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TOXICOLOGY AND CARCINOGENESIS STUDIES OF *N,N*-DIMETHYLANILINE

(CAS NO. 121-69-7)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *N,N*-DIMETHYLANILINE

(CAS NO. 121-69-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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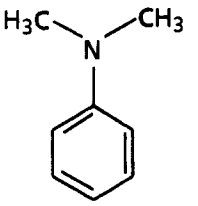
CONTENTS

APPENDIXES



N,N-DIMETHYLANILINE

CAS No. 121-69-7

$C_8H_{11}N$ Molecular weight 121.2

Synonyms: dimethylaminobenzene; *N,N*-dimethylbenzenamine; dimethylaniline; dimethylphenylamine; *N,N*-dimethylphenylamine

ABSTRACT

N,N-Dimethylaniline is used as a chemical intermediate in the synthesis of dyestuffs. Toxicology and carcinogenesis studies were conducted by administering *N,N*-dimethylaniline (greater than 98% pure) in corn oil by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex for 2 weeks, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse lymphoma cells, and Chinese hamster ovary (CHO) cells.

Two-Week and Thirteen-Week Studies: In the 2-week studies, doses were 94-1,500 mg/kg; deaths of rats and mice were observed in groups given doses of 750 or 1,500 mg/kg. The final mean body weights of male rats that received 375 or 750 mg/kg were 15% or 47% lower than that of vehicle controls; final mean body weights of other groups of rats and mice were similar to those of vehicle controls. Compound-related clinical signs observed included cyanosis in rats and lethargy and tremors in rats and mice. Splenomegaly occurred in nearly all dosed groups of rats and mice, and the incidences were dose related.

In the 13-week studies, doses were 32-500 mg/kg; no compound-related deaths occurred. The final mean body weights of male rats that received 250 or 500 mg/kg were 15% or 27% lower than that of vehicle controls. The final mean body weights of all groups of dosed female rats and male and female mice were within 12% of those of vehicle controls. Compound-related clinical signs included lethargy in rats and mice and cyanosis in rats. Splenomegaly was observed in all dosed groups of rats and mice; the severity was dose related. Compound-related extramedullary hematopoiesis and hemosiderosis occurred in the kidney or testis of dosed rats and liver and spleen of dosed rats and mice.

Two-year studies were conducted by administering 0, 3, or 30 mg/kg *N,N*-dimethylaniline in corn oil by gavage, 5 days per week for 103 weeks, to groups of 50 rats of each sex. The lower dose was selected to be one-tenth the higher dose to increase the likelihood that one dose would cause only a minimal nonneoplastic response. Groups of 50 mice of each sex were administered 0, 15, or 30 mg/kg on the same schedule.

Body Weight and Survival in the Two-Year Studies: Mean body weights of vehicle control and dosed rats and mice were similar throughout the studies. Survival rates of all respective groups were similar after 2 years, except for the lowered survival of vehicle control female rats (vehicle control, 21/50; low dose, 32/50; high dose, 36/50). This may reflect the large number (24/50) of vehicle control female rats killed when observed to be in a moribund state. Final survival for other groups was as follows: male rats--29/50; 32/50; 28/50; male mice--34/50; 30/50; 34/50; female mice--35/50; 39/50; 33/50.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: In these 2-year studies, the spleen was the expected site of chemical-related effects. Fatty metamorphosis and fibrosis in the spleen of high dose male rats were increased (fatty metamorphosis: vehicle control, 0/49; low dose, 1/49; high dose, 10/50; fibrosis: 5/49; 2/49; 22/50). Splenic hemosiderosis and hematopoiesis were present at an incidence greater than 85% in all groups of rats; however, the severity of the lesions was greater in dosed groups than in vehicle controls. Sarcomas of the spleen were seen in 3/50 high dose male rats, and an osteosarcoma was seen in another high dose male rat. One additional high dose male rat had a sarcoma of the thymus. Splenic sarcomas are uncommon in corn oil vehicle control male F344/N rats (NTP historical incidence 3/2,081, 0.1%), and thus, these neoplasms in high dose male rats (4/50, 8%) were considered to be chemically related.

Lower incidences of mononuclear cell leukemia (which apparently originates in the spleen) were seen in dosed male and female rats than in vehicle controls (male: 13/50; 4/50; 3/50; female: 11/50; 7/50; 0/50).

The incidence of squamous cell papillomas of the forestomach in high dose female mice was marginally greater than that in vehicle controls (2/50; 2/50; 8/50). No malignant forestomach neoplasms were observed.

Genetic Toxicology: *N,N*-Dimethylaniline was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of exogenous metabolic activation. In the mouse lymphoma assay, *N,N*-dimethylaniline produced a positive response with and without metabolic activation. In CHO cells, *N,N*-dimethylaniline induced both sister chromatid exchanges (SCEs) and chromosomal aberrations in the presence of exogenous metabolic activation. Without activation, an increase in chromosomal aberrations was observed, but no increase in SCEs occurred.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of *N,N*-dimethylaniline for male F344/N rats, as indicated by the increased incidences of sarcomas or osteosarcomas (combined) of the spleen. There was *no evidence of carcinogenic activity* of *N,N*-dimethylaniline for female F344/N rats given 3 or 30 mg/kg body weight by gavage for 2 years. There was *no evidence of carcinogenic activity* of *N,N*-dimethylaniline for male B6C3F$_1$ mice given 15 or 30 mg/kg body weight by gavage for 2 years. There was *equivocal evidence of carcinogenic activity* of *N,N*-dimethylaniline for female B6C3F$_1$ mice, as indicated by an increased incidence of squamous cell papillomas of the forestomach. Both rats and mice could have tolerated doses higher than those used in these studies.

There were decreased incidences of mononuclear cell leukemia in dosed male and high dose female rats. Compound-related splenic fibrosis, hemosiderosis, and fatty metamorphosis were increased in male rats.

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*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

SUMMARY OF THE TWO-YEAR GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 3, or 30 mg/kg *N,N*-dimethylaniline in corn oil, 5 d/wk	0, 3, or 30 mg/kg *N,N*-dimethylaniline in corn oil, 5 d/wk	0, 15, or 30 mg/kg *N,N*-dimethylaniline in corn oil, 5 d/wk	0, 15, or 30 mg/kg *N,N*-dimethylaniline in corn oil, 5 d/wk
Body weights			
Dosed and vehicle control groups similar	Dosed and vehicle control groups similar	Dosed and vehicle control groups similar	Dosed and vehicle control groups similar
Survival rates			
29/50; 32/50; 28/50	21/50; 32/50; 36/50	34/50; 30/50; 34/50	35/50; 39/50; 33/50
Nonneoplastic effects			
Splenic fibrosis and fatty metamorphosis; increase in the severity of hemosiderosis and hematopoiesis of the spleen	Increase in the severity of hemosiderosis and hematopoiesis of the spleen	None	None
Neoplastic effects			
Splenic sarcomas or osteosarcomas (combined): 0/49; 0/49; 4/50; decrease in the incidence of mononuclear cell leukemia (13/50; 4/50; 3/50)	Decrease in the incidence of mononuclear cell leukemia (11/50; 7/50; 0/50)	None	Squamous cell papillomas of the forestomach (2/50; 2/50; 8/50)
Level of evidence of carcinogenic activity*			
Some evidence	No evidence	No evidence	Equivocal evidence

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.

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 because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the *Technical Reports* series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

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

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic 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 incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of *N,N*-Dimethylaniline is based on 13-week studies that began in January 1980 and ended in April 1980 and on 2-year studies that began in March 1981 and ended in March 1983 at Springborn Institute for Bioresearch, Inc. (Spencerville, OH).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on *N,N*-dimethylaniline on March 13, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF *N,N*-DIMETHYLANILINE

On March 13, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of *N,N*-dimethylaniline received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (some evidence of carcinogenic activity for male rats, no evidence of carcinogenic activity for female rats, no evidence of carcinogenic activity for male mice, equivocal evidence of carcinogenic activity for female mice).

Dr. Perera, a principal reviewer, agreed with the conclusions. She asked that a comment be added to the last sentence in the conclusion that "Both rats and mice could have tolerated doses higher than those used in these studies," to indicate that the sensitivity of the studies for detecting the presence of carcinogenic responses was likely reduced. Dr. Abdo said that such a phrase would be added.

Dr. Garman, the second principal reviewer, agreed with the conclusions. He considered the doses selected for the 2-year studies to be adequate but wondered why the dose range was twofold for mice but tenfold for rats. Dr. Abdo indicated that the wider exposure range for rats was a successful attempt to administer a dose low enough that hemosiderosis would not be produced.

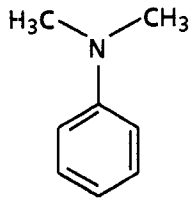
Dr. Popp commented that the lesions reported were very typical of the aniline class of compounds and stated that the comparison table in the discussion was a good idea.

Dr. Perera moved that the Technical Report on *N,N*-dimethylaniline be accepted with the conclusions as written, some evidence of carcinogenic activity for male rats, no evidence of carcinogenic activity for female rats and male mice, and equivocal evidence of carcinogenic activity for female mice. Dr. Garman seconded the motion, which was accepted unanimously by the Panel.

I. INTRODUCTION

Physical and Chemical Properties
Production and Use
Human Exposure and Health Effects
Toxicity in Humans
Toxicity in Animals
Carcinogenicity
Metabolism
Genetic Toxicology
Study Rationale

I. INTRODUCTION



N,N-DIMETHYLANILINE

CAS No. 121-69-7

$C_8H_{11}N$ Molecular weight 121.2

Synonyms: dimethylaminobenzene; *N,N*-dimethylbenzenamine; dimethylaniline; dimethylphenylamine; *N,N*-dimethylphenylamine

N,N-Dimethylaniline is a chemical intermediate used in the synthesis of dyestuffs. It is also used as a solvent and as an aid in methylation. *N,N*-Dimethylaniline is made by heating aniline, methyl alcohol, and sulfuric acid under pressure. The sulfate formed is converted to the free base with sodium hydroxide (Merck, 1983).

Physical and Chemical Properties

N,N-Dimethylaniline is an oily liquid with a density of 0.956, a boiling point of 192°-194° C, a melting point of 2.5° C, and a flashpoint of 61° C (Merck, 1983). This compound is insoluble in water but is freely soluble in alcohol, chloroform, and ether (Merck, 1983; Sax, 1984). It is also soluble in acetone, benzene, and other organic solvents (CRC, 1981).

Production and Use

According to the 1988 U.S. Environmental Protection Agency TSCA inventory, the United States production of *N,N*-dimethylaniline was between 2 and 20 million pounds. The import volume for *N,N*-dimethylaniline in 1985 was 1.9 million pounds (USDOC, 1986).

N,N-Dimethylaniline is used as an intermediate in the production of vanillin, Michler's ketone, and basic dyes (Merck, 1983). It is used as a solvent, as an activator for polyesters, and as an alkylating agent (Kirk-Othmer, 1978). It is also used as an acid scavenger or acceptor in the manufacture of semisynthetic penicillins and cephalosporins (Choi and Park, 1981) and as a rubber vulcanizing agent (Poisonindex, 1988).

Human Exposure and Health Effects

According to a national occupational exposure survey conducted from 1981 to 1983, the number of workers occupationally exposed to *N,N*-dimethylaniline was estimated at 21,300 (NIOSH, 1988). The American Conference of Governmental Industrial Hygienists adopted a threshold-limit value/time-weighted average of 5 ppm for this compound in the workplace air (ACGIH, 1988).

Because *N,N*-dimethylaniline is present as an impurity in β-lactam antibiotics (penicillins and cephalosporins) (Nachtmann and Gestrein, 1981), potential exposure of the public exists through their use. The allowable level in these drugs is limited to no more than 20 ppm (Quercia et al., 1980).

Toxicity in Humans

Toxic effects of *N,N*-dimethylaniline after inhalation exposure are similar to those of aniline and include inhibition of the nerve centers and circulatory system, with headache, cyanosis, dizziness, labored breathing, paralysis, and convulsion (Poisonindex, 1988). Increased blood methemoglobin levels, slight erythropenia, decreased hemoglobin concentration, and reticulocytosis were observed in workers exposed to *N,N*-dimethylaniline (Lazarev and Levine, 1976).

Toxicity in Animals

The reported oral LD_{50} for rats is 1,410 mg/kg (Smyth et al., 1962). Guinea pigs administered an oral or subcutaneous dose of *N,N*-dimethylaniline at 2 g/kg showed weakness, tremors, tonic and clonic convulsions, and slowing of breathing; death occurred due to respiratory failure (Sax, 1984).

Continuous inhalation exposure of male rats to *N,N*-dimethylaniline for 100 days, at a concentration of 300 µg/m^3 in the air, led to anemia, methemoglobinemia, leukopenia, and impairment of adrenal gland and liver functions (Markosyan, 1969). No toxicity was observed at 5 µg/m^3.

Carcinogenicity

N,N-Dimethylaniline administered by subcutaneous injection was not carcinogenic for Wistar rats (Walpole, 1963). In this study, the compound was administered at a rate of 50 mg/100 g body weight in arachis oil for up to 21 weeks (twice per week for the first 13 weeks and once per day thereafter), followed by a 19-week observation period. These studies are considered to be inadequate for evaluating potential carcinogenicity mainly because of the short duration and incomplete reporting.

Aniline hydrochloride (NCI, 1978) and several other compounds such as Dapsone, azobenzene, *p*-chloroaniline, *o*-toluidine hydrochloride, D & C Red No. 9, and *p*-chloroaniline hydrochloride were carcinogenic to F344/N rats and B6C3F$_1$ mice (NCI, 1977, 1979a,b,c; NTP, 1982, 1989). Most of these compounds induced splenic sarcomas in rats and hepatocellular adenomas and carcinomas in mice.

Metabolism

N,N-Dimethylaniline undergoes *N*-demethylation, *N*-oxidation, and ring hydroxylation in animals and in vitro when incubated with liver microsomal preparations. Urinary metabolites produced by dogs and rabbits injected subcutaneously with this compound included 4-aminophenol, 4-dimethylaminophenol, 2-aminophenol, and *N*-methylaniline (Williams, 1959; Kiese and Renner, 1974). Similar reactions were demonstrated in vitro with liver microsomal preparations from pigs, rats, rabbits, chickens, or guinea pigs (Fish et al., 1956; Ziegler and Pettit, 1964, 1966; Abou-Donia and Menzel, 1968). *N*-Oxidation of *N,N*-dimethylaniline was demonstrated with whole homogenates of human liver (Ziegler and Gold, 1971; Kitada et al., 1974). *N,N*-Dimethylaniline was also metabolized in the nasal and respiratory mucosa of F344 rats (McNulty et al., 1983). Alveolar type II cells from rabbit and rat lungs catalyzed the *N*-oxidation of this compound (Devereux and Fouts, 1974; Ohmiya and Mehendale, 1981). The rate of *N*-oxidation of *N,N*-dimethylaniline by lung tissue varies with species; rabbit lung homogenate was found to be three to five times more active than rat lung homogenate (Ohmiya and Mehendale, 1983). The microsomal preparation from rat seminal vesicles, when fortified with arachidonic acid, catalyzed the demethylation of *N,N*-dimethylaniline (Sivarajah et al., 1982).

Genetic Toxicology

N,N-Dimethylaniline was not mutagenic in several strains of *Salmonella typhimurium* at concentrations as high as 1,000 µg/plate with or without exogenous metabolic activation (Mori et al., 1980; Ho et al., 1981; Mortelmans et al., 1986; see Table H1). Results of in vitro cytogenetic tests with Chinese hamster ovary (CHO) cells conducted by the NTP were positive. In these NTP studies, *N,N*-dimethylaniline induced both chromosomal aberrations and sister chromatid exchanges (SCEs) in the presence of Aroclor 1254-induced male Sprague Dawley rat liver S9; in the absence of S9, there was a weakly positive response in the chromosomal aberration test, but results of the SCE test were negative (Loveday et al., 1989; see Tables H3 and H4).

Mutagenicity information is available on three metabolites of *N,N*-dimethylaniline: 4-aminophenol, 2-aminophenol, and *N*-methylaniline. Results of Salmonella tests for gene mutation induction were negative for two of the compounds (Lavoie et al., 1979; Mori et al., 1980; Thompson et al., 1983; Zeiger et al., 1988), but 2-aminophenol was found to induce reverse mutations in strain TA100 with and without S9 (Lavoie et al., 1979; Haworth et al., 1983; Thompson et al.,

1983). 4-Aminophenol and 2-aminophenol were reported to induce SCEs in human cells in vitro, both with S9 (Takehisa and Kanaya, 1982) and without S9 (Wilmer et al., 1981). 4-Aminophenol was also positive in tests with mice for chromosomal aberration induction (Mitra and Manna, 1971), micronucleus induction (Wild et al., 1980), and induction of sperm head abnormalities (Topham, 1979).

Aniline, a structural analog of *N,N*-dimethylaniline, has been tested extensively for genotoxic activity. Tests designed to measure primary DNA damage events gave mixed results. No increase in DNA repair was detected in hepatocytes from several rodent species after in vitro treatment with 3 mM aniline (McQueen et al., 1981; Williams, 1981). In vitro induction of SCEs by aniline was reported in human lymphoblastoid cells in the presence of S9 (Tohda et al., 1983) and in human fibroblasts without S9 (Wilmer et al., 1981), but not in human lymphocytes with or without S9 (Takehisa and Kanaya, 1982). NTP in vitro cytogenetics tests with CHO cells showed that aniline induced SCEs with and without S9 (Galloway et al., 1987). DNA strand breaks were detected in the liver and kidney cells of male Sprague Dawley rats after an intraperitoneal injection of up to 420 mg/kg aniline but not in the liver, kidney, or bone marrow cells of male Swiss mice similarly injected with aniline (Parodi et al., 1982). However, SCEs were induced in the bone marrow cells of male Swiss mice administered a single intraperitoneal injection of 210 or 420 mg/kg aniline (Parodi et al., 1983).

Aniline, like *N,N*-dimethylaniline, did not induce gene mutation in bacteria (McCann et al., 1975; Anderson and Styles, 1978; Simmon, 1979; Florin et al., 1980; Chung et al., 1981; De Flora, 1981; Haworth et al., 1983) or sex-linked recessive lethal mutations in *Drosophila melanogaster* (Yoon et al., 1985).

Amacher et al. (1980) reported a weak positive response with aniline in the mouse lymphoma L5178Y/TK$^{+/-}$ assay with S9; aniline was also positive in NTP mouse lymphoma assays both in the presence and absence of S9 (Mitchell et al., 1989; Myhr and Caspary, 1989).

NTP in vitro tests for induction of chromosomal aberrations in CHO cells by aniline gave weakly positive results; a small but significant increase in chromosomal aberrations was observed at the highest dose tested (5,000 µg/ml) in the presence of S9, and no increase was observed without S9 (Galloway et al., 1987). Ishidate (1983) reported induction of chromosomal aberrations in Chinese hamster lung cells in the presence of S9 at doses up to 2,000 µg/ml aniline.

Study Rationale

N,N-Dimethylaniline was nominated by the National Cancer Institute for evaluation of potential carcinogenicity in laboratory animals because of its structural similarity to other carcinogenic anilines. Because this compound is moderately volatile, the gavage route of administration was chosen.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *N,N*-DIMETHYLANILINE

CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY AND FIFTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *N,N*-DIMETHYLANILINE

N,N-Dimethylaniline was obtained in one lot (lot no. 0557019) from Buffalo Color Corporation (West Patterson, NJ). Purity and identity analyses were conducted at Midwest Research Institute, Kansas City, MO (Appendix G). The study chemical was identified as *N,N*-dimethylaniline by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Lot no. 0557019 was found to be greater than 98% pure as determined by elemental analysis, Karl Fischer water analysis, nonaqueous potentiometric titration of the tertiary amino group with 0.1 N perchloric acid, thin-layer chromatography, and gas chromatography.

The identity of the chemical at the study laboratory was confirmed by infrared spectroscopy. The stability of the study material was monitored by gas chromatography. No deterioration of the study material was seen over the course of the studies.

CHARACTERIZATION OF DOSE MIXTURES

The study chemical in corn oil (at 0.6% w/v) was found by gas chromatography to be stable for 3 weeks in the dark at room temperature; corn oil solutions were stable for 3 hours when exposed to light and air at room temperature. During the 13-week studies, *N,N*-dimethylaniline/corn oil mixtures were stored at 4° C for no longer than 1 week. During the 2-year studies, the dose mixtures were stored at 4° C for up to 2 weeks for rats and up to 3 weeks for mice.

Periodic analysis of formulated *N,N*-dimethylaniline/corn oil dose mixtures was conducted at the study laboratory and the analytical chemistry laboratory by extraction of the dose mixtures with methanol and spectrophotometric quantitation at 251 nm. During the 2-year studies the dose mixtures were analyzed at approximately 8-week intervals. The results of the analysis of the first several mixes indicated a problem with the analytical procedure. Reanalysis of the samples after the procedure was modified gave results that were within specifications.

For the *N,N*-dimethylaniline studies, the mixtures were formulated within ±10% of the target concentrations for all 44 analyses performed after the analytical procedure was modified (Table G3). Results of referee analysis periodically performed by the analytical chemistry laboratory indicated generally good agreement with results from the study laboratory (Table G4).

SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories; rats were observed for 14 days and mice for 15 days before the studies began.

Groups of five rats and five mice of each sex were administered a single dose of 350, 700, 1,410, 2,820, or 5,640 mg/kg *N,N*-dimethylaniline in corn oil by gavage. Animals were observed two times per day for 14 days. Details of animal maintenance are presented in Table 1.

FOURTEEN-DAY AND FIFTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 14 days before the studies began. The rats were approximately 6-7 weeks old when placed on study, and the mice were 6-8 weeks old.

Groups of five rats and five mice of each sex were administered 0, 94, 188, 375, 750, or 1,500 mg/kg *N,N*-dimethylaniline in corn oil by gavage for 14 consecutive days.

Animals were housed five per cage. Water and feed were available ad libitum. The rats and mice were observed two times per day and were weighed on days 0, 7, and 15. A necropsy was performed on all animals; histologic examinations were performed on selected animals. Details of animal maintenance are presented in Table 1.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Single-Administration Studies	Fourteen-Day and Fifteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses			
350, 700, 1,410, 2,820, or 5,640 mg/kg *N,N*-dimethylaniline in corn oil by gavage; dose vol--rats: 2-20 ml/kg; mice: 2.5-20 ml/kg	0, 94, 188, 375, 750, or 1,500 mg/kg *N,N*-dimethylaniline in corn oil by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	0, 31, 62, 125, 250, or 500 mg/kg *N,N*-dimethylaniline in corn oil by gavage; dose vol--rats: 5 ml/kg; mice: 10 ml/kg	Rats--0, 3, or 30 mg/kg *N,N*-dimethylaniline in corn oil by gavage; mice--0, 15, or 30 mg/kg; dose vol--rats: 5 ml/kg; mice: 10 ml/kg
Date of First Dose			
Rats--8/30/79; mice--8/31/79	10/26/79	1/10/80	Rats--3/30/81; mice--3/23/81
Date of Last Dose			
N/A	Rats--11/8/79; mice--11/9/79	4/9/80	Rats--3/18/83; mice--3/11/83
Duration of Dosing			
Single dose	14 (rats) or 15 (mice) consecutive d	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation			
Observed 2 × d; weighed initially	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed 1 × wk for 12 wk and at least 1 × mo thereafter
Necropsy and Histologic Examinations			
No necropsy or histologic exams performed	Necropsy performed on all animals; histologic exams performed on 3 male and 3 female rats from the 94 and 375 mg/kg groups and on 3 male and 3 female mice from the 375 mg/kg groups. Tissues examined include adrenal glands, brain, colon, duodenum, esophagus, gallbladder (mice), heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, salivary glands, testes or ovaries/uterus, skin, spleen, thymus, and trachea	Necropsy and histologic exams performed on all animals; the following tissues were examined: adrenal glands, brain, blood, bone marrow, colon, costochondral junction, duodenum, esophagus, external and middle ear, eyes, femur, gallbladder (mice), heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity, pancreas, parathyroids, pituitary gland, rectum, regional lymph nodes, salivary glands, sciatic nerve, seminal vesicles/prostate/testes or ovaries/uterus, skin, spinal cord, spleen, stomach, thigh muscle, tissue masses, thymus, thyroid gland, trachea, and urinary bladder	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups: adrenal glands, brain, epididymis/prostate/testes or ovaries/uterus, esophagus, eyes (if grossly abnormal), gross lesions and tissue masses with regional lymph nodes, heart, kidneys, large intestine, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroids, pharynx (if grossly abnormal), pituitary gland, salivary glands, skin, small intestine, spinal cord (if neurologic signs present), spleen, sternum or vertebrae or femur including marrow, stomach, thymus, thyroid gland, trachea, and urinary bladder; gross lesions examined in low dose groups; spleen and testes examined for low dose male rats; kidneys, liver, and spleen for low dose female rats; adrenal glands for low dose mice; liver and spleen for low dose female mice

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE (Continued)

Single-Administration Studies	Fourteen-Day and Fifteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species			
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory			
Springborn Institute for Bioresearch, Inc.	Springborn Institute for Bioresearch, Inc.	Springborn Institute for Bioresearch, Inc.	Springborn Institute for Bioresearch, Inc.
Method of Animal Identification			
Toe clip and ear punch	Ear notch and toe clip	Ear notch and toe clip	Toe clip and ear punch
Time Held Before Study			
Rats--14 d; mice--15 d	14 d	14 d	18 d
Age When Placed on Study			
6-7 wk	Rats--6-7 wk; mice--6-8 wk	Same as 14-d studies	Rats--7 wk; mice--8 wk
Age When Killed			
9 wk	Rats--8-9 wk; mice--8-10 wk	Rats--19-20 wk; mice--19-21 wk	Rats--111-112 wk; mice--112-113 wk
Necropsy or Kill Dates			
9/11/79	11/9/79	4/10/80-4/11/80	Rats--3/28/83-3/31/83; mice--3/21/83-3/24/83
Method of Animal Distribution			
According to a table of random numbers	Same as single-administration studies	Same as single-administration studies	Assigned to cages according to one table of random numbers and then to groups according to another table of random numbers
Diet			
NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Bedding			
Deotized board (Upjohn Co., Kalamazoo, MI)	Anipads (Ancare Corp., Manhasset, NY)	Ancubes (Ancare Corp., Manhasset, NY)	Heat-treated hardwood chips (Ancare Corp., Manhasset, NY)
Water			
Tap water from glass bottles; available ad libitum	Same as single-administration studies	Half deionized, half tap water from automatic watering system (Edstrom Industries, Waterford, WI)	Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum; approximately 90% of dissolved salts removed by a reverse osmosis unit
Cages			
Stainless steel with wire mesh bottoms (Shoreline)	Same as single-administration studies	Polycarbonate (Lab Products, Inc.)	Polycarbonate (Lab Products, Inc.)

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE (Continued)

Single-Administration Studies	Fourteen-Day and Fifteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Cage Filters			
None	None	100% polyester (Snow Filtration, Cincinnati, OH)	Nonwoven fiber filters (Snow Filtration, Cincinnati, OH)
Animals per Cage			
5	5	5	5
Other Chemicals on Study in the Same Room			
None	None	None	None
Animal Room Environment			
Temp--70°-74° F; hum--68%-74%; fluorescent light 12 h/d; 12 room air changes/h	Temp--70°-74° F; hum--48%-71%; fluorescent light 12 h/d; 12 room air changes/h	Temp--68°-76° F; hum--25%-76%; fluorescent light 12 h/d; 12 room air changes/h	Temp--62°-82° F; hum--14%-90%; fluorescent light 12 h/d;12 room air changes/h

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of *N,N*-dimethylaniline and to determine the doses to be used in the 2-year studies.

Four- to five-week-old male and female F344/N rats and 4- to 6-week-old male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 14 days, and then assigned to dose groups according to a table of random numbers.

Groups of 10 rats and 10 mice of each sex were administered 0, 31, 62, 125, 250, or 500 mg/kg *N,N*-dimethylaniline in corn oil by gavage, 5 days per week for 13 weeks.

Rats and mice were housed five per cage. Feed and water were available ad libitum. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 1.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 3, or 30 mg/kg *N,N*-dimethylaniline in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 0, 15, or 30 mg/kg on the same schedule.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 4-5 weeks (rats) or 5-6 weeks (mice) of age. The animals were quarantined at the study laboratory for 18 days. Thereafter, a complete

necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7 weeks of age and the mice at 8 weeks. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix E).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

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

Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed (Appendix F) and water were available ad libitum. The racks were rotated once per week. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed two times per day. Body weights were recorded one time per week for the first 12 weeks of the studies and at least once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, except for tissues that were excessively autolyzed or missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 1) were performed on all high dose and vehicle control animals and on low dose animals dying before the end of the studies. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were identified from the short-term studies or the literature and were determined by examination of the pathology data; these target organs/tissues in the lower dose groups were examined histopathologically.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Carcinogenesis Bioassay Data System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues, and all tissues from a randomly selected 10% of the animals were re-evaluated microscopically by a quality assessment pathologist. Target organs were the salivary gland of male and female rats; thyroid gland, spleen, stomach and testes of

male rats; liver of female rats; adrenal gland of male mice; and liver and spleen of female mice. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target organs, the randomly selected 10% of animals, and in tissues with unusual incidence patterns or trends. Tissues are generally not evaluated in a "blinded" fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle.

The quality assessment report and slides were submitted to a Pathology Working Group (PWG) Chairperson, who reviewed microscopically all potential target tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of potential chemical-related nonneoplastic lesions and neoplasms and examples of disagreements in diagnosis between the laboratory and quality assessment pathologists were shown to the PWG. The PWG, which includes the quality assessment pathologist and other pathologists experienced in rodent toxicology, examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final pathology data represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

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

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

Analysis of Tumor Incidence: The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was an incidental tumor 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, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined to obtain a single overall result.

In addition to incidental tumor analysis, 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 include pairwise comparisons of each dosed group with vehicle 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 data base (Haseman et al., 1984, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES

FIFTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

SINGLE-ADMINISTRATION STUDIES

All rats that received 5,640 mg/kg and female rats that received 1,410 or 2,820 mg/kg *N,N*-dimethylaniline died before the end of the studies (Table 2). Deaths of male rats were also seen at doses as low as 700 mg/kg. Compound-related effects included cyanosis and nasal discharge at the two highest doses and decreased activity at the three highest doses. One male and two female rats that received 5,640 mg/kg had body tremors for 1 day after they were dosed.

FOURTEEN-DAY STUDIES

All rats that received 1,500 mg/kg and 9/10 rats that received 750 mg/kg died before the end of the studies (Table 3). The final mean body weights of male rats that received 375 or 750 mg/kg were 15% or 47% lower than that of vehicle controls. Compound-related clinical signs in the two highest dose groups included cyanosis, lethargy, fine body tremors, diarrhea, and red ocular or nasal discharge. Splenomegaly was seen in the male rat that received 750 mg/kg and lived to the end of the studies, in all male and female rats that received 375 mg/kg, in 9/10 rats that received 188 mg/kg, and in 3/10 rats that received 94 mg/kg. Extramedullary hematopoiesis and an increased amount of hemosiderin were seen in the spleen of 3/3 males and 3/3 females at 375 mg/kg.

TABLE 2. SURVIVAL AND INITIAL MEAN BODY WEIGHTS OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Dose (mg/kg)	Survival (a)	Initial Mean Body Weight (grams) (b)
MALE (c)		
350	5/5	129 ± 2.5
700	(d) 4/5	128 ± 1.1
1,410	(e) 1/5	132 ± 1.4
2,820	(f) 2/5	126 ± 1.9
5,640	(g) 0/5	129 ± 3.3
FEMALE		
350	5/5	106 ± 2.7
700	5/5	103 ± 2.7
1,410	(h) 0/5	101 ± 1.6
2,820	(i) 0/5	103 ± 2.2
5,640	(j) 0/5	108 ± 3.4

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean; final body weights were not recorded.
(c) LD_{50} by probit analysis (95% confidence interval): 1,336 mg/kg (695-2,526 mg/kg)
(d) Day of death: 4
(e) Day of death: 2,2,3,3
(f) Day of death: all 3
(g) Day of death: 1,1,1,2,3
(h) Day of death: 2,3,3,3,3
(i) Day of death: 1,2,2,3,3
(j) Day of death: 1,1,1,2,2

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	126 ± 2	199 ± 6	+73 ± 5	
94	5/5	130 ± 5	194 ± 7	+64 ± 2	97
188	5/5	126 ± 3	187 ± 4	+61 ± 3	94
375	5/5	122 ± 4	169 ± 6	+47 ± 2	85
750	(d) 1/5	118 ± 4	105	−16	53
1,500	(e) 0/5	130 ± 3	(f)	(f)	(f)
FEMALE					
0	5/5	103 ± 2	135 ± 2	+32 ± 2	
94	5/5	97 ± 4	129 ± 3	+32 ± 2	96
188	5/5	97 ± 1	127 ± 2	+30 ± 2	94
375	5/5	105 ± 2	131 ± 5	+26 ± 3	97
750	(g) 0/5	91 ± 2	(f)	(f)	(f)
1,500	(e) 0/5	105 ± 2	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 4,4,6,6
(e) Day of death: all 3
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: all 4

THIRTEEN-WEEK STUDIES

No deaths occurred which were clearly compound related; no deaths occurred in the high dose female group, and other deaths occurred in the early weeks of the studies (Table 4), suggesting that the deaths were probably gavage related. The final mean body weights of male rats that received 250 or 500 mg/kg were 15% or 27% lower than that of vehicle controls. Compound-related clinical signs included cyanosis, excessive salivation, and lethargy. Compound-related histopathologic changes occurred in the spleen, liver, kidney, and bone marrow of male and female rats and in the testis of male rats (Table 5). The incidence and severity of these lesions increased with increasing doses. Compound-related effects were present in all dosed groups.

The spleen of dosed rats contained increased numbers of hematopoietic cells, which in some rats were abundant enough to produce splenic enlargement. In the red pulp, numerous prominent macrophages were filled with yellow-brown granular pigment. The pigment was identified as hemosiderin with Perl's stain. In contrast, the spleen of vehicle control rats contained few or no apparent hematopoietic cells and only small numbers of hemosiderin-filled macrophages, which is normal for the rat spleen. In the liver of dosed rats, Kupffer cells were enlarged and filled with yellow-brown granular pigment (hemosiderin), similar to that seen in the spleen. The pigment-containing Kupffer cells tended to localize in the centrilobular areas of the liver. In addition, the liver of some dosed rats contained scattered foci of hematopoietic cells. Cortical epithelial cells in the kidney of dosed rats also contained yellow-brown granular pigment, identified as hemosiderin with Perl's stain. Hyperplasia of the hematopoietic cells of the bone marrow occurred in rats administered doses of 62.5 mg/kg or more. The bone marrow of vehicle control rats consisted mainly of adipose cells mixed with small numbers of hematopoietic

cells, whereas the bone marrow of high dose rats was composed almost entirely of solid sheets of hematopoietic cells with very few adipose cells. The interstitium of the testis of dosed, but not vehicle control, rats also had small numbers of macrophages containing granular yellow-brown, iron-positive pigment in the cytoplasm.

