NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP Technical Report on the Toxicology and Carcinogenesis Studies of Pyridine (CAS No. 110-86-1) in F344/N Rats, Wistar Rats, and B6C3F$_1$ Mice (Drinking Water Studies)

NTP TR 470

MARCH 2000

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

PYRIDINE

(CAS NO. 110-86-1)

IN F344/N RATS, WISTAR RATS, AND B6C3F$_1$ MICE

(DRINKING WATER STUDIES)

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

March 2000

NTP TR 470

NIH Publication No. 00-3960

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

FOREWORD

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

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

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

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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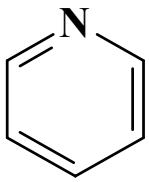
CONTENTS

ABSTRACT



PYRIDINE

CAS No. 110-86-1

Chemical Formula: C_5H_5N Molecular Weight: 79.10

Synonyms: Azabenzene, azine

Pyridine is used as a denaturant in alcohol and antifreeze mixtures, as a solvent for paint, rubber, and polycarbonate resins, and as an intermediate in the manufacture of insecticides, herbicides, and fungicides. It is used in the production of piperidine, an intermediate in the manufacture of rubber and mepiquat chloride, and as an intermediate and solvent in the preparation of vitamins and drugs, dyes, textile water repellants, and flavoring agents in food. Pyridine was nominated for study because of its large production volume and its use in a variety of food, medical, and industrial products. Male and female F344/N rats, male Wistar rats, and male and female B6C3F$_1$ mice were exposed to pyridine (approximately 99% pure) in drinking water for 13 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, cultured Chinese hamster ovary cells, *Drosophila melanogaster*, and mouse bone marrow cells.

13-WEEK STUDY IN F344/N RATS

Groups of 10 male and 10 female F344/N rats were exposed to pyridine in drinking water at concentrations of 0, 50, 100, 250, 500, or 1,000 ppm (equivalent to average daily doses of 5, 10, 25, 55, or 90 mg pyridine/kg body weight). Two females exposed to 1,000 ppm died during week 1. Final mean body weights of 1,000 ppm males and females and 500 ppm females were significantly less than controls. Water consumption by female rats exposed to 1,000 ppm was less than that by controls. At study termination, evidence of anemia persisted in the 500 and 1,000 ppm males and all exposed groups of females. There was evidence of hepatocellular injury and/or altered hepatic function demonstrated by increased serum alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations in 500 and 1,000 ppm rats. The estrous cycle length of 1,000 ppm females was significantly longer than that of the controls. Liver weights of males and females exposed to 250 ppm or greater were significantly greater than controls. In the liver, the incidences of centrilobular degeneration, hypertrophy, chronic inflammation, and pigmentation were generally increased in 500 and 1,000 ppm males and females relative to controls. In the kidney, the incidences of granular casts and hyaline degeneration (hyaline droplets) were significantly increased in 1,000 ppm males and slightly increased in 500 ppm males; these lesions are consistent with α2u-globulin nephropathy. Additionally, there were increased incidences and/or severities of protein casts, chronic inflammation, mineralization, and regeneration primarily in 500 and 1,000 ppm males.

13-WEEK STUDY IN MALE WISTAR RATS

Groups of 10 male Wistar rats were exposed to pyridine in drinking water at concentrations of 0, 50, 100, 250, 500, or 1,000 ppm (equivalent to average daily doses of 5, 10, 30, 60, or 100 mg/kg). One male rat exposed to 500 ppm died during week 1. Final mean body weights of rats exposed to 250, 500, or 1,000 ppm were significantly less than those of the controls. Water consumption by rats exposed to 1,000 ppm was lower than that by controls. There was evidence of hepatocellular injury and/or altered hepatic function in the 500 and 1,000 ppm groups, similar to that observed in the 13-week study in F344/N rats. Incidences of centrilobular degeneration, hypertrophy, chronic inflammation, and pigmentation in the liver of rats exposed to 500 or 1,000 ppm were significantly increased relative to controls.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F_1 mice were exposed to pyridine in drinking water at concentrations of 0, 50, 100, 250, 500, or 1,000 ppm (equivalent to average daily doses of 10, 20, 50, 85, or 160 mg/kg for males and 10, 20, 60, 100, or 190 mg/kg for females). One female mouse exposed to 250 ppm died during week 2. Final mean body weights of female mice exposed to 1,000 ppm were significantly less than those of controls. Water consumption by exposed female mice was lower than that by controls at week 1 but generally slightly higher than controls at week 13. Sperm motility in exposed male mice was significantly decreased relative to controls. Liver weights were significantly increased relative to controls in males exposed to 100 ppm or greater and in 250 and 500 ppm females. No chemical-related lesions were observed in male or female mice.

2-YEAR STUDY IN F344/N RATS

Groups of 50 male and 50 female F344/N rats were exposed to pyridine in drinking water at concentrations of 0, 100, 200, or 400 ppm (equivalent to average daily doses of 7, 14, or 33 mg/kg) for 104 (males) or 105 (females) weeks.

Survival, Body Weights, and Water Consumption

Survival of exposed males and females was similar to that of controls. Mean body weights of 400 ppm males and females were generally less than those of the controls throughout the study, and those of 200 ppm males and females were less during the second year of the study. Water consumption by males and females exposed to 200 or 400 ppm was generally greater than that by controls.

Pathology Findings

Incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in male rats exposed to 400 ppm were significantly increased compared to controls and exceeded the historical control ranges. The findings from an extended evaluation (step section) of the kidneys did not reveal additional carcinomas, but additional adenomas were observed in each group of males. In the standard evaluation, an increased incidence of renal tubule hyperplasia was observed in 400 ppm males compared to controls. Incidences of mononuclear cell leukemia in female rats were significantly increased in the 200 and 400 ppm groups, and the incidence in the 400 ppm group exceeded the historical control range.

Exposure concentration-related nonneoplastic liver lesions were observed in males and females, and the incidences were generally increased in groups exposed to 400 ppm. These included centrilobular cytomegaly, cytoplasmic vacuolization, periportal fibrosis, fibrosis, centrilobular degeneration and necrosis, and pigmentation. Bile duct hyperplasia occurred more often in exposed females than in controls.

2-YEAR STUDY IN MALE WISTAR RATS

Groups of 50 male Wistar rats were exposed to pyridine in drinking water at concentrations of 0, 100, 200, or 400 ppm (equivalent to average daily doses of 8, 17, or 36 mg/kg) for 104 weeks.

Survival, Body Weights, and Water Consumption

Survival of rats exposed to 200 or 400 ppm was significantly less than that of the controls. Mean body

weights of rats exposed to 100, 200, or 400 ppm were significantly less than controls. Water consumption was similar by control and exposed rats.

Pathology Findings

The incidence of testicular interstitial cell adenoma in rats exposed to 400 ppm was significantly increased compared to controls. Incidences of interstitial cell hyperplasia were observed in control and exposed groups and were slightly, but not significantly, increased in rats exposed to 200 or 400 ppm.

Severity of nephropathy was marked in all groups, and additional evidence of kidney disease, including mineralization in the glandular stomach, parathyroid gland hyperplasia, and fibrous osteodystrophy, was observed in 100 and 200 ppm rats. The incidences of hepatic centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and/or pigmentation were increased in one or more exposed groups.

2-YEAR STUDY IN MICE

Groups of 50 male B6C3F_1 mice were exposed to pyridine in drinking water at concentrations of 0, 250, 500, or 1,000 ppm (equivalent to average daily doses of 35, 65, or 110 mg/kg) for 104 weeks, and groups of 50 female B6C3F_1 mice were exposed to pyridine in drinking water at concentrations of 0, 125, 250, or 500 ppm (equivalent to average daily doses of 15, 35, or 70 mg/kg) for 105 weeks.

Survival, Body Weights, and Water Consumption

Survival of exposed males and females was similar to that of the controls. Mean body weights of 250 and 500 ppm females were less than controls. Water consumption by males exposed to 250 or 500 ppm was generally greater than that by controls during the last year of the study; male mice exposed to 1,000 ppm consumed less water than controls throughout the study. Water consumption by exposed females was generally lower than that by controls during the first year of the study, but greater than controls during the second year.

Pathology Findings

Hepatocellular neoplasms, including hepatoblastomas, in exposed male and female mice were clearly related to pyridine exposure. Additionally, many mice had multiple hepatocellular neoplasms. The incidences of hepatocellular neoplasms in exposed males and females generally exceeded the historical control ranges for drinking water studies. Neoplasms from control mice, 1,000 ppm males, and 500 ppm females were negative when stained for p53 protein.

GENETIC TOXICOLOGY

Pyridine was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 or in L5178Y mouse lymphoma cells, with or without S9 metabolic activation, and it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without S9. Pyridine was tested for induction of sex-linked recessive lethal mutations in adult male *Drosophila melanogaster*, and mixed results were obtained. In one experiment, administration by injection gave negative results, but feeding produced an equivocal response. A second experiment generated negative results by injection and feeding. A third experiment showed significant increases in sex-linked recessive lethal mutations in flies treated with pyridine by injection but not by feeding. Overall, results of the sex-linked recessive lethal mutations test in *Drosophila melanogaster* were considered negative by feeding and equivocal by injection. Results of a single reciprocal translocation test in male *Drosophila melanogaster* were negative. No induction of chromosomal aberrations or micronuclei was noted in bone marrow cells of male mice administered pyridine via intraperitoneal injection.

CONCLUSIONS

Under the conditions of these 2-year drinking water studies, there was *some evidence of carcinogenic activity** of pyridine in male F344/N rats based on increased incidences of renal tubule neoplasms. There was *equivocal evidence of carcinogenic activity* of pyridine in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was *equivocal evidence of carcinogenic activity* in male Wistar rats based on an increased incidence of interstitial cell adenoma of the testis. There was *clear evidence of carcinogenic activity* of pyridine in male and female B6C3F_1 mice based on increased incidences of malignant hepatocellular neoplasms.

In F344/N rats, exposure to pyridine resulted in increased incidences of centrilobular cytomegaly and degeneration, cytoplasmic vacuolization, and pigmentation in the liver of males and females; periportal fibrosis, fibrosis, and centrilobular necrosis in the liver of males; and bile duct hyperplasia in females. In male Wistar rats, pyridine exposure resulted in increased incidences of centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and pigmentation in the liver, and, secondary to kidney disease, mineralization in the glandular stomach and parathyroid gland hyperplasia.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 15.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Pyridine

	Male F344/N Rats	Female F344/N Rats	Male Wistar Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in drinking water	0, 100, 200, or 400 ppm	0, 100, 200, or 400 ppm	0, 100, 200, or 400 ppm	0, 250, 500, or 1,000 ppm	0, 125, 250, or 500 ppm
Body weights	200 and 400 ppm groups less than control group	200 and 400 ppm groups less than control group	Exposed groups less than control group	Exposed groups similar to control group	Exposed groups less than control group
Survival rates	25/50, 20/50, 25/50, 16/50	32/50, 37/50, 29/50, 26/50	22/50, 14/50, 11/50, 7/50	35/50, 28/50, 35/49, 35/50	32/50, 30/50, 22/50, 29/50
Nonneoplastic effects	Liver: centrilobular cytomegaly (0/50, 4/49, 8/50, 6/50); cytoplasmic vacuolization (4/50, 6/49, 13/50, 17/50); periportal fibrosis (0/50, 0/49, 2/50, 29/50); fibrosis (1/50, 1/49, 1/50, 10/50); centrilobular degeneration (1/50, 3/49, 2/50, 8/50); centrilobular necrosis (0/50, 3/49, 0/50, 5/50); pigmentation (4/50, 11/49, 20/50, 25/50)	Liver: centrilobular cytomegaly (0/50, 1/50, 4/50, 20/50); cytoplasmic vacuolization (10/50, 7/50, 9/50, 18/50); centrilobular degeneration (1/50, 2/50, 2/50, 7/50); bile duct hyperplasia (20/50, 29/50, 34/50, 29/50); pigmentation (6/50, 2/50, 6/50, 17/50)	Liver: centrilobular degeneration (1/50, 15/50, 25/50, 33/50); centrilobular necrosis (5/50, 6/50, 4/50, 23/50); fibrosis (1/50, 5/50, 26/50, 31/50); periportal fibrosis (0/50, 0/50, 5/50, 7/50); pigmentation (6/50, 15/50, 34/50, 42/50) Glandular Stomach: mineralization (8/49, 25/50, 16/48, 6/48) Parathyroid Gland: hyperplasia (16/48, 32/47, 29/48, 12/47)	None	None
Neoplastic effects	Kidney: renal tubule adenoma (standard evaluation - 1/50, 0/48, 2/50, 6/49; standard and extended evaluations combined- 2/50, 3/48, 6/50, 10/49); renal tubule adenoma or carcinoma (standard evaluation - 1/50, 1/48, 2/50, 6/49; standard and extended evaluations combined- 2/50, 4/48, 6/50, 10/49)	None	None	Liver: hepatocellular adenoma (29/50, 40/50, 34/49, 39/50); hepatocellular carcinoma (15/50, 35/50, 41/49, 40/50); hepatoblastoma (2/50, 18/50, 22/49, 15/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (38/50, 47/50, 46/49, 47/50)	Liver: hepatocellular adenoma (37/49, 39/50, 43/50, 34/50); hepatocellular carcinoma (13/49, 23/50, 33/50, 41/50); hepatoblastoma (1/49, 2/50, 9/50, 16/50); hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (41/49, 42/50, 45/50, 44/50)
Uncertain findings	None	Mononuclear cell leukemia: (12/50, 16/50, 22/50, 23/50)	Testis: interstitial cell adenoma (5/50, 6/49, 4/49, 12/50)	None	None
Level of evidence of carcinogenic activity	Some evidence	Equivocal evidence	Equivocal evidence	Clear evidence	Clear evidence

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Pyridine

Genetic toxicology	
Salmonella typhimurium gene mutations:	Negative in strains TA98, TA100, TA1535, and TA1537, with and without S9
Mouse lymphoma gene mutations:	Negative with and without S9
Sister chromatid exchanges	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Mouse bone marrow *in vivo*:	Negative
Sex-linked recessive lethal mutations	
Drosophila melanogaster:	Equivocal by injection; negative by feeding
Reciprocal translocations	
Drosophila melanogaster:	Negative
Micronucleated erythrocytes	
Mouse bone marrow *in vivo*:	Negative

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on pyridine on 10 December 1997 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 10 December 1997, the draft Technical Report on the toxicology and carcinogenesis studies of pyridine received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.K. Dunnick, NIEHS, introduced the toxicology and carcinogenesis studies of pyridine by discussing the uses of the chemical and the rationale for study, describing the experimental design, reporting on any survival and body weight effects, and commenting on compound-related neoplastic and nonneoplastic lesions in rats and mice. The proposed conclusions for the 2-year studies were *some evidence of carcinogenic activity* in male F344/N rats, *equivocal evidence of carcinogenic activity* in female F344/N rats and male Wistar rats, and *clear evidence of carcinogenic activity* in male and female B6C3F$_1$ mice.

Dr. Cullen, a principal reviewer, agreed with the proposed conclusions. He noted the large amount of inflammation in mouse livers and asked whether they had been screened for the possible presence of *Helicobacter hepaticus* infection. Dr. J.R. Hailey, NIEHS, said there was no frozen tissue available to perform PCR-based assays for identification of *H. hepaticus*. However, the liver lesions observed were not consistent with those typically associated with *H. hepaticus* infection.

Dr. Fischer, the second principal reviewer, agreed with the conclusions. She said the discussion should include comments on increased incidences of metastatic neoplasms in mice compared to rats. Dr. Dunnick agreed. Dr. Fischer expressed concern that the Wistar rats exposed to 400 ppm did not live long enough to produce neoplasms, and, thus, this experiment was not informative.

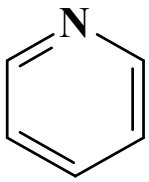
Dr. Bus, the third principal reviewer, did not agree with the proposed conclusions for female rats and mice and for male Wistar rats. He said the proposed conclusion of equivocal evidence in female rats was not warranted based on the lack of dose response, incidence values that only slightly exceeded recent NTP historical control values, and excessive body weight depressions that confound interpretation of chemical-associated neoplasms. Dr. Dunnick responded that by definition, the increases in the incidences of mononuclear cell leukemia were uncertain findings. With regard to male Wistar rats, Dr. Bus stated that the severe toxicity associated with markedly decreased survival and effects on body weight gain, especially at 200 and 400 ppm, compromised interpretation of the increased incidence of testicular adenomas in the 400 ppm group. Finally, he thought it difficult to understand a conclusion of clear evidence in female mice in view of the profound body weight loss over the last 25 weeks of the study, and though there was an exposure-related increase in the incidences of malignant liver neoplasms, liver adenomas and total neoplasms were not altered. Dr. Dunnick said the level of clear evidence was justified by the large exposure-related increased incidences of malignant neoplasms. The body weight loss was due in part to the development of liver neoplasms. Dr. J.K. Haseman, NIEHS, noted that while the incidence of liver neoplasms in control female mice may have been one of the highest seen in the NTP, almost all neoplasms were adenomas. On the other hand, almost every exposed animal that lived one year or longer developed a liver neoplasm, often multiple neoplasms, and often carcinomas or hepatoblastomas, with many neoplasms metastasizing to the lung, constituting one of the strongest carcinogenic effects ever seen at this site in his experience. Dr. Bus said this changed his perspective on the neoplasms in female mice.

