days from date of preparation	14 days from date of preparation	14 days from date of preparation
Storage Conditions		
Sealed in labeled serum vials and stored in the dark at 0 ± 5° C	Sealed in labeled serum vials and stored in the dark at approximately 4° C	Sealed in labeled serum vials containing magnetic stir bars and stored in the dark at 0 ± 5° C
Study Laboratory		
EG&G Mason Research Institute, Worcester, MA	EG&G Mason Research Institute, Worcester, MA	EG&G Mason Research Institute, Worcester, MA
Referee Laboratory		
Midwest Research Institute, Kansas City, MO	Midwest Research Institute, Kansas City, MO	Midwest Research Institute, Kansas City, MO

TABLE H2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 16-Day Gavage Studies of 2,4-Diaminophenol Dihydrochloride

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	% Difference from Target
8 June 1981	22 July 1981[c]	1.25	1.49	+19
		2.5	2.82	+13
		5.0	5.26	+5
8 June 1981	4 August 1981[c]	10.0	11.6	+16
		20.0	20.1	+1

[a] Rats: Dosing volume = 5 mL/kg; 1.25 mg/mL = 6 mg/kg; 2.5 mg/mL = 13 mg/kg; 5.0 mg/mL = 25 mg/kg; 10.0 mg/mL = 50 mg/kg; 20.0 mg/mL = 100 mg/kg.
Mice: Dosing volume = 10 mL/kg; 1.25 mg/mL = 13 mg/kg; 2.5 mg/mL = 25 mg/kg; 5.0 mg/mL = 50 mg/kg; 10 mg/mL = 100 mg/kg; 20 mg/mL = 200 mg/kg.
[b] Results of duplicate analyses
[c] Formulations stored during development of analysis method. Higher than theoretical recoveries possibly due to discoloration and higher absorbance readings which developed during storage.

TABLE H3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Gavage Studies of 2,4-Diaminophenol Dihydrochloride

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	% Difference from Target
15 October 1981	16 October 1981	0.5	0.70	+40[c]
		0.9	0.86	−4
		1.9	1.83	−4
	19 October 1981	2.4	2.33	−3
		3.8	3.70	−3
		5.0	4.74	−5
		7.5	7.26	−3
		10.0	10.1	+1
		20.0	15.3	−24[d]
		40.0	40.4	+1
16 December 1981	18 December 1981	0.5	0.53	+6
		0.9	0.80	−11[e]
		1.9	1.94	+2
		2.4	2.28	−5
		3.8	3.51	−7
		5.0	4.97	−1
		7.5	7.60	+1
		10.0	9.6	−4
		20.0	20.2	+1
		40.0	41.3	+3
21 December 1981	21 December 1981	0.9	1.00	+11[e]
22 December 1981	22 December 1981	0.9	0.73	−19[e]
23 December 1981	23 December 1981	0.9	0.95	+6

[a] Rats: Dosing volume = 5 mL/kg; 2.4 mg/mL = 12 mg/kg; 5.0 mg/mL = 25 mg/kg; 10 mg/mL = 50 mg/kg; 20 mg/mL = 100 mg/kg; 40 mg/mL = 200 mg/kg.
Mice: Dosing volume = 10 mL/kg; 0.5 mg/mL = 5 mg/kg; 0.9 mg/mL = 9 mg/kg; 1.9 mg/mL = 19 mg/kg; 3.8 mg/mL = 38 mg/kg; 7.5 mg/mL = 75 mg/kg
[b] Results of duplicate analyses
[c] Not within tolerance. Sample remixed. First remix out of tolerance; second remix within tolerance (−4% of target).
[d] Not within tolerance. Sample remixed; remix within tolerance (−4% of target).
[e] Not within tolerance. Sample remixed.