Dose Selection Rationale: Because of splenomegaly, the increase in the severity of hemosiderin accumulation, and extramedullary hematopoiesis and because a no-observable-effect level was not reached in the 13-week studies, doses selected for rats for the 2-year studies were 3 and 30 mg/kg *N,N*-dimethylaniline, administered in corn oil by gavage 5 days per week. The lower dose was selected to be one-tenth the higher dose to increase the likelihood that this dose would cause minimal or no nonneoplastic response.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	122 ± 3	345 ± 5	+223 ± 6	
31	10/10	123 ± 2	331 ± 8	+208 ± 7	96
62	10/10	128 ± 2	332 ± 5	+204 ± 3	96
125	10/10	127 ± 2	321 ± 5	+194 ± 4	93
250	10/10	124 ± 2	292 ± 5	+168 ± 3	85
500	(d) 9/10	122 ± 2	251 ± 9	+130 ± 8	73
FEMALE					
0	10/10	103 ± 2	193 ± 2	+90 ± 3	
31	10/10	98 ± 2	190 ± 2	+92 ± 2	98
62	(d) 9/10	96 ± 1	188 ± 2	+91 ± 2	97
125	(e) 9/10	100 ± 1	187 ± 2	+88 ± 2	97
250	(f) 9/10	99 ± 1	185 ± 2	+86 ± 2	96
500	10/10	99 ± 2	183 ± 4	+84 ± 4	95

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 2
(e) Week of death: 3
(f) Week of death: 7

TABLE 5. INCIDENCES OF RATS WITH SELECTED LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE (a)

Site/Lesion	Vehicle Control	31 mg/kg	62 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg
MALE						
Spleen						
Hematopoiesis, extramedullary	0/10	10/10 (2.3)	10/10 (2.0)	10/10 (2.8)	10/10 (3.5)	9/9 (4.0)
Hemosiderosis	0/10	10/10 (2.3)	10/10 (2.7)	10/10 (2.9)	10/10 (3.8)	9/9 (4.8)
Liver						
Pigmentation	0/10	0/10	2/10 (1.5)	9/10 (1.3)	10/10 (2.5)	9/9 (3.2)
Kidney						
Pigmentation	0/10	0/10	7/10 (1.1)	10/10 (2.0)	10/10 (3.7)	9/9 (4.2)
Testis						
Pigmentation	0/10	(b)	(b)	0/10	10/10 (1.0)	9/9 (1.0)
Bone marrow						
Hyperplasia	0/10	0/10	2/10 (1.0)	9/10 (1.3)	10/10 (2.1)	8/8 (3.0)
FEMALE						
Spleen						
Hematopoiesis, extramedullary	2/10 (2.0)	10/10 (2.1)	10/10 (2.4)	10/10 (2.9)	10/10 (2.9)	10/10 (3.9)
Hemosiderosis	0/10	10/10 (2.0)	9/10 (3.0)	9/10 (3.2)	9/10 (3.1)	10/10 (4.0)
Liver						
Pigmentation	0/10	0/10	6/10 (1.0)	9/10 (1.6)	9/10 (2.1)	10/10 (3.5)
Kidney						
Pigmentation	1/10 (1.0)	6/10 (1.0)	9/10 (1.3)	9/10 (2.1)	9/10 (3.6)	9/10 (3.6)
Bone marrow						
Hyperplasia	0/10	0/10	1/10 (1.0)	9/10 (1.4)	8/10 (2.1)	9/10 (1.9)

(a) Lesion incidence is the number of animals with the lesion/number of animals examined; number in parentheses denotes mean grade of severity (1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe).
(b) Not examined

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control rats were similar throughout the studies (Table 6 and Figure 1). No compound-related clinical signs were observed.

Survival

Estimates of the probabilities of survival for male and female rats administered *N,N*-dimethylaniline at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 2 and in Table 7. The survival of the high dose group of female rats was significantly greater than that of the vehicle controls after week 99.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the spleen, peripheral nerves, forestomach, liver, and hematopoietic system.

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 animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

TABLE 6. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	3 mg/kg Av. Wt. (grams)	3 mg/kg Wt. (percent of veh. controls)	3 mg/kg No. of Survivors	30 mg/kg Av. Wt. (grams)	30 mg/kg Wt. (percent of veh. controls)	30 mg/kg No. of Survivors
MALE								
0	143	50	146	102	50	146	102	50
1	168	49	171	102	49	169	101	50
2	196	49	198	101	49	197	101	50
3	212	49	225	106	49	226	107	50
4	241	49	244	101	49	242	100	49
5	252	49	255	101	48	254	101	47
6	267	49	270	101	48	257	96	47
7	273	49	283	104	48	271	99	47
8	292	49	294	101	48	296	101	47
9	301	49	300	100	48	297	99	47
10	310	49	316	102	48	308	99	47
11	321	49	326	102	48	321	100	47
12	329	49	331	101	48	321	98	47
16	355	49	352	99	48	339	95	47
20	393	49	395	101	48	393	100	47
24	396	49	401	101	48	395	100	47
28	408	49	418	102	48	405	99	47
32	416	49	434	104	48	417	100	47
36	434	49	445	103	48	432	100	47
40	437	49	448	103	48	435	100	47
44	431	49	439	102	48	428	99	45
48	444	49	462	104	48	446	100	45
52	451	49	461	102	48	448	99	45
60	459	49	465	101	46	457	100	45
64	460	49	471	102	46	461	100	44
68	462	49	475	103	46	465	101	44
72	464	49	478	103	46	462	100	44
76	476	49	460	97	46	454	95	44
80	459	46	469	102	45	462	101	42
84	459	45	464	101	44	466	102	38
90	456	41	456	100	42	450	99	37
94	450	39	455	101	40	444	99	33
98	445	33	444	100	35	442	99	30
102	422	30	433	103	32	436	103	29
FEMALE								
0	123	50	122	99	50	122	99	50
1	131	50	133	102	50	134	102	49
2	143	50	145	101	50	142	99	49
3	152	50	154	101	50	151	99	49
4	160	50	166	104	50	158	99	49
5	168	50	170	101	50	167	99	49
6	175	49	176	101	50	175	100	49
7	179	49	182	102	50	181	101	49
8	187	49	187	100	50	186	99	49
9	188	49	191	102	50	190	101	49
10	187	49	189	101	50	183	98	49
11	198	49	199	101	50	195	98	49
12	199	49	202	102	50	196	98	49
16	194	49	196	101	50	178	92	49
20	230	49	229	100	50	229	100	49
24	223	49	224	100	50	223	100	49
28	233	49	235	101	50	234	100	49
32	236	49	238	101	50	232	98	49
36	250	49	249	100	50	251	100	49
40	255	49	257	101	50	256	100	49
44	261	49	263	101	50	259	99	49
48	266	49	272	102	50	265	100	49
52	269	49	274	102	50	274	102	49
60	282	49	293	104	49	290	103	49
64	295	49	300	102	49	302	102	49
68	310	47	313	101	48	316	102	49
72	318	47	315	99	47	320	101	49
76	313	47	314	100	47	318	102	49
80	325	47	321	99	45	332	102	47
84	322	46	323	100	43	333	103	44
90	333	38	333	100	41	335	101	43
94	329	36	334	102	40	336	102	42
98	327	31	330	101	35	334	102	39
102	319	23	329	103	34	332	104	36

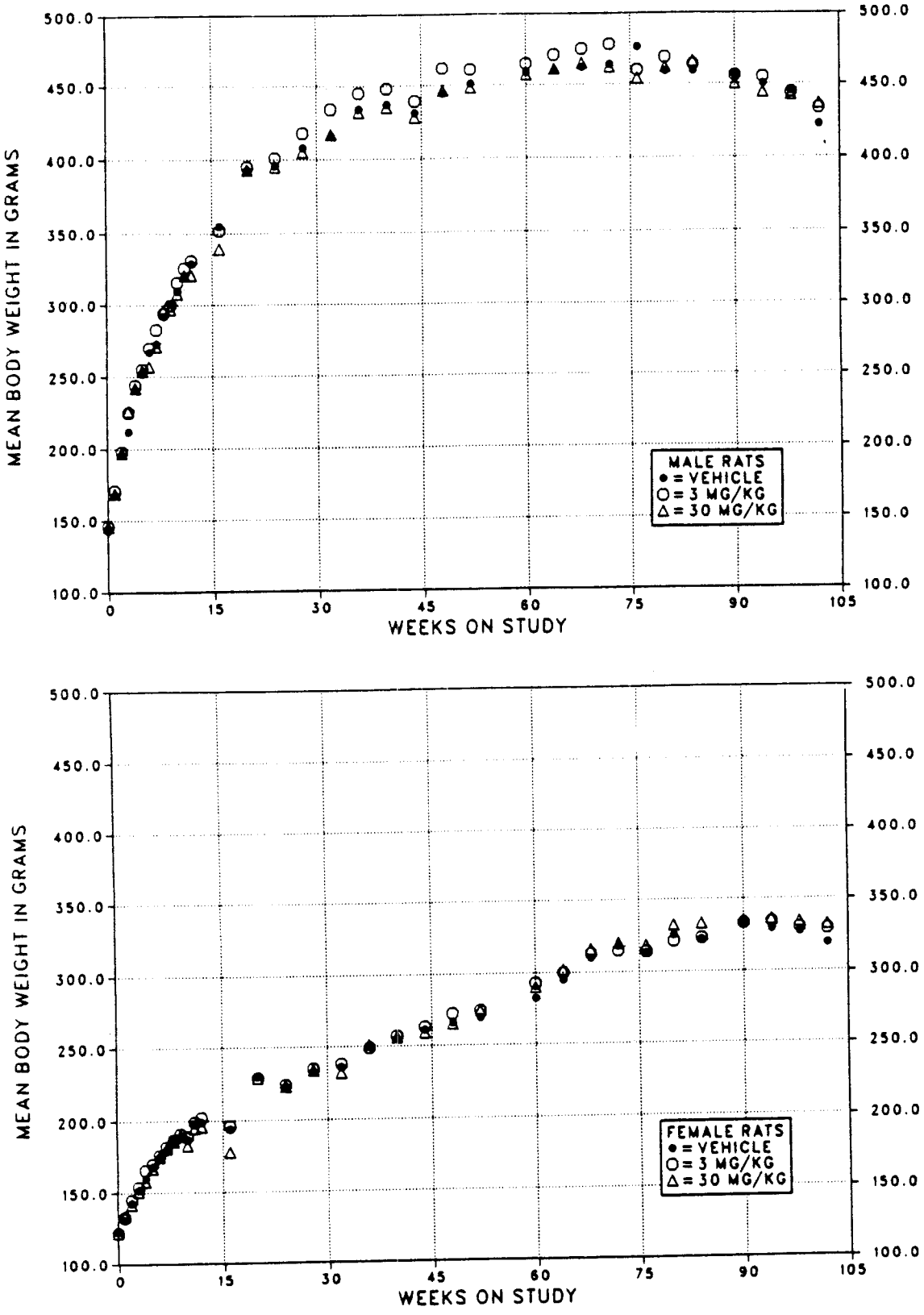


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED *N,N*-DIMETHYLANILINE IN CORN OIL BY GAVAGE FOR TWO YEARS

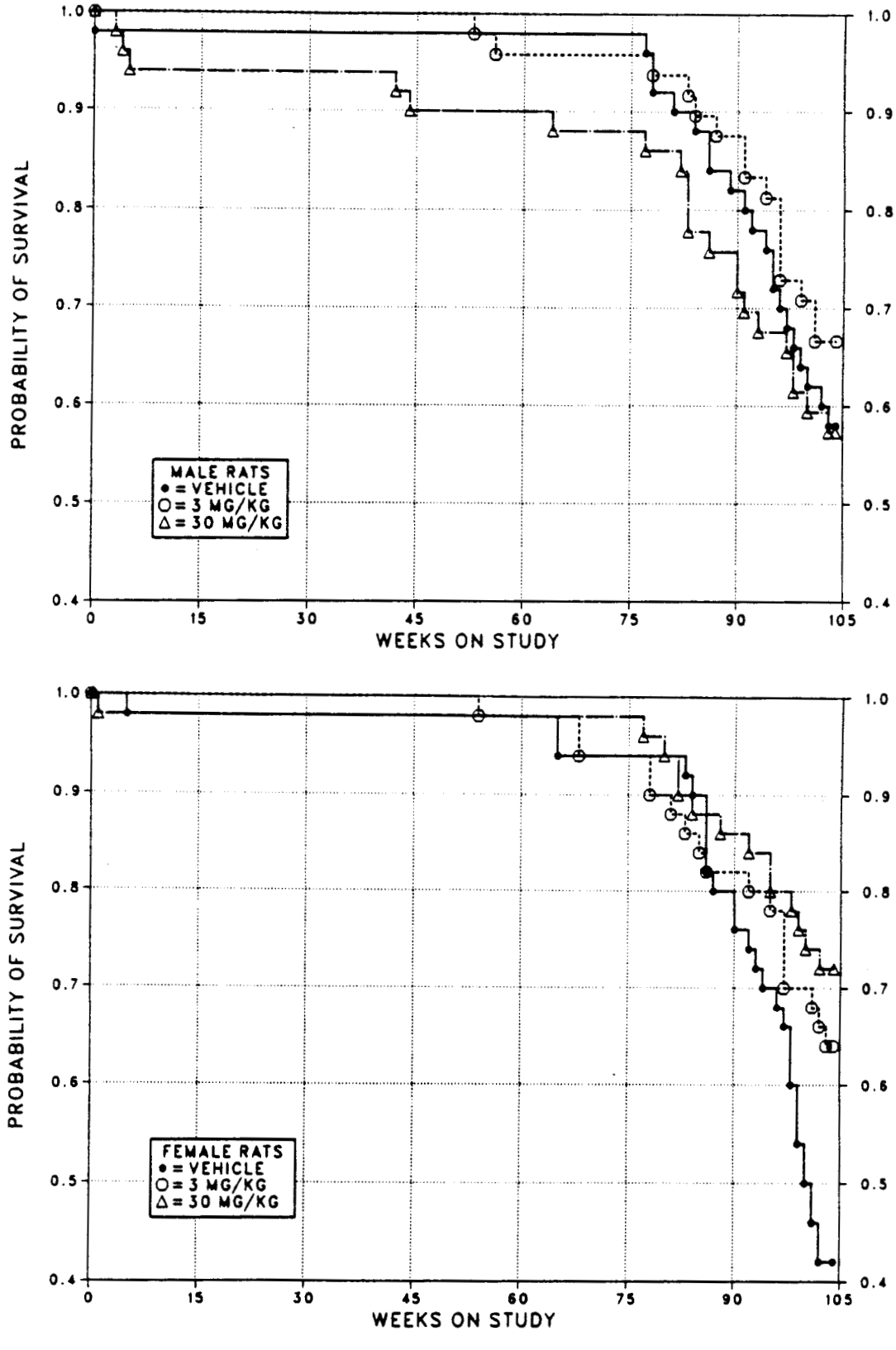


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED *N,N*-DIMETHYLANILINE IN CORN OIL BY GAVAGE FOR TWO YEARS

TABLE 7. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

	Vehicle Control	3 mg/kg	30 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	7	2	8
Moribund kills	14	14	13
Animals surviving until study termination	29	32	28
Killed accidentally	0	2	1
Survival P values (b)	0.530	0.470	0.888
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	5	7	5
Moribund kills	24	11	9
Animals surviving until study termination	21	32	36
Survival P values (b)	0.034	0.069	0.008

(a) Termination period: week 104
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

Spleen: Sarcomas were seen in 3/50 high dose male rats, and an osteosarcoma was seen in another high dose male rat (Table 8 and Figure 3). Although the incidence of sarcomas or osteosarcomas (combined) (4/50) was not significantly greater in high dose males than in vehicle controls (0/50), it exceeded the greatest historical incidence observed in corn oil vehicle control male F344/N rats (1/45). One sarcoma was observed in the spleen of a vehicle control female rat.

The splenic sarcomas had a varied morphology, ranging from poor to well demarcated and from dense collections of cells with vesiculate, angular nuclei and ill-defined cell borders to a well-differentiated osteosarcoma composed of dense osteoid seams and spindle-shaped cells. One sarcoma had features of hemangiosarcoma, with cavernous spaces that were either empty or filled with erythrocytes. One poorly differentiated sarcoma had a focus of minimal osteoid production, suggesting early differentiation toward osteosarcoma (Figure 4).

Compound-related nonneoplastic lesions seen in the spleen were hematopoiesis and hemosiderosis in males and females and fibrosis and fatty metamorphosis in males (Table 8 and Figure 5). The fibrotic lesions consisted of focal or diffuse deposits of highly cellular connective tissue. Fatty metamorphosis was characterized as a focal collection of lipid-laden cells having a morphology similar to that of adipose tissue cells. Although the incidences of hematopoiesis and hemosiderosis in all groups were similar, the lesions were more severe in the dosed groups of rats than in the vehicle controls. The splenic capsule was also thickened and had hypertrophic mesothelial cells on the surface. A normal spleen is shown in Figure 6.

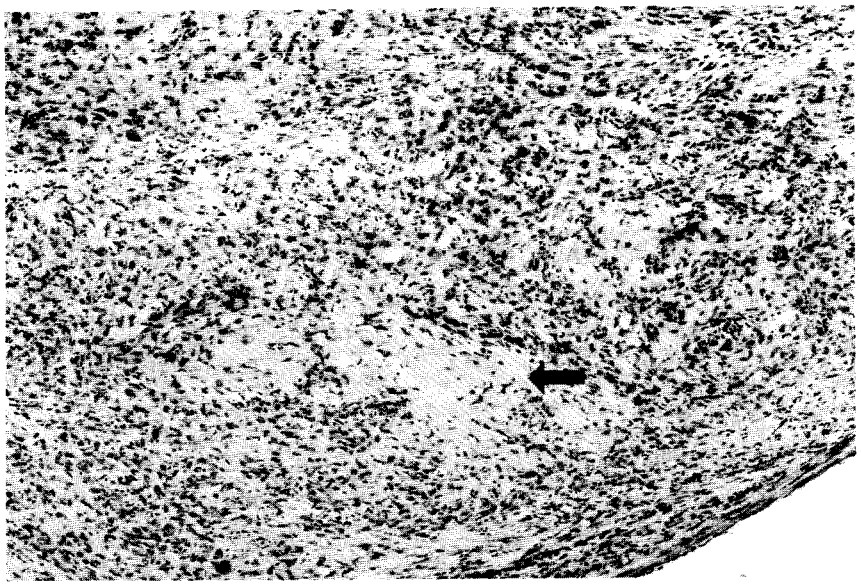


Figure 3. Splenic osteosarcoma from a high dose male rat (Animal No. 45) with large areas of osteoid (arrow).

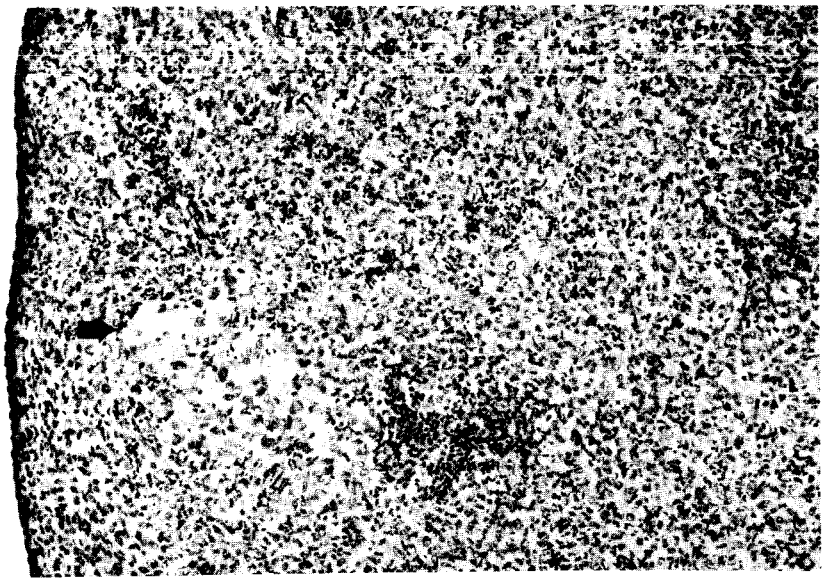


Figure 4. Splenic sarcoma from a high dose male rat (Animal No. 21) consisting of indistinct cells with vesiculate nuclei. Note focus of osteoid production (arrow).

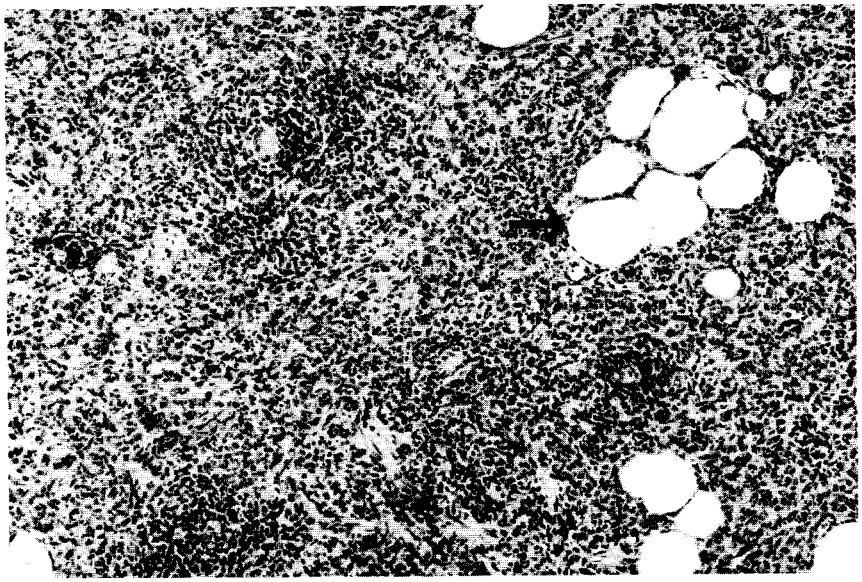


Figure 5. Spleen from a high dose male rat (Animal No. 12) showing fibrosis of the red pulp with focal fatty metamorphosis (arrow).

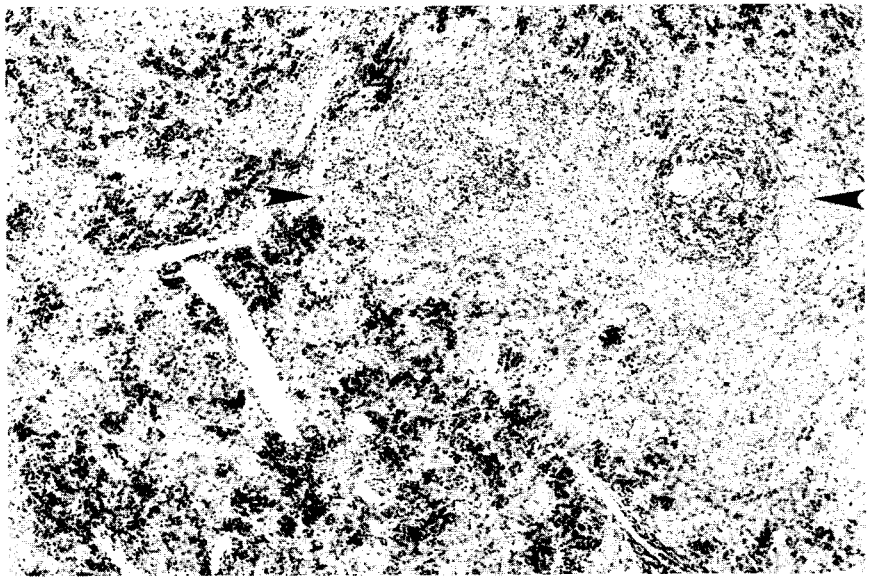


Figure 6. Normal spleen of a high dose male rat (Animal No. 8). Note the size of the lymphoid follicle (between arrows) compared with the fibrotic spleen (see Figure 5).

TABLE 8. SPLENIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE (a)

	Vehicle Control	3 mg/kg	30 mg/kg
MALE			
Hematopoiesis	44/49	48/49	50/50
Normal	5/49	1/49	0/50
Minimal	41/49	38/49	29/50
Mild	2/49	7/49	19/50
Moderate	0/49	3/49	2/50
Marked	1/49	0/49	0/50
Mean severity (b)	1.00 ± 0.09	1.24 ± 0.09	**1.46 ± 0.08
Hemosiderosis	43/49	47/49	49/50
Normal	6/49	2/49	1/50
Minimal	39/49	17/49	13/50
Mild	4/49	29/49	25/50
Moderate	0/49	1/49	11/50
Marked	0/49	0/49	0/50
Mean severity (b)	0.96 ± 0.06	**1.59 ± 0.09	**1.92 ± 0.11
Fibrosis	5/49	2/49	**22/50
Fatty Metamorphosis	0/49	1/49	**10/50
Sarcoma			
Overall Rates	0/49 (0%)	0/49 (0%)	3/50 (6%)
Incidental Tumor Tests	P=0.029	(c)	P=0.107
Osteosarcoma			
Overall Rates	0/49 (0%)	0/49 (0%)	1/50 (2%)
Sarcoma or Osteosarcoma (d)			
Overall Rates	0/49 (0%)	0/49 (0%)	4/50 (8%)
Incidental Tumor Tests	P=0.009	(c)	P=0.055
FEMALE			
Hematopoiesis	47/50	48/49	49/49
Normal	3/50	1/49	0/49
Minimal	25/50	16/49	9/49
Mild	22/50	30/49	38/49
Moderate	0/50	1/49	1/49
Marked	0/50	1/49	1/49
Mean severity (b)	1.38 ± 0.09	1.69 ± 0.09	**1.88 ± 0.08
Hemosiderosis	47/50	48/49	49/49
Normal	3/50	1/49	0/49
Minimal	10/50	5/49	1/49
Mild	37/50	29/49	20/49
Moderate	0/50	14/49	28/49
Marked	0/50	0/49	0/49
Mean severity (b)	1.68 ± 0.08	**2.14 ± 0.10	**2.55 ± 0.08
Fibrosis	2/50	0/49	2/49
Fatty Metamorphosis	0/50	1/49	0/49
Sarcoma	1/50	0/49	0/49

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Mean ± standard error; 0 = normal; 1 = minimal; 2 = mild; 3 = moderate; 4 = marked. P values by Mann Whitney U test (severity) (Hollander and Wolfe, 1973) or by incidental tumor test (nonneoplastic lesions).
(c) No P value is reported because no tumors were observed in the 3 mg/kg and vehicle control groups.
(d) Historical incidence of sarcomas at study laboratory (mean ± SD): 1/148 (0.7% ± 1%); historical incidence in NTP studies: 3/2,081 (0.1% ± 0.5%); no osteosarcomas have been observed.
**P<0.01 vs. vehicle controls

Peripheral Nerves: The combined incidences of neurilemomas from all sites were as follows: male--vehicle control, 2/50; low dose, 7/50; high dose, 7/50; female--3/50; 2/50; 2/50. The slightly increased incidences of neurilemomas in dosed males were not statistically significant and were not considered to be related to chemical administration. All the neurilemomas in the region of the salivary glands were observed grossly. The incidences of neurilemomas in dosed females were not increased over vehicle control females despite the better survival of the dosed females. Neurilemomas occur uncommonly, with an average historical incidence in male F344/N rats in NTP studies of 10/2,099 (0.5%); thus the number of neurilemomas observed in these studies is unusual. However, in two other contemporary studies (penicillin VK and benzofuran) at the same laboratory, there were high incidences of neurilemomas in both vehicle control and dosed rats. The incidence in vehicle control male rats in the benzofuran studies was 34% (penicillin VK--male: 4/50; 3/50; 2/50; female: 0/50; 3/50; 1/50; benzofuran--male: 17/50; 14/50; 12/50; female: 4/50; 9/50; 3/50). Neurilemomas were not considered to be compound related in either of these studies. Thus, an unusually high number of neurilemomas have occurred in vehicle control and dosed rats in studies of unrelated compounds conducted at this laboratory. The neurilemomas in these studies are considered to be unrelated to chemical administration.

Forestomach: Papillomas were observed in 2/50 high dose male rats (Table A1). The historical incidence of forestomach papillomas or carcinomas (combined) in corn oil vehicle control F344/N rats is 7/2,072 (0.3%). No more than one tumor has been observed in any vehicle control group. However, the incidence of papillomas in the high dose group was not statistically different from that in the concurrent vehicle controls and thus was not considered to be related to chemical administration.

Liver: Chronic focal inflammation was observed at increased incidences ($P<0.05$) in high dose female rats (male: none observed; female: vehicle control, 17/50; low dose, 20/46; high dose, 30/50).

Hematopoietic System: The incidences of mononuclear cell leukemia (which is believed to originate in the spleen) in high dose rats were significantly lower than those in vehicle controls (Table 9).

TABLE 9. HEMATOPOIETIC SYSTEM TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE (a)

	Vehicle Control	3 mg/kg	30 mg/kg
MALE			
Mononuclear Cell Leukemia (b)			
Overall Rates	13/50 (26%)	4/50 (8%)	3/50 (6%)
Terminal Rates	4/29 (14%)	2/32 (6%)	1/28 (4%)
Week of First Observation	91	99	83
Life Table Tests	P=0.057N	P=0.018N	P=0.017N
Incidental Tumor Tests	P=0.056N	P=0.022N	P=0.017N
FEMALE			
Mononuclear Cell Leukemia (c)			
Overall Rates	11/50 (22%)	7/50 (14%)	0/50 (0%)
Terminal Rates	2/21 (10%)	4/32 (13%)	0/36 (0%)
Week of First Observation	86	68	
Life Table Tests	P<0.001N	P=0.132N	P<0.001N
Incidental Tumor Tests	P=0.003N	P=0.391N	P=0.005N

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of leukemia in study laboratory (mean ± SD): 32/150 (21% ± 10%); historical incidence in NTP studies: 361/2,099 (17% ± 9%)
(c) Historical incidence of leukemia in study laboratory (mean ± SD): 38/150 (25% ± 3%); historical incidence in NTP studies: 403/2,100 (19% ± 8%)

SINGLE-ADMINISTRATION STUDIES

All mice that received 5,640 mg/kg died before the end of the studies (Table 10). Deaths occurred in all groups except the 350 mg/kg group of females. Decreased motor activity on the day of dosing was observed for mice that received 1,410 mg/kg or more *N,N*-dimethylaniline. Tremors were seen in one male and three female mice that received 5,640 mg/kg.

FIFTEEN-DAY STUDIES

All mice that received 750 or 1,500 mg/kg died before the end of the studies (Table 11). The death of one male receiving 188 mg/kg was not compound related. The final mean body weights of dosed and vehicle control mice were similar. Compound-related clinical signs included lethargy, excessive salivation, and tremors. Splenomegaly was seen in 2/5 male and 3/5 female mice receiving 375 mg/kg and in 1/5 males receiving 188 mg/kg. Congestion and increased extramedullary hematopoiesis or hemosiderin were seen in the spleen of 3/3 males and 3/3 females receiving 375 mg/kg.

TABLE 10. SURVIVAL AND INITIAL MEAN BODY WEIGHTS OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Dose (mg/kg)	Survival (a)	Initial Mean Body Weight (grams) (b)
MALE (c)		
350	(d) 4/5	26.4 ± 0.2
700	(d) 4/5	26.8 ± 0.2
1,410	(e) 2/4	25.6 ± 0.7
2,820	(f) 2/5	26.4 ± 0.6
5,640	(d) 0/5	26.0 ± 0.9
FEMALE (g)		
350	5/5	20.6 ± 0.2
700	(d) 3/5	21.0 ± 0.5
1,410	(d) 4/5	21.4 ± 0.4
2,820	(h) 1/5	21.6 ± 0.4
5,640	(d) 0/5	20.8 ± 0.2

(a) Number surviving/number initially in group; LD_{50} (95% confidence interval) by probit analysis.
(b) Initial group mean body weight ± standard error of the mean; final body weights were not recorded.
(c) LD_{50}: 1,376 mg/kg (530-3,475 mg/kg)
(d) Day of death: 1
(e) Day of death: 1,3
(f) Day of death: 1,2,3
(g) LD_{50}: 1,480 mg/kg (782-2,848 mg/kg)
(h) Day of death: 1,3,3,3,3

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FIFTEEN-DAY GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	25.2 ± 0.6	26.0 ± 0.6	+ 0.8 ± 0.2	
94	5/5	26.0 ± 1.4	28.1 ± 1.3	+ 2.1 ± 0.4	108.1
188	(d) 4/5	24.7 ± 0.4	26.6 ± 0.5	+ 2.1 ± 0.7	102.3
375	5/5	26.5 ± 0.8	28.6 ± 0.7	+ 2.1 ± 0.4	110.0
750	(e) 0/5	25.7 ± 1.0	(f)	(f)	(f)
1,500	(d) 0/5	25.8 ± 0.7	(f)	(f)	(f)
FEMALE					
0	5/5	19.8 ± 0.3	21.1 ± 0.3	+ 1.3 ± 0.4	
94	5/5	19.8 ± 0.7	21.3 ± 0.6	+ 1.5 ± 0.3	100.9
188	5/5	19.7 ± 0.8	21.3 ± 0.7	+ 1.6 ± 0.3	100.9
375	5/5	20.4 ± 0.6	22.8 ± 0.6	+ 2.4 ± 0.6	108.1
750	(g) 0/5	20.1 ± 0.6	(f)	(f)	(f)
1,500	(d) 0/5	19.6 ± 0.7	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: all 3
(e) Day of death: 4,6,6,6,12
(f) No data are reported due to 100% mortality in this group.
(g) Day of death: 6,6,6,6,9

THIRTEEN-WEEK STUDIES

No compound-related deaths occurred (Table 12). The final mean body weights of all groups of dosed male mice were approximately 8%-10% lower than that of the vehicle controls. The final mean body weights of dosed female mice were not clearly dose related. Compound-related clinical signs included blanching and lethargy. Compound-related histopathologic changes occurred in the spleen, liver, and kidney of male and female mice (Table 13). The incidence and/or severity of these lesions increased with increasing dose. These effects were present in all groups administered doses of 62 mg/kg or more.

The spleen of the affected mice contained increased numbers of hematopoietic cells, which in some mice were abundant enough to produce splenic enlargement and numerous prominent macrophages filled with yellow-brown granular pigment, identified as hemosiderin with Perl's stain. In contrast, the spleen of vehicle control mice contained few hematopoietic cells and only small numbers of hemosiderin-filled macrophages, which is normal for the mouse spleen. In the liver of dosed mice, Kupffer cells were enlarged and filled with yellow-brown to brown granular pigment (hemosiderin) similar to that seen in the spleen. These pigmented cells were scattered throughout the liver. In addition, the liver of some dosed mice contained scattered foci of hematopoietic cells. Cortical epithelial cells in the kidney of dosed mice also contained yellow-brown granular pigment. The pigment in the liver and kidney was identified as hemosiderin with Perl's stain.