Further discussion of whether hepatoblastomas should be viewed and weighed separately from hepatocellular carcinomas ensued. Dr. Hailey thought they should be viewed as part of a natural progression and that with chemicals having neoplasm promoter activity there is almost always an associated increase in hepatoblastomas. There was discussion about the appropriateness in general of combining benign and malignant neoplasms. Dr. J. Russo argued that combining can be misleading. Dr. Hailey commented that with some neoplasm types combining might be controversial but with the liver (mice) and the kidney (rats), the sites at issue here, there is a spectrum of lesions from foci or hyperplasia to adenoma to carcinoma that represents a

morphological and biological continuum, and combining seems appropriate. Dr. Bailer said that, based on the data in the report, he would have considered clear evidence as the proposed conclusion for male rats. Dr. Bucher observed that NTP is using its combined experience to delineate between some evidence and clear evidence based on its historical perspective.

Dr. Bus moved that the Technical Report on pyridine be accepted with the revisions discussed and the conclusions as written for male F344/N rats, *some evidence of carcinogenic activity*, and for male and female B6C3F$_1$ mice, *clear evidence of carcinogenic activity*. He moved that the conclusions for female F344/N rats and male Wistar rats be changed from *equivocal evidence of carcinogenic activity* to *inadequate study of carcinogenic activity*. Dr. Cullen seconded the motion. Dr. Haseman said that *inadequate study* is a category of evidence generally used only when there is some major flaw that makes the study uninterpretable. Dr. Bailer moved to amend the motion to keep the level of evidence for female F344/N rats and male Wistar rats as originally proposed, *equivocal evidence of carcinogenic activity*. Dr. Cullen seconded the amendment, which was accepted by six yes votes to one no vote (Dr. Bus). Dr. Bus's motion as amended by Dr. Bailer was accepted unanimously with seven votes.

INTRODUCTION



PYRIDINE

CAS No. 110-86-1

Chemical Formula: C_5H_5N Molecular Weight: 79.10

Synonyms: Azabenzene, azine

CHEMICAL AND PHYSICAL PROPERTIES

Pyridine is a slightly yellow or colorless, hygroscopic liquid with a characteristic nauseating odor and a burning taste. It is miscible with water, alcohols, diethyl ether, benzene, ligroin, and fatty oils and is slightly alkaline in reaction (pK_a of 5.19). Pyridine boils at approximately 115 C at 760 mm Hg and has a specific gravity of 0.982, a vapor pressure of approximately 20 torr at 25 C, and a vapor density of 2.73 (Jori *et al.*, 1983; *Hawley's*, 1987*; Merck Index*, 1989; Lewis, 1993). The liquid has a flash point (closed cup) of 20 C and is flammable when exposed to heat, flame, or oxidizers; the vapor explodes upon contact with a flame or spark. When heated to decomposition, it emits cyanide fumes (*Hawley's*, 1987; Sittig, 1991; Lewis, 1993).

PRODUCTION, USE, AND HUMAN EXPOSURE

Pyridine is produced by coal carbonization and recovery from coke-oven gases and coal tar middle oil. Since the 1950s it has also been produced synthetically from the vapor phase reaction of acetaldehyde and ammonia, with formaldehyde and methanol sometimes added (Jori *et al.*, 1983; NCI, 1985).

Pyridine is a solvent that is widely employed in industry and the laboratory. It is used as a denaturant in alcohol and antifreeze mixtures, as a solvent for paint, rubber, and polycarbonate resins, and as an intermediate in the manufacture of insecticides (chlorpyrifos), herbicides (paraquat and trichloropyr), and fungicides. It is used in the production of piperidine, an intermediate in the manufacture of rubber and mepiquat chloride. Pyridine is also used as an intermediate and solvent in the preparation of vitamins and drugs, dyes, textile water repellants, and flavoring agents in food (NCI, 1985; *Hawley's*, 1987; ATSDR, 1992).

Manufacturers and consumers used an estimated 300,000 kg pyridine in 1977. Approximately 4.5 to 8.9×10^6 kg pyridine was produced in the United States in 1975, 27×10^6 kg in 1976, and 11.6×10^6 kg in 1978 (Pyridine Task Force, correspondence from Chairmen to U.S. Environmental Protection Agency, Office of Toxic Substances, Washington, DC, 1978). No information on the current annual production of pyridine is available in the literature (ATSDR, 1992).

The greatest potential for exposure to pyridine is in the workplace. Occupational exposures, usually by inhalation or dermal absorption, may occur during pyridine

production or its use as a chemical intermediate or solvent (NCI, 1985). Exposure may also occur at coke-oven and oil-shale processing facilities. The U.S. Environmental Protection Agency (EPA) (1978) estimated that 249,000 persons were occupationally exposed to pyridine. The National Institute for Occupational Safety and Health (NIOSH) (1990) estimated the extent of potential human exposure between 1981 and 1983 at over 41,000 workers. The 8-hour, time-weighted average permissible exposure level for pyridine is 5 ppm (16 mg/m^3) (ACGIH, 1997). NIOSH (1985) determined the concentration immediately dangerous to life or health to be 3,600 ppm. The pungent odor of pyridine (odor threshold of 0.17 ppm in air) serves to limit voluntary exposure (NCI, 1985). The odor becomes objectionable to unaccustomed individuals at 10 ppm, and olfactory fatigue occurs at greater than 5 ppm (Jori *et al.*, 1983).

Pyridine has rarely been detected in ambient air, water, or soil except near industrial sources (ATSDR, 1992). Pyridine is released into the atmosphere as fugitive emissions from coal gasification and oil shale processing facilities, from ironworking and coking plants (Masek, 1981), and from the combustion of polyisocyanate foam products (Seader *et al.*, 1972; Junk and Ford, 1980). The Agency for Toxic Substances and Disease Registry estimated that 298,438 pounds of pyridine were released in air, 4,630 pounds in surface water, and 303,650 pounds in groundwater in 1987; 209,880 pounds of pyridine were disposed of in publicly owned wastewater treatment plants (ATSDR, 1992). Pyridine has been identified in effluent from waste-water treatment plants (Ellis *et al.*, 1982), natural waters (Shelton and Hites, 1978), and groundwater near an underground coal gasification site (Stuermer *et al.*, 1982). An estimated 28,656 pounds of pyridine were released from industrial sources to land in 1987 (ATSDR, 1992). Many states have regulations concerning the acceptable ambient air concentrations of pyridine. For an 8-hour period, ambient air limits have been set at 300 µg/m^3 in Connecticut, 150 µg/m^3 in Indiana, 0.357 µg/m^3 in Nevada, 0.3 µg/m^3 in Tampa, Florida, and 0.15 µg/m^3 in Vermont. Eighteen- and 24-hour limits have been set at 0.30 µg/m^3 and 250 µg/m^3 in North Dakota and Virginia, respectively, and annual limits have been set at 2.0 µg/m^3 in New York and 35.7 µg/m^3 in Kansas (NATICH, 1989).

In the United States, the general population may be exposed to low concentrations of pyridine by the ingestion of foods. Pyridine was detected among the natural volatile components of several foods, including fried chicken, cheese, and fried bacon (ATSDR, 1992). The EPA (1978) estimated the ingestion of pyridine in the United States to be about 500 mg per person per year. The FDA has approved the use of pyridine as a flavoring agent (21 CFR, § 172.515). Pyridine is also a coffee aroma constituent (ATSDR, 1992). Pyridine has been identified as a component of tobacco and marijuana smoke (Schmeltz and Hoffmann, 1977; Schumacher *et al.*, 1977; Meril *et al.*, 1981; Curvall *et al.*, 1984; Eatough *et al.*, 1989); the concentration of pyridine in indoor air contaminated with cigarette smoke may be as high as 16 µg/m^3 (ATSDR, 1992).

REGULATORY STATUS

The EPA Office of Toxic Substances has included pyridine in its toxic chemical release reporting rule (40 CFR, Part 372), its health and safety data reporting rule (40 CFR, § 716.120), and its preliminary assessment information reporting rule (40 CFR, § 712.30). The annual reportable quantity of pyridine release to the environment has been set at 1,000 pounds by the EPA Office of Emergency and Remedial Response (40 CFR, § 302.4). The EPA Office of Solid Wastes lists pyridine as a constituent of hazardous waste (40 CFR, Part 261), monitors its levels in groundwater (40 CFR, Part 264), and restricts its disposal on land (40 CFR, Part 268).

ENVIRONMENTAL IMPACT

Pyridine exists in the atmosphere as a vapor. Atmospheric pyridine may be slowly photodegraded by hydroxyl radicals in the troposphere; the estimated atmospheric lifetime is 23 to 46 days. A large fraction of the atmospheric pyridine vapor phase would tend to dissolve in water vapor (clouds and rain) due to its high water solubility. The magnitude of the Henry's law constant for aqueous solutions of pyridine indicates that much of the atmospheric pyridine is removed by precipitation and suggests that the pyridine in water does not volatilize readily into the atmosphere. The volatility and sorption of pyridine from water varies considerably and is pH dependent. The rate of removal of pyridine from unfiltered river water by biodegradation depends on the initial pyridine concentration. At concentrations less than 20 mg/L, pyridine degradation was virtually complete in 8 days or less. Pyridine in

water may partition to soils and sediments to an extent that depends on the pH of the water and the organic carbon content of the soil. Due to its low carbon/water partition coefficient, pyridine is highly mobile in soil. In laboratory screening tests, however, 94% to 100% of the pyridine added to municipal wastewater biodegraded in 2 to 21 days (ATSDR, 1992).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Pyridine is absorbed by inhalation and by oral or dermal exposure. Pyridine is eliminated in exhaled air, feces, and urine as free base and/or metabolites (Jori *et al.*, 1983; NCI, 1985).

Pyridine is metabolized primarily by N-methylation and/or aromatic hydroxylation; urinary excretion of metabolites and unchanged compound is the major route of elimination (NCI, 1985). The metabolic pathway in Figure 1 incorporates all the major urinary metabolites of pyridine that have been identified (ATSDR, 1992).

Experimental Animals

In a series of studies on pyridine N-methylation by D'Souza *et al.* (1980), a single dose of [^{14}C]-pyridine (7 mg/kg) was administered by intraperitoneal injection to groups of one to five female Wistar albino rats, female Tuck mice, male and female Dunkin-Hartley guinea pigs, female gerbils, female golden Syrian hamsters, male and female New Zealand White rabbits, and mongrel female cats. In the rat, mouse, guinea pig, gerbil, and hamster, 48% to 67% of the administered radiolabel was recovered in the urine within 24 hours. In both the cat and rabbit, 75% and 77% of the

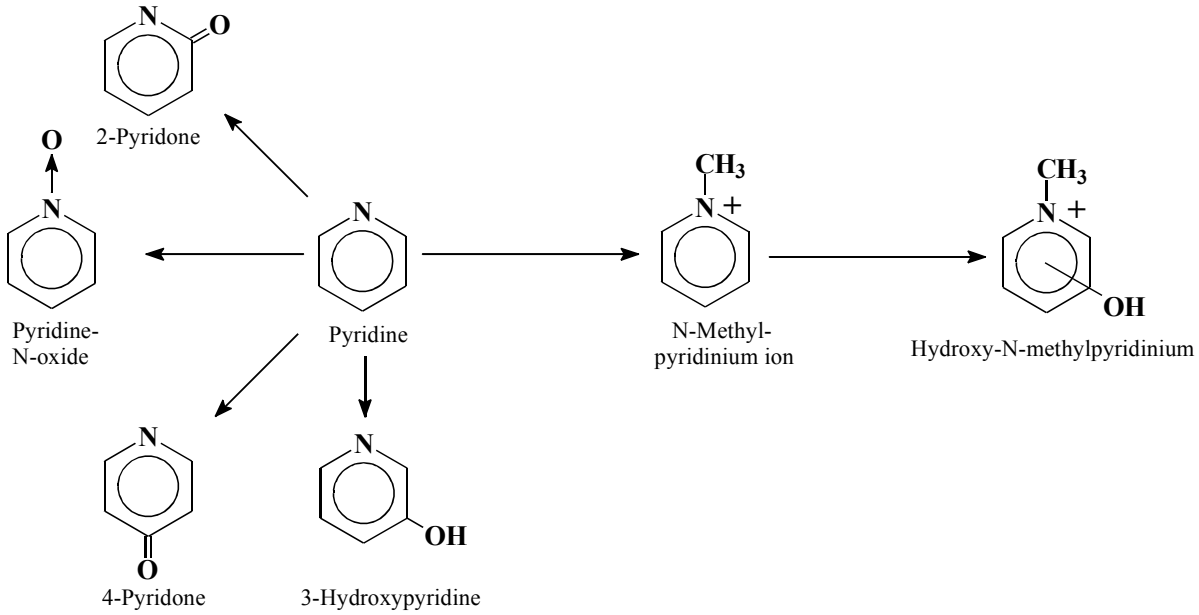


FIGURE 1
Proposed Metabolic Pathway for Pyridine (ATSDR, 1992)

administered radiolabel were recovered at 48 and 72 hours, respectively. Pyridine N-methylation was extensive (15% to 40% of the administered dose) in the guinea pig, gerbil, hamster, rabbit, and cat, and lower (approximately 5% to 12%) in the rat and mouse. To determine whether the N-methylpyridinium ion formed during the metabolism of pyridine is further metabolized, groups of three female rats and guinea pigs were injected intraperitoneally with 8 mg/kg N-methyl[2,6-^{14}C]-pyridinium as an aqueous solution of the iodide. Greater than 95% of the radiolabel recovered in the urine was unchanged compound, indicating that N-methylpyridinium is largely metabolically stable (D'Souza *et al.*, 1980).

The effects of route of administration, dose, and methionine supplementation on the N-methylation of pyridine were also investigated by D'Souza *et al.* (1980) in the rat (a poor pyridine methylator) and guinea pig (a good pyridine methylator). [^{14}C]-Pyridine was administered orally at doses of 7, 68, or 357 mg/kg or intraperitoneally at doses of 1, 7, or 500 mg/kg to groups of three animals. N-Methylation of pyridine was found to be independent of the route of administration but dependent on the dose. In rats given 7 mg/kg [^{14}C]-pyridine orally, 58% of the total ^{14}C was excreted within 24 hours, with 3.1% of the dose as the N-methylpyridinium ion; 48% of the total ^{14}C was excreted within 24 hours following intraperitoneal injection of 7 mg/kg, with 5.0% of the dose as N-methylpyridinium ion. In the guinea pig, 31% of the administered dose was recovered in the urine as the N-methylpyridinium ion, regardless of the route of administration (recovery of orally and intraperitoneally administered total ^{14}C was 76% and 66%, respectively). In contrast, a study by Okuda (1959) demonstrated that 2.5 times more N-methylpyridine was produced following subcutaneous administration than following oral administration of pyridine to dogs.

For both the rat and guinea pig (D'Souza *et al.*, 1980), overall urinary recovery of ^{14}C was inversely proportional to the dose. The metabolic reaction was saturable in both species. In another experiment (D'Souza *et al.*, 1980), rats were pretreated with an injection of 1 g DL-methionine/kg 24 hours prior to administration of 7 mg [^{14}C]-pyridine/kg and then maintained on a diet enriched with DL-methionine. The excretion of total ^{14}C and N-methylpyridinium ion were unaffected by methionine supplementation, which demonstrated that low N-methylation in the rat is unrelated to a relative deficiency of source methyl groups. In these same cross-species studies, Damani *et al.* (1982) identified 2-pyridine, 3-hydroxypyridine, and 4-pyridone in the urine of all species and pyridine N-oxide in all species except the rabbit, although the relative amounts of metabolites differed across species. In hamsters, guinea pigs, and cats, most of the urinary radioactivity was identified as unchanged pyridine and its C- and N-oxidized and N-methylated derivatives. A significant proportion of the excreted radioactivity in rats, gerbils, and rabbits could not be accounted for by the metabolites monitored in these studies, but 3-hydroxypyridine (not measured) was probably represented in the urine in a conjugated form. In rats, an unidentified cationic metabolite accounted for about 7.4% of the recovered radiolabel (Damani *et al.*, 1982).

D'Souza *et al.* (1980) suggested that N-methylation and quaternization of pyridine may result in the formation of a conjugation product (the N-methylpyridinium ion) more toxic than pyridine itself. The intraperitoneal LD_{50} for N-methylpyridinium ion in mice is 0.22 g/kg, compared to 1.2 g/kg for pyridine. Production of N-oxides, generally associated with detoxification and increased elimination in several animal species and humans, may conceivably result in an increase in toxicity or carcinogenicity, and the N-oxidation of pyridine may represent a route for bioactivation (NCI, 1985; Kim *et al.*, 1991a).