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride

Date Prepared	Date Analyzed	Target Concentration (mg/mL)[a]	Determined Concentration[b] (mg/mL)	% Difference from Target
15 September 1982	20 September 1982	2.5	2.50	0
		5.0	5.14	+3
	7 Octoberr 1982[c]	2.5	3.43	+37
		5.0	6.41	+28
6 October 1982	7 October 1982	1.9	1.24	-35[d]
		3.8	3.32	-13[d]
8 October 1982[e]	8 October 1982	1.9	1.88	-1
		3.8	3.70	-3
	27 October 1982[c]	1.9	1.84	-3
		3.8	3.52	-7
10 November 1982	11 November 1982	1.9	1.88	-1
		2.5	2.44	-2
		3.8	3.67	-3
		5.0	4.60	-8
	19 November 1982[c]	1.9	1.78	-6
		2.5	2.49	0
		3.8	3.91	+3
		5.0	4.86	-3
14 December 1982	15 December 1982	1.9	1.87	-2
		2.5	2.44	-2
		3.8	3.61	-5
		5.0	4.90	-2
23 February 1983	24 February 1983	1.9	1.84	-3
		2.5	2.40	-4
		3.8	3.67	-3
		5.0	4.92	-2
	8 March 1983[c]	1.9	1.9	0
		2.5	2.53	+1
		3.8	3.70	-3
		5.0	5.06	+1
6 April 1983	8 April 1983	1.9	1.80	-5
		2.5	2.48	-1
		3.8	3.93	+3
		5.0	5.04	+1
25 May 1983	26 May 1983	1.9	1.94	+2
		2.5	2.43	-3
		3.8	3.95	+4
		5.0	5.17	+3

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
13 July 1983	13 July 1983	1.9	1.92	+1
		2.5	2.46	-2
		3.8	3.79	0
		5.0	5.08	+2
	22 July 1983[c]	1.9	1.90	0
		2.5	2.53	+1
		3.8	3.82	+1
		5.0	5.01	0
17 August 1983	25 August 1983	3.8	3.90	+3
24 August 1983	25 August 1983	1.9	1.91	+1
		2.5	2.37	-5
		5.0	4.86	-3
16 November 1983	18 November 1983	1.9	1.93	+2
		2.5	1.99	-20[d]
		3.8	3.78	-1
		5.0	4.93	-1
19 November 1983[e]	19 November 1983	2.5	2.50	0
10 January 1984	12 January 1984	1.9	1.87	-2
		2.5	2.47	-1
		3.8	3.74	-2
		5.0	4.96	-1
	19 January 1984[c]	1.9	1.89	-1
		2.5	2.79	+12
		3.8	3.81	0
		5.0	5.37	+7
20 March 1984	21 March 1984	1.9	1.99	+5
		2.5	2.55	+2
		3.8	3.92	+3
		5.0	4.99	0
16 May 1984	17 May 1984	1.9	1.86	-2
		2.5	2.55	+2
		3.8	3.78	-1
		5.0	5.13	+3
3 July 1984	5 July 1984	1.9	1.84	-3
		2.5	2.48	-1
		3.8	3.97	+4
		5.0	5.13	+3

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
1 August 1984	2 August 1984	1.9	1.92	+1
		2.5	2.56	+2
		3.8	3.95	+4
		5.0	5.00	0
	13 August 1984[c]	1.9	1.94	+2
		2.5	2.62	+5
		3.8	3.77	-1
		5.0	5.15	+3
12 September 1984	13 September 1984	1.9	1.75	-8
		2.5	2.52	+1
		3.8	3.90	+3
		5.0	5.13	+3

[a] Rats: Dosing volume = 10 mL/kg; 2.5 mg/mL = 25 mg/kg; 5.0 mg/mL = 50 mg/kg.
Mice: Dosing volume = 10 mL/kg; 1.9 mg/mL = 19 mg/kg; 3.8 mg/mL = 38 mg/kg.
[b] Results of duplicate analyses
[c] Animal room samples
[d] Sample remixed
[e] Analysis results of remix

TABLE H5
Results of Referee Analysis of Dose Formulations in the 13-Week and 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride