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	9/10	30.5 ± 0.3	38.6 ± 1.0	+ 8.3 ± 0.8	
31.25	(d) 8/10	29.0 ± 0.9	34.8 ± 0.5	+ 5.5 ± 1.0	90.2
62.5	(e) 7/10	29.9 ± 0.6	35.1 ± 0.9	+ 5.4 ± 0.4	90.9
125	10/10	28.8 ± 0.5	33.9 ± 1.0	+ 5.1 ± 0.9	87.8
250	(f) 9/10	27.3 ± 0.8	34.9 ± 1.5	+ 7.6 ± 1.0	90.4
500	10/10	30.4 ± 0.4	35.3 ± 0.7	+ 4.9 ± 0.8	91.5
FEMALE					
0	10/10	23.4 ± 0.8	28.4 ± 1.2	+ 5.0 ± 0.7	
31.25	10/10	24.7 ± 0.4	26.4 ± 0.5	+ 1.7 ± 0.3	93.0
62.5	(g) 9/10	23.1 ± 0.4	26.7 ± 0.9	+ 3.5 ± 0.8	94.0
125	10/10	23.2 ± 0.4	25.9 ± 0.7	+ 2.7 ± 0.4	91.2
250	10/10	24.1 ± 0.3	28.0 ± 0.6	+ 3.9 ± 0.5	98.6
500	10/10	23.3 ± 0.4	27.8 ± 0.7	+ 4.5 ± 0.5	97.9

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 1,1
(e) Week of death: 2,3,8
(f) Week of death: 10
(g) Week of death: 12

TABLE 13. INCIDENCES OF MICE WITH SELECTED LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE (a)

Site/Lesion	Vehicle Control	31 mg/kg	62 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg
MALE						
Spleen						
Hematopoiesis, extramedullary	1/10 (1.0)	1/10 (2.0)	6/9 (1.4)	9/10 (1.9)	10/10 (2.2)	10/10 (3.9)
Hemosiderosis	1/10 (3.0)	0/10	5/9 (2.0)	9/10 (2.0)	9/10 (2.9)	10/10 (4.6)
Liver						
Pigmentation	1/10 (1.0)	1/10 (1.0)	0/10	9/9 (1.1)	9/10 (3.1)	9/10 (3.7)
Hematopoiesis, extramedullary	1/10 (1.0)	0/10	0/10	0/9	0/10	6/10 (2.3)
Kidney						
Pigmentation	0/10	0/10	0/3	(b)	0/10	8/10 (2.6)
FEMALE						
Spleen						
Hematopoiesis, extramedullary	0/10	0/10	8/10 (1.9)	10/10 (1.8)	10/10 (2.4)	10/10 (3.9)
Hemosiderosis	0/10	0/10	8/10 (2.1)	10/10 (2.0)	10/10 (2.9)	10/10 (5.0)
Liver						
Pigmentation	1/10 (1.0)	(b)	0/10	10/10 (1.0)	10/10 (3.2)	10/10 (3.3)
Hematopoiesis, extramedullary	0/10	(b)	0/10	0/10	0/10	8/10 (2.1)
Kidney						
Pigmentation	0/10	(b)	(b)	0/10	10/10 (1.2)	10/10 (2.8)

(a) Lesion incidence is the number of animals with the lesion/number of animals examined; number in parentheses denotes mean grade of severity (1 = minimal; 2 = mild; 3 = moderate; 4 = marked; 5 = severe).
(b) Not examined

Dose Selection Rationale: Because of splenomegaly and increases in the severity of hemosiderin accumulation and extramedullary hematopoiesis at higher doses, doses selected for mice for the 2-year studies were 15 and 30 mg/kg *N,N*-dimethylaniline, administered in corn oil by gavage 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control mice were similar throughout the studies (Table 14 and Figure 7). No compound-related clinical signs were observed.

TABLE 14. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Weeks on Study	Vehicle Control		15 mg/kg			30 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	25.1	50	23.5	94	50	24.2	96	50
1	25.8	50	30.0	116	50	27.4	106	50
2	27.4	50	31.3	114	50	29.4	107	50
3	26.9	50	28.1	104	50	27.4	102	50
4	30.8	50	29.3	95	50	31.7	103	50
5	31.2	50	32.9	105	50	35.6	114	50
6	34.3	50	40.6	118	50	38.1	111	50
7	28.7	50	31.5	110	50	30.0	105	50
8	30.7	50	31.0	101	50	30.4	99	50
9	33.3	50	35.9	108	50	34.7	104	50
10	32.0	50	33.4	104	50	32.8	103	50
11	30.7	50	32.0	104	50	31.4	102	50
12	34.4	49	35.7	104	50	34.5	100	50
16	36.1	49	36.7	102	50	35.6	99	50
20	36.7	47	37.1	101	50	36.3	99	50
24	38.1	47	37.6	99	50	37.1	97	50
28	38.7	47	39.0	101	49	38.0	98	50
32	40.2	47	40.4	100	49	38.6	96	50
36	40.6	47	41.7	103	49	40.2	99	50
40	40.5	47	42.7	105	49	40.8	101	50
44	42.2	47	41.1	97	49	42.2	100	50
48	43.3	47	43.6	101	49	43.7	101	50
52	42.5	47	41.3	97	49	43.4	102	50
56	43.5	46	44.8	103	49	44.6	103	50
60	44.7	46	44.6	100	49	45.2	101	50
64	45.3	46	46.6	103	49	45.8	101	50
68	46.1	46	46.1	100	49	46.5	101	50
72	46.3	46	45.6	98	48	46.2	100	50
76	46.1	46	45.1	98	47	46.3	100	50
80	45.8	46	46.8	102	45	46.5	102	47
84	45.8	45	45.5	99	41	46.2	101	47
90	44.0	43	44.2	100	38	44.5	101	42
96	43.7	37	44.7	102	35	44.3	101	39
100	42.1	35	43.9	104	33	44.3	105	36
102	43.6	34	42.7	98	31	45.6	105	35
FEMALE								
0	20.9	50	20.6	99	50	21.1	101	50
1	25.2	49	23.7	94	50	26.2	104	50
2	20.4	49	23.0	113	50	22.4	110	50
3	21.8	49	22.7	104	50	22.7	104	50
4	23.9	49	25.1	105	49	23.9	100	50
5	24.7	49	26.2	106	49	25.9	105	50
6	25.3	49	27.7	109	49	26.5	105	50
7	25.8	49	26.1	101	49	25.7	100	50
8	23.3	49	23.3	100	49	23.9	103	50
9	26.3	49	27.1	103	49	26.8	102	50
10	25.8	49	26.0	101	49	26.2	102	50
11	26.8	49	26.9	100	49	27.1	101	50
12	26.7	49	25.8	97	49	26.8	100	50
16	29.4	49	28.3	96	49	28.7	98	50
20	28.9	49	28.2	98	49	29.1	101	50
24	29.8	49	28.5	96	49	29.5	99	50
28	30.7	49	28.9	94	49	30.8	100	50
32	32.6	49	31.4	96	49	32.1	98	50
36	32.9	49	31.9	97	49	32.9	100	50
40	33.5	49	33.0	99	49	34.4	103	50
44	35.0	49	34.0	97	49	35.2	101	50
48	35.7	49	35.2	99	49	36.5	102	50
52	36.0	48	35.6	99	49	36.3	101	49
56	38.2	48	37.0	97	49	38.9	102	49
60	38.4	48	37.3	97	49	39.8	104	49
64	40.6	48	38.9	96	49	41.2	101	49
68	41.8	48	40.5	97	48	42.3	101	49
72	42.1	48	40.1	95	47	43.4	103	49
76	42.3	48	41.6	98	47	44.2	104	49
80	44.5	48	42.7	96	47	44.1	99	47
84	44.3	47	43.3	98	46	44.3	100	47
90	43.7	44	41.1	94	44	44.6	102	45
96	43.5	43	42.1	97	42	44.1	101	40
100	43.0	41	41.0	95	41	43.8	102	36
102	42.0	37	41.8	100	39	42.7	102	34

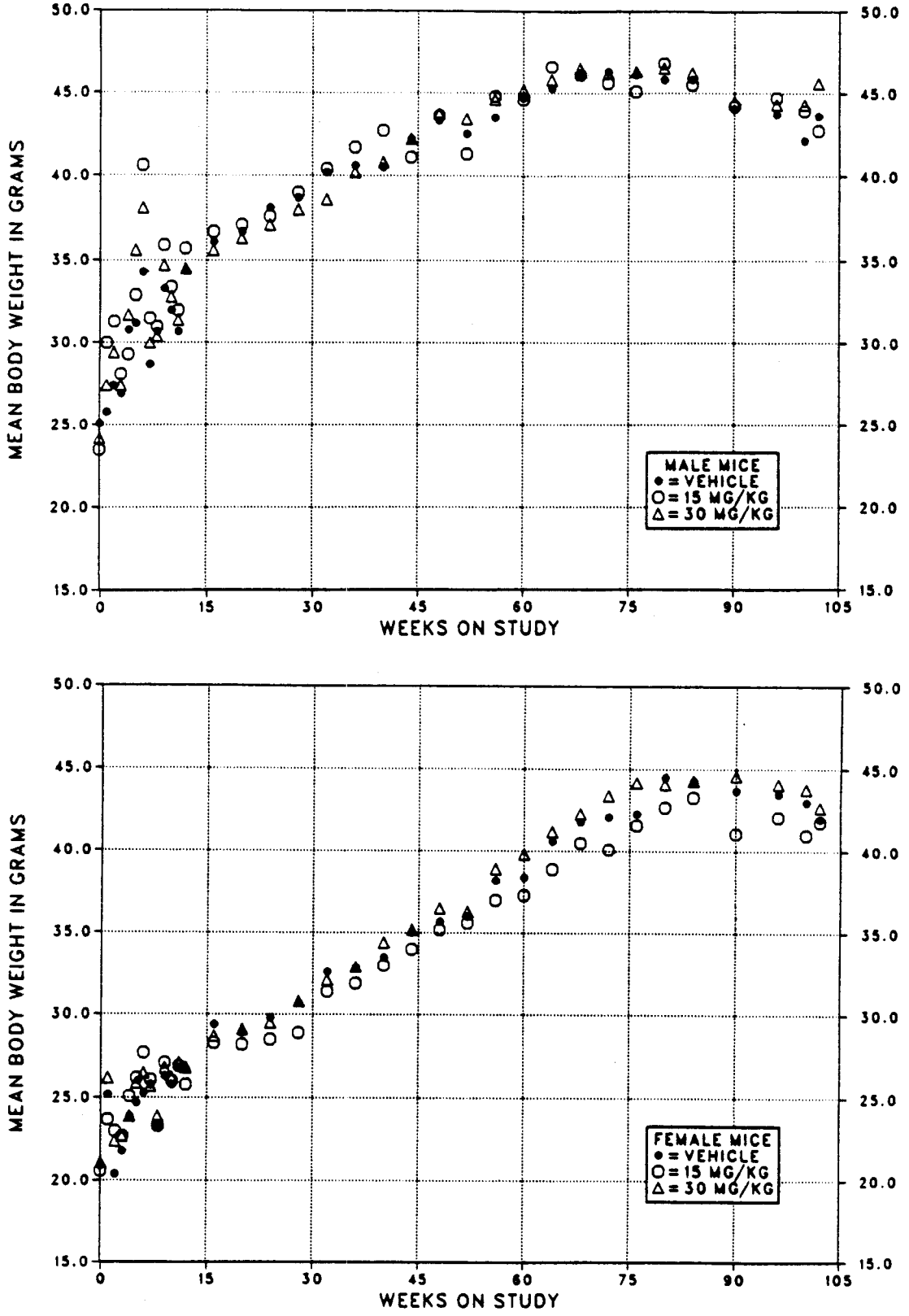


FIGURE 7. GROWTH CURVES FOR MICE ADMINISTERED *N,N*-DIMETHYLANILINE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered *N,N*-dimethylaniline at the doses used in these studies and for vehicle controls are shown in Table 15 and in the Kaplan and Meier curves in Figure 8. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the forestomach and pituitary gland.

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 animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice, respectively.

TABLE 15. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

	Vehicle Control	15 mg/kg	30 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	6	14	13
Moribund kills	6	6	3
Animals surviving to termination	34	30	34
Killed accidentally	4	0	0
Survival P values (b)	0.579	0.158	0.610
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	7	7	10
Moribund kills	8	3	7
Animals surviving to termination	35	39	33
Killed accidentally	0	1	0
Survival P values (b)	0.675	0.437	0.740

(a) Termination period: week 104
(b) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

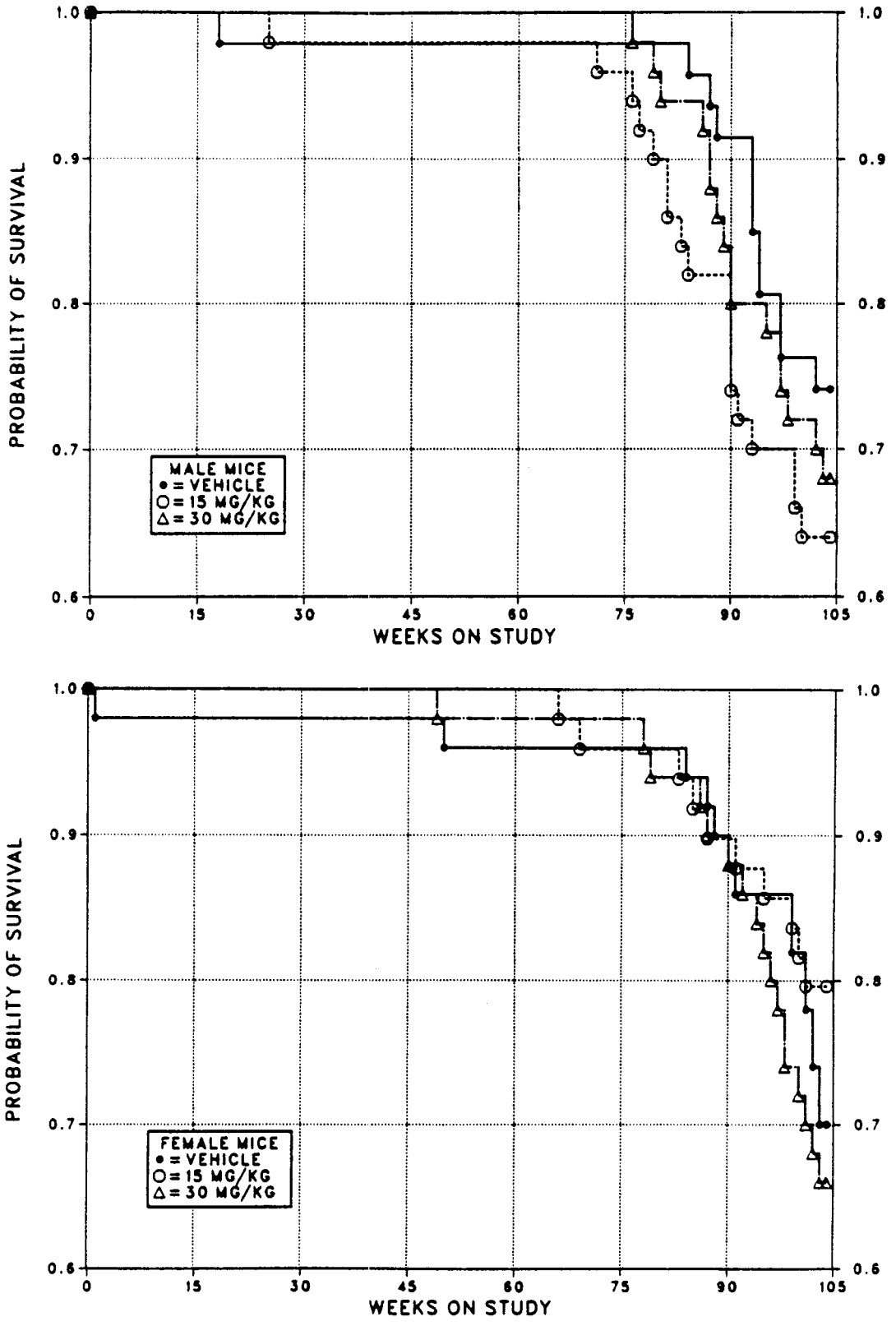


FIGURE 8. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED *N,N*-DIMETHYLANILINE IN CORN OIL BY GAVAGE FOR TWO YEARS

Forestomach: Squamous cell papillomas were seen in 2/50 vehicle control, 2/19 low dose, and 8/50 high dose female mice examined microscopically. The incidence of squamous cell papillomas in high dose female mice was significantly greater than that in vehicle controls (Table 16). The highest incidence of squamous cell neoplasms observed in a vehicle control group in previous studies is 5/44 (11%). The eight papillomas in the high dose female mice varied slightly in morphology. Most were exophytic papillary structures consisting of stratified squamous epithelium overlying a central core of connective tissue. Many of the papillomas had a narrow stalk, as shown in Figure 9, but some papillomas were more broad based. There were no squamous cell carcinomas identified in the stomach of female mice, suggesting that these papillomas might not be progressive. The incidences of focal epithelial hyperplasia were slightly increased in dosed female mice. Hyperplasia consisted of a focal increase in thickness of the stratified squamous epithelium that was, in some lesions, associated with an inflammatory reaction (Figure 10).

TABLE 16. LESIONS OF THE FORESTOMACH IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (a)

	Vehicle Control	15 mg/kg	30 mg/kg
Epithelial Hyperplasia			
Overall Rates	8/50 (16%)	(b) 11/19 (58%)	13/50 (26%)
Squamous Cell Papilloma (c)			
Overall Rates	2/50 (4%)	(b) 2/50 (4%)	8/50 (16%)
Terminal Rates	1/35 (3%)	1/39 (3%)	8/33 (24%)
Week of First Observation	99	100	104
Incidental Tumor Test	P=0.021	P=0.592	P=0.042

(a) For a complete explanation of the entries in this table, see Table D3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Nineteen forestomachs were examined microscopically.
(c) Historical incidence of squamous cell papillomas or carcinomas (combined) at study laboratory (mean ± SD): 7/141 (5% ± 6%); historical incidence in NTP studies: 32/2,047 (2% ± 3%)

Pituitary Gland: The incidences of adenomas and adenomas or carcinomas (combined) in high dose female mice were significantly lower than those in vehicle controls (Table 17). However, this decrease was not considered to be related to chemical adminstration because these neoplasms occur at a variable incidence in corn oil vehicle control female B6C3F$_1$ mice (Table D4b).

TABLE 17. PITUITARY GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (a)

	Vehicle Control	15 mg/kg	30 mg/kg
Chromophobe Cell Hyperplasia			
Overall Rates	10/45 (22%)	(b) 2/14 (14%)	16/44 (36%)
Adenoma			
Overall Rates	18/45 (40%)	(b) 5/14 (36%)	7/44 (16%)
Terminal Rates	17/34 (50%)		6/30 (20%)
Week of First Observation	102		103
Incidental Tumor Test			P=0.017N
Carcinoma			
Overall Rates	0/45 (0%)	(b) 0/14 (0%)	1/44 (2%)
Adenoma or Carcinoma (c)			
Overall Rates	18/45 (40%)	(b) 5/14 (36%)	8/44 (18%)
Terminal Rates	17/34 (50%)		6/30 (20%)
Week of First Observation	102		94
Incidental Tumor Test			P=0.031N

(a) For a complete explanation of the entries in this table, see Table D3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Incomplete sampling of tissues
(c) Historical incidence at study laboratory (mean ± SD): 36/134 (27% ± 12%); historical incidence in NTP studies: 418/1,893 (22% ± 10%)

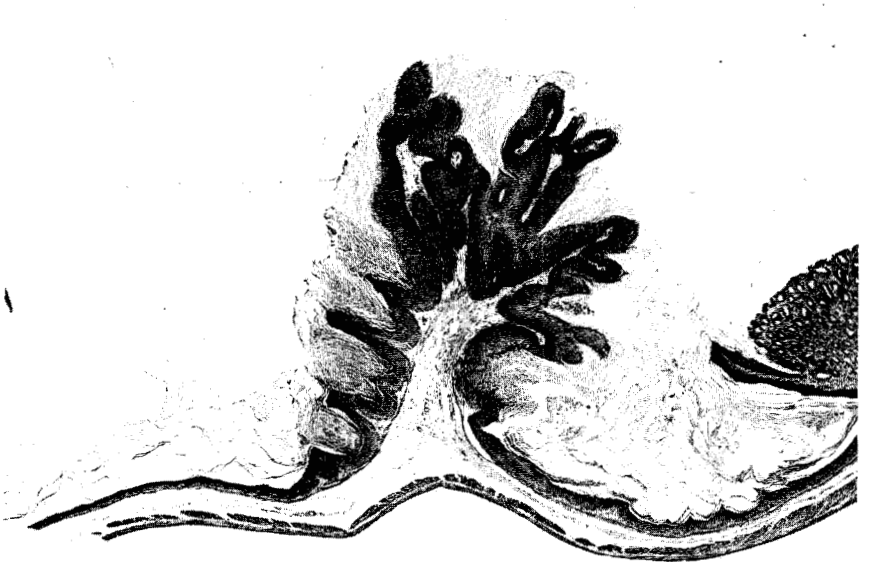


Figure 9. Forestomach papilloma from a high dose female mouse (Animal No. 4) showing fingerlike projections into the lumen. This example is representative of those seen in this dose group.

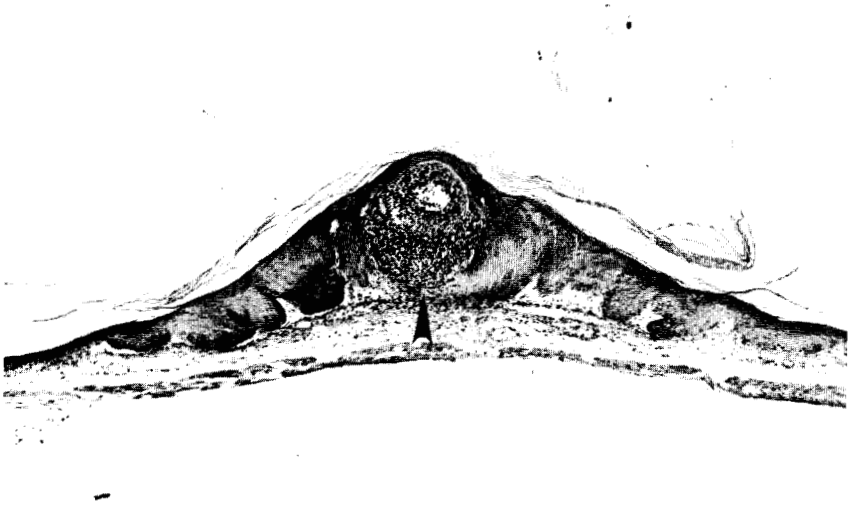


Figure 10. Forestomach focal hyperplasia from a high dose female mouse (Animal No. 15). Arrow indicates a central area of inflammation.

N,N-Dimethylaniline was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of exogenous metabolic activation. In the mouse lymphoma assay, *N,N*-dimethylaniline produced a positive response with and without metabolic activation. In Chinese hamster ovary cells, *N,N*-dimethylaniline induced both sister chromatid exchanges and chromosomal aberrations in the presence of exogenous metabolic activation. Without activation, an increase in chromosomal aberrations was observed (at the highest dose tested), but no increase in SCEs occurred.

The experimental procedures and results are presented in Appendix H.

IV. DISCUSSION AND CONCLUSIONS

Short-Term Studies
Genetic Toxicology
Two-Year Studies
Conclusions

IV. DISCUSSION AND CONCLUSIONS

N,N-Dimethylaniline, used in the manufacture of vanillin, Michler's ketone, and methyl violet and other dyes, was nominated for study largely because of its structural similarity to carcinogenic anilines. Short-term and long-term studies of *N,N*-dimethylaniline were conducted in F344/N rats and $B6C3F_1$ mice. This compound was administered in corn oil by gavage because of its volatility. As with other anilines, the major site of toxicity for *N,N*-dimethylaniline is the hematopoietic system.

Short-Term Studies

Oral LD_{50} values for *N,N*-dimethylaniline, as determined by probit analysis, were approximately 1,300 mg/kg for male rats, 1,375 mg/kg for male mice, and 1,500 mg/kg for female mice. The LD_{50} for female rats could not be calculated because 100% lethality occurred over a very narrow dose range.

Based on the incidences of splenomegaly, hemosiderin accumulation, and extramedullary hematopoiesis observed in the 14-day and 13-week studies, rats were more susceptible than mice to the toxic effects of this compound. No sex difference in toxicity was noted. In the 13-week studies, a no-observed-effect level was not reached for rats, whereas this level was found to be about 30 mg/kg for mice. All male and female rats administered 31 mg/kg or more had mild, chemically induced extramedullary hematopoiesis and hemosiderosis of the spleen.

Splenic enlargement and the hematopoiesis, hemosiderosis, and pigmentation observed in the spleen, liver, and kidney in dosed rats and mice and in the testis in dosed rats and the hyperplasia of the bone marrow observed in dosed rats may be related to erythrocyte destruction by intravascular hemolysis and increased phagocytosis. A similar enlargement of the spleen was found in rats dosed with aniline (Gralla et al., 1979) and in rats and mice exposed to *p*-chloroaniline hydrochloride (NTP, 1989). The splenic weight increases in aniline-dosed rats were due to excessive deposition of damaged erythrocytes as a result of aniline toxicity (Bus, 1983). Results of the 13-week *N,N*-dimethylaniline studies support this suggestion because rats and mice had splenic enlargement that was not accompanied by any histopathologic degenerative change. *N,N*-Dimethylaniline, as well as several other aniline derivatives, induced methemoglobin formation in rats and mice (NTP, 1989). Cyanosis observed in rats dosed with *N,N*-dimethylaniline was also indicative of erythrocyte destruction and reduced blood oxygenation, possibly as a result of methemoglobin formation.

The finding that rats are more susceptible than mice to the toxic effects of *N,N*-dimethylaniline was expected. Species differences in response to chemical inducers of methemoglobin have long been recognized. Humans were reported to be more susceptible than rats to the toxic effects of aniline (a compound known to cause methemoglobinemia, Heinz body formation, and splenic enlargement) (Jenkins et al., 1972). Susceptibility to the toxic effects of acetanilide (another methemoglobin former) was also reported to vary among species. The susceptibility of the various species to this compound, relative to that of the cat, were as follows: humans, 56%; dogs, 29%; rats, 5%; rabbits, 0%; and monkeys, 0% (Beard and Noe, 1981). These differences may be due to differences in methemoglobin reductase activity in the erythrocytes of the various species. Reductase activity of less susceptible species, such as rats and rabbits, is twofold to fourfold that of humans (Robin and Harley, 1966). Differences in mixed function oxidase activity of rats and mice may account for the difference in their susceptibility to *N,N*-dimethylaniline.

Mixed function oxidase activity resulting in the *N*-oxidative transformation of *N,N*-dimethylaniline to form a stable *N*-oxide has been observed in vitro with rat liver microsomal preparations (Ziegler and Pettit, 1964). In vivo, the primary transformations observed with *N,N*-dimethylaniline are *N*-demethylation and ring hydroxylation (Kiese and Renner, 1974). *N,N*-Dimethylaniline has a greater propensity for ring hydroxylation than does aniline because of the electrons that are contributed to the ring by the methyl groups on the nitrogen. Hydroxylation of the ring to form the urinary metabolites 4-aminophenol, 4-dimethylaminophenol, and 2-aminophenol could involve an electrophilic arene oxide intermediate capable of covalently

binding to macromolecules. For primary aromatic amines, *N*-hydroxylation is considered an important step in production of cyanosis and methemoglobinemia (Smith, 1986). No reports were found which indicate that an *N*-hydroxy derivative of this chemical is formed.

Genetic Toxicology

Aniline and six structurally related chemicals, including *N,N*-dimethylaniline, are genotoxic in short-term tests in vitro. D & C Red No. 9 (NTP, 1982), *p*-chloroaniline hydrochloride (NTP, 1989), azobenzene (NCI, 1979a), and *o*-toluidine hydrochloride (NCI, 1979c) all produce splenic neoplasms, and all are positive in the Salmonella gene mutation assay (Ashby and Tennant, 1988). Aniline, *N,N*-dimethylaniline, and Dapsone, although negative in Salmonella tests, were clastogenic in cultured mammalian cells. The clastogenic response with *N,N*-dimethylaniline is increased in the presence of S9 and is observed at lower doses than with aniline. These observations are consistent with the hypothesis that a DNA-reactive arene oxide intermediate may be involved in the clastogenic activity of *N,N*-dimethylaniline.

Two-Year Studies

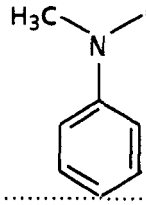
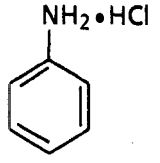
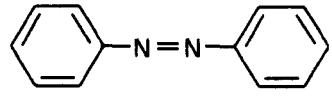
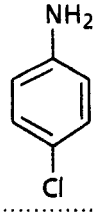
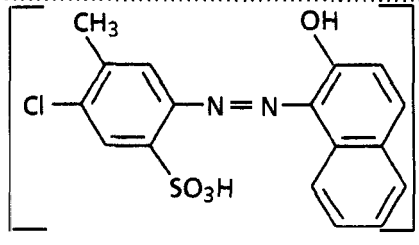
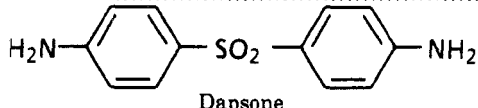
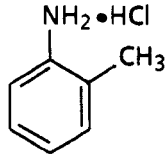
N,N-Dimethylaniline administered for up to 2 years at doses of 3 or 30 mg/kg for rats and 15 or 30 mg/kg for mice had no influence on body weight or survival. The apparent positive trend and significantly higher survival observed in high dose female rats is due to poor survival in the vehicle control group (21/50).

Sarcomas or osteosarcomas (combined) of the spleen occurred with a positive trend in male rats, and the incidence in high dose males (4/50) was greater than that ever seen in corn oil vehicle control F344/N male rats (1/45; mean historical incidence, 3/2,081, 0.1%). The splenic sarcomas were morphologically typical of those induced by other aniline compounds. These sarcomas are anaplastic neoplasms that exhibit a range of differentiation. Most have histologic characteristics of fibrosarcoma, but some have features of osteosarcoma or hemangiosarcoma. The rare splenic sarcomas that occur spontaneously in control F344 rats typically do not have the histologic features of those induced by aniline compounds. The sites of carcinogenicity and the sex differences in response to dosing with *N,N*-dimethylaniline were generally similar to that of aniline and other structurally related chemicals (Tables 18 and 19). All these compounds caused sarcomas in the spleen of male rats; female rats were less susceptible than males to induction of splenic tumors by these compounds, except in the case of the azobenzene and *o*-toluidine hydrochloride studies in which females were equally susceptible. Although high dose male rats in the current study showed an increase in the incidence of fatty metamorphosis and fibrosis of the spleen, such an increase was not seen in low dose males or dosed females (see Table 8).

Fibrosis in the spleen is considered a potential preneoplastic lesion that may progress to fibrosarcoma (Goodman et al., 1984). In a review of F344/N rat spleens from studies with D & C Red No. 9 and aniline, all groups of rats that had fatty metamorphosis also had splenic sarcomas; groups without this lesion did not exhibit splenic neoplasms (Weinberger et al., 1985). Retrospectively, it appears that the lack of compound-related increases in fatty metamorphosis, fibrosis, and sarcomas of the spleen in dosed female rats could be related to the doses used in the current studies. At the doses studied (3 or 30 mg/kg), *N,N*-dimethylaniline did not adversely affect survival or body weights of female rats, and thus the female rats might have tolerated higher doses. This could not have been predicted from the 13-week study results.

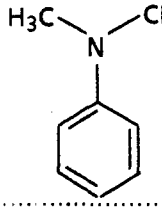
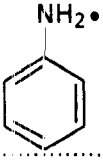
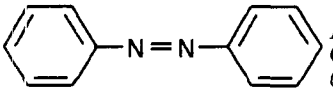
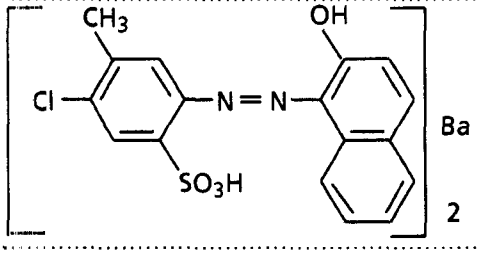
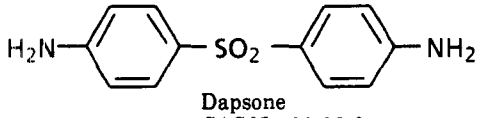
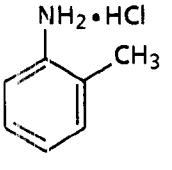
Weinberger et al. (1985) did not find any correlation between splenic hemosiderosis and the incidence of splenic neoplasms. In contrast, the incidence of hemosiderin classified as mild to moderate in male rats in the current 2-year study with *N,N*-dimethylaniline increased (vehicle control, 4/49; low dose, 30/49; high dose, 36/50) with the increased incidence of splenic sarcomas. A similar observation was noted with aniline hydrochloride (CIIT, 1982).