Pyridine, which is metabolized by cytochromes P2E1 and P4B (CYP2E1 and CYP4B), enhances the expression of various hepatic P_{450} isozymes in rats and rabbits (Kim and Novak, 1990; Kim *et al.*, 1991a, 1993; Nikula *et al.*, 1995). A series of studies demonstrated that pyridine enhances the expression of different gene subfamilies of rat hepatic cytochrome P_{450} including CYP2E1, CYP1A1, CYP1A2, CYP2B1, and CYP2B2 (Kim and Novak, 1990; Kim *et al.*, 1991a,b; Hotchkiss *et al.*, 1993; Iba *et al.*, 1993; Agarwal *et al.*, 1994).

Pyridine caused a dose-dependent, 4- to 22-fold elevation of hepatic CYP2B1/2B2 over the intraperitoneal dosing regimen of 100 to 400 mg/kg per day in Sprague-Dawley rats. Pyridine treatment increased CYP2B1 and CYP2B2 poly (A)+ RNA levels approximately 69- and 34-fold, respectively, while CYP2E poly (A)+ levels failed to increase (Kim *et al.*, 1993). Pyridine is similar to phenobarbital (Lubet *et al.*, 1989) and oxazepam (Griffin *et al.*, 1995) in this induction of CYP2B enzymes. Lubet *et al.* (1989) have associated

the strength of this CYP2B induction response to the strength of liver neoplasm promotion in the rat, although the mechanisms are not known. Rice *et al.* (1994) have also studied the association between CYP2B induction and liver neoplasm-promoting activity in the rat, and while there is a correlation with an induction of CYP2B and liver neoplasm promotion (after initiation with N-nitrosodiethylamine), other factors may be involved. Chemicals such as phenobarbital, which induces cytochrome P_{450}s in the rodent liver, induce a wide variety of enzyme systems (referred to as pleiotropic response), and it is likely that several effects of the chemical play a role in its liver neoplasm-promoting ability (McClain, 1990).

Male Sprague-Dawley rats were given intraperitoneal doses of 2.5 mmol of pyridine or a metabolite (including pyridine-N-oxide, 2-hydroxypyridine, 3-hydroxypyridine, 4-hydroxypyridine, and pyridinium methyl iodide) per kg of body weight for 1 to 5 days and sacrificed after the final dose. Only pyridine and 2-hydroxypyridine caused hepatotoxicity as measured by increases in serum sorbitol dehydrogenase. Pyridine, pyridine-N-oxide, 3-hydroxypyridine, and 4-hydroxypyridine were all effective inducers of CYP2E1-mediated metabolism (Carlson, 1996). As an inducer of cytochrome P_{450}2E1 in both liver and lung, pyridine has been shown to affect the metabolism of xenobiotics including 2-butanol (Page and Carlson, 1993), ethyl carbamate (urethane) (Page and Carlson, 1994), and carbon tetrachloride (Day *et al.*, 1993) in various species including rat, mouse, and/or rabbit.

Humans

N-Methylpyridinium ion (5.5% and 12% of the dose) was present in urine collected 24 hours after two human volunteers received 3.4 mg [^{14}C]-pyridine in orange juice (approximately 0.05 mg/kg) (D'Souza *et al.*, 1980). Pyridine-N-oxide was identified as a metabolite in the urine sample, accounting for 32% of the administered dose (Damani *et al.*, 1982). Approximately 25% of the urinary metabolites were not identified.

Pyridine and a number of its derivatives have been shown to cause selective inhibition of thromboxane synthetase *in vitro* in fresh citrated human blood (Miyamoto *et al.*, 1980) and in a test system employing the microsomal fraction of human platelet microsomes (Tai *et al.*, 1980); thromboxane A_2 is a potent labile inducer of platelet aggregation and vascular constriction. The inhibitory potency of pyridine on thromboxane synthetase in these systems was 60 µM in blood and 270 µM in platelet microsomes. In addition, pyridine (1.5 mM) inhibited the aggregation of human platelets induced by arachidonic acid or adenosine triphosphate (Tai *et al.*, 1980).

TOXICITY

Experimental Animals

Reported pyridine LD_{50}/LC_{50} values for rats are 891 to 1,580 mg/kg (oral), 360 mg/kg (intravenous), 866 to 1,150 mg/kg (subcutaneous), and approximately 8,000 to 9,000 ppm for 1 hour (inhalation) (Vernot *et al.*, 1977; Jori *et al.*, 1983; ATSDR, 1992). LD_{50} values for mice are 1,500 mg/kg (oral), 1,200 mg/kg (intraperitoneal), 420 mg/kg (intravenous), and 1,250 mg/kg (subcutaneous) (Jori *et al.*, 1983).

Pyridine has been reported to cause toxic effects in the liver and kidney in experimental animal model systems. Pyridine administration (oral gavage) to dogs has produced toxic effects in the liver and kidney (Jori *et al.*, 1983). Decreased glutamine concentration and increased ammonia excretion were observed in rats (age and strain not specified) exposed to pyridine vapors at a concentration of 5 to 10 mg/L for a single 40-minute exposure (ATSDR, 1992).

In a study in Sprague-Dawley rats (Anderson, 1987), pyridine was administered by gavage at 0, 0.24, 1, 10, 25, or 50 mg/kg per day in water for 90 consecutive days. No treatment-related deaths occurred during the study. Body weights relative to controls were significantly reduced in male rats in the 50 mg/kg per day group. Dose-related, mildly elevated serum cholesterol levels occurred in females at 25 and 50 mg/kg per day on days 30 and 90, and female rats that received 10 mg/kg or greater had significantly increased liver weights. Mild inflammatory hepatic lesions were seen in 70% of males and 20% of females in the 50 mg/kg groups; the incidence of inflammatory hepatic lesions was 10% in male and female control groups. Lesions included mixed peribiliary infiltrate, bile ductule proliferation, enlarged and vacuolated hepatocytes, and necrosis of hepatocytes. Liver lesions also occurred in the 10 and 25 mg/kg groups.

In a study in which rats were given subcutaneous injections of pyridine twice weekly for a year at doses of 3, 10, 30, or 100 mg/kg (Mason *et al.*, 1971),

survival rates and neoplasm incidences in pyridine-treated rats were similar to those in the controls. Mean body weights of the dosed groups ranged from 84% to 95% of those of the controls at the end of the study.

Inhalation of 5 or 444 ppm pyridine 6 hours per day for 4 days was associated with olfactory epithelial lesions in the nasal mucosa of male F344/N rats characterized by vacuolar degeneration of sustentacular cells, focal, marked attenuation of the epithelium, loss of sensory neurons, and intraepithelial luminal structures (Nikula and Lewis, 1994). These lesions were associated with induction of carboxylesterase (Nikula *et al.,* 1995).

Humans

There are no adequate studies on the toxicity of pyridine in humans. Several reports indicate that pyridine may be moderately toxic by the oral, dermal, intravenous, and inhalation routes. The chemical can cause skin irritation and severe eye damage (Sittig, 1991; Lewis, 1993).

In a review of the literature on pyridine, ATSDR (1992) reported the death of a man receiving pyridine as an intermittent medication for the treatment of epilepsy. The patient was also taking other medications (including phenobarbital), and it was not possible to attribute this death specifically to pyridine.

A 29-year-old man who accidentally swallowed ½ cup (approximately 125 mL) of pyridine experienced nausea, dizziness, abdominal pain, and lung congestion followed by death within 2 days (Jori *et al.*, 1983).

Inhalation is a primary route of exposure to pyridine, and mild symptoms of central nervous system injury may result from exposure to approximately 10 ppm (Jori *et al.*, 1983; NCI, 1985). Similar symptoms (headache, dizziness, insomnia, nausea, and anorexia) were reported in workers exposed to 125 ppm pyridine, 4 hours per day for 1 to 2 weeks (Jori *et al.*, 1983).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Injection of 10 or 20 mg pyridine into eggs caused muscular hypoplasia in 15% or 67% of chicks, respectively. The 20 mg dose induced defective beaks in 4.9% of the chicks and short or twisted necks in 1.1% (ATSDR, 1992). No information related to the reproductive or developmental toxicity of pyridine in humans was found in a search of the available literature.

CARCINOGENICITY

No information related to the carcinogenicity of pyridine in experimental animals or humans was found in a search of the available literature.

GENETIC TOXICITY

Pyridine has been tested in a variety of *in vivo* and *in vitro* assays, and with few exceptions, results were negative. No mutation induction (Pai *et al.*, 1978) or growth inhibition due to DNA damage was noted in *Escherichia coli* after treatment with pyridine (Warren *et al.*, 1981; Riebe *et al.*, 1982). No increases in gene mutation frequencies were observed in a variety of *Salmonella typhimurium* strains exposed to pyridine in the presence or the absence of S9 activation enzymes (Florin *et al.*, 1980; Kawachi *et al.*, 1980; Warren *et al.*, 1981; Riebe *et al.*, 1982; Haworth *et al.*, 1983). Zimmermann *et al.* (1986) reported induction of aneuploidy in *S. cerevisiae* D61.M after treatment with up to 1.1% pyridine, presumably resulting from disruption of microtubule assembly processes. No significant increases in mutant frequencies were seen in L5178Y mouse lymphoma cell cultures after incubation with pyridine, with or without S9 activation (McGregor *et al.*, 1988). There are two published data sets from *Drosophila melanogaster* sex-linked recessive lethal assays with pyridine, and the results are mixed. Valencia *et al.* (1985) reported negative results when pyridine was administered to adult male flies by injection (7,000 ppm) and equivocal results when feeding (700 ppm) was used as the route of administration. Mason *et al.* (1992) reported negative results in a sex-linked recessive lethal assay from a feeding study (500 ppm) but positive results after injection of 4,300 ppm pyridine. This positive result with pyridine in the sex-linked recessive lethal assay was followed by a test for induction of reciprocal translocations in male *Drosophila*, and negative results were obtained in this assay (Mason *et al.*, 1992).

Cytogenetic investigations in mammalian test systems yielded negative results with pyridine for induction of chromosomal aberrations and sister chromatid exchanges in cultured Chinese hamster ovary cells,

tested in the absence of S9 activation enzymes (Abe and Sasaki, 1977; Ishidate and Odashima, 1977; Kawachi *et al.*, 1980). *In vivo*, no induction of micronuclei in mouse bone marrow cells (Harper *et al.*, 1984) or chromosomal aberrations in rat bone marrow cells was reported after treatment with pyridine.

There are little mutagenicity data for metabolites of pyridine. Pyridine-1-oxide was negative in bacterial tests for gene mutation induction (Voogd *et al.*, 1980) and growth inhibition due to DNA damage, and it did not produce growth inhibition secondary to DNA damage in *S. cerevisiae* (Nagao and Sugimura, 1972). These tests were conducted without S9. 3-Hydroxypyridine, another pyridine metabolite, did not cause gene reversion in *S. typhimurium*, with or without S9 (Florin *et al.*, 1980).

In summary, there appears to be little evidence to indicate that pyridine is mutagenic in standard short-term tests.

STUDY RATIONALE

Pyridine was tested by the National Toxicology Program because of the large amount produced and its use in a variety of industrial products. The oral route of administration was selected to evaluate the systemic effects of pyridine. Pyridine has been shown to increase the severity of leukemia in a transplant model for leukemia in male F344/N rats (Dieter *et al.*, 1989), and male Wistar rats were added to these studies in order to evaluate the effects of pyridine in a rat model with a low spontaneous incidence of mononuclear cell leukemia.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PYRIDINE

Pyridine was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (00103BV). Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix K). Reports on analyses performed in support of the pyridine studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear, colorless liquid, was identified as pyridine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of lot 00103BV was determined by elemental analyses, Karl Fischer water analysis, functional group titration, and gas chromatography. Elemental analyses for hydrogen and nitrogen were in agreement with the theoretical values for pyridine; results for carbon were slightly low. Karl Fischer water analysis indicated 0.049% ± 0.003% water. Functional group titration indicated a purity of 99.8% ± 0.6%. Two gas chromatography systems indicated one major peak and no impurities with as much as 0.1% of the major peak area. The overall purity was determined to be greater than 99%.

Stability studies of the bulk chemical were performed by the analytical chemistry laboratory using gas chromatography. To ensure stability, the bulk chemical was stored at 1 to 8 C in amber glass bottles in the dark. Stability was monitored during the 13-week and 2-year studies using gas chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared as needed by mixing pyridine with deionized water (Table K1). Stability studies of a 0.01 mg/mL formulation were performed by the analytical chemistry laboratory using high-performance liquid chromatography. The stability of the dose formulation was confirmed for at least 3 weeks when stored in the dark at room temperature.

Periodic analyses of the dose formulations of pyridine were conducted at the study laboratory and analytical chemistry laboratory using high-performance liquid chromatography. For the 13-week studies, dose formulations were analyzed after preparation at the beginning, midpoint, and end of the studies (Table K2). During the 2-year studies, dose formulations were analyzed approximately every 6 to 10 weeks (Table K3). All dose formulations analyzed and used during the 13-week studies were within 10% of the target concentration. Of the dose formulations analyzed during the 2-year studies, 191 of 192 were within 10% of the target concentration. One formulation was 47% less than the target concentration; because records indicated that the proper amounts of pyridine and deionized water were used, it is possible that the wrong dose formulation was sampled for analysis. This dose formulation was remixed, and the remix was found to be within 10% of the target concentration. All animal room samples were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory during the 13-week studies agreed with the results obtained by the study laboratory (Table K4).

13-WEEK STUDIES

The 13-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to pyridine and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY); male Wistar rats were obtained from Charles River Laboratories (Kingston, NY). On receipt, rats and mice were approximately 5 weeks old. Animals were quarantined

for 12 to 14 days and were 7 or 8 weeks old on the first day of the studies. Before initiation of the studies, five male and five female F344/N rats and mice and five male Wistar rats were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female sentinel F344/N rats and mice and five male sentinel Wistar rats using the protocols of the NTP Sentinel Animal Program (Appendix N).

Groups of 10 male and 10 female F344/N rats and $B6C3F_1$ mice and 10 male Wistar rats were given drinking water containing 0, 50, 100, 250, 500, or 1,000 ppm pyridine (core study). Groups of 10 male and 10 female F344/N rats and 10 male Wistar rats exposed to the same concentrations were designated as special study animals for hematology and clinical chemistry analyses. Feed and water were available *ad libitum*; fresh control or treated water was provided twice weekly. Rats were housed five per cage, and mice were housed individually. Clinical findings were recorded weekly for rats and mice. Water consumption was recorded twice weekly by cage for core study animals. The animals were weighed initially and weekly thereafter. Details of the study design and animal maintenance are summarized in Table 1.

Blood from the retroorbital sinus was collected from special study rats on days 5 and 20 and core study rats at study termination for hematology and clinical chemistry analyses. Erythrocyte, leukocyte, and platelet counts; hemoglobin concentration; hematocrit, mean cell volume; mean cell hemoglobin; and mean cell hemoglobin concentration were measured with a Sysmex TOA E-2500. Blood smears were stained with Wright/Giemsa; differential leukocyte counts were based on classifying a minimum of 100 cells. Reticulocyte counts were done on a smear prepared from whole blood, stained with new methylene blue N, and incubated at room temperature; 1,000 erythrocytes were counted and the percent reticulocytes was determined. Clinical chemistry analyses were performed on the Roche Cobas FARA automated centrifugal analyzer (Roche Diagnostic Systems, Inc., Montclair, NJ). The hematology and clinical chemistry parameters measured are listed in Table 1.

At the end of the 13-week studies, blood was collected from the retroorbital sinus of all rats and mice for plasma pyridine concentration measurements. Pilot studies determined that samples could be collected between 8 a.m. and 10 a.m. The samples were taken in silicon-coated tubes which contained buffered sodium citrate. A plasma analysis procedure was developed and evaluated at the study laboratory for the analysis of plasma pyridine concentrations ranging from 0.063 to 100 µg/mL. Concentrations less than the experimental level of quantitation (0.063 µg/mL) should be considered approximations. Plasma samples were treated with sodium hydroxide and 3-methylpyridine, the internal standard. The samples were extracted with dichloromethane, then analyzed using gas chromatography with nitrogen-phosphorous detection. The gas chromatography was performed on a 20% Carbowax 20M-TPA on 80/100 Chromosorb column, with a nitrogen carrier gas at a flow rate of 30 mL/minute, and an oven temperature of 89 C for 7 minutes, then to 170 C at 20 C per minute, with a 2-minute hold. Three standard curve ranges were used to encompass the 1,600-fold quantitation range. Results from these analyses for rats are presented in Appendix J. Analyses of the samples for mice were not considered adequate and these data are not reported.