Date Mixed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies			
15 October 1981	5.0	4.74	4.76 ± 0.05
2-Year Studies			
15 September 1982	2.5	2.50	2.45 ± 0.04
6 April 1983	5.0	5.04	4.85 ± 0.11
16 November 1983	3.8	3.78	3.38 ± 0.05
20 March 1984	3.8	3.92	3.89 ± 0.10
1 August 1984	1.9	1.92	1.87 ± 0.01

[a] Results of duplicate analysis
[b] Results of triplicate analysis. Mean ± standard deviation

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

TABLE I1
Ingredients of NIH-07 Rat and Mouse Ration[a]

Ingredients[b]	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Dried brewer's yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

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

TABLE I2
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 I3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.76 ± 1.16	21.2–25.9	26
Crude fat (% by weight)	5.16 ± 0.58	4.2–6.3	26
Crude fiber (% by weight)	3.52 ± 0.37	2.8–4.5	26
Ash (% by weight)	6.68 ± 0.25	6.3–7.3	26
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.606	1.210–1.390	8
Cystine	0.306 ± 0.084	0.181–0.400	8
Glycine	1.150 ± 0.047	1.060–1.210	8
Histidine	0.576 ± 0.024	0.531–0.607	8
Isoleucine	0.917 ± 0.029	0.881–0.944	8
Leucine	1.946 ± 0.055	1.850–2.040	8
Lysine	1.270 ± 0.058	1.200–1.370	8
Methionine	0.448 ± 0.128	0.306–0.699	8
Phenylalanine	0.987 ± 0.140	0.665–1.110	8
Threonine	0.877 ± 0.042	0.824–0.940	8
Tryptophan	0.236 ± 0.176	0.107–0.671	8
Tyrosine	0.676 ± 0.105	0.564–0.794	8
Valine	1.103 ± 0.040	1.050–1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830–2.570	7
Linolenic	0.280 ± 0.040	0.210–0.320	7
Vitamins			
Vitamin A (IU/kg)	11,404 ± 4,343	4,200–22,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000–6,300	4
α-Tocopherol (ppm)	37.95 ± 9.41	22.50–48.90	8
Thiamine (ppm)	18.50 ± 3.82	12.0–31.0	26
Riboflavin (ppm)	7.92 ± 0.87	6.10–9.00	8
Niacin (ppm)	103.38 ± 26.59	65.0–150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0–34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60–14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80–3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19–0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6–65.0	8
Choline (ppm)	3,089 ± 329	2,400–3,430	8
Minerals			
Calcium (%)	1.23 ± 0.12	0.97–1.43	26
Phosphorus (%)	0.95 ± 0.05	0.86–1.10	26
Potassium (%)	0.883 ± 0.078	0.772–0.971	6
Chloride (%)	0.526 ± 0.092	0.380–0.635	8
Sodium (%)	0.313 ± 0.390	0.258–0.371	8
Magnesium (%)	0.168 ± 0.010	0.151–0.181	8
Sulfur (%)	0.280 ± 0.064	0.208–0.420	8
Iron (ppm)	361 ± 100	255.0–523.0	8
Manganese (ppm)	91.97 ± 6.01	81.70–99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10–64.50	8
Copper (ppm)	11.06 ± 2.50	8.090–15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52–4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04–2.09	8
Cobalt (ppm)	0.68 ± 0.14	0.490–0.780	4