TABLE 18. INCIDENCES OF SPLENIC NEOPLASMS AND LEUKEMIA/LYMPHOMAS IN MALE RATS INDUCED BY ANILINE HYDROCHLORIDE AND STRUCTURALLY RELATED CHEMICALS STUDIED BY THE NCI/NTP

Structure/Chemical CAS Number (Reference)	Dose (a)	Spleen Sarcomas (b)	Multiple Organs Leukemia/Lymphomas
 *N,N*-Dimethylaniline CAS No. 121-69-7 (NTP TR 360, current study	Route of administration: gavage in corn oil 0 mg/kg 0 µmol/kg 3 mg/kg 25 µmol/kg 30 mg/kg 248 µmol/kg	 0/49 0/49 4/50	 13/50 4/50 3/50
 Aniline hydrochloride CAS No. 142-04-1 (NCI TR 130, 1978)	Route of administration: feed 0 ppm 0 µmol/kg 3,000 ppm 810 µmol/kg 6,000 ppm 1,620 µmol/kg	 0/25 7/50 9/46	 1/25 3/50 0/48
 Azobenzene CAS No. 103-33-3 (NCI TR 154, 1979a)	Route of administration: feed 0 ppm 0 µmol/kg 200 ppm 38 µmol/kg 400 ppm 77 µmol/kg	 0/20 4/49 10/49	 3/20 1/49 8/50
 *p*-Chloroaniline CAS No. 106-47-8 (NCI TR 189, 1979b) *p*-Chloroaniline hydrochloride CAS No. 20265-96-7 (NTP TR 351, 1989)	Route of administration: feed 0 ppm 0 µmol/kg 250 ppm 71 µmol/kg 500 ppm 141 µmol/kg Route of administration: gavage in water 0 mg/kg 0 µmol/kg 2 mg/kg 12 µmol/kg 6 mg/kg 37 µmol/kg 18 mg/kg 110 µmol/kg	 0/20 0/49 3/49 0/49 1/50 3/50 36/50	 0/20 0/50 2/50 21/49 3/50 2/50 3/50
 D & C Red No. 9 CAS No. 5160-02-1 (NTP TR 225, 1982)	Route of administration: feed 0 ppm 0 µmol/kg 1,000 ppm 39 µmol/kg 3,000 ppm 118 µmol/kg	 0/50 0/50 26/48	 12/50 4/50 3/50
 Dapsone CAS No. 80-08-0 (NCI TR 20, 1977)	Route of administration: feed 0 ppm 0 µmol/kg 600 ppm 85 µmol/kg 1,200 ppm 169 µmol/kg	 0/14 0/34 6/32	 1/14 4/35 0/33
 *o*-Toluidine hydrochloride CAS No. 636-21-5 (NCI TR 153, 1979c)	Route of administration: feed 0 ppm 0 µmol/kg 3,000 ppm 658 µmol/kg 6,000 ppm 1,316 µmol/kg	 0/20 1/49 4/42	 4/20 2/50 0/49

(a) Gavage studies in milligrams per kilogram; feed studies in parts per million; micromoles per kilogram in feed studies based on 14 g feed per day for a 400-g male rat.
(b) Includes fibrosarcomas, osteosarcomas, and sarcomas, NOS

TABLE 19. INCIDENCES OF SPLENIC NEOPLASMS AND LEUKEMIA/LYMPHOMAS IN FEMALE RATS INDUCED BY ANILINE HYDROCHLORIDE AND STRUCTURALLY RELATED CHEMICALS STUDIED BY THE NCI/NTP

Structure/Chemical CAS Number (Reference)	Dose (a)		Spleen Sarcomas (b)	Multiple Organs Leukemia/Lymphomas
	Route of administration: gavage in corn oil			
N,N-Dimethylaniline CAS No. 121-69-7 (NTP TR 360, current study)	0 mg/kg	0 µmol/kg	1/50	11/50
	3 mg/kg	25 µmol/kg	0/50	7/50
	30 mg/kg	248 µmol/kg	0/50	0/50
	Route of administration: feed			
Aniline hydrochloride CAS No. 142-04-1 (NCI TR 130, 1978)	0 ppm	0 µmol/kg	0/23	3/24
	3,000 ppm	926 µmol/kg	0/50	4/50
	6,000 ppm	1,852 µmol/kg	3/50	0/50
	Route of administration: feed			
Azobenzene CAS No. 103-33-3 (NCI TR 154, 1979a)	0 ppm	0 µmol/kg	0/20	1/20
	200 ppm	44 µmol/kg	0/50	4/50
	400 ppm	88 µmol/kg	12/50	0/50
	Route of administration: feed			
p-Chloroaniline CAS No. 106-47-8 (NCI TR 189, 1979b)	0 ppm	0 µmol/kg	0/20	2/20
	250 ppm	78 µmol/kg	0/50	0/50
	500 ppm	157 µmol/kg	0/50	0/50
	Route of administration: gavage in water			
p-Chloroaniline hydrochloride CAS No. 20265-96-7 (NTP TR 351, 1989)	0 mg/kg	0 µmol/kg	0/50	10/50
	2 mg/kg	12 µmol/kg	0/50	2/50
	6 mg/kg	37 µmol/kg	1/50	1/50
	18 mg/kg	110 µmol/kg	1/50	1/50
	Route of administration: feed			
D & C Red No. 9 CAS No. 5160-02-1 (NTP TR 225, 1982)	0 ppm	0 µmol/kg	0/50	11/50
	1,000 ppm	45 µmol/kg	0/50	4/50
	3,000 ppm	135 µmol/kg	0/50	1/50
	Route of administration: feed			
Dapsone CAS No. 80-08-0 (NCI TR 20, 1977)	0 ppm	0 µmol/kg	0/15	0/15
	600 ppm	97 µmol/kg	0/34	0/34
	1,200 ppm	193 µmol/kg	0/35	0/35
	Route of administration: feed			
o-Toluidine hydrochloride CAS No. 636-21-5 (NCI TR 153, 1979c)	0 ppm	0 µmol/kg	0/20	1/20
	3,000 ppm	752 µmol/kg	2/49	3/50
	6,000 ppm	1,504 µmol/kg	4/49	0/49

(a) Gavage studies in milligrams per kilogram; feed studies in parts per million; micromoles per kilogram in feed studies based on 10 g feed per day for a 250-g female rat.
(b) Includes fibrosarcomas, osteosarcomas, and sarcomas, NOS

IV. DISCUSSION AND CONCLUSIONS

As with other aniline compounds, *N,N*-dimethylaniline caused a decrease in the incidence of mononuclear cell leukemia in rats (see Table 9). Male rats that had sarcomas of the spleen did not have leukemia. A review of NCI/NTP studies revealed an association between increased body weight and increased leukemia incidence in F344/N rats (Rao et al., 1987). In the current 2-year studies, final mean body weights of vehicle control and dosed rats were similar, so body weight was not considered a contributing factor. Because the major sites for the toxicity of *N,N*-dimethylaniline, as well as for other anilines, are the hematopoietic system and spleen, the decreased leukemia incidence may be a direct effect of the chemical on the mechanism responsible for the induction of leukemia in the aging rat. Splenectomy has been reported to greatly decrease the incidence of leukemia in F344 rats, suggesting that this neoplasm originates in the spleen (Moloney and King, 1973).

For mice as for rats, *N,N*-dimethylaniline had no effect on survival or body weights. Because no compound-related increases were noted for nonneoplastic or neoplastic lesions at any site in male mice and no clearly compound-related increases were noted in female mice, it appears that mice could have received higher doses of the compound.

The observation that *N,N*-dimethylaniline did not increase the incidence of splenic neoplasms in male or female mice is similar to results seen with other aromatic amines (Weisberger, 1983; NTP, 1989). However, unlike other aromatic amines, *N,N*-dimethylaniline did not cause an increase in liver neoplasms but did cause a slight increase in the incidence of forestomach papillomas in female mice. Papilloma is diagnosed when a proliferative lesion of the forestomach mucosa has an exophytic papillary form. The papillary structures consisted of a thickened, stratified squamous epithelium overlying a fibrous connective tissue core. Well-developed papillomas usually have a narrow stalk. It is uncertain if these proliferative lesions are true neoplasms or merely an advanced stage of hyperplasia. The forestomach papillomas may be preneoplastic lesions, since a squamous cell carcinoma has a greater probability of originating from a papilloma than from normal forestomach mucosa. Because no squamous cell carcinomas occurred in the forestomach of female mice, the papillomas seen in this study are considered to be early-stage lesions and might or might not have progressed to carcinomas. Furthermore, there was no increase in the low dose group. Therefore, the occurrence of the forestomach lesions is considered to be equivocal evidence of carcinogenic activity of *N,N*-dimethylaniline.

Conclusions

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenic activity** of *N,N*-dimethylaniline for male F344/N rats, as indicated by the increased incidences of sarcomas or osteosarcomas (combined) of the spleen. There was *no evidence of carcinogenic activity* of *N,N*-dimethylaniline for female F344/N rats given 3 or 30 mg/kg body weight by gavage for 2 years. There was *no evidence of carcinogenic activity* of *N,N*-dimethylaniline for male B6C3F$_1$ mice given 15 or 30 mg/kg body weight by gavage for 2 years. There was *equivocal evidence of carcinogenic activity* of *N,N*-dimethylaniline for female B6C3F$_1$ mice, as indicated by an increased incidence of squamous cell papillomas of the forestomach. Both rats and mice could have tolerated doses higher than those used in these studies.

There were decreased incidences of mononuclear cell leukemia in dosed male and high dose female rats. Compound-related splenic fibrosis, hemosiderosis, and fatty metamorphosis were increased in male rats.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Papilloma, NOS			1 (2%)
Squamous cell carcinoma	1 (2%)		1 (2%)
Basal cell tumor		1 (2%)	
Keratoacanthoma	1 (2%)	1 (2%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)	1 (2%)	1 (2%)
Fibroma	2 (4%)	3 (6%)	2 (4%)
Fibrosarcoma		1 (2%)	
Mesothelioma, invasive			1 (2%)
Neurilemoma, malignant	1 (2%)	5 (10%)	3 (6%)
RESPIRATORY SYSTEM			
#Trachea	(49)	(3)	(49)
Neurilemoma, invasive		1 (33%)	
#Lung	(49)	(10)	(50)
Carcinoma, NOS, metastatic		1 (10%)	
Alveolar/bronchiolar adenoma		1 (10%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (10%)	
Pheochromocytoma, metastatic	1 (2%)		
Sarcoma, NOS, metastatic		1 (10%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	13 (26%)	2 (4%)	3 (6%)
#Spleen	(49)	(49)	(50)
Leukemia, mononuclear cell		2 (4%)	
#Splenic red pulp	(49)	(49)	(50)
Sarcoma, NOS			3 (6%)
Osteosarcoma			1 (2%)
#Thymus	(24)	(4)	(26)
Sarcoma, NOS			1 (4%)
Neurilemoma, metastatic			1 (4%)
CIRCULATORY SYSTEM			
#Heart	(49)	(8)	(50)
Sarcoma, NOS, metastatic		1 (13%)	
#Heart/atrium	(49)	(8)	(50)
Mesothelioma, NOS		1 (13%)	
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Papilloma, NOS	1 (2%)	1 (2%)	
Squamous cell carcinoma	1 (2%)		
#Salivary gland	(48)	(14)	(48)
Carcinoma, NOS		1 (7%)	
Neurilemoma, malignant	1 (2%)	2 (14%)	3 (6%)
#Liver	(49)	(17)	(50)
Neoplastic nodule		1 (6%)	
Hepatocellular carcinoma	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Bile duct	(49)	(17)	(50)
Carcinoma, NOS		1 (6%)	
#Forestomach	(49)	(10)	(50)
Papilloma, NOS			2 (4%)
#Jejunum	(49)	(6)	(50)
Adenoma, NOS	1 (2%)		
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary	(47)	(16)	(45)
Glioma, NOS			1 (2%)
Meningioma		1 (6%)	
#Anterior pituitary	(47)	(16)	(45)
Adenoma, NOS	11 (23%)	10 (63%)	9 (20%)
Neurilemoma, malignant			1 (2%)
#Adrenal medulla	(49)	(7)	(49)
Pheochromocytoma	17 (35%)	2 (29%)	11 (22%)
Pheochromocytoma, malignant	1 (2%)		1 (2%)
#Thyroid	(49)	(14)	(50)
Follicular cell adenoma	1 (2%)		
Follicular cell carcinoma	1 (2%)	1 (7%)	
C-cell adenoma	7 (14%)	5 (36%)	2 (4%)
C-cell carcinoma	1 (2%)		2 (4%)
#Parathyroid	(34)	(1)	(32)
Adenoma, NOS	1 (3%)		
#Pancreatic islets	(48)	(4)	(49)
Islet cell adenoma	2 (4%)		
Islet cell carcinoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		
Fibroadenoma	2 (4%)	6 (12%)	2 (4%)
*Preputial gland	(50)	(50)	(50)
Adenoma, NOS	4 (8%)	1 (2%)	3 (6%)
Adenocarcinoma, NOS	1 (2%)		
#Prostate	(45)	(6)	(42)
Adenoma, NOS		1 (17%)	
Histiocytic sarcoma		1 (17%)	
#Testis	(48)	(50)	(50)
Interstitial cell tumor	46 (96%)	44 (88%)	45 (90%)
NERVOUS SYSTEM			
#Brain	(49)	(4)	(50)
Glioma, invasive			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		2 (4%)
MUSCULOSKELETAL SYSTEM			
None			

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
*Peritoneum	(50)	(50)	(50)
Mesothelioma, NOS		1 (2%)	
Mesothelioma, invasive			1 (2%)
*Peritoneal cavity	(50)	(50)	(50)
Mesothelioma, invasive	2 (4%)		
*Pleural cavity	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic		1 (2%)	
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS		1 (2%)	1 (2%)
Mesothelioma, malignant	2 (4%)		1 (2%)
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	2	8
Moribund sacrifice	14	14	13
Terminal sacrifice	29	32	28
Dosing accident		2	1
TUMOR SUMMARY			
Total animals with primary tumors**	48	46	46
Total primary tumors	125	99	105
Total animals with benign tumors	48	44	45
Total benign tumors	96	76	79
Total animals with malignant tumors	23	17	20
Total malignant tumors	28	19	25
Total animals with secondary tumors##	3	4	3
Total secondary tumors	3	5	4
Total animals with tumors-- uncertain benign or malignant	1	4	1
Total uncertain tumors	1	4	1

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: VEHICLE CONTROL

ANIMAL NUMBER	00071	00113	00132	00140	00226	00004	00008	00034	00118	00110	00009	00048	00330	00335	00155	00224	00123	00336	00133	00333	00447	00001	00203	00405
WEEKS ON STUDY	000	077	078	078	081	084	086	086	089	091	092	094	095	095	096	097	098	099	100	102	103	104	104	104
INTEGUMENTARY SYSTEM																								
Skin	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma											X													
Keratoacanthoma																								
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X													
Fibroma																			X					
Neurilemoma, malignant																								
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																								
Pheochromocytoma, metastatic																								
Trachea	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	−	−	A	+	−	+	+	+	+	+	−	+	−	+	+	−	−	−	−	+	−	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS																								
Squamous cell carcinoma		X																						
Salivary gland	+	+	+	+	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant							X																	
Liver	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																					X			
Bile duct	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS													X											
Large intestine	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X									X						X		X			
Adrenal	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma									X			X	X			X		X	X	X	X	X		
Pheochromocytoma, malignant																								
Thyroid	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma													X											
Follicular cell carcinoma																								
C-cell adenoma														X				X						X
C-cell carcinoma												X												
Parathyroid	−	−	+	−	A	−	−	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−
Adenoma, NOS																						X		
Pancreatic islets	+	+	+	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																	X							
REPRODUCTIVE SYSTEM																								
Mammary gland	N	N	N	N	N	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								
Fibroadenoma								X									X							
Testis	+	+	+	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X	X			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS						X																	X	
Adenocarcinoma, NOS																								
NERVOUS SYSTEM																								
Brain	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS												X												
BODY CAVITIES																								
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS															X									
Mesothelioma, invasive																								
Tunica vaginalis	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, malignant																								
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell										X	X	X	X			X	X	X	X	X			X	

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

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

ANIMAL NUMBER	0006	0014	0016	0017	0019	0020	0021	0022	0023	0025	0027	0028	0029	0031	0037	0038	0039	0041	0042	0043	0044	0045	0046	0049	0050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Keratoacanthoma																		X								1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma							X																			2
Neurilemoma, malignant																X										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma																	X									1
Pheochromocytoma, metastatic														X												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	−	+	−	+	−	−	−	−	−	+	+	−	−	−	−	+	−	−	+	+	+	+	−	+	+	24
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS					X																					1
Squamous cell carcinoma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neurilemoma, malignant																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	45
ENDOCRINE SYSTEM																										
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	47
Adenoma, NOS									X	X	X	X	X					X					X			11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma									X			X				X	X	X	X	X				X		17
Pheochromocytoma, malignant														X												1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										1
Follicular cell carcinoma								X																		1
C-cell adenoma				X			X											X							X	7
C-cell carcinoma																										1
Parathyroid	−	+	+	−	+	+	−	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	+	34
Adenoma, NOS																										1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																		X								2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS														X												1
Fibroadenoma																										2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	46
Prostate	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	45
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																			X		X					4
Adenocarcinoma, NOS									X																	1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										1
Mesothelioma, invasive																						X			X	2
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, malignant																						X			X	2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell																		X	X				X			13

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: LOW DOSE

ANIMAL NUMBER	0 1 8	0 4 6	0 1 5	0 0 2	0 1 7	0 4 9	0 3 0	0 2 0	0 1 0	0 3 5	0 0 9	0 0 5	0 2 3	0 3 2	0 4 2	0 5 0	0 1 6	0 1 9	0 0 1	0 0 3	0 0 4	0 0 6	0 0 7	0 0 8	0 1 1
WEEKS ON STUDY	0 0 0	0 0 4	0 5 3	0 5 6	0 7 8	0 8 3	0 8 4	0 8 7	0 9 1	0 9 1	0 9 4	0 9 6	0 9 6	0 9 6	0 9 6	0 9 9	1 0 1	1 0 1	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	N	N	N	N	N	N	N	N	N	+	N	N	+	N	N	N	+	N	N	N	N
Basal cell tumor														X											
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	N	N	N	N	N	N	N	N	N	+	N	N	+	N	N	N	+	N	N	N	N
Sarcoma, NOS								X																	
Fibroma																	X		X		X				
Fibrosarcoma																									
Neurilemoma, malignant				X	X		X								X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	−	−	+	−	−	−	−	−	−	−	−	−	+	−	−	−	−	+	−	−
Carcinoma, NOS, metastatic																									
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma																									
Sarcoma, NOS, metastatic								X																	
Trachea	−	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Neurilemoma, invasive					X																				
Nasal cavity	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																				X					
Lymph nodes	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Thymus	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	−	−	+	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−
Sarcoma, NOS, metastatic								X																	
Mesothelioma, NOS																									
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS																									
Salivary gland	+	+	+	+	+	−	+	+	−	−	−	+	+	−	+	+	−	−	−	−	−	−	−	−	−
Carcinoma, NOS																									
Neurilemoma, malignant												X	X												
Liver	+	+	+	+	−	+	+	+	−	−	+	−	−	−	−	+	+	+	−	−	+	−	−	−	−
Neoplastic nodule																		X							
Bile duct	+	+	+	+	−	+	+	+	−	−	+	−	−	−	−	+	+	+	−	−	+	−	−	−	−
Carcinoma, NOS																									
Pancreas	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Esophagus	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	−	+	+	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−
Small intestine	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Large intestine	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	−	+	−	−	+	−	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−
Urinary bladder	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	−	−	−	−	−	+	+	+	−	−	−	+	−	−	−	−	+	−	−	−	−	−
Adenoma, NOS											X				X					X					
Meningioma									X																
Adrenal	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Pheochromocytoma																									
Thyroid	−	+	+	+	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	+	−	−	−	−
Follicular cell carcinoma																									
C-cell adenoma													X								X				
Parathyroid	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N	+	N	N	N
Fibroadenoma												X										X			
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor					X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Prostate	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Adenoma, NOS																									
Histiocytic sarcoma																									
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, metastatic																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																						X			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																X		X							

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

ANIMAL NUMBER	012	013	014	021	022	024	025	026	027	028	029	031	033	034	036	037	038	039	040	041	043	044	045	047	048	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	ISSUES
INTEGUMENTARY SYSTEM																										
Skin	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	*50
Basal cell tumor																										1
Keratoacanthoma																							X			1
Subcutaneous tissue	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	*50
Sarcoma, NOS																										1
Fibroma																										3
Fibrosarcoma		X																								1
Neurilemoma, malignant			X																							5
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	–	–	–	–	+	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
Carcinoma, NOS, metastatic						X																				1
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma											X															1
Sarcoma, NOS, metastatic																										1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3
Neurilemoma, invasive																										1
Nasal cavity	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Spleen	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell																				X						2
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
Thymus	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	
Sarcoma, NOS, metastatic																										
Mesothelioma, NOS																									X	
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS																			X							1
Salivary gland	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	14
Carcinoma, NOS		X																								1
Neurilemoma, malignant																										2
Liver	–	–	–	+	+	+	–	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	17
Neoplastic nodule																										1
Bile duct	–	–	–	+	+	+	–	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	17
Carcinoma, NOS						X																				1
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	+	–	–	–	–	–	–	–	10
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–	6
Large intestine	–	–	–	–	–	+	–	–	–	–	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–	7
URINARY SYSTEM																										
Kidney	–	+	–	–	+	+	–	–	–	–	–	+	–	–	+	+	–	+	–	–	–	+	+	+	–	18
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
ENDOCRINE SYSTEM																										
Pituitary	–	+	–	–	+	+	–	–	+	–	–	–	+	+	+	–	–	+	–	–	–	–	+	–	–	16
Adenoma, NOS		X				X			X				X	X				X					X			10
Meningioma																										1
Adrenal	–	–	–	–	+	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	7
Pheochromocytoma					X									X												2
Thyroid	+	–	+	–	+	+	–	–	+	–	+	–	–	–	–	+	+	–	–	–	–	–	–	+	–	14
Follicular cell carcinoma					X																					1
C-cell adenoma						X										X	X									5
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	N	N	N	N	N	N	N	+	+	+	N	N	N	N	+	N	+	N	N	+	N	N	*50
Fibroadenoma		X										X	X					X								6
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	44
Prostate	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
Adenoma, NOS				X																						1
Histiocytic sarcoma					X																					1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																X										1
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcinoma, metast											X															1
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS									X																	1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell																										2

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: HIGH DOSE

ANIMAL NUMBER	0040	0018	0035	0007	0004	0026	0031	0023	0038	0006	0042	0050	0001	0024	0025	0033	0008	0048	0002	0028	0016	0010	0003	0005	0009
WEEKS ON STUDY	0003	0004	0005	0042	0044	0064	0077	0078	0082	0083	0083	0083	0086	0090	0090	0091	0093	0097	0098	0098	0100	0103	0104	0104	0104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Squamous cell carcinoma																						X			
Keratoacanthoma																			X						
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma											X														
Mesothelioma, invasive													X												
Neurilemoma, malignant												X		X						X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS									X										X						
Osteosarcoma																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	–	–	+	–	+	+	+	–	+	+	–	+	+	+	+	–	+	–	–	+
Sarcoma, NOS				X																					
Neurilemoma, metastatic														X											
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+
Neurilemoma, malignant							X										X								
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS													X												
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS															X	X								X	X
Glioma, NOS																					X				
Neurilemoma, malignant																									
Adrenal	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X								X	X	X		
Pheochromocytoma, malignant																	X								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
C-cell carcinoma														X											
Parathyroid	+	–	+	–	–	–	+	–	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+
Pancreatic islets	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	+	N	N	N	+	N	N	N	N	N	+	N	+	+	+	N	+	N	+	+	+
Fibroadenoma															X										
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS						X																			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, invasive																					X				
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS									X																
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, invasive													X												
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
Mesothelioma, malignant													X												
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell										X								X							

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

ANIMAL NUMBER	0111	0112	0113	0114	0115	0117	0119	0200	0211	0222	0227	0229	0230	0232	0234	0236	0237	0239	0241	0243	0244	0245	0246	0247	0249	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS						X																				1
Squamous cell carcinoma																										1
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																						X				1
Fibroma																									X	2
Mesothelioma, invasive																										1
Neurilemoma, malignant																										3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS									X																	3
Osteosarcoma																						X				1
Lymph nodes	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	−	−	−	−	−	+	−	+	+	+	−	+	−	+	−	−	−	−	+	−	+	−	−	+	−	26
Sarcoma, NOS																										1
Neurilemoma, metastatic																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neurilemoma, malignant														X												3
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma, NOS					X																					2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS						X		X			X											X		X		9
Glioma, NOS																										1
Neurilemoma, malignant													X													1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma							X		X		X		X				X					X			X	11
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma	X																X									2
C-cell carcinoma																		X								2
Parathyroid	−	+	−	−	−	−	−	−	−	+	+	−	+	+	−	+	+	+	+	+	+	+	−	+	+	32
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma					X																					1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma				X																						2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	45
Prostate	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	42
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS					X																	X				3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, invasive																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																			X							2
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, invasive																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS		X																								1
Mesothelioma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X																					3

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	3 mg/kg	30 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	6.5%	9.0%	5.9%
Terminal Rates (c)	1/29 (3%)	2/32 (6%)	1/28 (4%)
Week of First Observation	100	101	83
Life Table Tests (d)	P=0.605N	P=0.540	P=0.672
Incidental Tumor Tests (d)	P=0.622N	P=0.486	P=0.654
Cochran-Armitage Trend Test (d)	P=0.563N		
Fisher Exact Test (d)		P=0.500	P=0.691
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	8.8%	14.1%	9.4%
Terminal Rates (c)	1/29 (3%)	3/32 (9%)	2/28 (7%)
Week of First Observation	92	87	83
Life Table Tests (d)	P=0.537N	P=0.399	P=0.627
Incidental Tumor Tests (d)	P=0.501N	P=0.309	P=0.636
Cochran-Armitage Trend Test (d)	P=0.477N		
Fisher Exact Test (d)		P=0.357	P=0.661
Subcutaneous Tissue: Malignant Neurilemoma			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	3.4%	11.7%	8.0%
Terminal Rates (c)	1/29 (3%)	1/32 (3%)	0/28 (0%)
Week of First Observation	104	56	83
Life Table Tests (d)	P=0.521	P=0.116	P=0.283
Incidental Tumor Tests (d)	P=0.570	P=0.088	P=0.280
Cochran-Armitage Trend Test (d)	P=0.576		
Fisher Exact Test (d)		P=0.102	P=0.309
Salivary Glands: Malignant Neurilemoma			
Overall Rates (e)	1/48 (2%)	(f) 2/14 (14%)	3/48 (6%)
Adjusted Rates (b)	2.3%		8.5%
Terminal Rates (c)	0/29 (0%)		1/28 (4%)
Week of First Observation	86		77
Life Table Test (d)			P=0.274
Incidental Tumor Test (d)			P=0.273
Fisher Exact Test (d)			P=0.308
Subcutaneous Tissue or Salivary Glands: Malignant Neurilemoma			
Overall Rates (a)	2/50 (4%)	7/50 (14%)	6/50 (12%)
Adjusted Rates (b)	5.6%	16.3%	15.9%
Terminal Rates (c)	1/29 (3%)	1/32 (3%)	1/28 (4%)
Week of First Observation	86	56	77
Life Table Tests (d)	P=0.264	P=0.098	P=0.117
Incidental Tumor Tests (d)	P=0.267	P=0.053	P=0.108
Cochran-Armitage Trend Test (d)	P=0.325		
Fisher Exact Test (d)		P=0.080	P=0.134
All Sites: All Neurilemoma			
Overall Rates (a)	2/50 (4%)	7/50 (14%)	(g) 7/50 (14%)
Adjusted Rates (b)	5.6%	16.3%	19.0%
Terminal Rates (c)	1/29 (3%)	1/32 (3%)	2/28 (7%)
Week of First Observation	86	56	77
Life Table Tests (d)	P=0.163	P=0.098	P=0.071
Incidental Tumor Tests (d)	P=0.159	P=0.053	P=0.064
Cochran-Armitage Trend Test (d)	P=0.208		
Fisher Exact Test (d)		P=0.080	P=0.080

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	3 mg/kg	30 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	13/50 (26%)	(f,h) 4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	33.3%	11.6%	8.8%
Terminal Rates (c)	4/29 (14%)	2/32 (6%)	1/28 (4%)
Week of First Observation	91	99	83
Life Table Tests (d)	P=0.057N	P=0.018N	P=0.017N
Incidental Tumor Tests (d)	P=0.056N	P=0.022N	P=0.017N
Cochran-Armitage Trend Test (d)	P=0.031N		
Fisher Exact Test (d)		P=0.016N	P=0.007N
Spleen: Sarcoma			
Overall Rates (e)	0/49 (0%)	0/49 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	8.8%
Terminal Rates (c)	0/29 (0%)	0/31 (0%)	1/28 (4%)
Week of First Observation			82
Life Table Tests (d)	P=0.026	(i)	P=0.115
Incidental Tumor Tests (d)	P=0.029	(i)	P=0.107
Cochran-Armitage Trend Test (d)	P=0.032		
Fisher Exact Test (d)		(i)	P=0.125
Spleen: Sarcoma or Osteosarcoma			
Overall Rates (e)	0/49 (0%)	0/49 (0%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	12.2%
Terminal Rates (c)	0/29 (0%)	0/31 (0%)	2/28 (7%)
Week of First Observation			82
Life Table Tests (d)	P=0.008	(i)	P=0.060
Incidental Tumor Tests (d)	P=0.009	(i)	P=0.055
Cochran-Armitage Trend Test (d)	P=0.010		
Fisher Exact Test (d)		(i)	P=0.061
Anterior Pituitary Gland: Adenoma			
Overall Rates (e)	11/47 (23%)	(f) 10/16 (63%)	9/45 (20%)
Adjusted Rates (b)	33.9%		30.9%
Terminal Rates (c)	7/27 (26%)		7/26 (27%)
Week of First Observation	78		90
Life Table Test (d)			P=0.458N
Incidental Tumor Test (d)			P=0.493N
Fisher Exact Test (d)			P=0.444N
Adrenal Medulla: Pheochromocytoma			
Overall Rates (e)	17/49 (35%)	(f) 2/7 (29%)	11/49 (22%)
Adjusted Rates (b)	45.5%		35.1%
Terminal Rates (c)	9/29 (31%)		8/28 (29%)
Week of First Observation	89		86
Life Table Test (d)			P=0.191N
Incidental Tumor Test (d)			P=0.269N
Fisher Exact Test (d)			P=0.132N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (e)	18/49 (37%)	(f) 2/7 (29%)	12/49 (24%)
Adjusted Rates (b)	48.2%		37.0%
Terminal Rates (c)	10/29 (34%)		8/28 (29%)
Week of First Observation	89		86
Life Table Test (d)			P=0.202N
Incidental Tumor Test (d)			P=0.291N
Fisher Exact Test (d)			P=0.137N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	3 mg/kg	30 mg/kg
Thyroid Gland: C-Cell Adenoma			
Overall Rates (e)	7/49 (14%)	(f) 5/14 (36%)	2/50 (4%)
Adjusted Rates (b)	21.9%		7.1%
Terminal Rates (c)	5/29 (17%)		2/28 (7%)
Week of First Observation	95		104
Life Table Test (d)			P=0.095N
Incidental Tumor Test (d)			P=0.116N
Fisher Exact Test (d)			P=0.075N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (e)	8/49 (16%)	(f) 5/14 (36%)	4/50 (8%)
Adjusted Rates (b)	23.9%		13.1%
Terminal Rates (c)	5/29 (17%)		3/28 (11%)
Week of First Observation	94		90
Life Table Test (d)			P=0.216N
Incidental Tumor Test (d)			P=0.243N
Fisher Exact Test (d)			P=0.169N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	2/50 (4%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	5.1%	17.8%	6.2%
Terminal Rates (c)	0/29 (0%)	5/32 (16%)	1/28 (4%)
Week of First Observation	86	96	90
Life Table Tests (d)	P=0.377N	P=0.164	P=0.661
Incidental Tumor Tests (d)	P=0.365N	P=0.125	P=0.672
Cochran-Armitage Trend Test (d)	P=0.327N		
Fisher Exact Test (d)		P=0.134	P=0.691
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	8.4%	17.8%	6.2%
Terminal Rates (c)	1/29 (3%)	5/32 (16%)	1/28 (4%)
Week of First Observation	86	96	90
Life Table Tests (d)	P=0.293N	P=0.284	P=0.534N
Incidental Tumor Tests (d)	P=0.282N	P=0.234	P=0.528N
Cochran-Armitage Trend Test (d)	P=0.247N		
Fisher Exact Test (d)		P=0.243	P=0.500N
Preputial Gland: Adenoma			
Overall Rates (e)	4/50 (8%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	12.3%	3.1%	9.2%
Terminal Rates (c)	3/29 (10%)	1/32 (3%)	2/28 (7%)
Week of First Observation	84	104	64
Life Table Tests (d)	P=0.546	P=0.159N	P=0.533N
Incidental Tumor Tests (d)	P=0.579	P=0.176N	P=0.503N
Cochran-Armitage Trend Test (d)	P=0.591		
Fisher Exact Test (d)		P=0.181N	P=0.500N
Preputial Gland: Adenoma or Adenocarcinoma			
Overall Rates (e)	5/50 (10%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	15.7%	3.1%	9.2%
Terminal Rates (c)	4/29 (14%)	1/32 (3%)	2/28 (7%)
Week of First Observation	84	104	64
Life Table Tests (d)	P=0.624N	P=0.087N	P=0.389N
Incidental Tumor Tests (d)	P=0.592N	P=0.097N	P=0.362N
Cochran-Armitage Trend Test (d)	P=0.576N		
Fisher Exact Test (d)		P=0.102N	P=0.357N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	3 mg/kg	30 mg/kg
Testis: Interstitial Cell Tumor			
Overall Rates (e)	46/48 (96%)	44/50 (88%)	45/50 (90%)
Adjusted Rates (b)	100.0%	97.8%	100.0%
Terminal Rates (c)	29/29 (100%)	31/32 (97%)	28/28 (100%)
Week of First Observation	77	78	64
Life Table Tests (d)	P=0.260	P=0.214N	P=0.451
Incidental Tumor Tests (d)	P=0.139	P=0.202N	P=0.602
Cochran-Armitage Trend Test (d)	P=0.419N		
Fisher Exact Test (d)		P=0.148N	P=0.235N
All Sites: All Mesothelioma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	9.5%	9.4%	6.1%
Terminal Rates (c)	2/29 (7%)	3/32 (9%)	1/28 (4%)
Week of First Observation	96	104	86
Life Table Tests (d)	P=0.489N	P=0.618N	P=0.531N
Incidental Tumor Tests (d)	P=0.480N	P=0.642N	P=0.543N
Cochran-Armitage Trend Test (d)	P=0.441N		
Fisher Exact Test (d)		P=0.661	P=0.500N
All Sites: Benign Tumors			
Overall Rates (a)	48/50 (96%)	44/50 (88%)	45/50 (90%)
Adjusted Rates (b)	100.0%	97.8%	100.0%
Terminal Rates (c)	29/29 (100%)	31/32 (97%)	28/28 (100%)
Week of First Observation	77	78	64
Life Table Tests (d)	P=0.341	P=0.133N	P=0.558N
Incidental Tumor Tests (d)	P=0.136	P=0.137N	P=0.473
Cochran-Armitage Trend Test (d)	P=0.402N		
Fisher Exact Test (d)		P=0.135N	P=0.218N
All Sites: Malignant Tumors			
Overall Rates (a)	23/50 (46%)	17/50 (34%)	20/50 (40%)
Adjusted Rates (b)	55.6%	39.3%	48.0%
Terminal Rates (c)	11/29 (38%)	7/32 (22%)	7/28 (25%)
Week of First Observation	77	56	42
Life Table Tests (d)	P=0.448	P=0.148N	P=0.466N
Incidental Tumor Tests (d)	P=0.450	P=0.230N	P=0.554N
Cochran-Armitage Trend Test (d)	P=0.522N		
Fisher Exact Test (d)		P=0.154N	P=0.343N
All Sites: All Tumors			
Overall Rates (a)	48/50 (96%)	46/50 (92%)	46/50 (92%)
Adjusted Rates (b)	100.0%	97.9%	100.0%
Terminal Rates (c)	29/29 (100%)	31/32 (97%)	28/28 (100%)
Week of First Observation	77	56	42
Life Table Tests (d)	P=0.327	P=0.230N	P=0.508
Incidental Tumor Tests (d)	P=0.177	P=0.473N	P=0.374
Cochran-Armitage Trend Test (d)	P=0.418N		
Fisher Exact Test (d)		P=0.339N	P=0.339N

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined microscopically at the site
(f) Incomplete sampling of tissues
(g) Includes one malignant neurilemoma of the pituitary gland
(h) Two lymph nodes and 17 livers were examined microscopically.
(i) No P value is reported because no tumors were observed in the 3 mg/kg and vehicle control groups.

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

Study	Incidence of Sarcomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	0/49
Ampicillin trihydrate	1/50
Penicillin VK	0/49
TOTAL	1/148 (0.7%)
SD (b)	1.15%
Range (c)	
High	1/50
Low	0/49
Overall Historical Incidence	
TOTAL	(d) 3/2,081 (0.1%)
SD (b)	0.54%
Range (c)	
High	1/45
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Sarcomas, NOS; no osteosarcomas have been observed.