At the end of the 13-week studies, samples were collected for sperm motility and vaginal cytology evaluations on F344/N rats and mice exposed to 0, 250, 500, or 1,000 ppm. The parameters evaluated are listed in Table 1. Methods used were those described in the NTP's sperm morphology and vaginal cytology evaluations protocol (NTP, 1987). For 12 consecutive days prior to scheduled terminal sacrifice, the vaginal vaults of the females were moistened with saline, if necessary, and samples of vaginal fluid and cells were stained. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed. The tail of the epididymis (cauda epididymis) was then removed from the epididymal body (corpus epididymis) and weighed. Test yolk (rats) or modified Tyrode's buffer (mice) was applied to slides, and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in

buffered saline solution. Caudae were finely minced, and the tissue was incubated in the saline solution and then heat fixed at 65 C. Sperm density was then determined microscopically with the aid of a hemacytometer. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

A necropsy was performed on all core study animals. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 µm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on control and 1,000 ppm animals, and target organs were examined to the no-effect level. Table 1 lists the tissues and organs routinely examined. α2u-Globulin immunohistochemistry, using a primary antibody from Hazleton Laboratories, was assayed on selected animals from each exposure group.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female F344/N rats and 50 male Wistar rats were given drinking water containing 0, 100, 200, or 400 ppm pyridine for 104 (males) or 105 (females) weeks. Groups of 50 male $B6C3F_1$ mice were exposed to 0, 250, 500, or 1,000 ppm pyridine in drinking water for 104 weeks, and groups of 50 female $B6C3F_1$ mice were exposed to 0, 125, 250, or 500 ppm pyridine in drinking water for 105 weeks.

Source and Specification of Animals

Male and female F344/N rats and $B6C3F_1$ mice were obtained from Taconic Farms (Germantown, NY), and male Wistar rats were obtained from Charles River Laboratories (Portage, MI) for use in the 2-year studies. Rats and mice were quarantined for 12 to 14 days before the beginning of the studies. Five male and five female F344/N rats and mice and five male Wistar rats were randomly selected for parasite evaluation and gross observation of disease. Rats and mice were approximately 7 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix N).

Animal Maintenance

F344/N rats were housed five per cage, male Wistar rats were housed three per cage, and mice were housed individually. Feed and water were available *ad libitum*. Water consumption was measured weekly by cage for the first 13 weeks and every 4 weeks thereafter. Cages and racks were rotated every two weeks. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix M.

Clinical Examinations and Pathology

All animals were observed twice daily. Clinical findings were recorded at 4-week intervals, and body weights were recorded at the start of the study, weekly for the first 13 weeks, every 4 weeks until week 92 (F344/N rats), week 88 (male Wistar rats), or week 96 (mice), and then once every 2 weeks until study termination.

A complete necropsy and microscopic examination were performed on all rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. For extended evaluation of renal proliferative lesions in male rats, kidneys were step sectioned at 1-mm intervals, and four additional sections were obtained from each kidney. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year rat studies, a quality assessment pathologist evaluated slides from all tumors and all potential target

organs, which included the liver and kidney of male F344/N rats, the liver of female F344/N rats, and the liver, kidney, and testis of male Wistar rats. For the 2-year mouse studies, a quality assessment pathologist evaluated slides from all tumors and all potential target organs, which included the liver, nose, and spleen of male and female mice, the adrenal cortex and lung of male mice, and the ovary and pituitary gland of female mice.

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologists, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al.* (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on the guidelines of McConnell *et al.* (1986).

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Pyridine

13-Week Studies	2-Year Studies
Study Laboratory TSI Mason Research Institute (Worcester, MA)	TSI Mason Laboratories (Worcester, MA)
Strain and Species Rats: F344/N and Wistar Mice: B6C3F$_1$	Rats: F344/N and Wistar Mice: B6C3F$_1$
Animal Source F344/N rats: Taconic Farms (Germantown, NY) Wistar rats: Charles River Laboratories (Kingston, NY) Mice: Taconic Farms (Germantown, NY)	F344/N rats: Taconic Farms (Germantown, NY) Wistar rats: Charles River Laboratories (Portage, MI) Mice: Taconic Farms (Germantown, NY)
Time Held Before Studies F344/N rats: 14 days (males) or 12 days (females) Wistar rats: 13 days Mice: 13 days (males) or 14 days (females)	F344/N rats: 12 days (males) or 13 days (females) Wistar rats: 13 days Mice: 13 days (males) or 14 days (females)
Average Age When Studies Began 7 weeks, except special study F344/N rats at 8 weeks	7 weeks
Date of First Exposure Core Studies: F344/N rats: 24 January (males) or 22 January (females) 1990 Wistar rats: 8 February 1990 Mice: 20 December (males) or 21 December (females) 1989 Special Studies: F344/N rats: 3 February (males) or 1 February (females) 1990 Wistar rats: 1 March 1990	F344/N rats: 23 April (males) or 24 April (females) 1991 Wistar rats: 14 May 1991 Mice: 3 April (males) or 4 April (females) 1991
Duration of Exposure 13 weeks (core study animals) 19 days (special study F344/N rats) 20 days (special study Wistar rats)	F344/N and Wistar rats: 104 weeks (males) or 105 weeks (females) Mice: 104 weeks (males) or 105 weeks (females)
Date of Last Exposure Core Studies: F344/N rats: 25 April (males) or 23 April (females) 1990 Wistar rats: 30 May 1990 Mice: 21 March (males) or 22 March (females) 1990 Special Studies: F344/N rats: 22 February (males) or 20 February (females) 1990 Wistar rats: 20 March 1990	F344/N rats: 13 April (males) or 22 April (females) 1993 Wistar rats: 4 May 1993 Mice: 25 March (males) or 1 April (females) 1993
Necropsy Dates F344/N rats: 25 April (males) or 23 April (females) 1990 Wistar rats: 30 May 1990 Mice: 21 March (males) or 22 March (females) 1990	F344/N rats: 13 April (males) or 21-22 April (females) 1993 Wistar rats: 4 May 1993 Mice: 24-25 March (males) or 1 April (females) 1993
Average Age at Necropsy 19 weeks (core study)	F344/N and Wistar rats: 110 weeks (males) or 111 weeks (females) Mice: 110 weeks (males) or 111 weeks (females)
Size of Study Groups F344/N rats and mice: 10 males and 10 females Wistar rats: 10 males	F344/N rats and mice: 50 males and 50 females Wistar rats: 50 males

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Pyridine

13-Week Studies	2-Year Studies
Method of Distribution Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 13-week studies
Animals per Cage F344/N and Wistar rats: 5 Mice: 1	F344/N rats: 5 Wistar rats: 3 Mice: 1
Method of Animal Identification Tail tattoo	Tail tattoo
Diet NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 13-week studies
Water Deionized water via glass water bottles with stainless steel sipper tubes, available *ad libitum*, changed twice per week	Same as 13-week studies
Cages See-Through Systems polycarbonate, solid bottom (Lab Products, Inc., Rochelle Park, NJ), changed twice per week (rats) or weekly (mice)	Same as 13-week studies, except changed three times per week for male rats
Bedding F344/N and Wistar rats: Sani Chips (P.J. Murphy Products Corp., Montville, NJ), changed twice per week Mice: Beta Chips (P.J. Murphy Products Corp., Montville, NJ), changed weekly	Heat-treated hardwood chips (P.J. Murphy Forest Products, Montville, NJ), changed three times per week (male rats), twice per week (female rats), or weekly (mice)
Cage Filters Nonwoven fiber (Snow Filtration, Cincinnati, OH), changed once every 2 weeks	Same as 13-week studies
Racks Stainless steel (Lab Products, Inc., Rochelle Park, NJ), changed once every 2 weeks	Same as 13-week studies
Animal Room Environment Temperature: 20.6 -23.9 C (F344/N rats); 18.9 -23.3 C (Wistar rats); 20.6 -24.4 C (mice) Relative humidity: 31%-57% (F344/N rats); 35%-56% (Wistar rats); 26%-49% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour	Temperature: 19.4 -24.4 C (F344/N rats); 18.9 -26.7 C (Wistar rats); 20.0 -24.4 C (mice) Relative humidity: 24%-71% (F344/N rats); 25%-78% (Wistar rats); 20%-65% (mice) Room fluorescent light: 12 hours/day Room air changes: 10/hour
Exposure Concentrations 0, 50, 100, 250, 500, or 1,000 ppm	F344/N and Wistar rats: 0, 100, 200, or 400 ppm Mice: 0, 250, 500, or 1,000 ppm (males); 0, 125, 250, or 500 ppm (females)

TABLE 1
Experimental Design and Materials and Methods in the Drinking Water Studies of Pyridine

13-Week Studies	2-Year Studies
Type and Frequency of Observation Observed twice daily; animals were weighed initially and weekly thereafter; clinical findings were recorded weekly. Water consumption was recorded twice per week by cage.	Observed twice daily; animals were weighed initially, weekly for the first 13 weeks, every 4 weeks until week 92 (F344/N rats), week 88 (Wistar rats), or week 96 (mice), and then once every 2 weeks; clinical findings were recorded at 4-week intervals. Water consumption was measured weekly by cage for the first 13 weeks and every 4 weeks thereafter.
Method of Sacrifice CO_2	70%:30% CO_2:O_2
Necropsy Necropsy performed on all core study animals. Organs weighed were heart, right kidney, liver, lung, right testis, and thymus.	Necropsy performed on all animals.
Clinical Pathology Blood was collected from the retroorbital sinus of special study rats on days 5 and 20 and of core study rats at the end of the study for hematology and clinical chemistry analyses. ***Hematology:*** hematocrit; hemoglobin concentration; erythrocyte, reticulocyte, nucleated erythrocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte count and differentials ***Clinical chemistry:*** urea nitrogen, creatinine, protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbital dehyrodrogenase, bile acids	None
Histopathology Complete histopathology was performed on 0 and 1,000 ppm animals. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone (with marrow), brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (with adjacent skin), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach, testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus. The kidney of male rats and the liver of all rats were also examined in all other exposure groups.	Complete histopathology was performed on all rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone (with marrow), brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, liver, lung, lymph nodes (mandibular and mesenteric), mammary gland (with adjacent skin), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach, testis (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus.
Sperm Motility and Vaginal Cytology At the end of the studies, sperm samples were collected from male F344/N rats and mice in the 0, 250, 500, and 1,000 ppm groups for sperm motility evaluations. The following parameters were evaluated: spermatid heads per gram testis, spermatid heads per testis, sperm count, epididymal sperm concentration, and epididymal sperm motility. The left cauda, epididymis, and testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from all females exposed to 0, 250, 500, or 1,000 ppm for vaginal cytology evaluations. The following parameters were evaluated: estrous cycle length and relative frequency of estrous stages.	None
Determinations of Pyridine in Plasma At the end of the 13-week studies, blood was collected from the retroorbital sinus of all rats just before sacrifice for plasma pyridine concentration measurements.	None

STATISTICAL METHODS

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes or removed from study for other reasons were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B5, C1, C4, D1, D5, E1, and E5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, D3, and E3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., harderian gland, intestine, mammary gland, and skin) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on which a necropsy was performed. Tables A3, B3, C3, D3, and E3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and $B6C3F_1$ mice (Portier *et al.*, 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected tests were used in the analysis of lesion incidence, and reported P values are one sided. Values of P greater than 0.5 are presented as 1 P with the letter N added to indicate a lower incidence or negative trend in neoplasm occurrence relative to the control group (e.g., P=0.99 is presented as P=0.01N).

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972).

Hematology, clinical chemistry, plasma concentration, urinalysis, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison

methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to statistical analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations.

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

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

GENETIC TOXICOLOGY

The genetic toxicity of pyridine was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, mutations in L5178Y mouse lymphoma cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, sex-linked recessive lethal mutations in *Drosophila melanogaster*, and increases in the frequency of micronucleated erythrocytes in bone marrow of mice. The protocols for these studies and the results are given in Appendix F.

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

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests correlate less well with rodent carcinogenicity (Tennant *et al*., 1987; Zeiger *et al*., 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

The predictivity for carcinogenicity of a positive response in bone marrow chromosome aberration or micronucleus tests appears to be less than the *Salmonella* test (Shelby *et al.*, 1993; Shelby and Witt, 1995). Positive responses in long-term peripheral blood

micronucleus tests have not been formally evaluated for their predictivity for rodent carcinogenicity. But, because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical.

RESULTS

F344/N RATS

13-WEEK STUDY

Two females exposed to 1,000 ppm died during week 1; all other F344/N rats survived until the end of the study (Table 2). Final mean body weights of 1,000 ppm males and 500 and 1,000 ppm females and mean body weight gains of males and females exposed to 500 or 1,000 ppm were significantly less than those of the controls. Water consumption by female rats exposed to 1,000 ppm was less than that by the controls at week 1. Drinking water concentrations of 50, 100, 250, 500, or 1,000 ppm pyridine resulted in average daily doses of 5, 10, 25, 55, or 90 mg pyridine/kg body weight. There were no exposure-related clinical findings.

The hematology and clinical chemistry data for F344/N rats are listed in Table G1. On day 5, an erythrocytosis, demonstrated by increased hematocrit values, hemoglobin concentrations, and erythrocyte counts relative to controls, occurred in males exposed to 100 ppm or greater. An erythrocytosis would be consistent with dehydration, which can cause a relative erythrocytosis

TABLE 2
Survival, Body Weights, and Water Consumption of F344/N Rats in the 13-Week Drinking Water Study of Pyridine

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Water Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	149 ± 4	346 ± 9	197 ± 6		132	78
50	10/10	145 ± 4	345 ± 7	201 ± 5	100	138	76
100	10/10	149 ± 4	348 ± 6	199 ± 5	101	145	74
250	10/10	148 ± 4	346 ± 7	198 ± 4	100	136	82
500	10/10	150 ± 4	328 ± 5	177 ± 2**	95	131	90
1,000	10/10	150 ± 4	296 ± 5**	145 ± 4**	85	128	85
Female							
0	10/10	111 ± 2	206 ± 3	95 ± 2		126	91
50	10/10	110 ± 2	203 ± 4	93 ± 3	99	128	89
100	10/10	110 ± 2	202 ± 2	92 ± 2	98	127	93
250	10/10	111 ± 2	205 ± 4	95 ± 4	100	126	91
500	10/10	108 ± 2	193 ± 1**	85 ± 2*	94	123	98
1,000	8/10[d]	110 ± 2	187 ± 3**	78 ± 3**	91	85	89

* Significantly different (P 0.05) from the control group by Williams' test
** P 0.01
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Water consumption is expressed as grams of water consumed per kg body weight per day.
[d] Week of death: 1

due to decreased blood volume and hemoconcentration (Jain, 1986). On day 20, the erythrocytosis was replaced by a developing normocytic, normochromic, nonresponsive anemia, demonstrated by decreased hematocrit values, hemoglobin concentrations, and erythrocyte counts relative to controls in males and females exposed to 250 ppm or greater. Normocytosis, normochromia, and lack of an erythropoietic response were evidenced by the absence of changes relative to controls in mean cell volumes, mean cell hemoglobin concentrations, and reticulocyte counts, respectively. At week 13, evidence of the anemia persisted in 500 and 1,000 ppm males and expanded to all exposed females.

Albumin and total protein concentrations were increased relative to controls at various time points in males and females exposed to 100 ppm or greater. Increased albumin concentration would be consistent with dehydration and hemoconcentration; overproduction of albumin is not known to occur in any animal (Kaneko, 1989). The increase of total protein is probably a reflection of the increase of albumin. This evidence of dehydration could suggest that the severity of the anemia was tempered by the hemoconcentration and that the anemia may have been more severe than what the data indicate.

There was evidence of hepatocellular injury and/or altered hepatic function demonstrated by increased serum alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations that predominantly occurred in 500 and 1,000 ppm males and females relative to controls. Increases of bile acid concentrations also can indicate cholestasis. But activity of serum alkaline phosphatase, another biomarker of cholestasis, was decreased relative to controls in all exposed males and females at various time points; this suggests cholestasis was not involved. However, decreased alkaline phosphatase activity was not exposure concentration-related and, thus, could indicate chemical inhibition of the enzyme or interference with the assay method. Additionally, circulating alkaline phosphatase in a normal rat is primarily of intestinal and bone origin (Righetti and Kaplan, 1971), and fasting or food restriction causes decreases in serum alkaline phosphatase activity (Jenkins and Robinson, 1975). If rats decreased their food intake due to treatment-related toxicity or poor food palatability, decreases in alkaline phosphatase activity relative to controls might be related to loss of the normally circulating intestinal fraction. Thus, increases in alkaline phosphatase activity due to cholestasis could be counterbalanced by the negative effect of decreased food intake. Final mean body weights of 500 and 1,000 ppm males and females were significantly less than those of the controls, supporting the possibility of decreased food intake. Changes in other hematology and clinical chemistry variables were minimal, inconsistent between males and females, and within physiological values and thus were not considered toxicologically relevant.