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration

Contaminants	Mean ± Standard Deviation[a]	Range	Number of Samples
Arsenic (ppm)	0.55 ± 0.15	0.18–0.77	26
Cadmium (ppm)	0.12 ± 0.04	<0.10–0.20	26
Lead (ppm)	0.52 ± 0.20	0.24–1.00	26
Mercury (ppm)	<0.05		26
Selenium (ppm)	0.31 ± 0.06	0.21–0.45	26
Aflatoxins (ppb)	<5.0		26
Nitrate nitrogen (ppm)[b]	9.21 ± 3.89	2.50–19.0	26
Nitrite nitrogen (ppm)[b]	1.07 ± 1.37	<0.10–6.10	26
BHA (ppm)[c]	4.00 ± 4.99	<2.00–20.00	26
BHT (ppm)[c]	3.04 ± 2.58	<1.00–13.00	26
Aerobic plate count (CFU/g)[d]	146,296 ± 143,824	6,600–420,000	26
Coliform (MPN/g)[e]	496 ± 780	3.00–2,400	26
E. coli (MPN/g)[f]	3.80 ± 2.63	3.00–15.0	25
E. coli (MPN/g)[g]	9.42 ± 28.79	3.00–150	26
Total nitrosoamines (ppb)[h]	5.85 ± 5.89	0.80–30.30	26
N-Nitrosodimethylamine (ppb)[h]	5.01 ± 5.88	0.50–30.00	26
N-Nitrosopyrrolidine (ppb)[h]	0.84 ± 0.71	0.30–2.70	26
Pesticides (ppm)			
α-BHC[i]	<0.01		26
β-BHC	<0.02		26
γ-BHC	<0.01		26
δ-BHC	<0.01		26
Heptachlor	<0.01		26
Aldrin	<0.01		26
Heptachlor epoxide	<0.01		26
DDE	<0.01		26
DDD	<0.01		26
DDT	<0.01		26
HCB	<0.01		26
Mirex	<0.01		26
Methoxychlor	<0.05		26
Dieldrin	<0.01		26
Endrin	<0.01		26
Telodrin	<0.01		26
Chlordane	<0.05		26
Toxaphene	<0.1		26
Estimated PCBs	<0.2		26
Ronnel	<0.01		26
Ethion	<0.02		26
Trithion	<0.05		26
Diazinon	<0.1		26
Methyl parathion	<0.02		26
Ethyl parathion	<0.02		26
Malathion[j]	0.15 ± 0.15	0.05–0.81	26
Endosulfan I	<0.01		26
Endosulfan II	<0.01		26
Endosulfan sulfate	<0.03		26

TABLE I4
Contaminant Levels in NIH-07 Rat and Mouse Ration (continued)

[a] For values less than the limit of detection, the detection limit is given for the mean.
[b] Sources of contamination: alfalfa, grains, and fish meal
[c] Sources of contamination: soy oil and fish meal
[d] CFU = colony-forming unit
[e] MPN = most probable number
[f] Excludes one high value of 150 MPN/g obtained from the lot milled on 26 August 1983.
[g] Includes the high value obtained from the lot milled on 26 August 1983.
[h] All values were corrected for percent recovery.
[i] BHC = hexachlorocyclohexane or benzene hexachloride
[j] Fourteen lots contained more than 0.05 ppm.

APPENDIX J
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Rats

During the 13-week studies, five F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. At the termination of the 13-week studies, the animals were bled. Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM (pneumonia virus of mice)	Study termination
Sendai	Study termination
KRV (Kilham rat virus)	Study termination
H-1 (Toolan's H-1 virus)	Study termination
Complement Fixation	
RCV (rat corona virus)	Study termination

During the 2-year studies, 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Samples for viral screening at 24 months were collected from five diet control animals of each sex. Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM	6, 12, and 18 months
Sendai	6, 12, and 18 months
KRV	6, 12, 18, and 24 months
H-1	6, 12, 18, and 24 months
ELISA	
RCV/SDA (sialodacryoadenitis virus)	12, 18, and 24 months
Mycoplasma pulmonis	24 months
Mycoplasma arthritidis	24 months
PVM	24 months
Sendai	24 months
Complement Fixation	
RCV/SDA	6 months

Mice

During the 13-week studies, five B6C3F$_1$ mice of each sex were selected at the time of randomization and allocation of the animals to the various study groups. At the termination of the 13-week studies, the animals were bled. Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM	Study termination
Reovirus 3	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
Polyoma virus	Study termination
Sendai	Study termination
MVM (minute virus of mice)	Study termination
Ectromelia virus (mouse pox)	Study termination
Complement Fixation	
Mouse adenoma virus	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
ELISA	
MHV (mouse hepatitis virus)	Study termination