TABLE A4b. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM OR SALIVARY GLAND NEURILEMOMAS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Neurilemomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	(b) 2/50
Ampicillin trihydrate	0/50
Penicillin VK	4/50
TOTAL	(c) 6/150 (4.0%)
SD (d)	4.00%
Range (e)	
High	4/50
Low	0/50
Overall Historical Incidence	
TOTAL	(f) 10/2,099 (0.5%)
SD (d)	1.52%
Range (e)	
High	4/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks; unless otherwise specified, entries refer to benign neurilemomas of the integumentary system.
(b) Includes one neurilemoma of the salivary gland
(c) No malignant neurilemomas have been observed.
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes two benign neurilemomas of the salivary gland (2,061 examined) and one malignant neurilemoma of the integumentary system

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

Study	Incidence of Papillomas or Carcinomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	0/49
Ampicillin trihydrate	0/48
Penicillin VK	0/46
TOTAL	0/143 (0.0%)
SD (b)	0.00%
Range (c)	
High	0/49
Low	0/49
Overall Historical Incidence	
TOTAL	(d) 7/2,072 (0.3%)
SD (b)	0.76%
Range (c)	
High	1/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one papilloma, NOS, five squamous cell papillomas, and one squamous cell carcinoma

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

Study	Incidence of Leukemia in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	13/50
Ampicillin trihydrate	5/50
Penicillin VK	14/50
TOTAL	32/150 (21.3%)
SD (b)	9.87%
Range (c)	
High	14/50
Low	5/50
Overall Historical Incidence	
TOTAL	361/2,099 (17.2%)
SD (b)	9.04%
Range (c)	
High	(d) 22/50
Low	1/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Second highest: 15/50

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst		1 (2%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
Inflammation, acute	1 (2%)		
Granulation tissue	2 (4%)		
RESPIRATORY SYSTEM			
#Nasal mucosa	(48)		(50)
Lymphocytic inflammatory infiltrate	44 (92%)		47 (94%)
Inflammation, suppurative	5 (10%)		3 (6%)
Infection, fungal	1 (2%)		
#Lung/bronchus	(49)	(10)	(50)
Inflammation, suppurative	1 (2%)		
#Lung	(49)	(10)	(50)
Congestion, NOS	1 (2%)	1 (10%)	
Congestion, acute	4 (8%)		7 (14%)
Edema, NOS		1 (10%)	1 (2%)
Hemorrhage			1 (2%)
Inflammation, focal			1 (2%)
Inflammation, interstitial	1 (2%)		1 (2%)
Pneumonia, aspiration			1 (2%)
Pneumonia, interstitial chronic	1 (2%)	1 (10%)	3 (6%)
Inflammation, chronic focal			2 (4%)
Hyperplasia, alveolar epithelium			1 (2%)
#Lung/alveoli	(49)	(10)	(50)
Inflammation, interstitial	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Blood erythrocytes	(50)	(50)	(50)
Reticulocytosis	3 (6%)		4 (8%)
Normoblastosis	3 (6%)		1 (2%)
#Bone marrow	(49)	(4)	(49)
Hyperplasia, diffuse	1 (2%)		
Hyperplasia, erythroid	6 (12%)		7 (14%)
Hyperplasia, granulocytic	3 (6%)		1 (2%)
#Spleen	(49)	(49)	(50)
Hemosiderosis	43 (88%)	47 (96%)	49 (98%)
#Splenic red pulp	(49)	(49)	(50)
Congestion, NOS	14 (29%)	1 (2%)	8 (16%)
Congestion, acute	7 (14%)		1 (2%)
Fibrosis	5 (10%)	2 (4%)	22 (44%)
Necrosis, focal			1 (2%)
Metamorphosis, fatty		1 (2%)	10 (20%)
Plasmacytosis			1 (2%)
Hematopoiesis	44 (90%)	48 (98%)	50 (100%)
#Mandibular lymph node	(49)	(2)	(48)
Cyst, NOS			1 (2%)
Hyperplasia, focal			1 (2%)
Hyperplasia, diffuse	2 (4%)		2 (4%)
Plasmacytosis	1 (2%)		
Hyperplasia, lymphoid	18 (37%)		16 (33%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mediastinal lymph node	(49)	(2)	(48)
Hemorrhage	2 (4%)		1 (2%)
Hemosiderosis			1 (2%)
Hyperplasia, focal	1 (2%)		
Hyperplasia, lymphoid	2 (4%)		3 (6%)
#Pancreatic lymph node	(49)	(2)	(48)
Hemosiderosis			1 (2%)
Hyperplasia, lymphoid	1 (2%)		
#Mesenteric lymph node	(49)	(2)	(48)
Cyst, NOS	1 (2%)		
Hemorrhage			2 (4%)
Hemosiderosis			2 (4%)
Hyperplasia, diffuse	1 (2%)		2 (4%)
Histiocytosis			1 (2%)
Hyperplasia, lymphoid	11 (22%)		7 (15%)
#Renal lymph node	(49)	(2)	(48)
Cyst, NOS	1 (2%)		
#Lung/bronchus	(49)	(10)	(50)
Hyperplasia, lymphoid			1 (2%)
#Liver	(49)	(17)	(50)
Hematopoiesis	4 (8%)		
#Peyer's patch	(49)	(6)	(50)
Hyperplasia, lymphoid	5 (10%)		4 (8%)
#Adrenal	(49)	(7)	(49)
Hematopoiesis	1 (2%)		
#Adrenal cortex	(49)	(7)	(49)
Hematopoiesis			4 (8%)
#Thymus	(24)	(4)	(26)
Hyperplasia, epithelial			1 (4%)
CIRCULATORY SYSTEM			
#Spleen	(49)	(49)	(50)
Thrombosis, NOS			1 (2%)
#Heart/atrium	(49)	(8)	(50)
Thrombosis, NOS			1 (2%)
#Heart/ventricle	(49)	(8)	(50)
Dilatation, NOS		1 (13%)	1 (2%)
#Myocardium	(49)	(8)	(50)
Inflammation, granulomatous focal	1 (2%)		
Degeneration, NOS	36 (73%)	1 (13%)	31 (62%)
#Pancreas	(48)	(4)	(49)
Periarteritis	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(48)	(14)	(48)
Cyst, NOS		1 (7%)	
Fibrosis			1 (2%)
Focal cellular change	1 (2%)		
Atrophy, NOS		1 (7%)	
Atrophy, focal	3 (6%)	2 (14%)	5 (10%)
Hyperplasia, focal			2 (4%)
#Liver	(49)	(17)	(50)
Congestion, acute			2 (4%)
Necrosis, NOS		1 (6%)	
Necrosis, coagulative	1 (2%)		
Cytoplasmic vacuolization	2 (4%)		1 (2%)
Basophilic cyto change	16 (33%)	4 (24%)	16 (32%)
Focal cellular change	8 (16%)		5 (10%)
Eosinophilic cyto change	4 (8%)		2 (4%)
Clear cell change	2 (4%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Liver/centrilobular	(49)	(17)	(50)
Congestion, NOS			2 (4%)
Congestion, acute	3 (6%)		1 (2%)
Degeneration, NOS	9 (18%)		1 (2%)
Necrosis, coagulative			1 (2%)
Cytoplasmic vacuolization			1 (2%)
#Liver/periportal	(49)	(17)	(50)
Degeneration, NOS	1 (2%)		
#Bile duct	(49)	(17)	(50)
Hyperplasia, NOS	30 (61%)	6 (35%)	33 (66%)
Hyperplasia, focal	3 (6%)		3 (6%)
#Pancreas	(48)	(4)	(49)
Dilatation/ducts			1 (2%)
Atrophy, NOS	2 (4%)		1 (2%)
Atrophy, focal	5 (10%)		9 (18%)
#Esophagus	(49)	(4)	(47)
Inflammation, chronic			1 (2%)
#Gastric submucosa	(49)	(10)	(50)
Edema, NOS			1 (2%)
Inflammation, chronic	1 (2%)		
#Forestomach	(49)	(10)	(50)
Inflammation, suppurative	2 (4%)	2 (20%)	
Ulcer, chronic		1 (10%)	1 (2%)
Hyperkeratosis	1 (2%)		1 (2%)
Acanthosis	2 (4%)	3 (30%)	5 (10%)
Keratin pearl formation			1 (2%)
#Intestinal villus	(49)	(6)	(50)
Atrophy, NOS			1 (2%)
#Jejunum	(49)	(6)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
#Colon	(49)	(7)	(50)
Distention	16 (33%)		8 (16%)
Parasitism	4 (8%)		5 (10%)
#Cecum	(49)	(7)	(50)
Congestion, NOS		1 (14%)	
*Rectum	(50)	(50)	(50)
Distention			2 (4%)
URINARY SYSTEM			
#Kidney	(49)	(18)	(49)
Lymphocytic inflammatory infiltrate	1 (2%)		
Nephrosis, NOS	44 (90%)	14 (78%)	43 (88%)
#Kidney/tubule	(49)	(18)	(49)
Pigmentation, NOS	16 (33%)		11 (22%)
#Urinary bladder	(45)	(4)	(46)
Distention	5 (11%)		5 (11%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(47)	(16)	(45)
Cyst, NOS	2 (4%)		1 (2%)
Congestion, NOS		1 (6%)	
Hemorrhage	1 (2%)		
Hyperplasia, NOS	11 (23%)	2 (13%)	7 (16%)
Hyperplasia, focal	7 (15%)		6 (13%)
Hyperplasia, diffuse			1 (2%)
Angiectasis	3 (6%)		6 (13%)
#Adrenal cortex	(49)	(7)	(49)
Hyperplasia, NOS	1 (2%)		1 (2%)
Hyperplasia, focal	1 (2%)		5 (10%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(49)	(7)	(49)
Cyst, NOS	1 (2%)		
Hyperplasia, NOS	2 (4%)		1 (2%)
Hyperplasia, focal	11 (22%)		17 (35%)
#Thyroid	(49)	(14)	(50)
Follicular cyst, NOS			2 (4%)
Hyperplasia, C-cell	5 (10%)	5 (36%)	7 (14%)
#Parathyroid	(34)	(1)	(32)
Hyperplasia, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts		1 (2%)	
Hyperplasia, NOS	3 (6%)		2 (4%)
Hyperplasia, diffuse			1 (2%)
*Mammary duct	(50)	(50)	(50)
Distention	3 (6%)	3 (6%)	6 (12%)
*Preputial gland	(50)	(50)	(50)
Retention of content	1 (2%)	3 (6%)	1 (2%)
Inflammation, suppurative	1 (2%)		
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal	29 (58%)		16 (32%)
Inflammation, chronic suppurative	6 (12%)		5 (10%)
Hyperplasia, NOS			1 (2%)
#Prostate	(45)	(6)	(42)
Inflammation, suppurative	2 (4%)		2 (5%)
Inflammation, chronic suppurative	16 (36%)		18 (43%)
*Seminal vesicle	(50)	(50)	(50)
Distention		1 (2%)	
Atrophy, NOS	6 (12%)	4 (8%)	4 (8%)
Atrophy, diffuse			1 (2%)
#Testis	(48)	(50)	(50)
Edema, NOS			1 (2%)
Hyperplasia, interstitial cell	7 (15%)	8 (16%)	10 (20%)
#Spermatid	(48)	(50)	(50)
Dysplasia, NOS	5 (10%)		9 (18%)
*Epididymis	(50)	(50)	(50)
Cytoplasmic vacuolization	23 (46%)	12 (24%)	6 (12%)
NERVOUS SYSTEM			
#Brain stem	(49)	(4)	(50)
Hemorrhage	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Cataract	1 (2%)		
Phthisis bulbi		1 (2%)	1 (2%)
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		
*Ear canal	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	31 (62%)		27 (54%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteosclerosis			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
BODY CAVITIES			
*Peritoneal cavity	(50)	(50)	(50)
Hemorrhage			1 (2%)
*Pleural cavity	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Adhesion, fibrous		1 (2%)	
*Pericardium	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
Inflammation, chronic			1 (2%)
*Mesentery	(50)	(50)	(50)
Necrosis, fat	4 (8%)	10 (20%)	3 (6%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
Autolysis/necropsy/no histology	1		

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

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Keratoacanthoma	2 (4%)		
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)	1 (2%)	
Fibroma	1 (2%)		1 (2%)
Fibrosarcoma	2 (4%)		1 (2%)
Neurilemoma	1 (2%)		
Neurilemoma, malignant	1 (2%)	1 (2%)	2 (4%)
RESPIRATORY SYSTEM			
#Lung	(50)	(5)	(49)
Neurilemoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	11 (22%)	7 (14%)	
#Splenic red pulp	(50)	(49)	(49)
Sarcoma, NOS	1 (2%)		
#Lumbar lymph node	(50)	(4)	(50)
Sarcoma, NOS, metastatic		1 (25%)	
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Papilloma, NOS	1 (2%)		
#Salivary gland	(50)	(8)	(49)
Sarcoma, NOS		1 (13%)	1 (2%)
Neurilemoma	1 (2%)		
Neurilemoma, malignant		1 (13%)	
#Large intestine	(50)	(3)	(50)
Adenomatous polyp, NOS	1 (2%)		
#Colon	(50)	(3)	(50)
Adenomatous polyp, NOS			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Lipoma	1 (2%)	1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(32)	(50)
Adenoma, NOS	27 (55%)	22 (69%)	24 (48%)
Ganglioneuroma			1 (2%)
#Adrenal	(50)	(8)	(50)
Cortical adenoma	1 (2%)		
#Adrenal medulla	(50)	(8)	(50)
Pheochromocytoma	2 (4%)	3 (38%)	1 (2%)
Pheochromocytoma, malignant			2 (4%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(49)	(3)	(48)
Follicular cell adenoma	1 (2%)		
C-cell adenoma	1 (2%)	1 (33%)	2 (4%)
C-cell carcinoma	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
Adenocarcinoma, NOS	1 (2%)		3 (6%)
Fibroadenoma	21 (42%)	21 (42%)	23 (46%)
*Clitoral gland	(50)	(50)	(50)
Adenoma, NOS	4 (8%)	2 (4%)	4 (8%)
#Uterus	(49)	(14)	(49)
Endometrial stromal polyp	7 (14%)	6 (43%)	8 (16%)
#Ovary	(49)	(7)	(49)
Granulosa cell tumor	1 (2%)		
Leiomyosarcoma			1 (2%)
NERVOUS SYSTEM			
#Brain	(49)	(4)	(50)
Astrocytoma	1 (2%)		
Oligodendroglioma			1 (2%)
Meningioma		1 (25%)	
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
Site unknown			
Sarcoma, NOS	1		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	7	5
Moribund sacrifice	24	11	9
Terminal sacrifice	21	32	36

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	48	42	42
Total primary tumors	94	68	77
Total animals with benign tumors	43	37	42
Total benign tumors	73	56	65
Total animals with malignant tumors	18	12	11
Total malignant tumors	20	12	12
Total animals with secondary tumors##	1	1	
Total secondary tumors	1	1	
Total animals with tumors-- uncertain benign or malignant	1		
Total uncertain tumors	1		

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: VEHICLE CONTROL

ANIMAL NUMBER	0026	0027	0029	0020	0050	0005	0041	0042	0047	0024	0017	0031	0049	0036	0012	0040	0038	0004	0030	0037	0028	0039	0046	0010	0033
WEEKS ON STUDY	005	065	085	083	084	086	086	086	086	087	090	090	092	093	094	096	097	098	098	098	099	099	099	100	100
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																			X						
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma													X												
Fibrosarcoma																									
Neurilemoma																X									
Neurilemoma, malignant														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, metastatic														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	−	−	+	+	+	−	+	+	+	−	+	−	−	+	+	+	+	−	+	−	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papilloma, NOS						X																			
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma										X															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS						X																			
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																X									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X		X	X			X					X	X		X	X	X	X	X	X	X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma							X																		
Pheochromocytoma																				X					
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma																			X						
C-cell carcinoma																									
Parathyroid	−	−	+	+	+	−	+	+	+	−	+	−	+	−	−	+	+	+	−	+	−	+	+	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X		
Adenocarcinoma, NOS																							X		
Fibroadenoma	X			X								X		X	X	X	X		X	X			X	X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS					X																				
Uterus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp										X			X						X					X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell							X	X			X	X			X		X				X	X	X		
Site unknown																									
Sarcoma, NOS																X									

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

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

ANIMAL NUMBER	00 07	00 25	00 02	01 13	00 01	00 03	00 06	00 08	00 09	01 11	01 14	01 15	01 16	01 18	01 19	02 21	02 22	02 23	03 32	03 34	03 35	04 43	04 44	04 45	04 48	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	101	101	102	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma									X																	2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS			X																							1
Fibroma																										1
Fibrosarcoma		X				X																				2
Neurilemoma																										1
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																				X						1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	−	−	−	−	+	+	+	+	−	−	+	+	+	+	−	+	+	+	+	+	−	−	+	32
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papilloma, NOS			X																							1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
creas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenomatous polyp, NOS																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X			X					X		X		X	X		X	X			X		X	X		X	27
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma																							X			2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma															X											1
C-cell adenoma																										1
C-cell carcinoma					X																					1
Parathyroid	+	+	−	−	+	−	+	+	+	+	−	+	+	−	+	−	+	+	+	−	+	+	−	+	+	32
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																										1
Fibroadenoma	X			X	X	X				X		X					X	X	X					X		21
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS									X	X							X									4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp						X							X						X							7
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor							X																			1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma		X																								1
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell																			X		X					11
Site unknown																										
Sarcoma, NOS																										1

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: LOW DOSE

ANIMAL NUMBER	041	007	038	020	039	031	024	044	016	009	046	021	033	043	050	030	032	015	001	002	003	004	005	006	008
WEEKS ON STUDY	054	068	068	078	078	081	083	085	086	092	095	097	097	097	097	101	102	103	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	N	+	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS	X																								
Neurilemoma, malignant														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–
Trachea	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Nasal cavity	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	–	+	–	–	–	+	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Sarcoma, NOS, metastatic	X																								
Thymus	+	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
DIGESTIVE SYSTEM																									
Salivary gland	+	–	+	–	–	–	–	–	+	–	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–
Sarcoma, NOS									X																
Neurilemoma, malignant																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+
Pancreas	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Esophagus	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Stomach	+	–	+	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Small intestine	+	–	+	–	–	+	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Large intestine	–	–	+	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
ENDOCRINE SYSTEM																									
Pituitary	+	–	+	–	+	–	–	+	–	+	–	+	–	+	+	+	+	+	+	+	–	+	+	–	+
Adenoma, NOS			X		X			X		X				X		X		X	X	X			X		
Adrenal	+	–	+	+	–	–	–	–	+	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–
Pheochromocytoma																X									
Thyroid	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
C-cell adenoma																									
Parathyroid	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	+	N	+	+	+	+	+	+	+	+	+	N	N	N	+	+
Fibroadenoma												X	X	X	X	X		X		X				X	X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS										X															
Uterus	+	–	+	–	–	+	–	–	–	–	–	–	–	–	+	–	–	+	–	–	–	+	–	–	–
Endometrial stromal polyp															X										
Ovary	+	–	+	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–
NERVOUS SYSTEM																									
Brain	+	–	+	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Meningioma					X																				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X					X				X														

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

ANIMAL NUMBER	0110	0111	0112	0113	0114	0117	0118	0119	0122	0123	0125	0126	0127	0128	0129	0134	0135	0136	0137	0140	0142	0145	0147	0148	0149	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	*50
Sarcoma, NOS																										1
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
Nasal cavity	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	49
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Sarcoma, NOS, metastatic																										1
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
DIGESTIVE SYSTEM																										
Salivary gland	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–	8
Sarcoma, NOS																										1
Neurilemoma, malignant																				X						1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	46
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	46
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma									X																	1
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
ENDOCRINE SYSTEM																										
Pituitary	–	–	+	+	–	+	–	+	–	–	–	+	+	–	+	+	+	+	+	+	+	–	+	+	+	32
Adenoma, NOS				X				X					X		X	X	X	X	X	X	X		X		X	22
Adrenal	–	–	–	–	–	–	–	–	+	–	–	+	–	–	–	–	–	–	–	–	–	+	–	–	–	8
Pheochromocytoma												X										X				3
Thyroid	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	3
C-cell adenoma												X														1
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	N	+	+	N	N	+	N	N	N	N	+	+	+	N	N	N	+	+	N	+	*50
Fibroadenoma		X	X	X	X		X	X			X						X	X				X	X		X	21
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS								X																		2
Uterus	+	+	–	–	–	+	–	–	–	+	–	–	+	–	–	–	+	–	–	–	–	+	–	+	–	14
Endometrial stromal polyp		X				X											X					X		X		6
Ovary	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	7
NERVOUS SYSTEM																										
Brain	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Meningioma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell								X				X	X					X								7

* Animals necropsied

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: HIGH DOSE

ANIMAL NUMBER	042	010	026	045	048	017	028	011	014	024	021	035	036	032	001	002	003	004	005	006	007	008	009	012	013
WEEKS ON STUDY	001	077	080	082	082	084	088	092	095	095	098	099	100	102	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma																									
Neurilemoma, malignant												X											X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	−	−	−	+	+	+	−	+	−	+	+	+	−	+	+	−	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS									X																
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X	X	X	X			X	X	X	X	X	X	X						X		X		X	
Ganglioneuroma																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma													X												
Pheochromocytoma, malignant			X										X												
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma								X																	
C-cell carcinoma																									
Parathyroid	−	−	+	−	+	−	+	+	+	+	+	−	−	+	−	+	+	−	−	−	+	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS								X			X														
Fibroadenoma			X						X		X			X	X	X	X		X	X		X	X	X	X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																		X							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp									X	X				X											X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma																									

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

ANIMAL NUMBER	0115	0116	0118	0119	0200	0222	0223	0225	0227	0229	0230	0231	0233	0234	0237	0238	0239	0240	0241	0243	0244	0246	0247	0249	0250	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	ISSUES
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																									X	1
Fibrosarcoma			X																							1
Neurilemoma, malignant																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	48
Spleen	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	−	+	+	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenomatous polyp, NOS	X																									1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X	X	X						X	X	X					X		X	X				X		24
Ganglioneuroma																					X					1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										1
Pheochromocytoma, malignant																										2
Thyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma																	X									2
C-cell carcinoma											X															1
Parathyroid	+	+	+	+	−	+	−	+	−	−	+	+	+	+	−	−	−	+	+	+	+	+	−	+	−	30
REPRODUCTIV																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS								X																		3
Fibroadenoma	X		X			X		X	X				X	X	X			X		X						23
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS				X			X																		X	4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	49
Endometrial stromal polyp		X						X							X			X								8
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Leiomyosarcoma																			X							1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma								X																		1

* Animals necropsied

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	3 mg/kg	30 mg/kg
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted Rates (b)	11.0%	0.0%	5.6%
Terminal Rates (c)	1/21 (5%)	0/32 (0%)	2/36 (6%)
Week of First Observation	92		104
Life Table Tests (d)	P=0.625N	P=0.079N	P=0.314N
Incidental Tumor Tests (d)	P=0.623	P=0.176N	P=0.484N
Cochran-Armitage Trend Test (d)	P=0.613		
Fisher Exact Test (d)		P=0.121N	P=0.500N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	14.8%	2.0%	5.6%
Terminal Rates (c)	1/21 (5%)	0/32 (0%)	2/36 (6%)
Week of First Observation	92	54	104
Life Table Tests (d)	P=0.380N	P=0.118N	P=0.168N
Incidental Tumor Tests (d)	P=0.600N	P=0.217N	P=0.390N
Cochran-Armitage Trend Test (d)	P=0.494N		
Fisher Exact Test (d)		P=0.181N	P=0.339N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	11/50 (22%)	7/50 (14%)	0/50 (0%)
Adjusted Rates (b)	30.2%	18.3%	0.0%
Terminal Rates (c)	2/21 (10%)	4/32 (13%)	0/36 (0%)
Week of First Observation	86	68	
Life Table Tests (d)	P<0.001N	P=0.132N	P<0.001N
Incidental Tumor Tests (d)	P=0.003N	P=0.391N	P=0.005N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.218N	P<0.001N
Anterior Pituitary Gland: Adenoma			
Overall Rates (e)	27/49 (55%)	(f) 22/32 (69%)	24/50 (48%)
Adjusted Rates (b)	69.4%		50.9%
Terminal Rates (c)	10/21 (48%)		13/36 (36%)
Week of First Observation	65		77
Life Table Test (d)			P=0.047N
Incidental Tumor Test (d)			P=0.470
Fisher Exact Test (d)			P=0.307N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (e)	2/49 (4%)	(f) 1/3 (33%)	3/48 (6%)
Adjusted Rates (b)	7.6%		7.9%
Terminal Rates (c)	1/21 (5%)		2/35 (6%)
Week of First Observation	98		92
Life Table Test (d)			P=0.662
Incidental Tumor Test (d)			P=0.509
Fisher Exact Test (d)			P=0.490
Mammary Gland: Fibroadenoma			
Overall Rates (a)	(g) 21/50 (42%)	21/50 (42%)	23/50 (46%)
Adjusted Rates (b)	58.5%	55.1%	57.2%
Terminal Rates (c)	8/21 (38%)	15/32 (47%)	19/36 (53%)
Week of First Observation	5	97	80
Life Table Tests (d)	P=0.249N	P=0.173N	P=0.147N
Incidental Tumor Tests (d)	P=0.436	P=0.390	P=0.452
Cochran-Armitage Trend Test (d)	P=0.382		
Fisher Exact Test (d)		P=0.580	P=0.420

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	3 mg/kg	30 mg/kg
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	(f) 1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	3.3%	0.0%	7.4%
Terminal Rates (c)	0/21 (0%)	0/32 (0%)	1/36 (3%)
Week of First Observation	99		92
Life Table Tests (d)	P=0.160	P=0.469N	P=0.410
Incidental Tumor Tests (d)	P=0.054	P=0.638N	P=0.151
Cochran-Armitage Trend Test (d)	P=0.111		
Fisher Exact Test (d)		P=0.500N	P=0.309
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	(f) 21/50 (42%)	21/50 (42%)	24/50 (48%)
Adjusted Rates (b)	58.5%	55.1%	58.2%
Terminal Rates (c)	8/21 (38%)	15/32 (47%)	19/36 (53%)
Week of First Observation	5	97	80
Life Table Tests (d)	P=0.318N	P=0.173N	P=0.194N
Incidental Tumor Tests (d)	P=0.336	P=0.390	P=0.350
Cochran-Armitage Trend Test (d)	P=0.298		
Fisher Exact Test (d)		P=0.580	P=0.344
Clitoral Gland: Adenoma			
Overall Rates (e)	4/50 (8%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	16.1%	5.5%	11.1%
Terminal Rates (c)	3/21 (14%)	1/32 (3%)	4/36 (11%)
Week of First Observation	84	92	104
Life Table Tests (d)	P=0.604N	P=0.219N	P=0.375N
Incidental Tumor Tests (d)	P=0.611	P=0.306N	P=0.410N
Cochran-Armitage Trend Test (d)	P=0.476		
Fisher Exact Test (d)		P=0.339N	P=0.642
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	7/50 (14%)	(h) 6/50 (12%)	8/50 (16%)
Adjusted Rates (b)	24.0%	17.8%	20.2%
Terminal Rates (c)	3/21 (14%)	5/32 (16%)	5/36 (14%)
Week of First Observation	87	97	95
Life Table Tests (d)	P=0.526N	P=0.286N	P=0.405N
Incidental Tumor Tests (d)	P=0.406	P=0.501N	P=0.422
Cochran-Armitage Trend Test (d)	P=0.407		
Fisher Exact Test (d)		P=0.500N	P=0.500
All Sites: Benign Tumors			
Overall Rates (a)	43/50 (86%)	37/50 (74%)	42/50 (84%)
Adjusted Rates (b)	93.3%	87.9%	89.3%
Terminal Rates (c)	18/21 (86%)	27/32 (84%)	31/36 (86%)
Week of First Observation	5	68	77
Life Table Tests (d)	P=0.060N	P=0.005N	P=0.007N
Incidental Tumor Tests (d)	P=0.486	P=0.125N	P=0.536N
Cochran-Armitage Trend Test (d)	P=0.405		
Fisher Exact Test (d)		P=0.106N	P=0.500N
All Sites: Malignant Tumors			
Overall Rates (a)	18/50 (36%)	12/50 (24%)	11/50 (22%)
Adjusted Rates (b)	49.0%	28.2%	25.6%
Terminal Rates (c)	5/21 (24%)	5/32 (16%)	5/36 (14%)
Week of First Observation	86	54	80
Life Table Tests (d)	P=0.075N	P=0.065N	P=0.022N
Incidental Tumor Tests (d)	P=0.430N	P=0.266N	P=0.380N
Cochran-Armitage Trend Test (d)	P=0.166N		
Fisher Exact Test (d)		P=0.138N	P=0.093N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	3 mg/kg	30 mg/kg
All Sites: All Tumors			
Overall Rates (a)	48/50 (96%)	42/50 (84%)	42/50 (84%)
Adjusted Rates (b)	98.0%	89.2%	89.3%
Terminal Rates (c)	20/21 (95%)	27/32 (84%)	31/36 (86%)
Week of First Observation	5	54	77
Life Table Tests (d)	P=0.008N	P=0.007N	P<0.001N
Incidental Tumor Tests (d)	P=0.204N	P=0.108N	P=0.075N
Cochran-Armitage Trend Test (d)	P=0.164N		
Fisher Exact Test (d)		P=0.046N	P=0.046N