Epididymis and testis weights of 1,000 ppm males were significantly less than controls but were probably related to decreased body weights (Table I1). The estrous cycle length of 1,000 ppm females was significantly longer than that of the controls (Table I2).

Absolute and relative liver weights of males exposed to 250, 500, or 1,000 ppm and of females exposed to 100, 250, 500, or 1,000 ppm were significantly greater than controls (Table H1). At the end of the study, plasma concentrations of pyridine in 50, 100, 250, and 500 ppm females were greater than those in males; however, plasma concentration in 1,000 ppm females was less than in males (Table J1).

Multiple hepatic alterations were observed in the livers of males and females exposed to 500 or 1,000 ppm (Table 3). Incidences of centrilobular degeneration and hypertrophy were increased relative to controls in males and females exposed to 500 or 1,000 ppm. Incidences of chronic inflammation were increased in 1,000 ppm males and females and 500 ppm males compared to controls. Incidences of pigmentation were significantly increased in 500 and 1,000 ppm males and females and 250 ppm females relative to controls. Degeneration consisted of clusters of hepatocytes, primarily centrilobular, that were strikingly ballooned and whose rarefied cytoplasm had strands or granules of eosinophilic material. Hypertrophy was a minimal increase in the size of centrilobular hepatocytes. Chronic inflammation consisted of lymphocytes, macrophages, and fibrous connective tissue that was primarily centrilobular but bridged across lobules in more severe cases. The macrophages often contained a yellow-brown pigment that special stains showed had characteristics

of both lipofuscin and hemosiderin. The pigment was positive with PAS, Perl's, and Schmorl's staining but was acid-fast negative.

In the kidney, the incidences of granular casts and hyaline degeneration (hyaline droplets) of minimal severity were significantly increased in 1,000 ppm males and slightly increased in 500 ppm males (Table 3). Lumens from one to three tubules per kidney were filled with a granular eosinophilic material (granular casts) thought to represent cellular debris from dead and sloughed renal tubule epithelial cells from a more proximal region of the tubule.

Hyaline droplets were characterized by eosinophilic proteinaceous material within the cytoplasm of renal tubular epithelial cells. This change occurred in all kidneys from males in the 13-week study but was only diagnosed when the quantity exceeded that observed in control males. An immunohistochemical stain specific for α2u-globulin was positive in both control and exposed males; the intensity of staining appeared slightly greater in the 1,000 ppm group. These changes, consistent with α2u-globulin nephropathy, were minimal in 1,000 ppm males. There was marginal evidence of an effect in the 500 ppm group and a no-effect level in the 250 ppm group.

TABLE 3
Incidences of Selected Nonneoplastic Lesions in F344/N Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm		50 ppm		100 ppm		250 ppm		500 ppm		1,000 ppm	
Male												
Liver[a]	10		10		10		10		10		10	
Centrilobular, Degeneration[b]	0		0		0		0		9**	(1.0)[c]	9**	(1.8)
Hypertrophy	0		0		0		0		9**	(1.0)	9**	(1.0)
Inflammation, Chronic	1	(1.0)	1	(1.0)	1	(1.0)	1	(1.0)	7**	(1.0)	9**	(1.9)
Pigmentation	0		0		0		0		6**	(1.0)	10**	(1.1)
Kidney	10		10		10		10		10		10	
Casts	0		0		3	(1.0)	3	(1.0)	9**	(1.0)	9**	(1.0)
Inflammation, Chronic	0		0		0		2	(1.0)	4*	(1.0)	9**	(1.0)
Mineralization	2	(1.0)	2	(1.0)	2	(1.0)	6	(1.0)	9**	(1.0)	10**	(1.0)
Renal Tubule, Regeneration	10	(1.0)	10	(1.0)	10	(1.0)	10	(1.1)	10	(1.6)	10	(1.4)
Casts Granular	0		0		0		0		3	(1.0)	8**	(1.0)
Renal Tubule, Hyaline Degeneration	1	(1.0)	0		1	(1.0)	1	(1.0)	3	(1.0)	7**	(1.0)
Female												
Liver	10		10		10		10		10		10	
Centrilobular, Degeneration	0		0		0		0		9**	(1.0)	9**	(1.8)
Hypertrophy	0		0		0		0		9**	(1.0)	8**	(1.0)
Inflammation, Chronic	0		0		0		0		1	(1.0)	4*	(1.8)
Pigmentation	0		0		0		7**	(1.0)	7**	(1.0)	8**	(1.1)
Kidney	10										10	
Casts	0										2	(1.0)
Mineralization	10	(1.6)									10	(1.3)

* Significantly different (P 0.05) from the control group by the Fisher exact test
** P 0.01
[a] Number examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Additionally, there were increased incidences and/or severities of protein casts, chronic inflammation, mineralization, and regeneration primarily in 500 and 1,000 ppm males. These lesions are qualitatively similar to those associated with spontaneous nephropathy observed in young control male F344/N rats and may have been exacerbated by administration of pyridine. Exacerbation of these lesions also occurs with α2u-globulin nephropathy and may have contributed to the increases observed in this study.

Exposure Concentration Selection Rationale: The highest exposure concentration selected for the 2-year F344/N rat study was 400 ppm based on increased incidences and severities of liver (including increased alanine aminotransferase and sorbitol dehydrogenase activities and bile acids concentrations) and kidney lesions and lower final mean body weights and body weight gains relative to controls in rats exposed to 500 or 1,000 ppm in the 13-week study. Lesions observed in the liver of female rats exposed to 250 ppm consisted of only scant pigment in macrophages in the vicinity of the central veins, and there was no effect on the kidney. Pyridine plasma levels were measured at the end of the 13-week studies in rats (Tables J1 and J2). A clear inflection point in the serum levels cannot be determined from the pyridine data, but the serum levels at 500 and 1,000 ppm appear disproportionally high when compared to those at 100 and 250 ppm.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female F344/N rats are shown in Table 4 and in the Kaplan-Meier survival curves (Figure 2). Survival of exposed males and females was not significantly different from controls.

Body Weights, Water and Compound Consumption, and Clinical Findings

Mean body weights of 400 ppm males and females were generally less than those of controls throughout the study, and those of 200 ppm males and females were generally less during the second year of the study (Figure 3; Tables 5 and 6). Water consumption by 400 ppm males and females was greater than that by controls throughout the study, and water consumption by 200 ppm males and females was greater during the second year of the study (Tables L1 and L2). Drinking water concentrations of 100, 200, or 400 ppm pyridine resulted in average daily doses of 7, 14, or 33 mg/kg. There were no treatment-related clinical findings.

TABLE 4
Survival of F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	11	13	15	10
Natural deaths	14	17	10	24
Animals surviving to study termination	25	20	25	16
Percent probability of survival at end of study[a]	50	40	50	32
Mean survival (days)[b]	663	666	665	646
Survival analysis[c]	P=0.124	P=0.403	P=1.000	P=0.095
Female				
Animals initially in study	50	50	50	50
Moribund	3	8	7	2
Natural deaths	15	5	14	22
Animals surviving to study termination	32	37	29	26
Percent probability of survival at end of study	64	74	58	52
Mean survival (days)	694	703	693	672
Survival analysis	P=0.055	P=0.392N	P=0.700	P=0.204

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. Lower mortality in an exposure group is indicated by **N**.

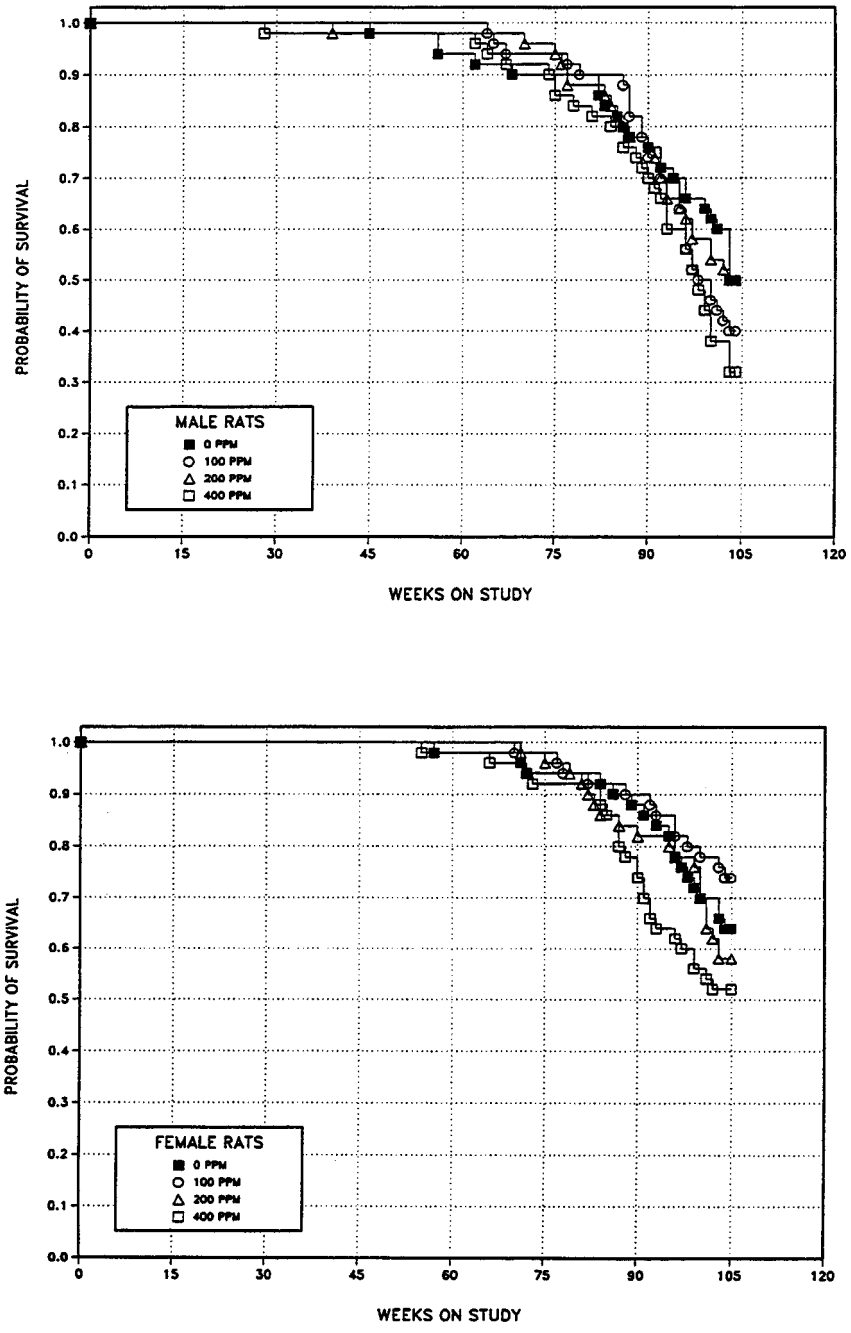


FIGURE 2
Kaplan-Meier Survival Curves for Male and Female F344/N Rats Exposed to Pyridine in Drinking Water for 2 Years

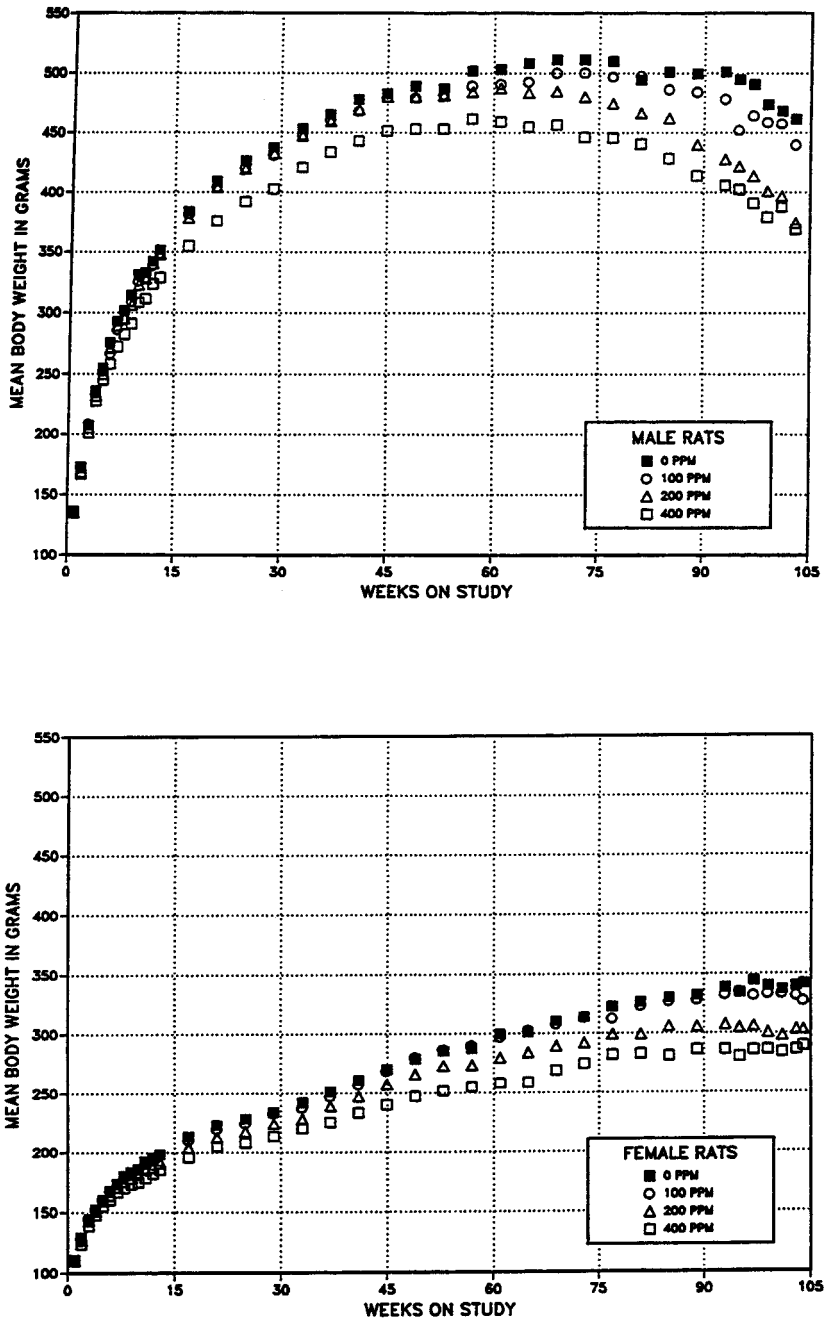


FIGURE 3
Growth Curves for Male and Female F344/N Rats Exposed to Pyridine in Drinking Water for 2 Years

TABLE 5
Mean Body Weights and Survival of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

Weeks on Study	0 ppm		100 ppm			200 ppm			400 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	136	50	135	99	50	135	99	50	136	100	50
2	173	50	172	100	50	169	98	50	167	97	50
3	207	50	208	101	50	206	99	50	201	97	50
4	236	50	234	99	50	232	98	50	227	96	50
5	255	50	253	99	50	250	98	50	245	96	50
6	275	50	267	97	50	272	99	50	258	94	50
7	293	50	286	98	50	289	99	50	272	93	50
8	302	50	295	98	50	295	98	50	282	94	50
9	314	50	309	98	50	306	97	50	291	93	50
10	331	50	326	99	50	323	98	50	309	93	50
11	333	50	329	99	50	328	99	50	311	94	50
12	342	50	339	99	50	340	100	50	323	95	50
13	351	50	349	99	50	348	99	50	328	94	50
17	384	50	382	100	50	378	99	50	355	93	50
21	409	50	405	99	50	404	99	50	376	92	50
25	426	50	420	99	50	420	98	50	392	92	50
29	437	50	431	99	50	433	99	50	403	92	49
33	453	50	448	99	50	448	99	50	421	93	49
37	465	50	461	99	50	460	99	50	434	93	49
41	478	50	468	98	50	469	98	49	443	93	49
45	483	50	480	99	50	480	100	49	452	94	49
49	489	49	479	98	50	480	98	49	453	93	49
53	487	49	482	99	50	482	99	49	453	93	49
57	502	47	489	98	50	484	97	49	462	92	49
61	503	47	491	98	50	487	97	49	459	91	49
65	508	46	492	97	49	484	95	49	455	90	47
69	511	45	500	98	47	485	95	49	457	89	46
73	511	45	500	98	47	480	94	48	446	87	46
77	510	45	497	98	47	475	93	46	446	87	43
81	494	45	497	101	45	467	94	44	441	89	42
85	501	42	486	97	45	462	92	41	428	86	40
89	499	39	484	97	41	440	88	39	414	83	37
93	501	36	478	95	35	428	85	35	406	81	33
95	495	35	452	91	35	422	85	33	403	81	30
97	491	33	464	95	28	414	84	30	391	80	28
99	474	33	459	97	25	401	85	29	379	80	24
101	468	31	458	98	23	397	85	27	388	83	19
103	461	29	440	95	21	374	81	26	369	80	19
Mean for weeks											
1-13	273		269	99		269	99		258	95	
14-52	447		442	99		441	99		414	93	
53-103	495		479	97		449	91		425	86	