During the 2-year studies, 15 B6C3F$_1$ mice of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Samples for viral screening at 24 months were collected from five diet control animals of each sex. Blood collected from each animal was allowed to clot, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates, Inc. (Bethesda, MD) for determination of the antibody titers. The following tests were performed:

Method of Analysis	Time of Analysis
Hemagglutination Inhibition	
PVM	6, 12, and 18 months
Reovirus 3	6, 12, and 18 months
GDVII	6, 12, and 18 months
Polyoma virus	6, 12, 18, and 24 months
Sendai	6, 12, and 18 months
MVM	6, 12, 18, and 24 months
Ectromelia virus	6, 12, and 18 months
Complement Fixation	
Mouse adenoma virus	6, 12, and 18 months
LCM	6, 12, 18, and 24 months
Immunofluorescent Antibody	
EDIM (epizootic diarrhea of infant mice)	24 months

Method of Analysis (continued)	Time of Analysis
ELISA	
PVM	24 months
Reovirus 3	24 months
GDVII	24 months
Sendai	24 months
Ectromelia virus	24 months
Mouse adenoma virus	24 months
Mycoplasma pulmonis	24 months
Mycoplasma arthritidis	24 months
MHV	6, 12, 18, and 24 months

TABLE J1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Gavage Studies of 2,4-Diaminophenol Dihydrochloride

	Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies			
Rats	13 weeks	0/10	None positive
Mice	13 weeks	0/10	None positive
2-Year Studies			
Rats	6 months	0/10	None positive
	12 months	10/10	Sendai
		9/10	RCV/SDA
	18 months	10/10	Sendai
		10/10	RCV/SDA
	24 months	10/10	Sendai
		8/10	RCV/SDA
		2/10	*M. arthritidis*[a]
Mice	6 months	9/10	MHV
	12 months	3/9	MHV
	18 months	1/9	MHV
	24 months	5/10	MHV
		4/10	*M. arthritidis*[a]
		7/10	EDIM

[a] Possible *Mycoplasma arthritidis*

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichloroethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	Telone II® (1,3-Dichloropropene)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3
336	Penicillin VK
337	Nitrofurazone

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TR No.	CHEMICAL
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	*a*-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3'-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
385	Methyl Bromide
386	Tetranitromethane
387	Amphetamine Sulfate
388	Ethylene Thiourea
389	Sodium Azide
390	3,3′-Dimethylbenzidine Dihydrochloride
391	Tris(2-chloroethyl) Phosphate
392	Chlorinated Water and Chloraminated Water
393	Sodium Fluoride
395	Probenecid
396	Monochloroacetic Acid
399	Titanocene Dichloride
405	C.I. Acid Red 114
406	γ-Butyrolactone
407	C.I. Pigment Red 3
410	Naphthalene
415	Polysorbate 80

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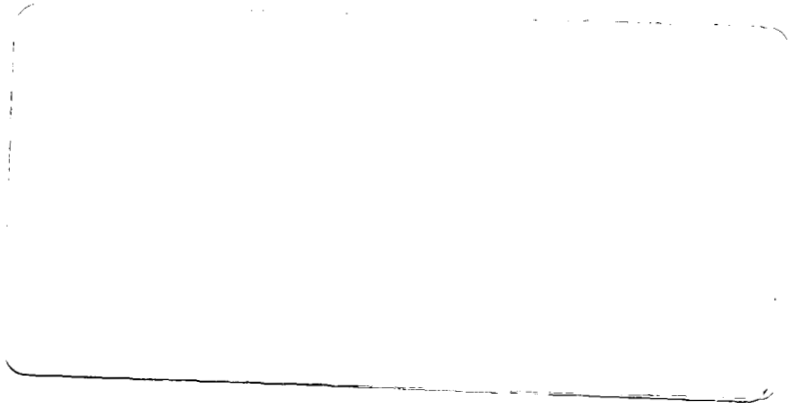

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