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

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

Study	Incidence of Leukemia in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,N-Dimethylaniline	11/50
Ampicillin trihydrate	14/50
Penicillin VK	13/50
TOTAL	38/150 (25.3%)
SD (b)	3.06%
Range (c)	
High	14/50
Low	11/50
Overall Historical Incidence	
TOTAL	403/2,100 (19.2%)
SD (b)	7.95%
Range (c)	
High	21/50
Low	2/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Granulation tissue	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal mucosa	(50)		(50)
Lymphocytic inflammatory infiltrate	47 (94%)		42 (84%)
Inflammation, suppurative			1 (2%)
#Tracheal submucosa	(50)	(2)	(50)
Granulation tissue	1 (2%)		
#Lung/bronchus	(50)	(5)	(49)
Edema, NOS	1 (2%)		
#Lung	(50)	(5)	(49)
Congestion, NOS		1 (20%)	1 (2%)
Congestion, acute	2 (4%)		2 (4%)
Hemorrhage			2 (4%)
Lymphocytic inflammatory infiltrate		1 (20%)	
Inflammation, interstitial	1 (2%)		1 (2%)
Inflammation, suppurative	1 (2%)		
Pneumonia, interstitial chronic			1 (2%)
Proteinosis, alveolar			1 (2%)
Hyperplasia, alveolar epithelium			1 (2%)
#Lung/alveoli	(50)	(5)	(49)
Histiocytosis			1 (2%)
HEMATOPOIETIC SYSTEM			
*Blood erythrocytes	(50)	(50)	(50)
Reticulocytosis			2 (4%)
Normoblastosis	1 (2%)		3 (6%)
#Bone marrow	(47)	(2)	(48)
Hyperplasia, erythroid	4 (9%)		6 (13%)
Hyperplasia, granulocytic	1 (2%)		4 (8%)
Hyperplasia, lymphoid	1 (2%)		
#Spleen	(50)	(49)	(49)
Congestion, NOS	1 (2%)	1 (2%)	2 (4%)
Fibrosis	1 (2%)		
Metamorphosis, fatty		1 (2%)	
Hemosiderosis	47 (94%)	48 (98%)	49 (100%)
#Splenic red pulp	(50)	(49)	(49)
Congestion, NOS	3 (6%)	1 (2%)	5 (10%)
Fibrosis	1 (2%)		2 (4%)
Atrophy, focal	1 (2%)		
Hematopoiesis	47 (94%)	48 (98%)	49 (100%)
#Mandibular lymph node	(50)	(4)	(50)
Hyperplasia, diffuse	4 (8%)		2 (4%)
Hyperplasia, lymphoid	19 (38%)		16 (32%)
#Mediastinal lymph node	(50)	(4)	(50)
Hemorrhage	1 (2%)		1 (2%)
Inflammation, chronic	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
#Pancreatic lymph node	(50)	(4)	(50)
Hemorrhage	2 (4%)		
Hyperplasia, lymphoid		1 (25%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(50)	(4)	(50)
Hemorrhage	2 (4%)		1 (2%)
Hyperplasia, diffuse	1 (2%)		
Hyperplasia, lymphoid	6 (12%)	1 (25%)	4 (8%)
#Lung/bronchus	(50)	(5)	(49)
Hyperplasia, lymphoid	1 (2%)		
#Liver	(50)	(46)	(50)
Hematopoiesis	1 (2%)	1 (2%)	
#Peyer's patch	(50)	(5)	(50)
Hyperplasia, lymphoid		1 (20%)	2 (4%)
CIRCULATORY SYSTEM			
#Myocardium	(50)	(2)	(50)
Inflammation, chronic	1 (2%)		
Inflammation, granulomatous focal	1 (2%)		
Degeneration, NOS	24 (48%)		20 (40%)
#Adrenal cortex	(50)	(8)	(50)
Thrombus, organized	1 (2%)		
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Inflammation, chronic suppurative	1 (2%)		
#Salivary gland	(50)	(8)	(49)
Hemorrhage		1 (13%)	
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, suppurative	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Atrophy, focal	5 (10%)	3 (38%)	6 (12%)
#Liver	(50)	(46)	(50)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal	17 (34%)	20 (43%)	30 (60%)
Necrosis, focal	2 (4%)		1 (2%)
Cytoplasmic vacuolization	2 (4%)	2 (4%)	1 (2%)
Basophilic cyto change	40 (80%)	37 (80%)	49 (98%)
Eosinophilic cyto change	2 (4%)	2 (4%)	
Clear cell change	4 (8%)	3 (7%)	5 (10%)
Hyperplasia, nodular	1 (2%)	1 (2%)	
Angiectasis		2 (4%)	1 (2%)
#Liver/centrilobular	(50)	(46)	(50)
Congestion, acute	1 (2%)		1 (2%)
Degeneration, NOS	6 (12%)	1 (2%)	
Necrosis, NOS			1 (2%)
#Bile duct	(50)	(46)	(50)
Hyperplasia, NOS	14 (28%)	19 (41%)	15 (30%)
#Pancreas	(49)	(2)	(50)
Inflammation, chronic focal	1 (2%)		
Atrophy, NOS			3 (6%)
Atrophy, focal	3 (6%)		5 (10%)
#Esophagus	(50)	(3)	(50)
Necrosis, NOS		1 (33%)	
#Gastric mucosa	(50)	(3)	(50)
Fibrosis	11 (22%)		11 (22%)
#Forestomach	(50)	(3)	(50)
Inflammation, suppurative			2 (4%)
Ulcer, chronic		1 (33%)	
Hyperkeratosis	3 (6%)		4 (8%)
Acanthosis	5 (10%)		9 (18%)
#Large intestine	(50)	(3)	(50)
Hemorrhage	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Colon	(50)	(3)	(50)
Distention	3 (6%)		5 (10%)
Parasitism	3 (6%)		3 (6%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hamartoma	1 (2%)		
Inflammation, suppurative	1 (2%)		
Infection, bacterial	1 (2%)		
Nephrosis, NOS	37 (74%)	1 (2%)	37 (74%)
Infarct, healed	1 (2%)		
#Kidney/tubule	(50)	(50)	(50)
Pigmentation, NOS	48 (96%)	50 (100%)	49 (98%)
Atrophy, focal		1 (2%)	
#Urinary bladder	(50)	(2)	(48)
Distention	3 (6%)		1 (2%)
Hyperplasia, epithelial			1 (2%)
Hyperplasia, adenomatous			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(32)	(50)
Hyperplasia, NOS	1 (2%)		
#Anterior pituitary	(49)	(32)	(50)
Cyst, NOS	3 (6%)	1 (3%)	3 (6%)
Hemorrhage	2 (4%)		
Hyperplasia, NOS	15 (31%)	4 (13%)	12 (24%)
Hyperplasia, focal	1 (2%)	1 (3%)	4 (8%)
Hyperplasia, diffuse			1 (2%)
Angiectasis	17 (35%)		15 (30%)
#Adrenal cortex	(50)	(8)	(50)
Hemorrhagic cyst			1 (2%)
Cytoplasmic vacuolization	3 (6%)		
Hypertrophy, focal	1 (2%)		
Hyperplasia, NOS	1 (2%)		1 (2%)
Hyperplasia, focal	3 (6%)		5 (10%)
#Adrenal medulla	(50)	(8)	(50)
Hyperplasia, focal	3 (6%)	2 (25%)	15 (30%)
#Thyroid	(49)	(3)	(48)
Hyperplasia, C-cell	1 (2%)		2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts		2 (4%)	
Hyperplasia, NOS	3 (6%)	1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)	1 (2%)	
*Mammary duct	(50)	(50)	(50)
Distention	12 (24%)		20 (40%)
Dysplasia, NOS		1 (2%)	
*Vulva	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
*Clitoral gland	(50)	(50)	(50)
Retention of content		3 (6%)	
Inflammation, suppurative	3 (6%)	3 (6%)	2 (4%)
Inflammation, chronic	3 (6%)	2 (4%)	
Inflammation, chronic focal	5 (10%)		
Inflammation, chronic suppurative	2 (4%)		6 (12%)
Hyperplasia, focal	2 (4%)	1 (2%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Uterus	(49)	(14)	(49)
Hydrometra	9 (18%)	2 (14%)	12 (24%)
Hematometra			2 (4%)
Pyometra			1 (2%)
Adenomyosis	1 (2%)		
#Cervix uteri	(49)	(14)	(49)
Epidermal inclusion cyst			1 (2%)
Inflammation, suppurative			1 (2%)
#Uterus/endometrium	(49)	(14)	(49)
Hyperplasia, NOS		1 (7%)	
Hyperplasia, cystic	3 (6%)		1 (2%)
Hyperplasia, stromal		1 (7%)	
#Ovary	(49)	(7)	(49)
Cyst, NOS	4 (8%)	4 (57%)	4 (8%)
NERVOUS SYSTEM			
#Brain	(49)	(4)	(50)
Hydrocephalus, NOS		1 (25%)	
Inflammation, chronic focal	1 (2%)		
Infection, bacterial	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Cataract	1 (2%)		
Phthisis bulbi		1 (2%)	
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	4 (8%)		1 (2%)
*Ear canal	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	31 (62%)		26 (52%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteosclerosis	1 (2%)		
*Skull	(50)	(50)	(50)
Osteosclerosis		1 (2%)	
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Necrosis, fat	11 (22%)	9 (18%)	7 (14%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	1 (2%)		
Fibrosarcoma	3 (6%)	4 (8%)	1 (2%)
Neurilemoma, malignant	1 (2%)		2 (4%)
RESPIRATORY SYSTEM			
#Lung/bronchiole	(50)	(29)	(50)
Papilloma, NOS	1 (2%)		
#Lung	(50)	(29)	(50)
Hepatocellular carcinoma, metastatic	3 (6%)	2 (7%)	1 (2%)
Alveolar/bronchiolar adenoma	6 (12%)	10 (34%)	6 (12%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (7%)	6 (12%)
Follicular cell carcinoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)		1 (2%)
Malignant lymphoma, undifferentiated type		1 (2%)	1 (2%)
Malignant lymphoma, lymphocytic type		1 (2%)	
Malignant lymphoma, mixed type	3 (6%)	5 (10%)	1 (2%)
#Spleen	(49)	(21)	(50)
Malignant lymphoma, NOS		1 (5%)	
#Mandibular lymph node	(48)	(20)	(49)
Neurilemoma, invasive	1 (2%)		
#Mesenteric lymph node	(48)	(20)	(49)
Malignant lymphoma, undifferentiated type		1 (5%)	
Malignant lymphoma, histiocytic type			1 (2%)
Malignant lymphoma, mixed type	1 (2%)		
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
#Spleen	(49)	(21)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma	1 (2%)	1 (5%)	2 (4%)
#Liver	(50)	(30)	(49)
Hemangiosarcoma	1 (2%)	1 (3%)	3 (6%)
#Ileum	(50)	(13)	(44)
Hemangiosarcoma, metastatic	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(13)	(48)
Neurilemoma, invasive	1 (2%)		
#Liver	(50)	(30)	(49)
Hepatocellular adenoma	7 (14%)	12 (40%)	10 (20%)
Hepatocellular carcinoma	4 (8%)	5 (17%)	5 (10%)
Histiocytic sarcoma		1 (3%)	
#Forestomach	(50)	(23)	(49)
Squamous cell papilloma	3 (6%)	5 (22%)	1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary	(40)	(13)	(44)
Adenoma, NOS	1 (3%)		1 (2%)
#Adrenal/capsule	(47)	(44)	(49)
Adenoma, NOS	1 (2%)		2 (4%)
#Adrenal medulla	(47)	(44)	(49)
Pheochromocytoma	1 (2%)		
Pheochromocytoma, malignant	2 (4%)		
#Thyroid	(45)	(13)	(44)
Follicular cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
#Testis	(50)	(14)	(50)
Interstitial cell tumor	1 (2%)		2 (4%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Papillary adenoma	2 (4%)	3 (6%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Carcinoma, NOS, unclear primary or metastatic		1 (2%)	
Paraganglioma, NOS			1 (2%)
Neurilemoma, metastatic			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Fibrosarcoma	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	14	13
Moribund sacrifice	6	6	3
Terminal sacrifice	34	30	34
Dosing accident	4		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	32	37	33
Total primary tumors	45	55	47
Total animals with benign tumors	20	22	22
Total benign tumors	25	30	23
Total animals with malignant tumors	17	22	20
Total malignant tumors	20	24	23
Total animals with secondary tumors##	6	2	2
Total secondary tumors	7	2	2
Total animals with tumors-- uncertain benign or malignant			1
Total uncertain tumors			1
Total animals with tumors-- uncertain primary or metastatic		1	
Total uncertain tumors		1	

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: VEHICLE CONTROL

ANIMAL NUMBER	02 7	04 2	04 4	04 8	01 5	00 6	01 1	03 1	00 3	02 0	04 3	01 7	04 6	00 5	02 5	02 8	00 1	00 2	00 4	00 7	00 8	00 9	01 0	01 2	01 3
WEEKS ON STUDY	01 1	01 7	01 8	05 2	08 4	08 7	08 8	09 0	09 3	09 3	09 3	09 4	09 4	09 7	09 7	10 2	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma					X																				
Fibrosarcoma										X				X		X									
Neurilemoma, malignant												X													
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS								X																	
Hepatocellular carcinoma, metastatic																				X		X			
Alveolar/bronchiolar adenoma								X						X											
Alveolar/bronchiolar carcinoma						X																			
Follicular cell carcinoma, metastatic																									
Trachea	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Hemangiosarcoma											X														
Lymph nodes	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, invasive												X													
Malignant lymphoma, mixed type								X																	
Thymus	+	+	+	+	–	+	–	–	–	–	–	+	–	–	–	+	–	–	+	–	–	–	–	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, invasive												X													
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X																				
Hepatocellular carcinoma																				X		X			
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	N	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+
Pancreas	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic											X														
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	–
Adenoma, NOS																							X		
Adrenal	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma																									
Pheochromocytoma, malignant									X																
Thyroid	+	–	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Follicular cell carcinoma																									
Parathyroid	–	–	+	+	–	–	–	–	–	+	–	–	+	+	–	–	+	+	–	–	–	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma						X																			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma													X												
Malignant lymphoma, NOS							X																		
Malignant lymphoma, mixed type									X	X					X										

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

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

ANIMAL NUMBER	0014	0016	0018	0019	0021	0022	0023	0024	0026	0029	0030	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0045	0047	0049	0050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Fibrosarcoma																										3
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma, NOS																										1
Hepatocellular carcinoma, metastatic																									X	3
Alveolar/bronchiolar adenoma				X										X						X		X				6
Alveolar/bronchiolar carcinoma																										1
Follicular cell carcinoma, metastatic																	X									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																									X	1
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neurilemoma, invasive																										1
Malignant lymphoma, mixed type																										1
Thymus	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	27
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, invasive																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X	X				X									X			X	X							7
Hepatocellular carcinoma																					X				X	4
Hemangiosarcoma																		X								1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X							X						X											3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	−	−	+	+	−	+	−	+	+	+	+	+	+	+	−	+	+	+	+	−	40
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS			X																							1
Pheochromocytoma															X											1
Pheochromocytoma, malignant																		X								2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	45
Follicular cell carcinoma																	X									1
Parathyroid	+	−	+	+	−	−	+	−	+	+	+	+	−	+	+	−	+	−	−	+	+	+	+	+	−	27
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor															X											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma																							X			2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										1
Malignant lymphoma, NOS																										1
Malignant lymphoma, mixed type																										3

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: LOW DOSE

ANIMAL NUMBER	0028	0020	0033	0044	0040	0037	0048	0041	0026	0004	0007	0021	0034	0030	0042	0005	0015	0018	0006	0032	0001	0002	0003	0008	0009
WEEKS ON STUDY	0025	0071	0076	0077	0079	0081	0081	0083	0084	0090	0090	0090	0090	0091	0093	0099	0099	0100	0102	0102	0104	0104	0104	0104	0104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	N	N	+	N	N	N	N	N	N	N
Fibrosarcoma			X					X	X					X											
Hemangiosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	−	−	−	−	+	−	−
Hepatocellular carcinoma, metastatic															X										
Alveolar/bronchiolar adenoma							X		X			X						X					X		
Alveolar/bronchiolar carcinoma														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
Nasal cavity	+	+	+	+	+	−	−	+	−	+	+	+	+	−	−	−	−	+	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	−	−	−	−	−	−	+
Hemangiosarcoma																									
Malignant lymphoma, NOS																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	−	−	−	−	−	−	−
Malignant lymphoma, undifferentiated type					X																				
Thymus	−	−	−	−	−	−	−	−	−	−	+	+	−	−	−	−	−	+	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	−	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	−	+	+
Hepatocellular adenoma											X		X					X			X			X	X
Hepatocellular carcinoma						X									X				X	X					
Histiocytic sarcoma																									
Hemangiosarcoma																				X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	−	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	+	N	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	−	+	+	+	+	+	−	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
Esophagus	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	+	−	−	−	−	−	+
Squamous cell papilloma																			X						X
Small intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−
Large intestine	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	−	+	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
Adrenal	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
Parathyroid	−	−	+	+	+	+	−	+	+	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	+	−	−	−	−	−	−
Prostate	+	+	−	+	+	+	+	−	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma			X								X	X													
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, unclear primary or metastatic						X																			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undifferentiated type				X																					
Malignant lymphoma, lymphocytic type										X															
Malignant lymphoma, mixed type							X										X	X							

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

ANIMAL NUMBER	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 6	0 1 7	0 1 9	0 2 2	0 2 3	0 2 4	0 2 5	0 2 7	0 2 9	0 3 1	0 3 5	0 3 6	0 3 8	0 3 9	0 4 3	0 4 5	0 4 6	0 4 7	0 4 9	0 5 0	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	*50
Fibrosarcoma																										4
Hemangiosarcoma										X																1
RESPIRATORY SYSTEM																										
Lungs and bronchi	−	−	+	+	−	−	−	−	+	+	+	−	−	−	+	+	+	+	−	−	−	+	−	+	+	29
Hepatocellular carcinoma, metastatic																		X								2
Alveolar/bronchiolar adenoma			X	X											X	X									X	10
Alveolar/bronchiolar carcinoma											X															2
Trachea	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
Nasal cavity	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	11
HEMATOPOIETIC SYSTEM																										
Bone marrow	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	14
Spleen	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	+	−	+	+	−	−	−	−	−	21
Hemangiosarcoma						X																				1
Malignant lymphoma, NOS																			X							1
Lymph nodes	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	+	−	−	+	−	−	+	−	−	20
Malignant lymphoma, undifferent. type																										1
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	3
CIRCULATORY SYSTEM																										
Heart	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
DIGESTIVE SYSTEM																										
Salivary gland	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	13
Liver	−	+	+	−	−	−	−	+	−	−	+	+	−	−	−	−	−	+	−	−	−	+	+	−	−	30
Hepatocellular adenoma		X	X					X			X	X						X								12
Hepatocellular carcinoma																		X								5
Histiocytic sarcoma																							X			1
Hemangiosarcoma																										1
Bile duct	−	+	+	−	−	−	−	+	−	−	+	+	−	−	−	−	−	+	−	−	−	+	+	−	−	30
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	*50
Pancreas	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	12
Esophagus	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	12
Stomach	−	+	+	+	−	−	−	+	−	−	−	−	+	−	−	−	+	−	−	−	−	+	+	−	−	23
Squamous cell papilloma		X		X				X																		5
Small intestine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
Large intestine	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	15
URINARY SYSTEM																										
Kidney	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	14
Urinary bladder	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
ENDOCRINE SYSTEM																										
Pituitary	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
Adrenal	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	44
Thyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
Parathyroid	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	9
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	14
Prostate	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	11
NERVOUS SYSTEM																										
Brain	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	13
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma																										3
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS, uncl. primary or meta																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undifferent. type																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type																	X			X						5

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: HIGH DOSE

ANIMAL NUMBER	019	005	015	035	023	043	021	020	036	042	049	013	018	039	001	041	002	003	004	006	007	008	009	011	011
WEEKS ON STUDY	078	079	080	086	087	087	088	089	090	090	095	097	097	098	102	103	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma															X										
Neurilemoma, malignant								X					X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic										X															
Alveolar/bronchiolar adenoma																	X		X						
Alveolar/bronchiolar carcinoma																					X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Lymph nodes	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, histiocytic type																									
Thymus	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	+	+	+	−	+	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X						X	X			X	X					X				
Hepatocellular carcinoma			X							X	X														
Hemangiosarcoma				X																		X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	N	N	N	+	N	N	+	N	N	N	N	N	N	+	N	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	−	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	−	+	+	−	+	+	−	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X																							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																						X			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	+	+	−	+	−	+	−	+	+	−	−	−	−	+	+	+	+	−	+	−	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Paraganglioma, NOS																	X								
Neurilemoma, metastatic								X																	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																X									
Malignant lymphoma, undifferentiated type							X																		
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	012	014	016	017	022	024	025	026	027	028	029	030	031	032	033	034	037	038	040	044	045	046	047	048	050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
Neurilemoma, malignant																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma	X								X		X			X												6
Alveolar/bronchiolar carcinoma				X	X						X													X	X	6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X	X									2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, histiocytic type																	X									1
Thymus	−	+	+	+	+	−	+	+	−	−	−	+	−	−	−	+	+	+	+	+	+	+	+	−	+	24
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma								X								X			X			X			10
Hepatocellular carcinoma	X															X										5
Hemangiosarcoma																	X									3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma															X											1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Large intestine	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	46
ENDOCRINE SYSTEM																										
Pituitary	−	+	+	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	44
Adenoma, NOS																										1
Adrenal	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X																							2
Thyroid	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	+	−	+	+	+	+	44
Parathyroid	+	+	+	+	−	+	+	+	+	−	−	+	−	+	+	−	−	+	+	−	−	+	+	+	+	31
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor		X												X												2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma										X																1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Paraganglioma, NOS																										1
Neurilemoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										1
Malignant lymphoma, undifferent. type																										1
Malignant lymphoma, mixed type										X																1

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	15 mg/kg	30 mg/kg
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	7.7%	9.2%	2.8%
Terminal Rates (c)	0/34 (0%)	0/30 (0%)	0/34 (0%)
Week of First Observation	93	76	102
Life Table Tests (d)	P=0.254N	P=0.459	P=0.303N
Incidental Tumor Tests (d)	P=0.156N	P=0.527N	P=0.403N
Cochran-Armitage Trend Test (d)	P=0.252N		
Fisher Exact Test (d)		P=0.500	P=0.309N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	9.7%	9.2%	2.8%
Terminal Rates (c)	0/34 (0%)	0/30 (0%)	0/34 (0%)
Week of First Observation	84	76	102
Life Table Tests (d)	P=0.152N	P=0.596	P=0.180N
Incidental Tumor Tests (d)	P=0.060N	P=0.283N	P=0.178N
Cochran-Armitage Trend Test (d)	P=0.146N		
Fisher Exact Test (d)		P=0.643	P=0.181N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (e)	6/50 (12%)	(f) 10/29 (34%)	6/50 (12%)
Adjusted Rates (b)	16.1%		17.6%
Terminal Rates (c)	4/34 (12%)		6/34 (18%)
Week of First Observation	90		104
Life Table Test (d)			P=0.619N
Incidental Tumor Test (d)			P=0.593N
Fisher Exact Test (d)			P=0.620
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (e)	1/50 (2%)	(f) 2/29 (7%)	6/50 (12%)
Adjusted Rates (b)	2.2%		17.6%
Terminal Rates (c)	0/34 (0%)		6/34 (18%)
Week of First Observation	87		104
Life Table Test (d)			P=0.060
Incidental Tumor Test (d)			P=0.077
Fisher Exact Test (d)			P=0.056
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (e)	7/50 (14%)	(f) 12/29 (41%)	11/50 (22%)
Adjusted Rates (b)	18.0%		32.4%
Terminal Rates (c)	4/34 (12%)		11/34 (32%)
Week of First Observation	87		104
Life Table Test (d)			P=0.220
Incidental Tumor Test (d)			P=0.266
Fisher Exact Test (d)			P=0.218
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	4/50 (8%)	(f,g) 5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	9.5%	14.0%	2.9%
Terminal Rates (c)	0/34 (0%)	2/30 (7%)	1/34 (3%)
Week of First Observation	90	81	104
Life Table Tests (d)	P=0.169N	P=0.451	P=0.189N
Incidental Tumor Tests (d)	P=0.155N	P=0.503	P=0.174N
Cochran-Armitage Trend Test (d)	P=0.158N		
Fisher Exact Test (d)		P=0.500	P=0.181N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	5/50 (10%)	(f,g) 9/50 (18%)	4/50 (8%)
Adjusted Rates (b)	11.5%	22.6%	10.6%
Terminal Rates (c)	0/34 (0%)	3/30 (10%)	2/34 (6%)
Week of First Observation	88	77	88
Life Table Tests (d)	P=0.438N	P=0.175	P=0.503N
Incidental Tumor Tests (d)	P=0.314N	P=0.401	P=0.414N
Cochran-Armitage Trend Test (d)	P=0.439N		
Fisher Exact Test (d)		P=0.194	P=0.500N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	(f,g) 3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	5.3%	9.6%	10.8%
Terminal Rates (c)	1/34 (3%)	2/30 (7%)	3/34 (9%)
Week of First Observation	93	102	86
Life Table Tests (d)	P=0.272	P=0.444	P=0.339
Incidental Tumor Tests (d)	P=0.269	P=0.414	P=0.375
Cochran-Armitage Trend Test (d)	P=0.264		
Fisher Exact Test (d)		P=0.500	P=0.339
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	3/50 (6%)	(f,g) 3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	8.1%	9.6%	10.8%
Terminal Rates (c)	2/34 (6%)	2/30 (7%)	3/34 (9%)
Week of First Observation	93	102	86
Life Table Tests (d)	P=0.424	P=0.603	P=0.500
Incidental Tumor Tests (d)	P=0.424	P=0.578	P=0.538
Cochran-Armitage Trend Test (d)	P=0.421		
Fisher Exact Test (d)		P=0.661	P=0.500
Liver: Hepatocellular Adenoma			
Overall Rates (e)	7/50 (14%)	(f) 12/30 (40%)	10/49 (20%)
Adjusted Rates (b)	19.4%		25.2%
Terminal Rates (c)	6/34 (18%)		5/34 (15%)
Week of First Observation	84		87
Life Table Test (d)			P=0.314
Incidental Tumor Test (d)			P=0.281
Fisher Exact Test (d)			P=0.282
Liver: Hepatocellular Carcinoma			
Overall Rates (e)	4/50 (8%)	(f) 5/30 (17%)	5/49 (10%)
Adjusted Rates (b)	11.8%		12.3%
Terminal Rates (c)	4/34 (12%)		2/34 (6%)
Week of First Observation	104		80
Life Table Test (d)			P=0.507
Incidental Tumor Test (d)			P=0.575
Fisher Exact Test (d)			P=0.487
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (e)	11/50 (22%)	(f) 16/30 (53%)	13/49 (27%)
Adjusted Rates (b)	30.9%		31.0%
Terminal Rates (c)	10/34 (29%)		6/34 (18%)
Week of First Observation	84		80
Life Table Test (d)			P=0.422
Incidental Tumor Test (d)			P=0.464
Fisher Exact Test (d)			P=0.385

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	3/50 (6%)	(h) 5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	8.8%	16.0%	2.9%
Terminal Rates (c)	3/34 (9%)	4/30 (13%)	1/34 (3%)
Week of First Observation	104	102	104
Life Table Tests (d)	P=0.266N	P=0.292	P=0.304N
Incidental Tumor Tests (d)	P=0.281N	P=0.279	P=0.304N
Cochran-Armitage Trend Test (d)	P=0.264N		
Fisher Exact Test (d)		P=0.357	P=0.309N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (e)	3/47 (6%)	0/44 (0%)	0/49 (0%)
Adjusted Rates (b)	8.3%	0.0%	
Terminal Rates (c)	2/33 (6%)	0/26 (0%)	0/33 (0%)
Week of First Observation	93		
Life Table Tests (d)	P=0.044N	P=0.162N	P=0.126N
Incidental Tumor Tests (d)	P=0.047N	P=0.175N	P=0.132N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.133N	P=0.113N
Harderian Gland: Papillary Adenoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	5.1%	6.9%	2.9%
Terminal Rates (c)	1/34 (3%)	0/30 (0%)	1/34 (3%)
Week of First Observation	87	76	104
Life Table Tests (d)	P=0.398N	P=0.476	P=0.497N
Incidental Tumor Tests (d)	P=0.208N	P=0.449N	P=0.409N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.500	P=0.500N
All Sites: Benign Tumors			
Overall Rates (a)	20/50 (40%)	22/50 (44%)	22/50 (44%)
Adjusted Rates (b)	51.9%	56.6%	54.5%
Terminal Rates (c)	16/34 (47%)	14/30 (47%)	16/34 (47%)
Week of First Observation	84	76	79
Life Table Tests (d)	P=0.402	P=0.273	P=0.437
Incidental Tumor Tests (d)	P=0.518	P=0.575N	P=0.517
Cochran-Armitage Trend Test (d)	P=0.381		
Fisher Exact Test (d)		P=0.420	P=0.420
All Sites: Malignant Tumors			
Overall Rates (a)	17/50 (34%)	22/50 (44%)	20/50 (40%)
Adjusted Rates (b)	37.8%	48.9%	45.8%
Terminal Rates (c)	6/34 (18%)	8/30 (27%)	11/34 (32%)
Week of First Observation	87	76	80
Life Table Tests (d)	P=0.350	P=0.167	P=0.373
Incidental Tumor Tests (d)	P=0.459	P=0.453	P=0.440
Cochran-Armitage Trend Test (d)	P=0.304		
Fisher Exact Test (d)		P=0.206	P=0.339
All Sites: All Tumors			
Overall Rates (a)	32/50 (64%)	37/50 (74%)	33/50 (66%)
Adjusted Rates (b)	69.6%	78.5%	71.4%
Terminal Rates (c)	20/34 (59%)	20/30 (67%)	21/34 (62%)
Week of First Observation	84	76	79
Life Table Tests (d)	P=0.483	P=0.127	P=0.514
Incidental Tumor Tests (d)	P=0.342N	P=0.465	P=0.466N
Cochran-Armitage Trend Test (d)	P=0.457		
Fisher Exact Test (d)		P=0.194	P=0.500

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

(a) Number of tumor-bearing animals/number of animals examined grossly at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined microscopically at the site
(f) Incomplete sampling of tissues
(g) Twenty-one spleens and 30 livers were examined microscopically.
(h) Twenty-three stomachs were examined microscopically.

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
Inflammation, acute/chronic	2 (4%)	1 (2%)	
Inflammation, chronic focal	1 (2%)		
Fibrosis, diffuse			2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
Fibrosis, diffuse			1 (2%)
RESPIRATORY SYSTEM			
#Nasal mucosa	(47)	(11)	(50)
Hemorrhage			1 (2%)
Degeneration, hyaline	29 (62%)	6 (55%)	30 (60%)
#Nasopharynx	(47)	(11)	(50)
Inflammation, acute			1 (2%)
Inflammation, acute focal			1 (2%)
#Bronchial submucosa	(50)	(29)	(50)
Inflammation, acute focal			1 (2%)
#Lung	(50)	(29)	(50)
Congestion, NOS	1 (2%)	4 (14%)	6 (12%)
Hemorrhage	2 (4%)	1 (3%)	5 (10%)
Lymphocytic inflammatory infiltrate	20 (40%)		22 (44%)
Inflammation, interstitial			1 (2%)
Alveolar macrophages	1 (2%)		2 (4%)
Hyperplasia, adenomatous	1 (2%)		1 (2%)
Hyperplasia, alveolar epithelium		4 (14%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)		
*Blood	(50)	(50)	(50)
Leukocytosis, NOS	1 (2%)		4 (8%)
*Subcutaneous tissue	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)	
#Bone marrow	(50)	(14)	(50)
Fibrosis, focal	1 (2%)	1 (7%)	
Fibrosis, diffuse	2 (4%)		
Hyperplasia, granulocytic	19 (38%)	8 (57%)	16 (32%)
#Spleen	(49)	(21)	(50)
Congestion, NOS	1 (2%)		1 (2%)
Hemosiderosis	1 (2%)		2 (4%)
Hyperplasia, lymphoid	9 (18%)	3 (14%)	7 (14%)
Hematopoiesis	11 (22%)	3 (14%)	10 (20%)
#Lymph node	(48)	(20)	(49)
Congestion, NOS			1 (2%)
Hyperplasia, lymphoid	4 (8%)		2 (4%)
#Mandibular lymph node	(48)	(20)	(49)
Hemorrhage	1 (2%)		
Inflammation, acute focal			1 (2%)
Pigmentation, NOS	1 (2%)		
Hemosiderosis	3 (6%)		6 (12%)
Hyperplasia, lymphoid	2 (4%)	1 (5%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(48)	(20)	(49)
Congestion, NOS	20 (42%)	1 (5%)	20 (41%)
Hemorrhage	1 (2%)	1 (5%)	
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Hemosiderosis	1 (2%)		
Hyperplasia, lymphoid	3 (6%)	4 (20%)	1 (2%)
Hematopoiesis	7 (15%)		10 (20%)
#Inguinal lymph node	(48)	(20)	(49)
Hyperplasia, lymphoid		1 (5%)	
#Liver	(50)	(30)	(49)
Leukocytosis, NOS	1 (2%)		
Hematopoiesis	1 (2%)	1 (3%)	
#Jejunum	(50)	(13)	(44)
Hyperplasia, lymphoid	1 (2%)		
#Cecum	(50)	(15)	(47)
Hyperplasia, lymphoid	1 (2%)	2 (13%)	
#Thymus	(27)	(3)	(24)
Ectopia			1 (4%)
Ultimobranchial cyst	4 (15%)		5 (21%)
Cyst, NOS	1 (4%)		
Hyperplasia, epithelial	1 (4%)		
CIRCULATORY SYSTEM			
*Site unknown	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
#Mesenteric lymph node	(48)	(20)	(49)
Lymphangiectasis		1 (5%)	
#Lung	(50)	(29)	(50)
Thrombosis, NOS	1 (2%)		
#Heart	(50)	(13)	(50)
Thrombosis, NOS			1 (2%)
Degeneration, NOS		1 (8%)	
#Myocardium	(50)	(13)	(50)
Fibrosis, focal			1 (2%)
*Artery	(50)	(50)	(50)
Periarteritis			1 (2%)
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Dysplasia, NOS	7 (14%)		7 (14%)
#Salivary gland	(50)	(13)	(48)
Cyst, NOS		1 (8%)	
Edema, NOS	1 (2%)		
Hemorrhage	1 (2%)		
Lymphocytic inflammatory infiltrate	11 (22%)	2 (15%)	15 (31%)
Atrophy, focal			1 (2%)
Atrophy, diffuse			1 (2%)
#Liver	(50)	(30)	(49)
Congestion, NOS		2 (7%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
Inflammation, acute focal		1 (3%)	
Inflammation, acute/chronic	2 (4%)		
Inflammation, chronic focal	1 (2%)		1 (2%)
Degeneration, granular		1 (3%)	
Necrosis, focal	2 (4%)	2 (7%)	4 (8%)
Metamorphosis, fatty	1 (2%)	1 (3%)	4 (8%)
Cytoplasmic vacuolization	6 (12%)		7 (14%)
Basophilic cyto change		1 (3%)	1 (2%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(30)	(49)
Eosinophilic cyto change			1 (2%)
Clear cell change			2 (4%)
Atrophy, diffuse			1 (2%)
Hyperplasia, nodular			1 (2%)
Angiectasis			1 (2%)
#Intrahepatic bile duct	(50)	(30)	(49)
Inflammation, chronic focal	2 (4%)		
Inflammation, chronic diffuse		1 (3%)	
Degeneration, hyaline		1 (3%)	
Hyperplasia, focal	1 (2%)		
#Liver/centrilobular	(50)	(30)	(49)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute/chronic			1 (2%)
Necrosis, NOS			1 (2%)
Necrosis, focal			1 (2%)
Necrosis, diffuse	1 (2%)	1 (3%)	
Metamorphosis, fatty	8 (16%)		7 (14%)
Cytoplasmic vacuolization		1 (3%)	5 (10%)
Atrophy, diffuse			1 (2%)
#Liver/periportal	(50)	(30)	(49)
Degeneration, granular	1 (2%)		
Metamorphosis, fatty	2 (4%)		
#Liver/hepatocytes	(50)	(30)	(49)
Pleomorphism	1 (2%)		1 (2%)
Atrophy, focal		1 (3%)	1 (2%)
*Gallbladder	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Inflammation, acute	1 (2%)		
Inflammation, acute diffuse			1 (2%)
Inflammation, acute/chronic			2 (4%)
Degeneration, hyaline	1 (2%)		2 (4%)
#Pancreas	(49)	(12)	(48)
Dilatation/ducts		1 (8%)	
Lymphocytic inflammatory infiltrate			2 (4%)
Inflammation, chronic focal	1 (2%)		
Atrophy, focal	2 (4%)		4 (8%)
Atrophy, diffuse		2 (17%)	
#Stomach	(50)	(23)	(49)
Edema, NOS			1 (2%)
Inflammation, acute focal	1 (2%)		1 (2%)
Inflammation, acute/chronic	2 (4%)		4 (8%)
#Gastric mucosa	(50)	(23)	(49)
Foreign body, NOS	1 (2%)		
Ulcer, NOS			1 (2%)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute focal			2 (4%)
Inflammation, acute/chronic	1 (2%)		
Hyperplasia, diffuse	1 (2%)		
Hyperkeratosis	6 (12%)	3 (13%)	9 (18%)
#Forestomach	(50)	(23)	(49)
Hyperplasia, epithelial	11 (22%)	6 (26%)	13 (27%)
#Jejunum	(50)	(13)	(44)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
#Colon	(50)	(15)	(47)
Hyperplasia, epithelial			1 (2%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(50)	(14)	(50)
Hydronephrosis		2 (14%)	
Lymphocytic inflammatory infiltrate	20 (40%)		22 (44%)
Inflammation, acute/chronic		1 (7%)	
Glomerulonephritis, subacute	2 (4%)	1 (7%)	
Nephropathy	1 (2%)		
Infarct, NOS	1 (2%)		
Infarct, focal			1 (2%)
Metaplasia, osseous	1 (2%)		
#Kidney/tubule	(50)	(14)	(50)
Cyst, NOS	2 (4%)		
Degeneration, NOS	5 (10%)	1 (7%)	4 (8%)
Metamorphosis, fatty	37 (74%)	5 (36%)	41 (82%)
#Urinary bladder	(48)	(13)	(46)
Edema, NOS	1 (2%)	2 (15%)	
Hemorrhage		1 (8%)	
Lymphocytic inflammatory infiltrate	1 (2%)		2 (4%)
Inflammation, chronic diffuse		1 (8%)	
#Urinary bladder/mucosa	(48)	(13)	(46)
Hyperplasia, diffuse	1 (2%)		
*Prostatic urethra	(50)	(50)	(50)
Hyperplasia, papillary			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary	(40)	(13)	(44)
Cyst, NOS	3 (8%)		
Hyperplasia, chromophobe cell			1 (2%)
#Adrenal/capsule	(47)	(44)	(49)
Amyloid, NOS		1 (2%)	
Hyperplasia, focal	36 (77%)	36 (82%)	43 (88%)
Hyperplasia, diffuse	7 (15%)	4 (9%)	1 (2%)
#Adrenal cortex	(47)	(44)	(49)
Hypertrophy, focal	7 (15%)	6 (14%)	3 (6%)
Hyperplasia, nodular			1 (2%)
Hyperplasia, focal	1 (2%)	1 (2%)	2 (4%)
#Adrenal medulla	(47)	(44)	(49)
Fibrosis, diffuse	1 (2%)		
Hyperplasia, focal	1 (2%)	1 (2%)	
#Thyroid	(45)	(13)	(44)
Ultimobranchial cyst	2 (4%)		1 (2%)
Follicular cyst, NOS	6 (13%)		1 (2%)
Inflammation, acute/chronic	1 (2%)		
Hyperplasia, follicular cell			1 (2%)
#Thyroid follicle	(45)	(13)	(44)
Degeneration, cystic	2 (4%)		
Hyperplasia, papillary			1 (2%)
#Parathyroid	(27)	(9)	(31)
Ectopia			1 (3%)
Ultimobranchial cyst	1 (4%)		
Cyst, NOS	1 (4%)		
#Pancreatic islets	(49)	(12)	(48)
Hyperplasia, focal	16 (33%)	2 (17%)	14 (29%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
Inflammation, acute/chronic	5 (10%)	6 (12%)	12 (24%)
Inflammation, chronic	2 (4%)	1 (2%)	
Inflammation, chronic diffuse	4 (8%)	2 (4%)	2 (4%)
Degeneration, cystic	6 (12%)	9 (18%)	9 (18%)
Hyperkeratosis	4 (8%)	2 (4%)	4 (8%)
#Prostate	(48)	(11)	(49)
Lymphocytic inflammatory infiltrate	6 (13%)	1 (9%)	2 (4%)
Inflammation, acute		1 (9%)	
Inflammation, acute focal			1 (2%)
Inflammation, acute/chronic		1 (9%)	1 (2%)
Inflammation, chronic diffuse			1 (2%)
Degeneration, cystic			4 (8%)
Hyperplasia, focal	2 (4%)		
Hyperplasia, papillary			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	9 (18%)	11 (22%)	6 (12%)
*Coagulating gland	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
#Testis	(50)	(14)	(50)
Granuloma, spermatic			1 (2%)
Amyloidosis			1 (2%)
Atrophy, focal	1 (2%)		3 (6%)
Atrophy, diffuse	1 (2%)	1 (7%)	
Hyperplasia, interstitial cell	1 (2%)		
*Epididymis	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, chronic focal	3 (6%)		1 (2%)
Fibrosis, diffuse		1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(49)	(13)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Brain	(49)	(13)	(50)
Compression, NOS			1 (2%)
#Brain/thalamus	(49)	(13)	(50)
Mineralization	31 (63%)	4 (31%)	25 (50%)
*Thoracic spinal cord	(50)	(50)	(50)
Congenital lordosis		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
Phthisis bulbi	1 (2%)		
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, acute			1 (2%)
Inflammation, acute focal		1 (2%)	2 (4%)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal	5 (10%)	1 (2%)	3 (6%)
Necrosis, fat			1 (2%)
Hyperplasia, focal	2 (4%)		
Hyperplasia, papillary	2 (4%)	1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy	2 (4%)		
Osteosclerosis			1 (2%)
*Ankle joint	(50)	(50)	(50)
Ankylosis	11 (22%)	8 (16%)	6 (12%)
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Inflammation, acute diffuse	1 (2%)		1 (2%)
Inflammation, acute/chronic	2 (4%)		
*Mediastinum	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, acute diffuse			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
*Pleura	(50)	(50)	(50)
Inflammation, acute diffuse	1 (2%)		1 (2%)
*Mesentery	(50)	(50)	(50)
Necrosis, fat	2 (4%)	2 (4%)	4 (8%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Congestion, NOS			2 (4%)
Lymphocytic inflammatory infiltrate	7 (14%)		2 (4%)
Amyloidosis	1 (2%)		
Site unknown			
Hemorrhage	1		
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	Low Dose	High Dose
Animals in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosarcoma	1 (2%)		1 (2%)
Osteosarcoma			1 (2%)
Neurilemoma, malignant			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(49)	(12)	(50)
Carcinoma, NOS, metastatic	1 (2%)		
Adenocarcinoma, NOS, metastatic		1 (8%)	
Hepatocellular carcinoma, metastatic	1 (2%)		1 (2%)
Alveolar/bronchiolar adenoma	2 (4%)	3 (25%)	5 (10%)
Alveolar/bronchiolar carcinoma	2 (4%)		1 (2%)
Fibrosarcoma, metastatic	1 (2%)		
Osteosarcoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS			2 (4%)
Malignant lymphoma, undifferentiated type	2 (4%)		1 (2%)
Malignant lymphoma, lymphocytic type	1 (2%)	1 (2%)	1 (2%)
Malignant lymphoma, histiocytic type	2 (4%)	1 (2%)	
Malignant lymphoma, mixed type	7 (14%)	3 (6%)	9 (18%)
#Spleen	(49)	(50)	(49)
Malignant lymphoma, mixed type		1 (2%)	
#Mediastinal lymph node	(49)	(12)	(49)
Malignant lymphoma, lymphocytic type			1 (2%)
#Mesenteric lymph node	(49)	(12)	(49)
Histiocytic sarcoma	1 (2%)		
Malignant lymphoma, mixed type			1 (2%)
#Renal lymph node	(49)	(12)	(49)
Adenocarcinoma, NOS, metastatic		1 (8%)	
#Duodenum	(50)	(7)	(47)
Malignant lymphoma, undifferentiated type		1 (14%)	
#Jejunum	(50)	(7)	(47)
Malignant lymphoma, mixed type			1 (2%)
#Uterus	(49)	(41)	(50)
Malignant lymphoma, histiocytic type		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma			3 (6%)
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)		2 (4%)
#Bone marrow	(50)	(7)	(50)
Hemangiosarcoma	1 (2%)		
Hemangiosarcoma, metastatic	1 (2%)		
#Spleen	(49)	(50)	(49)
Hemangiosarcoma		1 (2%)	1 (2%)
Hemangiosarcoma, metastatic	1 (2%)		
#Liver	(50)	(50)	(50)
Hemangioma	2 (4%)		
Hemangiosarcoma		2 (4%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Urinary bladder	(50)	(8)	(50)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Bile duct carcinoma			1 (2%)
Hepatocellular adenoma	4 (8%)	3 (6%)	6 (12%)
Hepatocellular carcinoma	1 (2%)	2 (4%)	3 (6%)
Histiocytic sarcoma	1 (2%)	1 (2%)	
#Glandular stomach	(50)	(19)	(50)
Carcinoma, NOS		1 (5%)	
#Forestomach	(50)	(19)	(50)
Squamous cell papilloma	2 (4%)	2 (11%)	8 (16%)
URINARY SYSTEM			
#Kidney	(50)	(12)	(50)
Adenocarcinoma, NOS, metastatic		1 (8%)	
Tubular cell adenocarcinoma		1 (8%)	
ENDOCRINE SYSTEM			
#Pituitary	(45)	(14)	(44)
Carcinoma, NOS			1 (2%)
Adenoma, NOS	18 (40%)	5 (36%)	7 (16%)
#Adrenal	(49)	(6)	(50)
Pheochromocytoma		1 (17%)	
#Thyroid	(46)	(6)	(48)
Follicular cell adenoma			1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
#Uterus	(49)	(41)	(50)
Adenocarcinoma, NOS	1 (2%)	1 (2%)	1 (2%)
Sarcoma, NOS		1 (2%)	
Endometrial stromal polyp	2 (4%)	1 (2%)	2 (4%)
Neurilemoma, malignant		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
Papillary adenoma	2 (4%)	1 (2%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)	1 (2%)
Fibrosarcoma	1 (2%)		
Neurilemoma, malignant			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	7	10
Moribund sacrifice	8	3	7
Terminal sacrifice	35	39	33
Accidentally killed, NOS		1	
TUMOR SUMMARY			
Total animals with primary tumors**	39	27	41
Total primary tumors	55	36	67
Total animals with benign tumors	28	15	21
Total benign tumors	32	16	31
Total animals with malignant tumors	21	17	30
Total malignant tumors	23	20	36
Total animals with secondary tumors##	4	1	2
Total secondary tumors	5	3	3