TABLE 6
Mean Body Weights and Survival of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

Weeks on Study	0 ppm		100 ppm			200 ppm			400 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	110	50	110	100	50	110	101	50	111	101	50
2	129	50	128	99	50	127	99	50	124	96	50
3	144	50	145	100	50	143	99	50	139	96	50
4	152	50	152	100	50	151	99	50	148	97	50
5	160	50	160	100	50	159	100	50	155	97	50
6	167	50	167	100	50	164	98	50	160	96	50
7	173	50	173	100	50	171	98	50	167	96	50
8	180	50	179	100	50	176	98	50	170	95	50
9	183	50	183	100	50	178	97	50	173	94	50
10	186	50	185	100	50	181	98	50	175	94	50
11	192	50	190	99	50	185	96	50	178	93	50
12	196	50	194	99	50	187	96	50	182	93	50
13	198	50	197	100	50	191	97	50	185	93	50
17	213	50	210	99	50	204	96	50	196	92	50
21	223	50	220	99	50	212	95	50	205	92	50
25	228	50	225	99	50	218	95	50	208	91	50
29	234	50	233	100	50	224	96	50	214	91	50
33	242	50	238	98	50	228	94	50	220	91	50
37	251	50	247	98	50	239	95	50	225	90	50
41	261	50	257	99	50	247	95	50	234	90	50
45	270	50	269	100	50	257	95	50	240	89	50
49	279	50	280	101	50	266	95	50	247	89	50
53	285	50	287	101	50	273	96	50	252	88	50
57	288	50	290	101	50	273	95	50	255	89	49
61	299	49	297	99	50	280	94	50	258	86	49
65	301	49	302	100	50	284	94	50	259	86	49
69	310	49	308	99	50	290	93	50	269	87	48
73	314	47	313	100	49	292	93	49	275	88	47
77	322	47	313	97	49	299	93	48	282	88	46
81	326	47	323	99	47	299	92	47	283	87	46
85	330	46	327	99	46	306	93	43	281	85	44
89	331	45	328	99	45	306	92	42	286	86	39
93	338	43	332	98	44	307	91	41	286	85	33
95	334	42	335	100	43	305	91	41	281	84	32
97	344	38	332	96	41	306	89	39	286	83	30
99	340	36	333	98	40	301	89	38	286	84	29
101	337	35	333	99	39	298	89	35	284	85	28
103	340	35	332	98	39	303	89	31	286	84	26
Mean for weeks											
1-13	167		166	99		163	98		159	95	
14-52	245		242	99		233	95		221	90	
53-103	321		318	99		295	92		276	86	

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the kidney, liver, and lung and incidences of mononuclear cell leukemia. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male F344/N rats and Appendix B for female F344/N rats.

Kidney: In the standard evaluation, the number of renal tubule adenomas in male rats exposed to 400 ppm was significantly greater than in the controls and exceeded the historical control range (Tables 7, A3, and A4). One renal tubule carcinoma was observed in a 100 ppm male. Additional step sections of kidneys were prepared from residual wet tissue so that each kidney yielded four additional sections spaced 1 mm apart. The step sections did not reveal additional carcinomas, but additional adenomas were observed in each group of exposed and control males (Table 7). The incidence of renal tubule hyperplasia was increased in 400 ppm males in single sections compared to controls (Tables 7 and A5).

Renal tubule hyperplasia consisted of multiple layers rather than the normal single layer of epithelium, frequently resulting in an increased tubule diameter (Plate 1). Severity of hyperplasia depended on the number of layers and the complexity of their patterns. Some had papillary projections, but cells retained their orientation to the basement membrane. The renal tubule adenomas in both single and step sections were typical of those occurring spontaneously. Adenomas were masses of epithelial cells five or more tubule diameters in size (Plate 2). Cells in the adenomas were disorganized and had lost their orientation to the tubule basement membrane. The renal tubule carcinoma observed in the single sections was approximately 3 mm in diameter and had densely packed, widely pleomorphic epithelial cells that infiltrated the adjacent parenchyma.

TABLE 7
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Kidney	50	48	50	49
Single Sections (Standard Evaluation)				
Nephropathy[a]	47 (2.3)[b]	47 (2.3)	49 (2.5)	49 (2.6)
Renal Tubule, Hyperplasia	1 (1.0)	0	4 (3.0)	7* (1.7)
Renal Tubule, Adenoma[c] (includes multiple)				
Overall rate[d]	1/50 (2%)	0/48 (0%)	2/50 (4%)	6/49 (12%)
Adjusted rate[e]	2.4%	0.0%	4.9%	15.9%
Terminal rate[f]	1/25 (4%)	0/20 (0%)	1/25 (4%)	2/16 (13%)
First incidence (days)	722 (T)	—[h]	708	644
Poly-3 test[g]	P=0.003	P=0.510N	P=0.498	P=0.042
Renal Tubule, Carcinoma[i]	0	1	0	0
Renal Tubule, Adenoma or Carcinoma[c]				
Overall rate	1/50 (2%)	1/48 (2%)	2/50 (4%)	6/49 (12%)
Adjusted rate	2.4%	2.6%	4.9%	15.9%
Terminal rate	1/25 (4%)	1/20 (5%)	1/25 (4%)	2/16 (13%)
First incidence (days)	722 (T)	722 (T)	708	644
Poly-3 test	P=0.008	P=0.750	P=0.498	P=0.042

TABLE 7
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Step Sections (Extended Evaluation)				
Renal Tubule, Hyperplasia	9 (2.0)	7 (2.1)	11 (3.0)	15 (2.4)
Renal Tubule, Adenoma	1	3	5	9**
Single Sections and Step Sections (Combined)				
Renal Tubule, Hyperplasia	10 (1.9)	7 (2.1)	14 (3.1)	16 (2.4)
Renal Tubule, Adenoma				
Overall rate	2/50 (4%)	3/48 (6%)	6/50 (12%)	10/49 (20%)
Adjusted rate	4.9%	7.6%	14.5%	26.3%
Terminal rate	2/25 (8%)	2/20 (10%)	3/25 (12%)	5/16 (31%)
First incidence (days)	722 (T)	673	627	644
Poly-3 test	P=0.002	P=0.480	P=0.133	P=0.008
Renal Tubule, Carcinoma	0	1	0	0
Renal Tubule, Adenoma or Carcinoma				
Overall rate	2/50 (4%)	4/48 (8%)	6/50 (12%)	10/49 (20%)
Adjusted rate	4.9%	10.2%	14.5%	26.3%
Terminal rate	2/25 (8%)	3/20 (15%)	3/25 (12%)	5/16 (31%)
First incidence (days)	722 (T)	673	627	644
Poly-3 test	P=0.003	P=0.316	P=0.133	P=0.008
Stomach, Glandular	50	49	50	49
Mineralization	0	2 (2.0)	2 (1.5)	8** (2.0)
Parathyroid Gland	50	50	50	48
Hyperplasia	0	1 (2.0)	3 (2.3)	3 (2.0)
Bone	50	50	50	50
Fibrous Osteodystrophy	2 (3.0)	1 (3.0)	4 (2.3)	6 (2.5)

* Significantly different (P 0.05) from the control group by the Poly-3 test
** P 0.01
(T)Terminal sacrifice
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year drinking water studies with untreated control groups (mean ± standard deviation): 1/327 (0.3% ± 0.8%); range, 0%-2%
[d] Number of animals with neoplasm per number of animals with kidney examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by **N**.
[h] Not applicable; no neoplasms in animal group
[i] Historical incidence: 0/327

The severity of nephropathy was not significantly increased in males (Table 7). Incidences of mineralization of the stomach, parathyroid gland hyperplasia, and fibrous osteodystrophy were observed in a few exposed males, and the incidence of stomach mineralization in 400 ppm males was significantly increased compared to controls (Tables 7 and A5). These extrarenal lesions are indicative of kidney disease.

Mononuclear Cell Leukemia: Incidences of mononuclear cell leukemia in female rats were significantly increased in the 200 and 400 ppm groups compared to controls, and the incidence in the 400 ppm group exceeded the historical control range (Tables 8, B3, and B4). In all animals with this neoplasm, neoplastic cells were found in the spleen and usually also in the liver. Infiltrations in the lung, bone marrow, lymph nodes, adrenal gland, and kidney were also common. Incidences of mononuclear cell leukemia in male rats were similar to those in controls (0 ppm, 29/50; 100 ppm, 32/50; 200 ppm, 26/50; 400 ppm, 27/50; Table A3).

TABLE 8
Incidences of Mononuclear Cell Leukemia in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Mononuclear Cell Leukemia[a]				
Overall rate[b]	12/50 (24%)	16/50 (32%)	22/50 (44%)	23/50 (46%)
Adjusted rate[c]	26.5%	34.3%	45.4%	48.7%
Terminal rate[d]	8/32 (25%)	12/37 (32%)	8/29 (28%)	5/26 (19%)
First incidence (days)	636	546	496	380
Poly-3 test[e]	P=0.013	P=0.279	P=0.043	P=0.020

[a] Historical incidence for 2-year drinking water studies with untreated control groups (mean ± standard deviation): 102/330 (30.9% ± 10.0%); range, 16%-44%
[b] Number of animals necropsied
[c] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[d] Observed incidence at terminal kill
[e] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.

Liver: Incidences of hepatocellular neoplasms were not significantly increased in exposed rats compared to controls, but exposure concentration-related nonneoplastic liver lesions were observed (Tables 9, A5, and B5). Incidences of centrilobular cytomegaly and cytoplasmic vacuolization were increased in males exposed to 200 or 400 ppm and females exposed to 400 ppm relative to controls. In 400 ppm males, incidences of periportal fibrosis, fibrosis, and centrilobular degeneration and necrosis were significantly increased relative to controls. The incidence of centrilobular degeneration was increased in 400 ppm females compared to controls. Bile duct hyperplasia was observed in control and exposed males and females, and the incidences were significantly increased in exposed females compared to controls. Incidences of pigmentation increased compared to controls in all exposed groups of males and in 400 ppm females. Incidences of basophilic foci were decreased relative to controls in 200 and 400 ppm males and all exposed groups of females. The incidence of clear cell foci relative to controls was decreased in 100 ppm males; incidences of clear cell foci were increased relative to controls in 200 and 400 ppm females. The incidence of eosinophilic foci was increased relative to controls in 100 ppm males.

Centrilobular cytomegaly consisted of an increased amount of cytoplasm containing varying amounts of homogeneous eosinophilic material that enlarged hepatocytes. Cytoplasmic vacuolization referred to vacuolized hepatocytes in noncentrilobular areas. Periportal fibrosis consisted of bands of fibrous connective tissue in portal areas. Fibrosis was defined as fibrous connective tissue under the capsule of the liver and extending downward along the vasculature. Bile duct hyperplasia was a cluster of six or more bile ducts. Pigmentation was yellowish brown material in

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm		100 ppm		200 ppm		400 ppm	
Male								
Number Examined Microscopically	50		49		50		50	
Basophilic Focus[a]	12		5		0**		1**	
Clear Cell Focus	7		1*		7		4	
Eosinophilic Focus	14		23*		23		13	
Centrilobular, Cytomegaly	0		4	(1.3)[b]	8**	(1.3)	6*	(2.0)
Vacuolization Cytoplasmic	4	(1.5)	6	(1.8)	13*	(1.7)	17**	(2.4)
Periportal Fibrosis	0		0		2	(2.5)	29**	(1.8)
Fibrosis	1	(2.0)	1	(2.0)	1	(1.0)	10**	(1.6)
Centrilobular, Degeneration	1	(2.0)	3	(2.3)	2	(2.0)	8*	(2.1)
Centrilobular, Necrosis	0		3	(1.7)	0		5*	(2.2)
Bile Duct, Hyperplasia	46	(1.4)	43	(1.5)	44	(1.6)	49	(1.6)
Pigmentation	4	(1.0)	11*	(1.3)	20**	(1.3)	25**	(2.0)
Hepatocellular Adenoma	1		1		0		3	
Hepatocellular Carcinoma	0		0		1		0	
Hepatocellular Adenoma or Carcinoma	1		1		1		3	
Female								
Number Examined Microscopically	50		50		50		50	
Basophilic Focus	38		28*		11**		0**	
Clear Cell Focus	4		9		11*		16**	
Eosinophilic Focus	19		24		22		15	
Centrilobular, Cytomegaly	0		1	(1.0)	4	(1.0)	20**	(1.4)
Vacuolization Cytoplasmic	10	(1.8)	7	(1.0)	9	(1.8)	18*	(1.6)
Centrilobular, Degeneration	1	(2.0)	2	(2.5)	2	(1.5)	7*	(1.1)
Bile Duct, Hyperplasia	20	(1.0)	29*	(1.1)	34**	(1.0)	29*	(1.0)
Pigmentation	6	(1.5)	2	(1.5)	6	(2.3)	17**	(1.6)
Hepatocellular Adenoma	1		0		1		0	

* Significantly different (P 0.05) from the control group by the Poly-3 test
** P 0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

macrophages, often present in areas of fibrosis. Centrilobular degeneration was used to denote vacuolated hepatocytes in the center of hepatic lobules.

Lung: Incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in males occurred with a positive trend (1/50, 0/50, 2/50, 4/50; Table A3). Alveolar epithelial hyperplasia was also observed in the 100 and 400 ppm groups (0/50, 3/50, 0/50, 3/50; Table A5). Although these neoplasms are relatively uncommon, incidences up to eight of 50 have occurred in untreated control groups from other recent NTP 2-year carcinogenicity studies. This marginally increased neoplasm incidence was not considered to be chemical-related.

WISTAR RATS

13-WEEK STUDY

One male rat exposed to 500 ppm died during the first week of the study (Table 10). Final mean body weights and body weight gains of rats exposed to 250, 500, or 1,000 ppm were significantly less than those of the controls. Water consumption by rats exposed to 1,000 ppm was lower than that by controls. Drinking water concentrations of 50, 100, 250, 500, or 1,000 ppm pyridine resulted in average daily doses of 5, 10, 30, 60, or 100 mg/kg. There were no treatment-related clinical findings.

TABLE 10
Survival, Body Weights, and Water Consumption of Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Water Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
0	10/10	161 ± 3	511 ± 9	350 ± 9		169	120
50	10/10	161 ± 3	476 ± 13	315 ± 11	93	152	118
100	10/10	159 ± 3	490 ± 7	331 ± 8	96	148	116
250	10/10	159 ± 3	463 ± 17**	304 ± 16**	91	136	95
500	9/10[d]	157 ± 4	443 ± 8**	286 ± 6**	87	141	127
1,000	10/10	159 ± 3	420 ± 15**	260 ± 14**	82	111	74

** Significantly different (P 0.01) from the control group by Williams' test
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] Water consumption is expressed as grams of water consumed per kg body weight per day.
[d] Week of death: 1

The hematology and clinical chemistry data for Wistar rats are presented in Table G2. Similar to male F344/N rats, an erythrocytosis, demonstrated by increased hematocrit values, hemoglobin concentrations, and erythrocyte counts, occurred in 500 and 1,000 ppm rats on day 5. An erythrocytosis would be consistent with dehydration, which can cause a relative erythrocytosis due to decreased blood volume and hemoconcentration. Hemoconcentration would be supported by the increased albumin concentration in 1,000 ppm rats relative to controls. Additionally, urea nitrogen concentrations were increased relative to controls in 500 and 1,000 ppm rats on days 5 and 20; creatinine concentration, another marker of renal function, was unaffected. Urea nitrogen concentration can be influenced by many extrarenal factors: high protein diets, dehydration, liver function, animal health, and nutritional status (Finco, 1989). Serum creatinine, a product of muscle metabolism, is not as affected by extrarenal factors (Ragan, 1989). A nonrenal effect, such as dehydration caused by decreased water intake due to poor palatability of dosed water, could result in a urea nitrogen concentration increase, while creatinine concentration remains unchanged.

Also similar to F344/N rats, there was evidence of hepatocellular injury and/or altered hepatic function demonstrated by increased serum alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations at all time points in 500 and 1,000 ppm rats relative to controls. Decreased alkaline phosphatase activity relative to controls was observed, but with less consistency, in 250 and 1,000 ppm rats.

Organ weights of exposed rats were not significantly different from those of controls (Table H2). Plasma concentrations of pyridine increased with increasing dose (Table J2).

Incidences of centrilobular degeneration, hypertrophy, chronic inflammation, and pigmentation in the liver of rats exposed to 500 or 1,000 ppm were significantly increased relative to controls (Table 11). Two types of enlarged centrilobular hepatocytes were separately diagnosed. Degeneration consisted of mildly to moderately enlarged, palely stained hepatocytes, primarily centrilobular, that had lacy to vacuolated cytoplasm containing an eosinophilic granular to flocculent material. Hypertrophy was a minimal increase in size of centrilobular hepatocytes without vacuolated or lacy cytoplasm. Chronic inflammation consisted of lymphocytes, macrophages, and fibrous connective tissue that was primarily centrilobular and bridged across lobules in more severe cases. The macrophages often contained a yellow-brown pigment that special stains showed had characteristics of both lipofuscin and hemosiderin. The pigment was positive with PAS, Perl's, and Schmorl's staining but was acid-fast negative.

Incidences of kidney lesions in exposed rats were not significantly different from those of controls (Table 11). Many lesions (protein casts, inflammation mineralization, and regeneration of renal tubule epithelium) are components of spontaneous nephropathy that is common in male rats. The incidences of spontaneous nephropathy in control Wistar males were high, and possible nephrotoxicity was not clear. Granular casts, which indicate more severe renal tubule damage than protein casts, were noted in one rat in the 1,000 ppm group. The incidence, but not the severity, of hyaline degeneration was increased, although not significantly, in the 1,000 ppm group. Hyaline degeneration refers to eosinophilic refractile protein material in the cytoplasm of renal tubule epithelium. Immunohistochemistry for α2u-globulin was positive in all males tested.

Exposure Concentration Selection Rationale: The highest exposure concentration selected for the 2-year Wistar rat study was 400 ppm based on increased incidences and severities of liver lesions (including increased alanine aminotransferase and sorbitol dehydrogenase activities and bile acid concentrations) in rats exposed to 500 or 1,000 ppm compared to controls. Pyridine plasma levels were measured at the end of the 13-week studies in rats (Tables J1 and J2). A clear inflection point in the serum levels could not be determined from the pyridine data, but the serum levels at 500 and 1,000 ppm appeared disproportionally high when compared to those at 100 and 250 ppm.

TABLE 11
Incidences of Selected Nonneoplastic Lesions in Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Liver[a]	10	10	10	10	9	10
Centrilobular, Degeneration[b]	0	0	0	0	9** (1.7)[c]	9** (1.4)
Hypertrophy	0	0	0	0	9** (1.0)	10** (1.0)
Inflammation, Chronic	0	0	0	2 (1.0)	9** (1.7)	9** (2.2)
Pigmentation	0	0	0	0	9** (1.0)	9** (1.3)
Kidney	10	10	10	10	9	10
Casts	3 (1.0)	3 (1.0)	4 (1.0)	4 (1.5)	4 (1.0)	5 (1.0)
Inflammation, Chronic	0	1 (1.0)	1 (2.0)	0	0	2 (1.0)
Mineralization	7 (1.0)	5 (1.2)	4 (1.0)	8 (1.3)	8 (1.0)	10 (1.0)
Renal Tubule, Regeneration	5 (1.0)	6 (1.0)	5 (1.0)	9 (1.0)	7 (1.0)	8 (1.1)
Casts Granular	0	0	0	0	0	1 (1.0)
Renal Tubule, Hyaline Degeneration	2 (1.0)	0	0	2 (1.0)	3 (1.0)	6 (1.0)

** Significantly different (P 0.01) from the control group by the Fisher exact test
[a] Number examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesion in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male Wistar rats are shown in Table 12 and in the Kaplan-Meier survival curves (Figure 4). Survival of rats exposed to 200 or 400 ppm was significantly less than that of the controls.

Body Weights, Water and Compound Consumption, and Clinical Findings

Mean body weights of rats exposed to 100, 200, or 400 ppm were significantly less than controls (Figure 5 and Table 13). Water consumption by exposed rats was similar to that by controls (Table L3). Drinking water concentrations of 100, 200, or 400 ppm pyridine resulted in average daily doses of 8, 17, or 36 mg/kg. There were no treatment-related clinical findings.

TABLE 12
Survival of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Animals initially in study	50	50	50	50
Moribund	2	9	9	10
Natural deaths	26	27	30	33
Animals surviving to study termination	22	14	11	7
Percent probability of survival at end of study[a]	44	28	22	14
Mean survival (days)[b]	661	625	618	577
Survival analysis[c]	P<0.001	P=0.090	P=0.020	P<0.001

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns.

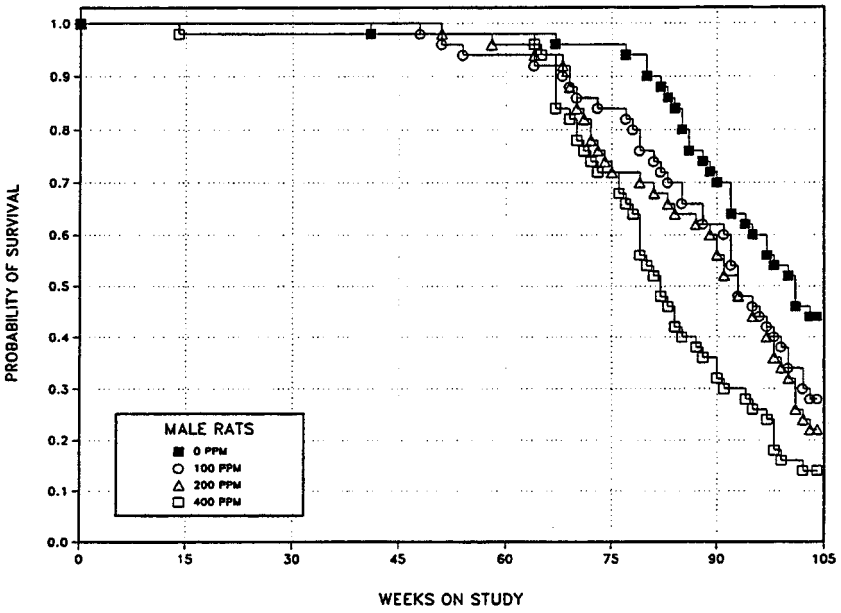


FIGURE 4
Kaplan-Meier Survival Curves for Male Wistar Rats Exposed to Pyridine in Drinking Water for 2 Years

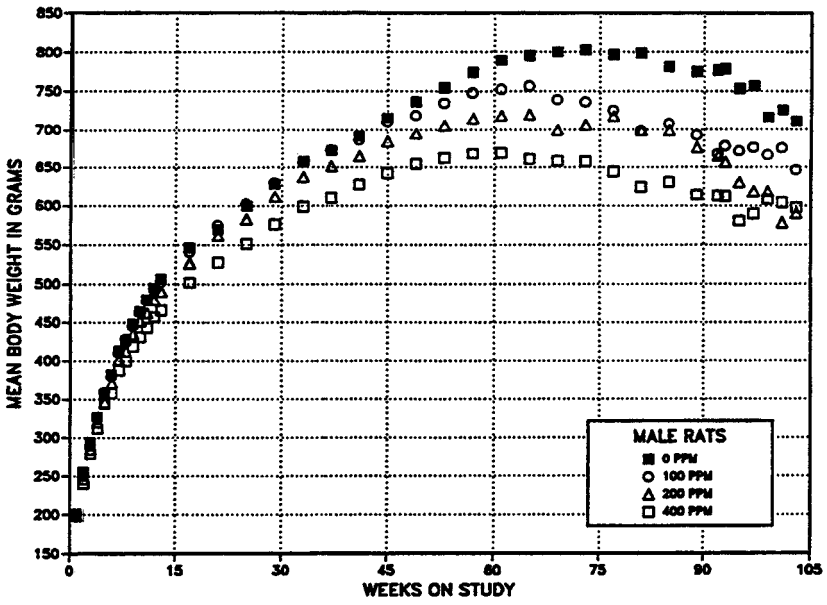


FIGURE 5
Growth Curves for Male Wistar Rats Exposed to Pyridine in Drinking Water for 2 Years

TABLE 13
Mean Body Weights and Survival of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

Weeks on Study	0 ppm		100 ppm			200 ppm			400 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	201	50	198	98	50	199	99	50	198	98	50
2	255	50	250	98	50	246	97	50	240	94	50
3	294	50	289	98	50	285	97	50	280	95	50
4	327	50	326	100	50	321	98	50	312	95	50
5	357	50	359	101	50	347	97	50	345	96	50
6	382	50	380	99	50	372	97	50	358	94	50
7	413	50	411	100	50	402	97	50	388	94	50
8	426	50	428	101	50	412	97	50	400	94	50
9	448	50	446	100	50	435	97	50	419	94	50
10	464	50	463	100	50	452	97	50	431	93	50
11	479	50	478	100	50	463	97	50	443	93	50
12	494	50	492	100	50	479	97	50	457	93	50
13	506	50	503	99	50	490	97	50	466	92	50
17	546	50	542	99	50	527	97	50	502	92	49
21	569	50	575	101	50	562	99	50	528	93	49
25	599	50	602	101	50	583	97	50	552	92	49
29	627	50	630	100	50	612	98	50	576	92	49
33	658	50	657	100	50	638	97	50	599	91	49
37	672	50	673	100	50	651	97	50	610	91	49
41	691	50	686	99	50	664	96	50	627	91	49
45	715	49	711	99	50	684	96	50	642	90	49
49	736	49	719	98	49	695	94	50	654	89	49
53	755	49	735	97	48	705	93	49	662	88	49
57	774	49	748	97	47	714	92	49	668	86	49
61	789	49	753	95	47	718	91	48	669	85	49
65	795	49	757	95	46	720	91	47	661	83	48
69	800	48	739	92	45	699	87	46	658	82	42
73	803	48	736	92	43	706	88	39	657	82	37
77	797	48	725	91	42	717	90	36	644	81	34
81	799	45	698	87	38	698	88	34	624	78	27
85	782	41	707	91	35	699	89	32	630	81	21
89	775	37	692	89	31	676	87	31	614	79	18
92	777	35	667	86	29	665	86	26	613	79	15
93	779	32	678	87	27	657	84	25	612	79	15
95	753	31	671	89	24	630	84	24	581	77	14
97	757	30	675	89	22	618	82	22	590	78	13
99	715	27	666	93	20	618	86	17	609	85	8
101	725	25	675	93	17	578	80	16	604	83	8
103	710	23	646	91	15	591	83	12	598	84	7
Mean for weeks											
1-13	388		386	99		377	97		364	94	
14-52	646		644	100		624	97		588	91	
53-103	770		704	91		671	87		629	82	

Pathology and Statistical Analyses

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

Testis: The incidence of testicular interstitial cell adenoma in rats exposed to 400 ppm was significantly increased compared to controls (Tables 14 and C3). Interstitial cell hyperplasia was observed in control and exposed groups and the incidences were slightly, but not significantly, increased in rats exposed to 200 or 400 ppm (Tables 14 and C4). The appearance of interstitial cells was similar in both hyperplasia and adenoma and the diagnoses were based on size. Some interstitial cell neoplasms nearly replaced normal tissue (Plate 3). Hyperplasia was defined as a proliferation no larger than the diameter of a seminiferous tubule, and interstitial cell adenoma was larger.

TABLE 14
Incidences of Neoplasms and Nonneoplastic Lesions of the Testis in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Number Examined Microscopically	50	49	49	50
Interstitial Cell Hyperplasia[a]	3 (2.3)[b]	4 (2.0)	7 (2.3)	7 (2.9)
Adenoma (interstitial cell)				
Overall rate[c]	5/50 (10%)	6/49 (12%)	4/49 (8%)	12/50 (24%)
Adjusted rate[d]	12.3%	16.9%	11.9%	36.6%
Terminal rate[e]	3/22 (14%)	3/14 (21%)	1/11 (9%)	3/7 (43%)
First incidence (days)	592	486	660	464
Poly-3 test[f]	P=0.008	P=0.404	P=0.618N	P=0.012

[a] Number examined microscopically
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Number of animals with neoplasm per number of animals with testis examined microscopically
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by **N**.

Kidney: Incidences of renal tubule neoplasms in exposed rats were not significantly different from control incidences in the standard evaluation (Tables 15, C1, and C3). Renal tubule adenomas were observed in control and exposed rats and were similar to those observed in F344/N rats. Cells in renal tubule adenomas were disorganized and had lost their orientation to the tubule basement membrane. One renal tubule carcinoma approximately 5 cm in diameter was observed in the 400 ppm group. This neoplasm had multiple large, solid, irregular proliferations of densely packed, enlarged epithelial cells interspersed with areas of necrosis and inflammatory cells. In an extended evaluation, kidneys were step sectioned because of the carcinoma in the 400 ppm group, because of increased incidences of renal tubule hyperplasia in 100 ppm males relative to controls (Tables 15 and C4), and for comparison with F344/N male rats. Step sections were prepared from residual wet tissue so that each kidney yielded four additional sections spaced 1 mm apart. Step sectioning did not detect any significant treatment-related increase in incidences of renal tubule hyperplasia, adenoma, or carcinoma.

TABLE 15
Incidences of Selected Neoplasms and Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm		100 ppm		200 ppm		400 ppm	
Kidney[a]	50		50		50		50	
Single Sections (Standard Evaluation)								
Renal Tubule, Hyperplasia[b]	6	(1.7)[c]	17**	(2.1)	8	(2.4)	5	(2.6)
Nephropathy	50	(3.3)	50	(3.6)	50	(3.4)	50	(3.2)
Cyst	21	(2.0)	31	(2.5)	19	(2.5)	16	(2.1)
Mineralization	8	(1.5)	17	(2.1)	8	(1.9)	5	(1.4)
Inflammation, Acute	0		2	(3.0)	0		1	(1.0)
Renal Tubule, Adenoma (includes multiple)	2		5		1		2	
Renal Tubule, Carcinoma	0		0		0		1	
Renal Tubule, Adenoma or Carcinoma	2		5		1		3	
Step Sections (Extended Evaluation)								
Renal Tubule, Hyperplasia	5	(2.2)	13	(2.8)	10	(2.1)	9	(2.8)
Renal Tubule, Oncocytoma	0		1		0		0	
Renal Tubule, Adenoma	1		2		4		2	
Renal Tubule, Carcinoma	0		0		1		0	
Renal Tubule, Adenoma or Carcinoma	1		2		5		2	
Single Sections and Step Sections (Combined)								
Renal Tubule, Hyperplasia	10	(1.8)	22	(2.5)	14	(2.4)	13	(2.8)
Renal Tubule, Adenoma	3		6		5		4	
Renal Tubule, Carcinoma	0		0		1		1	
Renal Tubule, Adenoma or Carcinoma	3		6		6		4	
Stomach, Glandular	49		50		48		48	
Mineralization	8	(2.8)	25**	(2.8)	16*	(2.5)	6	(2.7)
Parathyroid Gland	48		47		48		47	
Hyperplasia	16	(3.3)	32**	(3.2)	29**	(3.0)	12	(2.5)
Bone	50		50		50		50	
Fibrous Osteodystrophy	10	(2.8)	21*	(2.8)	16	(2.9)	6	(1.7)

* Significantly different (P 0.05) from the control group by the Poly-3 test
** P 0.01
[a] Number examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Hyperplasia consisted of multiple layers rather than the normal single layer of cells, frequently with an increased diameter of the tubule. Severity of hyperplasia depended on the number of layers and the complexity of their patterns. Some had papillary projections, but all maintained their orientation to the basement membrane. Nephropathy was observed in all control and exposed rats (Tables 15 and C4). Nephropathy is a common spontaneous kidney disease that increases in severity with increasing age. Lesions associated with nephropathy include renal cysts, mineralization of basement membranes, and inflammation of the renal parenchyma (Tables 15 and C4). Nephropathy was moderately severe in control and exposed groups of Wistar males and was considered to be the cause of their high mortality in this study. Probably because the kidney lesions were so severe in the controls, no treatment-related increase in the severity of nephropathy could be detected. However, incidences of extrarenal lesions of kidney disease such

as mineralization in the glandular stomach, parathyroid gland hyperplasia, and fibrous osteodystrophy were generally increased in rats exposed to 100 or 200 ppm compared to controls. These extrarenal lesions suggest that nephropathy was generally more severe in these groups. Kidney disease in 400 ppm rats may have been less severe because of their reduced survival and lower body weights.

Liver: Incidences of hepatocellular neoplasms were not increased in exposed Wistar rats compared to controls, but exposure-related nonneoplastic liver lesions were observed (Tables 16, C1, and C4). Incidences of centrilobular degeneration (cytoplasmic vacuolization) occurred in exposed groups and increased with increasing exposure concentration, and the severities of cytoplasmic vacuolization were slightly increased in the exposed groups. The incidence of centrilobular necrosis was increased in the 400 ppm group compared to controls. Incidences of fibrosis and periportal fibrosis were increased in the 200 and 400 ppm groups relative to controls. Incidences of pigmentation were increased in each exposed group compared to controls. The incidences of eosinophilic foci decreased compared to controls in rats exposed to 200 or 400 ppm. In general, these liver lesions were more severe in Wistar rats than in F344/N rats.