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: VEHICLE CONTROL

ANIMAL NUMBER	0002	0033	0032	0339	0444	0005	0299	0288	0355	0077	0188	0088	0225	0222	0477	0011	0033	0044	0066	0099	0110	0111	0112	0113	0114
WEEKS ON STUDY	0001	0501	0804	0887	0888	0900	0911	0999	0999	1001	1011	1022	1022	1033	1033	1041	1044	1044	1044	1044	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma								X																	
Hemangiosarcoma													X												
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic								X																	
Hepatocellular carcinoma, metastatic			X																						
Alveolar/bronchiolar adenoma				X						X															
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic		X																							
Trachea	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic													X												
Spleen	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic													X												
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Thymus	−	−	−	+	−	−	−	−	−	−	−	−	+	−	−	+	+	−	+	+	−	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																				X					X
Hepatocellular carcinoma			X																						
Histiocytic sarcoma										X															
Hemangioma														X											
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	+	N	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	−	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X																
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X							X			X		X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	−	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS								X																	
Papillary adenoma									X																
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma		X																							
Malignant lymphoma, undifferentiated type												X			X										
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, histiocytic type							X																		
Malignant lymphoma, mixed type														X						X			X	X	

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

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

ANIMAL NUMBER	0 1 5	0 1 6	0 1 7	0 1 9	0 2 0	0 2 1	0 2 3	0 2 4	0 2 6	0 2 7	0 3 0	0 3 1	0 3 4	0 3 6	0 3 7	0 3 8	0 4 0	0 4 1	0 4 2	0 4 3	0 4 5	0 4 6	0 4 8	0 4 9	0 5 0	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*50	
Fibrosarcoma																									1	
Hemangiosarcoma																									1	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Carcinoma, NOS, metastatic																									1	
Hepatocellular carcinoma, metastatic																									1	
Alveolar/bronchiolar adenoma																									2	
Alveolar/bronchiolar carcinoma																						X		X	2	
Fibrosarcoma, metastatic																									1	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hemangiosarcoma								X																	1	
Hemangiosarcoma, metastatic																									1	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Hemangiosarcoma, metastatic																									1	
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Histiocytic sarcoma																									1	
Thymus	+	−	+	+	−	+	+	−	−	+	+	+	+	+	+	−	−	+	+	+	+	+	+	−	27	
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Hepatocellular adenoma											X												X		4	
Hepatocellular carcinoma																									1	
Histiocytic sarcoma																									1	
Hemangioma																						X			2	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Squamous cell papilloma												X													2	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	45	
Adenoma, NOS		X	X	X		X	X		X			X	X			X	X			X			X	X	18	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	49	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	46	
Parathyroid	+	+	−	−	+	+	+	−	−	−	+	+	−	+	+	+	+	−	+	−	−	+	−	+	−	35
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	N	+	+	N	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																			X							1
Endometrial stromal polyp															X			X								2
Ovary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	−	+	+	44
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Papillary adenoma														X												2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										1
Malignant lymphoma, undifferent. type																										2
Malignant lymphoma, lymphocytic type													X													1
Malignant lymphoma, histiocytic type								X																		2
Malignant lymphoma, mixed type					X									X			X									7

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: LOW DOSE

ANIMAL NUMBER	00808	00909	04909	02707	03010	04505	00606	04303	02404	00707	01101	00101	00202	00303	00404	00505	01010	01212	01313	01414	01515	01616	01717	01818	01919
WEEKS ON STUDY	00303	00606	00609	00808	00805	00807	00901	00905	00909	01000	01001	01004	01004	01004	01004	01004	01004	01004	01004	01004	01004	01004	01004	01004	01004
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−
Adenocarcinoma, NOS, metastatic								X																	
Alveolar/bronchiolar adenoma								X																	
Trachea	+	−	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Nasal cavity	−	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Malignant lymphoma, mixed type													X												
Lymph nodes	+	−	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	+	−	+	−	−	−	−	−
Adenocarcinoma, NOS, metastatic								X																	
Thymus	−	−	+	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																	X					X			
Hepatocellular carcinoma																								X	
Histiocytic sarcoma																									
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	N	+	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N
Pancreas	+	−	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Esophagus	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	+	+	+	−	−	+	+	−	−	+	−	+	−	−	−	−	−	−	+	−	−	−	−	+	−
Carcinoma, NOS			X																						
Squamous cell papilloma										X															
Small intestine	+	−	+	−	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Malignant lymphoma, undifferentiated type																									
Large intestine	+	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	−	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−
Adenocarcinoma, NOS, metastatic								X																	
Tubular cell adenocarcinoma													X												
Urinary bladder	+	+	+	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Adenoma, NOS									X																
Adrenal	+	−	−	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Pheochromocytoma																									
Thyroid	+	−	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
Parathyroid	+	−	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Uterus	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Adenocarcinoma, NOS								X																	
Sarcoma, NOS																									
Endometrial stromal polyp																									
Neurilemoma, malignant																									
Malignant lymphoma, histiocytic type															X										
Ovary	+	−	+	+	+	+	+	−	−	−	+	−	+	+	+	−	−	+	+	+	−	+	−	−	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma					X																				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Histiocytic sarcoma																		X							
Malignant lymphoma, lymphocytic type							X																		
Malignant lymphoma, histiocytic type																				X					
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	020	021	022	023	025	026	028	029	031	032	033	034	035	036	037	038	039	040	041	042	044	046	047	048	050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	12
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma									X																X	3
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
Nasal cavity	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Malignant lymphoma, mixed type																										1
Lymph nodes	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	+	–	–	–	+	–	–	–	–	12
Adenocarcinoma, NOS, metastatic																										1
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	2
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	7
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																						X				3
Hepatocellular carcinoma																	X									2
Histiocytic sarcoma												X														1
Hemangiosarcoma																		X	X							2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	*50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
Stomach	–	–	+	+	–	+	+	+	–	–	–	+	+	+	–	–	–	–	–	+	–	+	–	–	–	19
Carcinoma, NOS																										1
Squamous cell papilloma			X																							2
Small intestine	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	7
Malignant lymphoma, undifferent. type		X																								1
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
URINARY SYSTEM																										
Kidney	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	12
Adenocarcinoma, NOS, metastatic																										1
Tubular cell adenocarcinoma																										1
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
ENDOCRINE SYSTEM																										
Pituitary	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	+	+	+	+	–	–	+	14
Adenoma, NOS										X										X	X				X	5
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	6
Pheochromocytoma																			X							1
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	6
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Uterus	+	+	+	+	+	+	+	–	+	+	–	+	+	–	–	+	+	+	+	+	–	+	–	+	–	41
Adenocarcinoma, NOS																										1
Sarcoma, NOS													X													1
Endometrial stromal polyp																X										1
Neurilemoma, malignant																						X				1
Malignant lymphoma, histiocytic type																										1
Ovary	+	+	+	–	–	–	+	–	–	–	–	–	+	+	+	–	+	–	–	–	–	+	–	+	–	25
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	7
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Histiocytic sarcoma																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type													X				X				X					3

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE: HIGH DOSE

ANIMAL NUMBER	0121	0111	0455	0236	0009	0033	0411	0011	0489	0196	0277	0221	0222	0440	0336	0399	0302	0024	0404	0505	0606	0707	0808	0910	1013
WEEKS ON STUDY	049	078	079	086	087	090	092	094	095	096	097	098	098	100	101	102	103	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Fibrosarcoma						X																			
Hemangiosarcoma																				X					
Osteosarcoma																X									
Neurilemoma, malignant																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																						X			
Alveolar/bronchiolar adenoma							X							X									X		
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, metastatic																X									
Trachea	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, lymphocytic type																X									
Malignant lymphoma, mixed type																									
Thymus	–	+	–	–	–	–	+	–	–	–	–	+	–	–	–	+	–	–	+	+	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	–	+	–	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct carcinoma																						X			
Hepatocellular adenoma																						X	X		X
Hepatocellular carcinoma	X																					X		X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	N	N	N	+	+	+	+	N	+	+	+	N	+	+	+	N	+	+	+	+	+	+
Pancreas	+	+	+	–	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X						
Small intestine	+	+	+	–	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS								X																	
Adenoma, NOS																	X						X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									X
Parathyroid	–	+	–	–	+	–	–	+	–	+	+	+	–	–	+	+	+	–	+	+	+	+	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	+	N	N	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS								X																	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Endometrial stromal polyp							X																		
Malignant lymphoma, histiocytic type																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma							X																		
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, metastatic																						X			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Histiocytic sarcoma		X																							
Hemangiosarcoma										X		X					X								
Neurilemoma, malignant													X												
Malignant lymphoma, NOS				X					X																
Malignant lymphoma, undifferentiated type														X											
Malignant lymphoma, lymphocytic type																	X								
Malignant lymphoma, mixed type															X						X				

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

ANIMAL NUMBER	0114	0115	0116	0117	0118	0120	0124	0125	0126	0128	0129	0131	0132	0134	0135	0136	0137	0138	0142	0143	0144	0146	0147	0149	0150	TOTAL:
WEEKS ON STUDY	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
Hemangiosarcoma											X															2
Osteosarcoma																										1
Neurilemoma, malignant																			X							1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma						X				X																5
Alveolar/bronchiolar carcinoma									X																	1
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type			X																							1
Thymus	–	+	–	+	+	+	–	–	–	+	+	+	+	–	+	–	+	+	–	+	+	+	+	–	+	26
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct carcinoma																										1
Hepatocellular adenoma					X					X			X													6
Hepatocellular carcinoma																										3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X	X	X						X									X		X	X				8
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malignant lymphoma, mixed type										X																1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma						X																				1
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	44
Carcinoma, NOS																										1
Adenoma, NOS							X													X			X		X	7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																										1
Parathyroid	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	33
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																								X		1
Endometrial stromal polyp																				X						2
Malignant lymphoma, histiocytic type														X												1
Ovary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatocellular carcinoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Histiocytic sarcoma																										1
Hemangiosarcoma																										3
Neurilemoma, malignant																										1
Malignant lymphoma, NOS																										2
Malignant lymphoma, undifferent. type																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type		X						X								X		X		X			X		X	9

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	15 mg/kg	30 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/49 (4%)	(b) 3/12 (25%)	5/50 (10%)
Adjusted Rates (c)	4.5%		13.6%
Terminal Rates (d)	0/35 (0%)		3/33 (9%)
Week of First Observation	87		92
Life Table Test (e)			P=0.201
Incidental Tumor Test (e)			P=0.259
Fisher Exact Test (e)			P=0.226
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/49 (8%)	(b) 3/12 (25%)	6/50 (12%)
Adjusted Rates (c)	10.0%		16.4%
Terminal Rates (d)	2/35 (6%)		4/33 (12%)
Week of First Observation	87		92
Life Table Test (e)			P=0.338
Incidental Tumor Test (e)			P=0.404
Fisher Exact Test (e)			P=0.383
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (f)	7/50 (14%)	4/50 (8%)	11/50 (22%)
Adjusted Rates (c)	19.4%	10.3%	32.2%
Terminal Rates (d)	6/35 (17%)	4/39 (10%)	10/33 (30%)
Week of First Observation	103	104	101
Life Table Tests (e)	P=0.125	P=0.205N	P=0.173
Incidental Tumor Tests (e)	P=0.143	P=0.238N	P=0.195
Cochran-Armitage Trend Test (e)	P=0.161		
Fisher Exact Test (e)		P=0.263N	P=0.218
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (f)	12/50 (24%)	8/50 (16%)	17/50 (34%)
Adjusted Rates (c)	30.5%	19.8%	43.2%
Terminal Rates (d)	8/35 (23%)	7/39 (18%)	11/33 (33%)
Week of First Observation	91	91	86
Life Table Tests (e)	P=0.120	P=0.175N	P=0.156
Incidental Tumor Tests (e)	P=0.163	P=0.259N	P=0.208
Cochran-Armitage Trend Test (e)	P=0.148		
Fisher Exact Test (e)		P=0.227N	P=0.189
Circulatory System: Hemangiosarcoma			
Overall Rates (f)	2/50 (4%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (c)	5.3%	7.4%	16.1%
Terminal Rates (d)	1/35 (3%)	2/39 (5%)	3/33 (9%)
Week of First Observation	102	100	96
Life Table Tests (e)	P=0.077	P=0.529	P=0.120
Incidental Tumor Tests (e)	P=0.115	P=0.406	P=0.157
Cochran-Armitage Trend Test (e)	P=0.090		
Fisher Exact Test (e)		P=0.500	P=0.134
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (f)	4/50 (8%)	3/50 (6%)	7/50 (14%)
Adjusted Rates (c)	10.6%	7.4%	18.9%
Terminal Rates (d)	2/35 (6%)	2/39 (5%)	4/33 (12%)
Week of First Observation	102	100	96
Life Table Tests (e)	P=0.169	P=0.463N	P=0.231
Incidental Tumor Tests (e)	P=0.235	P=0.625N	P=0.298
Cochran-Armitage Trend Test (e)	P=0.195		
Fisher Exact Test (e)		P=0.500N	P=0.262

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (c)	11.4%	7.7%	18.2%
Terminal Rates (d)	4/35 (11%)	3/39 (8%)	6/33 (18%)
Week of First Observation	104	104	104
Life Table Tests (e)	P=0.260	P=0.441N	P=0.330
Incidental Tumor Tests (e)	P=0.260	P=0.441N	P=0.330
Cochran-Armitage Trend Test (e)	P=0.297		
Fisher Exact Test (e)		P=0.500N	P=0.370
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (c)	2.1%	5.1%	7.9%
Terminal Rates (d)	0/35 (0%)	2/39 (5%)	2/33 (6%)
Week of First Observation	84	104	49
Life Table Tests (e)	P=0.210	P=0.520	P=0.297
Incidental Tumor Tests (e)	P=0.177	P=0.499	P=0.239
Cochran-Armitage Trend Test (e)	P=0.222		
Fisher Exact Test (e)		P=0.500	P=0.30
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	8/50 (16%)
Adjusted Rates (c)	13.3%	12.8%	22.8%
Terminal Rates (d)	4/35 (11%)	5/39 (13%)	7/33 (21%)
Week of First Observation	84	104	49
Life Table Tests (e)	P=0.189	P=0.571N	P=0.245
Incidental Tumor Tests (e)	P=0.169	P=0.583N	P=0.214
Cochran-Armitage Trend Test (e)	P=0.221		
Fisher Exact Test (e)		P=0.630	P=0.277
Forestomach: Squamous Cell Papilloma			
Overall Rates (f)	2/50 (4%)	(g) 2/50 (4%)	8/50 (16%)
Adjusted Rates (c)	5.1%	4.9%	24.2%
Terminal Rates (d)	1/35 (3%)	1/39 (3%)	8/33 (24%)
Week of First Observation	99	100	104
Life Table Tests (e)	P=0.015	P=0.675N	P=0.037
Incidental Tumor Tests (e)	P=0.021	P=0.592	P=0.042
Cochran-Armitage Trend Test (e)	P=0.021		
Fisher Exact Test (e)		P=0.691	P=0.046
Pituitary Gland: Adenoma			
Overall Rates (a)	18/45 (40%)	(b) 5/14 (36%)	7/44 (16%)
Adjusted Rates (c)	51.3%		22.4%
Terminal Rates (d)	17/34 (50%)		6/30 (20%)
Week of First Observation	102		103
Life Table Test (e)			P=0.019N
Incidental Tumor Test (e)			P=0.017N
Fisher Exact Test (e)			P=0.010N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	18/45 (40%)	(b) 5/14 (36%)	8/44 (18%)
Adjusted Rates (c)	51.3%		24.2%
Terminal Rates (d)	17/34 (50%)		6/30 (20%)
Week of First Observation	102		94
Life Table Test (e)			P=0.038N
Incidental Tumor Test (e)			P=0.031N
Fisher Exact Test (e)			P=0.021N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Harderian Gland: Papillary Adenoma or Carcinoma, NOS			
Overall Rates (f)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (c)	7.4%	2.2%	2.3%
Terminal Rates (d)	1/35 (3%)	0/39 (0%)	0/33 (0%)
Week of First Observation	99	85	92
Life Table Tests (e)	P=0.221N	P=0.304N	P=0.338N
Incidental Tumor Tests (e)	P=0.187N	P=0.442N	P=0.272N
Cochran-Armitage Trend Test (e)	P=0.202N		
Fisher Exact Test (e)		P=0.309N	P=0.309N
All Sites: Benign Tumors			
Overall Rates (f)	28/50 (56%)	15/50 (30%)	21/50 (42%)
Adjusted Rates (c)	69.7%	34.7%	58.1%
Terminal Rates (d)	23/35 (66%)	11/39 (28%)	18/33 (55%)
Week of First Observation	87	85	92
Life Table Tests (e)	P=0.148N	P=0.004N	P=0.183N
Incidental Tumor Tests (e)	P=0.095N	P=0.009N	P=0.125N
Cochran-Armitage Trend Test (e)	P=0.094N		
Fisher Exact Test (e)		P=0.008N	P=0.115N
All Sites: Malignant Tumors			
Overall Rates (f)	21/50 (42%)	17/50 (34%)	30/50 (60%)
Adjusted Rates (c)	47.3%	39.2%	64.9%
Terminal Rates (d)	12/35 (34%)	13/39 (33%)	17/33 (52%)
Week of First Observation	50	69	49
Life Table Tests (e)	P=0.046	P=0.212N	P=0.063
Incidental Tumor Tests (e)	P=0.058	P=0.335N	P=0.077
Cochran-Armitage Trend Test (e)	P=0.044		
Fisher Exact Test (e)		P=0.269N	P=0.055
All Sites: All Tumors			
Overall Rates (f)	39/50 (78%)	27/50 (54%)	41/50 (82%)
Adjusted Rates (c)	84.7%	59.8%	87.2%
Terminal Rates (d)	28/35 (80%)	21/39 (54%)	27/33 (82%)
Week of First Observation	50	69	49
Life Table Tests (e)	P=0.276	P=0.009N	P=0.286
Incidental Tumor Tests (e)	P=0.409	P=0.013N	P=0.450
Cochran-Armitage Trend Test (e)	P=0.370		
Fisher Exact Test (e)		P=0.010N	P=0.401

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

TABLE D4a. HISTORICAL INCIDENCE OF FORESTOMACH SQUAMOUS CELL TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Papillomas or Carcinomas in Vehicle Controls
Historical Incidence at Springborn Institute for Bioresearch, Inc.	
N,*N*-Dimethylaniline	2/50
Ampicillin trihydrate	0/47
Penicillin VK	5/44
TOTAL	7/141 (5.0%)
SD (b)	5.76%
Range (c)	
High	5/44
Low	0/47
Overall Historical Incidence	
TOTAL	(d) 33/2,047 (1.6%)
SD (b)	2.76%
Range (c)	
High	5/44
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two papillomas, NOS, and one squamous cell carcinoma; all other tumors were squamous cell papillomas.

TABLE D4b. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Springborn Institute for Bioresearch, Inc.			
N,*N*-Dimethylaniline	18/45	0/45	18/45
Ampicillin trihydrate	7/44	1/44	8/44
Penicillin VK	10/45	0/45	10/45
TOTAL	35/134 (26.1%)	1/134 (0.7%)	36/134 (26.9%)
SD (b)	12.49%	1.31%	11.61%
Range (c)			
High	18/45	1/44	18/45
Low	7/44	0/45	8/44
Overall Historical Incidence			
TOTAL	(d) 395/1,893 (20.9%)	(e) 23/1,893 (1.2%)	(d,e) 418/1,893 (22.1%)
SD (b)	10.02%	2.29%	10.23%
Range (c)			
High	20/49	5/47	21/49
Low	2/44	0/49	2/44

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes 38 chromophobe adenomas and 1 acidophil adenoma
(e) Includes six adenocarcinomas, NOS, and one acidophil carcinoma

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE

	Vehicle Control	Low Dose	High Dose
Animals in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Necrosis, fat	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal mucosa	(48)	(6)	(49)
Inflammation, acute focal	1 (2%)		
Degeneration, hyaline	36 (75%)	5 (83%)	35 (71%)
Amyloid, NOS	1 (2%)		
#Trachea	(48)	(6)	(47)
Hemorrhage	2 (4%)		
#Lung	(49)	(12)	(50)
Congestion, NOS	4 (8%)	1 (8%)	2 (4%)
Hemorrhage	1 (2%)		1 (2%)
Lymphocytic inflammatory infiltrate	12 (24%)	2 (17%)	12 (24%)
Inflammation, acute/chronic	1 (2%)		
Alveolar macrophages	3 (6%)		
Hyperplasia, adenomatous	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemoid reaction	1 (2%)		1 (2%)
Hyperplasia, lymphoid			1 (2%)
*Blood	(50)	(50)	(50)
Leukocytosis, NOS	1 (2%)		1 (2%)
#Bone marrow	(50)	(7)	(50)
Congestion, NOS	1 (2%)		
Angiectasis			2 (4%)
Myelofibrosis		1 (14%)	
Hyperplasia, granulocytic	13 (26%)	2 (29%)	7 (14%)
#Spleen	(49)	(50)	(49)
Congestion, NOS			1 (2%)
Hemosiderosis	45 (92%)	45 (90%)	43 (88%)
Hyperplasia, reticulum cell			1 (2%)
Hyperplasia, lymphoid	8 (16%)	9 (18%)	7 (14%)
Hematopoiesis	7 (14%)	6 (12%)	13 (27%)
#Mandibular lymph node	(49)	(12)	(49)
Pigmentation, NOS	7 (14%)		
Hemosiderosis	1 (2%)		
Hyperplasia, lymphoid	4 (8%)	1 (8%)	2 (4%)
#Mediastinal lymph node	(49)	(12)	(49)
Hyperplasia, lymphoid	1 (2%)		2 (4%)
#Mesenteric lymph node	(49)	(12)	(49)
Congestion, NOS	2 (4%)		
Hemorrhage		1 (8%)	
Hemosiderosis	1 (2%)		
Hyperplasia, lymphoid	5 (10%)		1 (2%)
Hematopoiesis	1 (2%)		
#Liver	(50)	(50)	(50)
Hematopoiesis	6 (12%)	1 (2%)	5 (10%)
#Thymus	(27)	(2)	(26)
Ultimobranchial cyst	2 (7%)	1 (50%)	1 (4%)
Cyst, NOS	1 (4%)		3 (12%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
CIRCULATORY SYSTEM			
#Mesenteric lymph node	(49)	(12)	(49)
Lymphangiectasis			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(47)	(7)	(45)
Lymphocytic inflammatory infiltrate	7 (15%)	2 (29%)	12 (27%)
Atrophy, NOS	1 (2%)		
#Liver	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	7 (14%)	3 (6%)	8 (16%)
Inflammation, chronic focal	1 (2%)		
Necrosis, focal	2 (4%)	3 (6%)	1 (2%)
Necrosis, diffuse			2 (4%)
Infarct, NOS	1 (2%)		
Metamorphosis, fatty	2 (4%)		
Hemosiderosis	2 (4%)		1 (2%)
Cytoplasmic vacuolization	11 (22%)	20 (40%)	29 (58%)
#Intrahepatic bile duct	(50)	(50)	(50)
Cyst, NOS		1 (2%)	1 (2%)
*Gallbladder	(50)	(50)	(50)
Edema, NOS	1 (2%)		
Degeneration, hyaline	2 (4%)		
Hyperplasia, papillary		2 (4%)	
#Pancreas	(49)	(4)	(45)
Dilatation/ducts	1 (2%)		
Cyst, NOS			1 (2%)
Cystic ducts			1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		2 (4%)
Inflammation, chronic diffuse			1 (2%)
Focal cellular change			1 (2%)
Atrophy, focal	1 (2%)		1 (2%)
Atrophy, diffuse	2 (4%)		
#Stomach	(50)	(19)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		2 (4%)
Inflammation, chronic diffuse		1 (5%)	
#Gastric mucosa	(50)	(19)	(50)
Ulcer, NOS	2 (4%)	2 (11%)	
Hyperkeratosis	2 (4%)		2 (4%)
#Forestomach	(50)	(19)	(50)
Hyperplasia, epithelial	8 (16%)	11 (58%)	13 (26%)
#Ileum	(50)	(7)	(47)
Amyloidosis			1 (2%)
#Colon	(50)	(8)	(50)
Impaction, NOS		1 (13%)	
Cyst, NOS	1 (2%)		1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(12)	(50)
Hydronephrosis	1 (2%)		
Lymphocytic inflammatory infiltrate	16 (32%)	2 (17%)	20 (40%)
Glomerulonephritis, membranous	1 (2%)		
Necrosis, focal	1 (2%)		
Infarct, focal	3 (6%)	1 (8%)	1 (2%)
Amyloidosis	1 (2%)		1 (2%)
Metaplasia, osseous			1 (2%)
#Kidney/tubule	(50)	(12)	(50)
Degeneration, NOS	1 (2%)		2 (4%)
Degeneration, hyaline	2 (4%)	2 (17%)	1 (2%)
Metamorphosis, fatty		1 (8%)	2 (4%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
URINARY SYSTEM (Continued)			
#Urinary bladder	(50)	(8)	(50)
Edema, NOS		1 (13%)	
Lymphocytic inflammatory infiltrate	6 (12%)		9 (18%)
ENDOCRINE SYSTEM			
#Pituitary	(45)	(14)	(44)
Cyst, NOS			1 (2%)
Hemorrhagic cyst			1 (2%)
Hyperplasia, chromophobe cell	10 (22%)	2 (14%)	16 (36%)
Angiectasis		1 (7%)	
#Adrenal	(49)	(6)	(50)
Ectopia			1 (2%)
#Adrenal/capsule	(49)	(6)	(50)
Hyperplasia, focal	1 (2%)		3 (6%)
Hyperplasia, diffuse	43 (88%)	4 (67%)	40 (80%)
#Adrenal cortex	(49)	(6)	(50)
Congestion, NOS	1 (2%)		
Degeneration, lipoid	2 (4%)		
Hypertrophy, diffuse			1 (2%)
Hyperplasia, nodular	1 (2%)	1 (17%)	1 (2%)
#Adrenal medulla	(49)	(6)	(50)
Ectopia			1 (2%)
Mineralization			1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Thyroid	(46)	(6)	(48)
Follicular cyst, NOS	3 (7%)	1 (17%)	4 (8%)
Inflammation, chronic focal			1 (2%)
Hyperplasia, follicular cell	1 (2%)		2 (4%)
#Thyroid follicle	(46)	(6)	(48)
Hyperplasia, papillary	2 (4%)		2 (4%)
#Parathyroid	(35)	(4)	(33)
Ectopia		1 (25%)	
Ultimobranchial cyst	3 (9%)		
#Pancreatic islets	(49)	(4)	(45)
Hyperplasia, NOS	1 (2%)		1 (2%)
Hyperplasia, focal	9 (18%)	1 (25%)	8 (18%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	8 (16%)		9 (18%)
Inflammation, active chronic			1 (2%)
Hyperplasia, diffuse	1 (2%)		
#Uterus	(49)	(41)	(50)
Dilatation, NOS	5 (10%)	1 (2%)	
Hemorrhagic cyst	3 (6%)		2 (4%)
Inflammation, acute diffuse			2 (4%)
Angiectasis	1 (2%)	2 (5%)	
#Uterus/endometrium	(49)	(41)	(50)
Hyperplasia, cystic			1 (2%)
#Endometrial gland	(49)	(41)	(50)
Cyst, NOS	37 (76%)	31 (76%)	39 (78%)
Hyperplasia, cystic		1 (2%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF *N,N*-DIMETHYLANILINE (Continued)

	Vehicle Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
#Ovary	(44)	(25)	(48)
Cyst, NOS	9 (20%)	11 (44%)	19 (40%)
Hemorrhagic cyst	14 (32%)		12 (25%)
Inflammation, NOS	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)		2 (4%)
Inflammation, acute		1 (4%)	
Inflammation, acute/chronic		2 (8%)	
Inflammation, chronic		1 (4%)	
Inflammation, chronic diffuse	1 (2%)		
Fibrosis	1 (2%)		
Hyperplasia, papillary			1 (2%)
NERVOUS SYSTEM			
*Nerve tract	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Brain	(50)	(7)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
#Brain/thalamus	(50)	(7)	(50)
Mineralization	41 (82%)	1 (14%)	24 (48%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, chronic			2 (4%)
Inflammation, chronic focal	9 (18%)		7 (14%)
Hyperplasia, focal	1 (2%)		3 (6%)
Hyperplasia, diffuse	3 (6%)		
Hyperplasia, papillary	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy	30 (60%)		35 (70%)
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Inflammation, chronic diffuse	1 (2%)		
*Mediastinum	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, acute diffuse	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
Necrosis, fat	3 (6%)	1 (2%)	2 (4%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	14 (28%)		5 (10%)
Inflammation, acute/chronic	1 (2%)		
Broad ligament			
Lymphocytic inflammatory infiltrate	1		4
Necrosis, fat			2

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

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. SENTINEL ANIMAL PROGRAM

Method

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

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex 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. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

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

Results

Results are presented in Table E1.

TABLE E1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	10/10	PVM
	2/10	RCV
12	10/10	PVM
	2/10	KRV
	10/10	RCV
18	9/9	PVM
	9/9	KRV
	8/9	Sendai
	5/8	RCV
MICE		
6	9/10	PVM
	2/10	MVM
12	3/6	PVM
	5/9	MHV
18	7/9	PVM
	2/9	Sendai

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing; samples were sent to Microbiological Associates (Bethesda, MD) for determination of antibody titers.

APPENDIX F

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

Pelleted Diet: January 1981 to February 1983

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

TABLE F1. 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 F2. 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 F3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.97 ± 0.93	22.7-26.3	23
Crude fat (percent by weight)	5.02 ± 0.45	4.2-5.7	23
Crude fiber (percent by weight)	3.41 ± 0.53	2.9-5.6	23
Ash (percent by weight)	6.39 ± 0.38	5.7-7.1	23
Amino Acids (percent of total diet)			
Arginine	1.32 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.05	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	10,883 ± 2,705	3,600-18,000	23
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	16.64 ± 2.08	13.0-21.0	23
Riboflavin (ppm)	7.6 ± 0.85	6.10-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.23 ± 0.18	0.72-1.63	23
Phosphorus (percent)	0.99 ± 0.12	0.88-1.47	23
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.46 ± 0.12	0.29-0.83	23
Cadmium (ppm)	<0.10		23
Lead (ppm)	1.01 ± 0.75	0.48-3.37	23
Mercury (ppm) (a)	<0.05		23
Selenium (ppm)	0.28 ± 0.07	0.13-0.40	23
Aflatoxins (ppb) (b)	<10.0		23
Nitrate nitrogen (ppm) (c)	9.60 ± 4.19	3.80-22.0	23
Nitrite nitrogen (ppm) (c)	2.10 ± 1.56	0.40-6.90	23
BHA (ppm) (d)	6.11 ± 4.98	0.04-17.0	23
BHT (ppm) (d)	3.39 ± 2.63	0.90-12.0	23
Aerobic plate count (CFU/g) (e)	38,383 ± 29,013	4,900-880,000	23
Coliform (MPN/g) (f)	35.35 ± 95.28	3.00-460	23
E. coli (MPN/g)	<3.0		23
Total nitrosamines (ppb) (g,h)	3.80 ± 2.66	1.70-9.0	22
Total nitrosamines (ppb) (g,i)	20.18 ± 58.69	1.70-266.20	23
N-Nitrosodimethylamine (ppb) (g,j)	2.66 ± 2.56	0.80-8.30	22
N-Nitrosodimethylamine (ppb) (g,k)	18.99 ± 58.56	0.80-265.0	23
N-Nitrosopyrrolidine (ppb) (g)	1.19 ± 0.57	0.50-2.90	23
Pesticides (ppm)			
α-BHC (a,l)	<0.01		23
β-BHC (a)	<0.02		23
γ-BHC (a)	<0.01		23
δ-BHC (a)	<0.01		23
Heptachlor (a)	<0.01		23
Aldrin (a)	<0.01		23
Heptachlor epoxide (a)	<0.01		23
DDE (a)	<0.01		23
DDD (a)	<0.01		23
DDT (a)	<0.01		23
HCB (a)	<0.01		23
Mirex (a)	<0.01		23
Methoxychlor (m)	<0.05	0.09	23
Dieldrin (a)	<0.01		23
Endrin (a)	<0.01		23
Telodrin (a)	<0.01		23
Chlordane (a)	<0.05		23
Toxaphene (a)	<0.1		23
Estimated PCBs (a)	<0.2		23
Ronnel (a)	<0.01		23
Ethion (a)	<0.02		23
Trithion (a)	<0.05		23
Diazinon (a)	<0.1		23
Methyl parathion (a)	<0.02		23
Ethyl parathion (a)	<0.02		23
Malathion (n)	0.09 ± 0.06	0.05-0.27	23
Endosulfan I (a)	<0.01		23
Endosulfan II (a)	<0.01		23
Endosulfan sulfate (a)	<0.03		23

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) Detection limit was reduced from 10 ppb to 5 ppb after July 1981.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) CFU = colony-forming unit
(f) MPN = most probable number
(g) All values were corrected for percent recovery.
(h) Mean, standard deviation, and range exclude extremely high values of 117.60 and 266.20 ppb obtained for the lots produced on January 26, 1981, and April 27, 1981, respectively.
(i) Mean, standard deviation, and range include extremely high values given in (h).
(j) Mean, standard deviation, and range exclude extremely high values of 115.00 and 265.00 ppb obtained in the lots produced on January 26, 1981, and April 27, 1981, respectively.
(k) Mean, standard deviation, and range include extremely high values given in (j).
(l) BHC = hexachlorocyclohexane or benzene hexachloride
(m) One observation, on August 26, 1981, was above the detection limit; the high value is given under the range.
(n) Eleven lots contained more than 0.05 ppm.

APPENDIX G

CHEMICAL CHARACTERIZATION, ANALYSIS, AND DOSE PREPARATION OF *N,N*-DIMETHYLANILINE FOR THE TOXICOLOGY STUDIES

APPENDIX G. CHEMICAL CHARACTERIZATION

Procurement and Characterization of *N,N*-Dimethylaniline

N,N-Dimethylaniline was obtained in one lot (lot no. 0557019) from Buffalo Color Corporation (West Patterson, NJ). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the *N,N*-dimethylaniline studies are on file at the National Institute of Environmental Health Sciences.

The study chemical was identified as *N,N*-dimethylaniline by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared spectrum (Figure G1) was identical to a literature spectrum (Aldrich, 1975) and the nuclear magnetic resonance spectrum (Figure G2) was consistent with that expected for the structure and with the literature spectrum (Sadtler Standard Spectra). The observed maxima of the ultraviolet/visible spectrum were consistent with the literature values (CRC, 1975).

The purity of lot no. 0557019 was determined by elemental analysis, Karl Fischer water analysis, nonaqueous potentiometric titration of the tertiary amino group with 0.1 N perchloric acid, thin-layer chromatography, and gas chromatography. Gas chromatography was performed with flame ionization detection and either a 10% Carbowax 20M-TPA column (system 1) or a 3% OV-225 column (system 2). Cumulative data indicated that the study material was greater than 98% pure. Results of elemental analysis for carbon, hydrogen, and nitrogen were in agreement with theoretical values. No impurities were detected by thin-layer chromatography with either silica gel plates and a hexanes: acetone (98:2) solvent system or $KC_{18}F$ plates and methanol:water (80:20). Titration of the amino function indicated a purity of 98.2%. The water content was determined to be 0.076%. Gas chromatographic system 1 indicated three impurities totaling 0.16% of the major peak area; system 2 indicated two impurities totaling 0.21%. Stability studies performed with gas chromatographic system 2 indicated that *N,N*-dimethylaniline was stable as a bulk chemical when stored for 2 weeks in the dark at temperatures up to 60° C. Confirmation of the stability of the bulk chemical during the 2-year studies was obtained by nonaqueous titration of the tertiary amino group and by gas chromatographic analysis. No deterioration of the study material was seen over the course of the studies. The identity of the chemical at the study laboratory was confirmed by infrared spectroscopy.

Preparation and Characterization of Dose Mixtures

The appropriate amounts of *N,N*-dimethylaniline and corn oil were mixed (w/v) to give the desired concentrations (Table G1). The stability of *N,N*-dimethylaniline in corn oil was determined by gas chromatography with a 3% SP2100-DB column after extraction with methanol; undecane was used as the internal standard. The chemical in corn oil (at 0.6% w/v) was found to be stable for 3 weeks in the dark at room temperature; corn oil solutions were stable for 3 hours when exposed to light and air at room temperature. During the 13-week studies, *N,N*-dimethylaniline/corn oil mixtures were stored at 4° C for no longer than 1 week. During the 2-year studies, the dose mixtures were stored at 4° C for up to 2 weeks for rats and up to 3 weeks for mice.

Periodic analysis of formulated *N,N*-dimethylaniline/corn oil dose mixtures was conducted at the study laboratory and the analytical chemistry laboratory by extraction of the dose mixtures with methanol and spectrophotometric quantitation at 251 nm. Results were compared with a standard curve of freshly prepared *N,N*-dimethylaniline in methanol. Dose mixtures were analyzed twice during the 13-week studies; the results were variable, ranging from 118% to 95% of the target concentrations (Table G2).

During the 2-year studies the dose mixtures were analyzed at approximately 8-week intervals. The results of the analysis of the mix and remix of May 19, 1981, indicated a problem, which was diagnosed as an analytical variable. Reanalysis of the samples, after the procedure was modified to

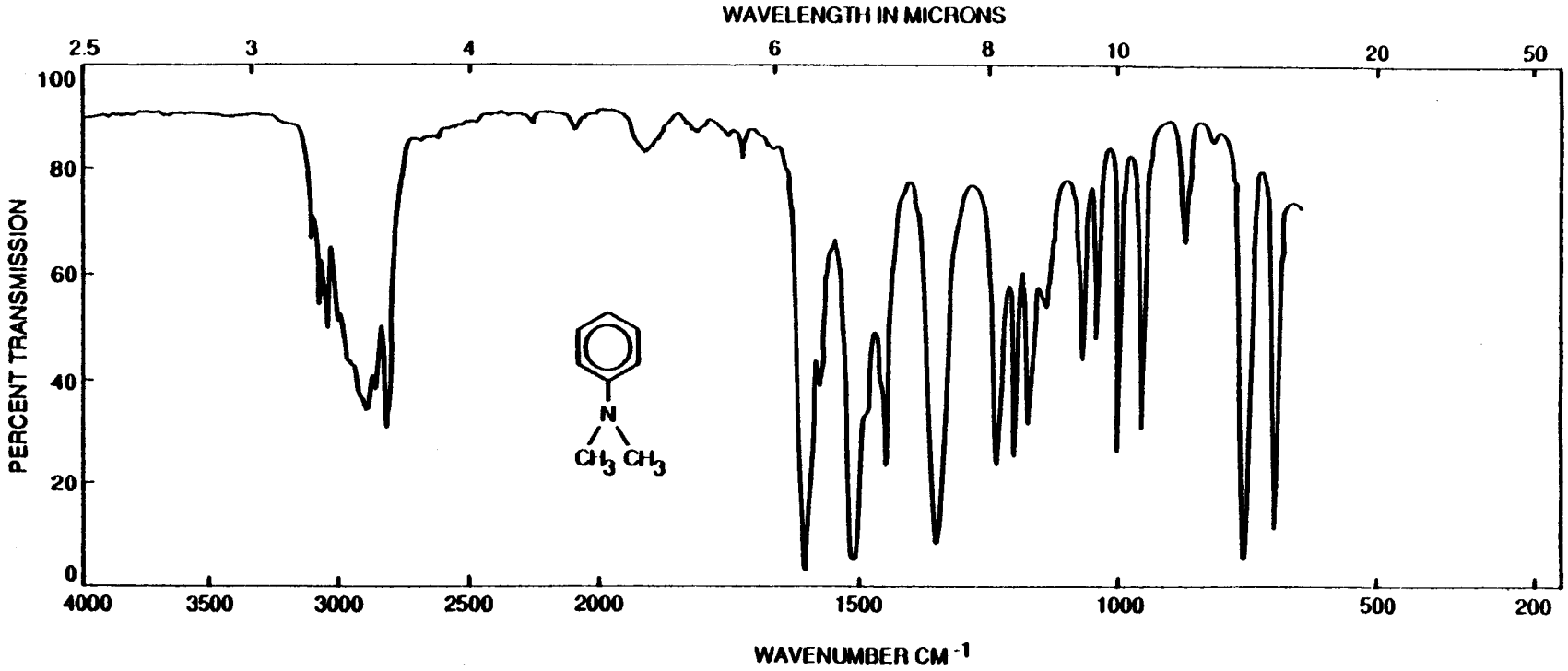

FIGURE G1. INFRARED ABSORPTION SPECTRUM OF *N,N*-DIMETHYLANILINE (LOT NO. 0557019)

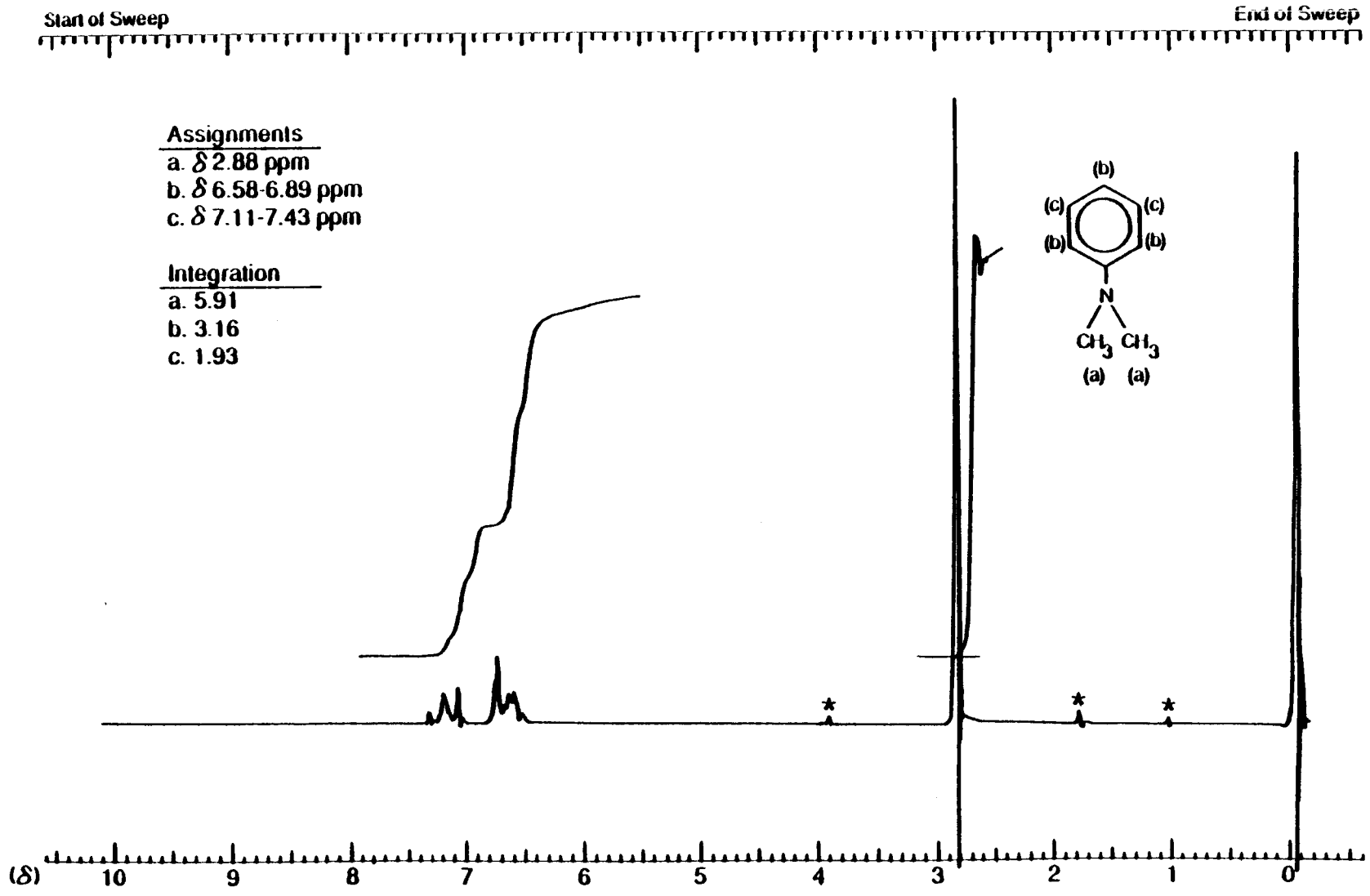

FIGURE G2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF *N,N*-DIMETHYLANILINE (LOT NO. 0557019)

TABLE G1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
Weighed amount of *N,N*-dimethylaniline combined with corn oil in a volumetric flask and mixed by inversion	Same as single-administration studies	Stock solution prepared by mixing weighed amount of *N,N*-dimethylaniline with corn oil in a volumetric flask with a stir bar and magnetic mixer. Dose mixtures prepared by dilution of stock solution with corn oil	Weighed amount of *N,N*-dimethylaniline combined with corn oil in a volumetric flask with a stir bar and magnetic stirrer
Maximum Storage Time			
N/A	1 wk	1 wk	Rats--2 wk; mice--3 wk
Storage Conditions			
N/A	Approximately 4° C	Same as 14-d studies	Same as 14-d studies; daily doses placed in individual vials

TABLE G2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Date Mixed	Concentration of *N,N*-Dimethylaniline in Corn Oil (percent w/v)		Determined as a Percent of Target
	Target	Determined	
01/08/80	0.3125	(a,b) 0.356	114
	0.625	(a) 0.622	99.5
	1.25	(a,b) 1.48	118
	2.5	(a) 2.37	95
	5	(a) 4.87	97
	10	(a) 9.67	97
01/28/80	0.3125	(b,c) 0.369	118
	0.625	(c) 0.683	110
	1.25	(c) 1.20	96
	2.5	(c) 2.55	102
	5	(c) 5.48	110
	10	(c) 10.24	102
03/17/80	0.3125	(b,c) 0.357	114
03/24/80	0.3125	(b,c,d) 0.369	118

(a) Results of a single analysis
(b) Out of specifications
(c) Results of duplicate analysis
(d) Remix; out of specifications.

include the use of *N,N*-dimethylaniline standards spiked in corn oil at each dose concentration, gave results that were within specifications.

For the *N,N*-dimethylaniline studies, the mixtures were formulated within ±10% of the target concentrations 100% of the time for the 44 analyses performed after the analytical procedure was modified in August 1981 (Table G3). Results of referee analysis periodically performed by the analytical chemistry laboratory indicated generally good agreement with results from the study laboratory (Table G4).

TABLE G3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Date Mixed	Concentration of *N,N*-Dimethylaniline in Corn Oil for Target Concentration (percent w/v) (a)			
	0.06	0.15	0.30	0.60
03/18/81	--	0.140	0.280	--
03/25/81	(b) 0.070	--	--	0.590
05/19/81	0.058	0.140	(c) 0.237	0.648
05/21/81	--	--	(d) 0.240	--
05/22/81	--	--	(d) 0.245	--
09/09/81	0.056	0.155	0.308	0.645
11/04/81	0.055	0.164	0.270	0.581
12/30/81	0.056	0.147	0.310	0.600
02/17/82	0.060	0.150	0.300	0.600
04/14/82	0.057	0.147	0.293	0.591
06/09/82	0.056	0.146	0.295	0.592
08/18/82	0.055	0.162	0.324	0.611
10/12/82	0.060	0.140	0.293	0.583
12/07/82	0.060	0.147	0.290	0.599
02/02/83	0.056	0.146	0.289	0.584
03/01/83	0.057	0.143	0.287	0.592
Mean (percent w/v)	0.058	0.148	0.290	0.601
Standard deviation	0.0040	0.0078	0.0211	0.0217
Coefficient of variation (percent)	6.9	5.3	7.3	3.6
Range (percent w/v)	0.055-0.070	0.140-0.164	0.237-0.324	0.581-0.648
Number of samples	13	13	13	13

(a) Results of duplicate analysis
(b) Out of specifications; used in the studies.
(c) Out of specifications; not used in the studies.
(d) Remix; not included in the mean.

TABLE G4. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF *N,N*-DIMETHYLANILINE

Date Mixed	Target Concentration (percent w/v)	Determined Concentration (percent w/v)	
		Study Laboratory (a)	Referee Laboratory (b)
11/04/81	0.30	0.270	0.28
06/09/82	0.06	0.056	0.062
12/07/82	0.15	0.147	0.147
03/01/83	0.60	0.592	0.602

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

APPENDIX H

GENETIC TOXICOLOGY OF *N,N*-DIMETHYLANILINE

METHODS

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Haworth et al. (1983) and Mortelmans et al. (1986). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Chemicals were tested in a series (four strains used) or in a hierarchy (initial testing in TA98 and TA100; if results were negative, then the chemical was tested further in additional strains). If all results were negative, the chemical was retested in all strains with a different concentration of S9.

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 1 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response.

A positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was 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 Myhr et al. (1985) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 800 nl/ml. Mouse L5178Y lymphoma 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 thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

All doses within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 ml of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with the study chemical continued for 4 hours, after 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 express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with Tft 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 under 5% carbon dioxide for 10-12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P<0.05$) for a chemical to be considered capable of inducing Tft resistance; a single significant response led to an "equivocal" 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; if a clearly positive response was not obtained, the experiment was repeated with induced S9.

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Loveday et al. (1989) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

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 (2 mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing the study chemical was removed and replaced with fresh medium plus BrdU and colcemid, and incubation was continued for 2 more 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 chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no study chemical; 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 chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; colcemid was added, and incubation was continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the chromosomal aberration 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 10 hours in fresh medium, with colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the chromosomal aberration test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

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 usually scored for frequency of SCEs per cell from each dose; 100 first-division metaphase cells were scored at each dose for the chromosomal aberration 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 both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.003$) trend test or a significantly increased dose point ($P<0.05$) was sufficient to indicate a chemical effect.

RESULTS

N,N-Dimethylaniline was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested at doses up to 1,000 µg/plate with or without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Table H1). In the mouse lymphoma assay for induction of Tft resistance in L5178Y/TK cells, treatment with 400-600 nl/ml *N,N*-dimethylaniline in the absence of S9 produced a significant increase in resistant cells but with concomitant severe toxicity (relative total growth less than 10%) (Table H2). When tested in the presence of Aroclor 1254-induced male F344 rat liver S9, *N,N*-dimethylaniline induced a significant, dose-related increase in resistant cells over a concentration range of 20-60 nl/ml with good survival at the effective doses . In vitro treatment of CHO cells with 30-1,010 µg/ml *N,N*-dimethylaniline induced significant, dose-related increases in SCEs in the presence, but not the absence, of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Table H3). *N,N*-dimethylaniline induced chromosomal aberrations in CHO cells both in the presence and absence of S9 (Table H4). In the one trial performed without S9, a marginally significant increase in aberrations was detected only at the highest dose tested (830 µg/ml), and there was no trend; with S9, the response was much stronger and was observed over a range of doses (83-1,010 µg/ml).

TABLE H1. MUTAGENICITY OF *N,N*-DIMETHYLANILINE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA98	0	14 ± 0.3	15 ± 1.9	27 ± 1.5	30 ± 1.2	17 ± 1.8	25 ± 3.8
	3	18 ± 0.7	15 ± 4.5	--	27 ± 6.6	--	25 ± 0.6
	10	14 ± 0.7	12 ± 2.2	23 ± 5.0	29 ± 2.1	19 ± 3.5	24 ± 2.6
	33	11 ± 2.7	8 ± 0.3	25 ± 0.9	23 ± 4.0	22 ± 2.8	22 ± 3.9
	100	10 ± 1.5	8 ± 0.9	25 ± 2.4	24 ± 3.0	22 ± 2.0	22 ± 2.8
	333	9 ± 1.8	12 ± 2.5	26 ± 3.4	22 ± 2.5	22 ± 1.9	20 ± 0.7
	1,000	--	--	(c) 4 ± 0.3	--	(c) 8 ± 4.6	--
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		1,034 ± 21.2	354 ± 30.5	1,104 ± 32.4	1,444 ± 62.5	402 ± 17.0	404 ± 29.7
TA100	0	85 ± 2.7	93 ± 3.7	123 ± 10.0	87 ± 3.1	97 ± 2.2	94 ± 9.0
	3	107 ± 3.2	107 ± 8.5	--	104 ± 4.7	--	108 ± 11.7
	10	89 ± 5.6	102 ± 8.0	112 ± 8.7	89 ± 6.0	110 ± 7.9	108 ± 4.8
	33	104 ± 11.3	97 ± 10.3	113 ± 1.8	104 ± 3.0	110 ± 6.2	101 ± 6.2
	100	109 ± 12.5	95 ± 9.9	102 ± 9.3	87 ± 3.3	113 ± 4.5	105 ± 2.6
	333	102 ± 3.5	81 ± 3.7	122 ± 12.7	93 ± 2.7	119 ± 11.1	102 ± 8.1
	1,000	--	--	(c) 40 ± 9.3	--	(c) 78 ± 13.4	--
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		382 ± 7.7	345 ± 17.7	1,336 ± 56.6	1,132 ± 40.3	461 ± 26.6	441 ± 9.1
TA1535	0	23 ± 1.9	28 ± 3.7	9 ± 1.9	6 ± 0.3	8 ± 0.6	10 ± 1.2
	3	14 ± 0.9	20 ± 3.8	--	7 ± 1.0	--	9 ± 0.3
	10	14 ± 3.2	21 ± 2.2	10 ± 1.2	7 ± 2.8	7 ± 0.7	8 ± 2.2
	33	16 ± 1.5	18 ± 1.9	8 ± 0.3	4 ± 1.2	6 ± 0.0	7 ± 0.7
	100	15 ± 0.3	18 ± 2.8	6 ± 0.3	7 ± 0.6	7 ± 0.9	6 ± 1.0
	333	15 ± 2.1	20 ± 2.9	7 ± 1.2	6 ± 1.0	6 ± 1.0	5 ± 0.9
	1,000	--	--	(c) 2 ± 1.0	--	(c) 3 ± 1.2	--
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		519 ± 6.8	324 ± 21.2	438 ± 43.0	452 ± 9.8	158 ± 11.5	187 ± 9.9
TA1537	0	7 ± 0.9	7 ± 2.7	8 ± 2.3	6 ± 1.7	6 ± 1.9	3 ± 0.9
	3	3 ± 0.3	5 ± 1.8	--	9 ± 1.8	--	7 ± 0.6
	10	4 ± 1.5	5 ± 0.0	3 ± 0.9	4 ± 1.2	5 ± 0.7	7 ± 0.0
	33	4 ± 0.3	4 ± 0.9	5 ± 0.6	5 ± 0.7	3 ± 0.6	4 ± 0.9
	100	6 ± 2.2	3 ± 0.0	7 ± 0.3	7 ± 0.9	5 ± 1.2	3 ± 0.7
	333	2 ± 1.5	5 ± 1.7	5 ± 0.6	6 ± 2.1	5 ± 0.9	4 ± 0.0
	1,000	--	--	(c) 2 ± 0.9	--	(c) 7 ± 1.2	--
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (d)		556 ± 5.2	154 ± 23.7	298 ± 10.1	339 ± 18.3	128 ± 3.9	105 ± 6.2

(a) Study performed at SRI International. The detailed protocol is presented by Mortelmans et al. (1986). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Slight toxicity
(d) Positive control; 2-aminoanthracene was used with all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE H2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY *N,N*-DIMETHYLANILINE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (nl/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
−S9					
Trial 1					
Ethanol (d)		90.0	99.8	68.0	25.0
N,N-Dimethylaniline	200	79.0	44.3	66.3	28.3
	300	70.3	27.7	77.7	36.7
	400	58.3	9.7	86.7	(e) 53.3
	(f) 500	67.0	9.0	82.0	(e) 40.5
	600	Lethal	--	--	--
Methyl methanesulfonate (g)	5	49.5	38.0	406.5	(e) 282.0
Trial 2					
Ethanol (d)		76.3	100.0	97.5	43.0
N,N-Dimethylaniline	200	66.0	77.0	58.3	30.0
	300	72.7	56.7	87.7	40.3
	400	83.5	56.0	102.3	41.0
	500	68.7	25.7	123.0	59.0
	600	72.7	25.7	153.3	(e) 70.3
	800	Lethal	--	--	--
Methyl methanesulfonate (g)	5	72.0	64.0	561.5	(e) 264.5
+S9 (h)					
Trial 1					
Ethanol (d)		95.8	100.0	134.8	47.0
N,N-Dimethylaniline	10	74.3	89.0	136.0	62.3
	20	82.0	85.3	167.3	(e) 70.0
	30	80.7	80.0	204.7	(e) 86.0
	40	72.7	59.7	264.7	(e) 121.0
	50	83.7	49.7	433.7	(e) 174.7
	60	68.7	38.7	369.3	(e) 180.3
Methylcholanthrene	2.5	63.0	34.0	821.7	(e) 445.0
Trial 2					
Ethanol (d)		92.0	100.0	178.8	66.0
N,N-Dimethylaniline	20	61.3	54.3	314.7	(e) 176.7
	30	66.0	28.0	542.3	(e) 276.0
	40	49.78	11.3	839.3	(e) 566.3
	(f) 50	41.0	4.5	709.5	(e) 622.5
	(f) 60	36.5	5.0	783.5	(e) 735.5
	80	Lethal	--	--	--
Methylcholanthrene	2.5	23.0	6.0	612.7	(e) 888.7

TABLE H2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY *N,N*-DIMETHYLANILINE IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate except as noted; the average of the 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 (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
(b) Mean ± standard error from three replicate plates of approximately 1×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.
(c) Mutant fraction (frequency) is a ratio of the Tft-resistant cells to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.
(d) Data presented are average of four tests.
(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.
(f) Data presented are for two tests; the dose in one test was lethal.
(g) Data presented are for two tests.
(h) Tests conducted with metabolic activation were performed as described in (a) except that S9, prepared from the liver of Aroclor 1254-induced F344 rats, was added at the same time as the study chemical and/or solvent.

TABLE H3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY *N,N*-DIMETHYLANILINE (a)

Compound	Dose (µg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
–S9 (c)--Summary: Negative								
Dimethyl sulfoxide		50	1,045	499	0.48	10.0	26.0	
N,N-Dimethylaniline	29.9	50	1,042	441	0.42	8.8	26.0	88.0
	99.5	50	1,052	447	0.42	8.9	26.0	89.0
	299	50	1,038	530	0.51	10.6	26.0	106.0
Mitomycin C	0.002	50	1,043	628	0.60	12.6	26.0	126.0
	0.01	10	208	317	1.52	31.7	26.0	317.0
+S9 (d)								
Trial 1--Summary: Positive								
Dimethyl sulfoxide		50	1,041	462	0.44	9.2	26.0	
N,N-Dimethylaniline	101	50	1,039	982	0.95	19.6	26.0	213.0
	302	50	1,043	1,066	1.02	21.3	26.0	231.5
	1,010	50	1,037	1,254	1.21	25.1	26.0	272.8
Cyclophosphamide	0.5	50	1,043	852	0.82	17.0	26.0	184.8
	2.5	10	210	400	1.90	40.0	26.0	434.8
Trial 2--Summary: Positive								
Dimethyl sulfoxide		50	1,051	441	0.42	8.8	25.5	
N,N-Dimethylaniline	10	50	1,045	510	0.49	10.2	25.5	115.9
	30	50	1,050	919	0.88	18.4	25.5	209.1
	100	50	1,052	1,427	1.36	28.5	25.5	323.9
Cyclophosphamide	0.4	50	1,048	909	0.87	18.2	25.5	206.8
	2.5	10	208	616	2.96	61.6	25.5	700.0

(a) Study performed at Bioassay Systems Corp. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Loveday et al. (1989). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) 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) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent.
(c) In the absence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) In the presence of S9, cells were incubated with study compound 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 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE H4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY *N,N*-DIMETHYLANILINE (a)

−S9 (b)					+S9 (c)				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time 10.5 h					Trial 1--Harvest time 12.0 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	1	0.01	1.0		100	1	0.01	1.0
N,N-Dimethylaniline					*N,N*-Dimethylaniline				
83	100	1	0.01	1.0	83	100	11	0.11	9.0
415	100	1	0.01	1.0	415	100	15	0.15	15.0
830	100	9	0.09	8.0	830	100	19	0.19	13.0
	Summary: Weakly positive					Summary: Positive			
Mitomycin C					Cyclophosphamide				
5	100	54	0.54	37.0	50	100	58	0.58	37.0
					Trial 2--Harvest time 12.0 h				
					Dimethyl sulfoxide				
						100	4	0.04	3.0
					N,N-Dimethylaniline				
					505	100	36	0.36	23.0
					755	100	63	0.63	35.0
					1,010	100	46	0.46	27.0
						Summary: Positive			
					Cyclophosphamide				
					50	100	84	0.84	50.0

(a) Study performed at Bioassay Systems Corp. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Loveday et al. (1989). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft (October 1988) of NTP Technical Report No. 360 for the 2-year studies of *N,N*-dimethylaniline in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by quality assurance, resource support contractors. The audit included review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records including protocol, correspondence, animal husbandry, environmental conditions, dosing, external masses, mortality, animal identification, and serology.
(3) Body weight and clinical observation data for a random 10% sample of animals in each study group.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning date of death, disposition code, condition code, tissue accountability, correlation of masses or clinical signs recorded at or near the last inlife observation with gross observations and microscopic diagnoses, and correlations between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory and wet tissues from a random 20% sample of animals in all study groups, plus other relevant cases, to evaluate the integrity of individual animal identity and to examine for untrimmed potential lesions.
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group, plus animals with less than complete or correct identification, to examine for proper match and inventory.
(8) Necropsy record forms for data entry errors and all microscopic diagnoses for a random 20% sample of animals, plus all redlined diagnoses on the preliminary pathology tables, to verify incorporation of changes into the final tables.
(9) The extent of correlation between the data, factual information, and procedures for the 2-year studies presented in the draft Technical Report and the records available at the NTP Archives.

Most procedures and events for the exposure phase of the studies were documented adequately. Review of data for the entire exposure phase indicated that the animal care procedures were followed adequately during the course of the studies. According to the records, the doses were prepared, stored, analyzed, and administered to animals according to protocols. Of the external masses observed inlife, 119/124 in rats and 61/71 in mice were correlated with necropsy observations. Survival records for all unscheduled-death animals were found to be complete and internally consistent except for the dates of death for three rats and one mouse and the disposition codes (natural death vs. moribund kill) assigned to four rats and six mice; review of pathology specimens gave no indication of other inconsistencies, and these discrepancies had no effect on the overall survival values for the respective study groups.

Individual animal identifiers (punched ears and clipped toes) were present and correct in the residual tissue bags for 68/71 rats and 63/73 mice examined. Review of the entire data trail for animals with less than complete and correct identifiers indicated that the integrity of individual animal identity had been maintained, except for the cagemate switching of two low dose rats and four low dose mice. For the remaining rat and six mice, the corresponding ears and feet were not identifiable. One untrimmed potential lesion was found in one rat, and six were found in four mice; none involved target organs. Intestinal segments were not completely opened for 15/71 rats and 14/73 mice; however, no potential lesions were evident by external examination. All gross observations made at necropsy were correlated with microscopic observations, except for five that involved nontarget organs of five rats. Tissue blocks and slides matched each other properly. All post-Pathology Working Group changes in diagnoses had been incorporated into the final pathology tables.

Full details about these and other audit findings are presented in audit reports that are on file at NIEHS. In conclusion, the data and results presented in the draft Technical Report for the 2-year gavage studies of *N*,*N*-dimethylaniline are supported by the records at the NTP Archives.