The overall structure was maintained, but exposed rats tended to have centrilobular hepatocytes that were necrotic or had an altered appearance with an increase in fibrous connective tissue in portal areas and extending downward from the liver capsule. Fibrosis was defined as fibrous connective tissue under the capsule of the liver and extending downward along the vasculature. Periportal fibrosis consisted of bands of fibrous connective tissue in portal areas. Pigmentation consisted of yellow-brown material in macrophages.

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm		100 ppm		200 ppm		400 ppm	
Number Examined Microscopically	50		50		50		50	
Basophilic Focus[a]	0		0		0		2	
Clear Cell Focus	15		7		8		8	
Eosinophilic Focus	14		12		4*		2**	
Vacuolization Cytoplasmic	18	(1.6)[b]	18	(1.9)	12	(1.8)	15	(1.9)
Centrilobular, Degeneration	1	(1.0)	15**	(1.8)	25**	(2.1)	33**	(2.4)
Centrilobular, Necrosis	5	(2.8)	6	(2.0)	4	(2.8)	23**	(2.5)
Fibrosis	1	(2.0)	5	(1.4)	26**	(1.6)	31**	(1.8)
Periportal Fibrosis	0		0		5*	(2.0)	7**	(2.4)
Pigmentation	6	(1.5)	15*	(1.3)	34**	(1.8)	42**	(1.8)
Hepatocellular Adenoma	2		0		1		0	

* Significantly different (P 0.05) from the control group by the Poly-3 test
** P 0.01
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

MICE

13-WEEK STUDY

One female mouse exposed to 250 ppm died during week 2 (Table 17). Final mean body weights and body weight gains of female mice exposed to 1,000 ppm were significantly less than those of controls; final mean body weights and body weight gains of all other exposed groups were similar to controls. Water consumption by exposed female mice was lower than that by controls at week 1 but was generally slightly higher than controls at week 13; water consumption by exposed and control male mice was similar. Estimated water consumption declined over the course of the study. Drinking water concentrations of 50, 100, 250, 500, or 1,000 ppm pyridine resulted in average daily doses of 10, 20, 50, 85, or 160 mg/kg for males and 10, 20, 60, 100, or 190 mg/kg for females. There were no treatment-related clinical findings.

TABLE 17
Survival, Body Weights, and Water Consumption of Mice in the 13-Week Drinking Water Study of Pyridine

Concentration (ppm)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)	Water Consumption[c]	
		Initial	Final	Change		Week 1	Week 13
Male							
0	10/10	23.7 ± 0.4	39.4 ± 0.9	15.7 ± 0.8		395	147
50	10/10	23.5 ± 0.3	38.4 ± 1.1	14.9 ± 1.0	97	349	162
100	10/10	23.8 ± 0.3	39.3 ± 0.9	15.4 ± 0.8	100	318	186
250	10/10	23.8 ± 0.3	40.2 ± 1.1	16.3 ± 1.0	102	364	167
500	10/10	23.4 ± 0.3	39.1 ± 0.8	15.8 ± 0.6	99	336	146
1,000	10/10	23.7 ± 0.3	37.2 ± 0.7	13.5 ± 0.6	94	377	121
Female							
0	10/10	19.0 ± 0.3	33.6 ± 1.1	14.6 ± 1.0		441	149
50	10/10	18.7 ± 0.3	37.4 ± 1.1	18.8 ± 1.1	111	278	147
100	10/10	18.9 ± 0.1	34.4 ± 0.9	15.5 ± 0.8	102	271	192
250	9/10[d]	18.7 ± 0.3	34.2 ± 1.1	15.4 ± 1.0	102	375	214
500	10/10	19.4 ± 0.3	33.2 ± 0.9	13.8 ± 0.8	99	292	172
1,000	10/10	18.7 ± 0.2	29.7 ± 0.9**	11.0 ± 0.8**	88	201	195

** Significantly different (P 0.01) from the control group by Williams' or Dunnett's test
[a] Number of animals surviving at 13 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the studies.
[c] Water consumption is expressed as grams of water consumed per kg body weight per day.
[d] Week of death: 2

Sperm motility in exposed male mice was decreased relative to controls (Table I3). There were no significant differences in estrous cycle lengths between control and exposed females (Table I4).

Absolute and relative liver weights were significantly increased relative to controls in males exposed to 100 ppm or greater and in 250 and 500 ppm females (Table H3). No histopathologic lesions were observed in the liver despite the increased liver weights, nor were any chemical-related lesions observed in any other tissue.

Exposure Concentration Selection Rationale: The highest exposure concentration for the 2-year male mouse study was set at 1,000 ppm based on the lack of target organ lesions in the 13-week study. The highest exposure concentration for the 2-year female mouse study was set at 500 ppm based on decreased mean body weight gains relative to controls and decreased water consumption.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 18 and in the Kaplan-Meier survival curves (Figure 6). Survival of exposed males and females was similar to that of the controls.

Body Weights, Water and Compound Consumption, and Clinical Findings

Mean body weights of exposed males were similar to those of the controls; mean body weights of 250 and 500 ppm females were less than controls (Tables 19 and 20; Figure 7). Water consumption by males exposed to 250 or 500 ppm was generally greater than that by controls during the last year of the study; male mice exposed to 1,000 ppm consumed less water than controls throughout the study (Table L4). Water consumption by exposed females was generally lower than that by controls during the first year of the study, but greater than controls during the second year (Table L5). Drinking water concentrations of 250, 500, or 1,000 ppm pyridine resulted in average daily doses of 35, 65, or 110 mg/kg for male mice and concentrations of 125, 250, or 500 ppm pyridine resulted in average daily doses of 15, 35, or 70 mg/kg for female mice. There were no treatment-related clinical findings.

TABLE 18
Survival of Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Male				
Animals initially in study	50	50	50	50
Accidental deaths[a]	2	1	1	3
Other[a]	0	0	1	0
Moribund	2	3	3	1
Natural deaths	11	18	11	11
Animals surviving to study termination	35	28	34	35
Percent probability of survival at end of study[b]	73	57	71	75
Mean survival (days)[c]	685	660	670	656
Survival analysis[d]	P=0.507N	P=0.138	P=0.928	P=1.000N
	0 ppm	**125 ppm**	**250 ppm**	**500 ppm**
Female				
Animals initially in study	50	50	50	50
Accidental deaths[a]	3	6	4	5
Moribund	3	2	3	5
Natural deaths	12	12	21	11
Animals surviving to study termination	32	30	22	29
Percent probability of survival at end of study	68	68	48	65
Mean survival (days)	671	640	638	624
Survival analysis	P=0.487	P=1.000N	P=0.090	P=0.755

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[d] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the exposed group columns. A negative trend or lower mortality in an exposure group is indicated by **N**.

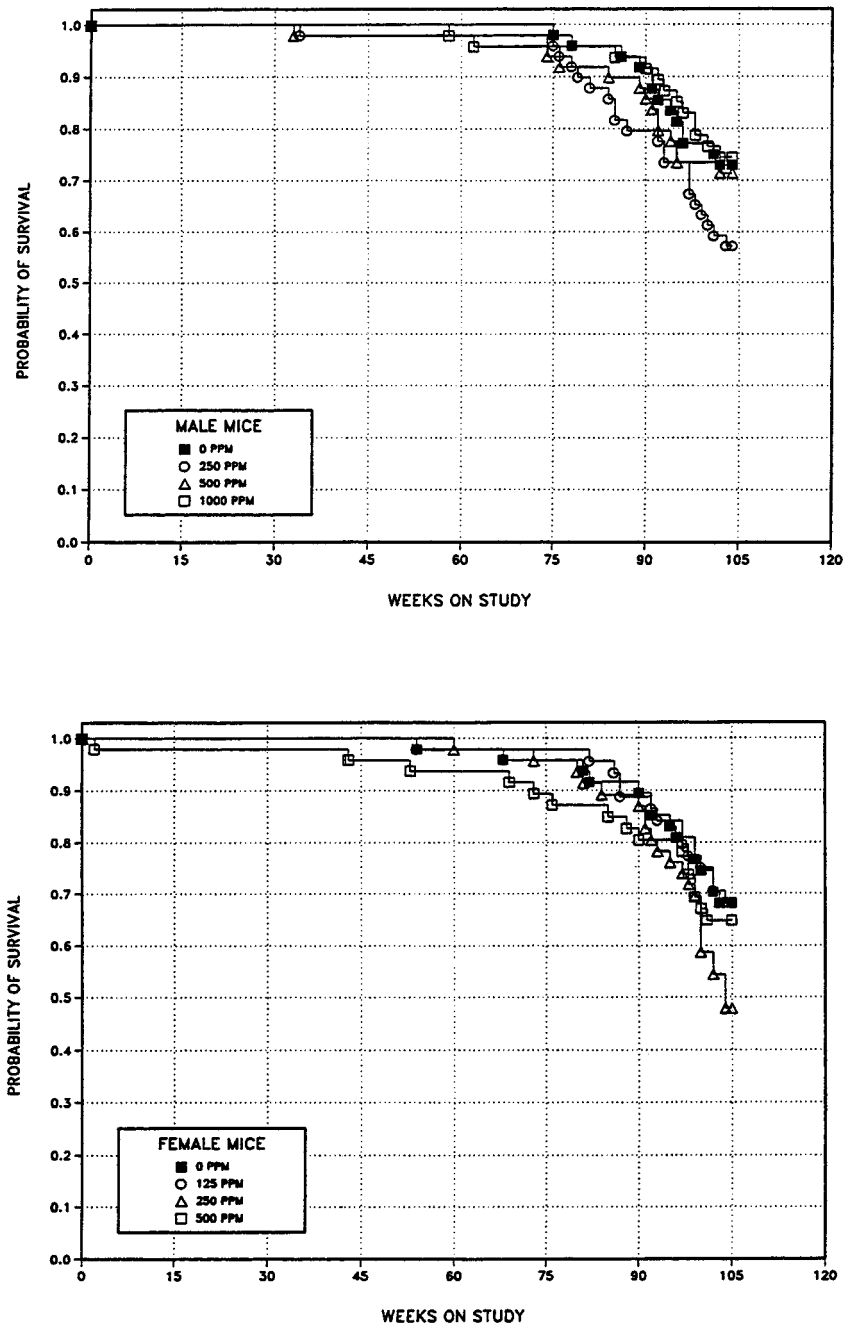


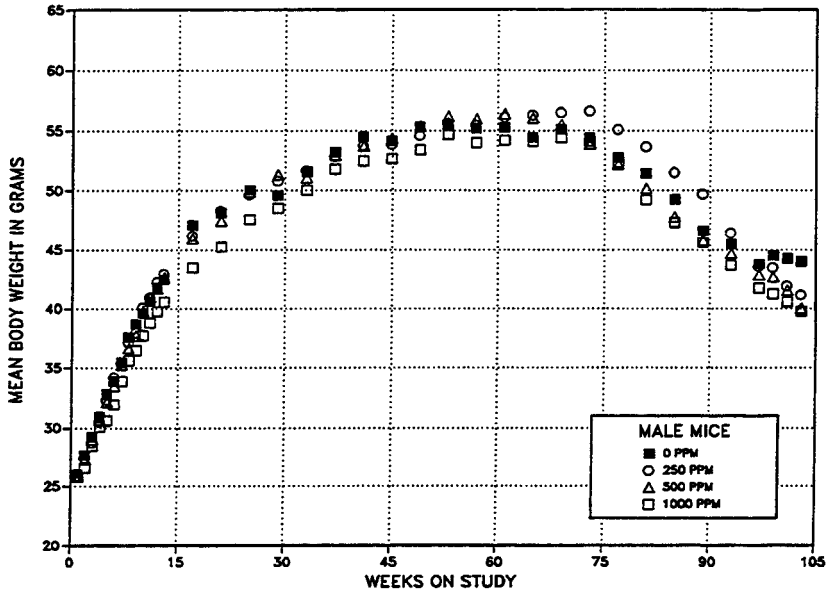
FIGURE 6
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Pyridine in Drinking Water for 2 Years

TABLE 19
Mean Body Weights and Survival of Male Mice in the 2-Year Drinking Water Study of Pyridine

Weeks on Study	0 ppm		250 ppm			500 ppm			1,000 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	26.1	50	25.9	99	50	25.8	99	50	25.8	99	50
2	27.6	50	27.4	99	49	27.3	99	49	26.6	96	49
3	29.2	50	28.7	98	49	29.0	99	49	28.4	97	48
4	30.9	50	30.5	99	49	30.7	99	49	30.1	97	48
5	32.8	50	32.3	99	49	32.2	98	49	30.6	93	48
6	33.9	50	34.2	101	49	33.5	99	49	32.0	94	48
7	35.4	50	35.4	100	49	35.3	100	49	33.9	96	48
8	37.6	50	37.1	99	49	36.7	98	49	35.6	95	48
9	38.7	50	37.9	98	49	37.7	97	49	36.5	94	48
10	39.6	50	40.1	101	49	39.8	101	49	37.7	95	47
11	40.6	50	41.0	101	49	41.0	101	49	38.8	96	47
12	41.8	50	42.3	101	49	41.7	100	49	39.8	95	47
13	42.4	50	42.9	101	49	42.7	101	49	40.6	96	47
17	47.0	50	46.2	98	49	45.9	98	49	43.5	93	47
21	48.1	49	48.3	100	49	47.4	99	49	45.2	94	47
25	50.0	49	49.6	99	49	49.9	100	49	47.5	95	47
29	49.6	49	50.8	102	49	51.3	103	49	48.5	98	47
33	51.6	49	51.7	100	49	51.1	99	49	50.0	97	47
37	53.2	49	52.9	99	48	53.0	100	48	51.8	97	47
41	54.5	49	53.8	99	48	53.7	99	48	52.5	96	47
45	54.1	49	53.9	100	48	54.4	101	48	52.7	97	47
49	55.3	49	54.6	99	48	55.4	100	48	53.4	97	47
53	55.4	49	55.6	100	48	56.2	101	48	54.7	99	47
57	55.2	49	55.4	100	48	56.0	101	48	54.0	98	47
61	55.2	49	56.1	102	48	56.4	102	48	54.2	98	46
65	54.4	49	56.3	104	48	56.1	103	48	54.1	99	45
69	55.1	49	56.5	103	48	55.5	101	48	54.4	99	45
73	54.4	49	56.6	104	48	53.9	99	48	54.1	99	45
77	52.8	48	55.1	104	46	52.2	99	45	52.4	99	45
81	51.4	47	53.7	105	44	50.2	98	45	49.2	96	45
85	49.2	46	51.5	105	42	47.8	97	44	47.3	96	45
89	46.6	45	49.7	107	39	45.8	98	44	45.6	98	44
93	45.5	41	46.4	102	37	44.7	98	39	43.7	96	42
97	43.8	37	43.6	100	36	42.9	98	36	41.8	95	39
99	44.5	37	43.5	98	32	42.7	96	36	41.2	93	37
101	44.2	37	41.9	95	30	41.6	94	36	40.6	92	36
103	44.0	35	41.2	94	28	40.0	91	35	39.8	91	35
Mean for weeks											
1-13	35.1		35.1	100		34.9	99		33.6	96	
14-52	51.5		51.3	100		51.3	100		49.5	96	
53-103	50.1		50.9	102		49.5	99		48.5	97	

TABLE 20
Mean Body Weights and Survival of Female Mice in the 2-Year Drinking Water Study of Pyridine

Weeks on Study	0 ppm		125 ppm			250 ppm			500 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	20.8	50	20.7	100	50	20.6	99	50	20.5	99	50
2	21.8	50	21.4	98	49	21.6	99	49	21.5	99	50
3	23.2	50	22.8	98	49	22.8	98	49	22.6	97	47
4	24.1	50	24.0	100	47	23.9	99	49	23.7	98	47
5	25.5	50	25.3	99	47	25.5	100	49	25.6	100	47
6	26.7	50	26.5	99	47	26.3	99	48	26.9	101	47
7	28.2	50	28.4	101	47	28.8	102	47	28.5	101	47
8	29.6	50	29.9	101	47	29.8	101	47	30.0	101	47
9	31.1	50	30.1	97	47	30.8	99	47	30.4	98	47
10	31.7	49	32.0	101	47	32.7	103	47	32.9	104	47
11	33.3	49	33.2	100	47	33.7	101	47	33.7	101	47
12	34.1	49	34.2	100	47	35.2	103	47	35.1	103	47
13	35.8	49	35.5	99	47	36.5	102	47	36.3	101	47
17	40.2	49	39.4	98	47	40.5	101	47	40.4	101	47
21	41.1	49	40.0	97	47	41.6	101	47	41.4	101	47
25	45.9	48	44.2	96	47	45.8	100	47	45.1	98	47
29	45.7	48	44.9	98	46	47.2	103	46	46.5	102	46
33	49.1	48	47.7	97	46	49.5	101	46	48.7	99	46
37	51.0	48	49.4	97	46	51.0	100	46	50.1	98	46
41	53.1	48	51.1	96	46	53.2	100	46	52.0	98	46
45	54.0	48	52.5	97	46	54.1	100	46	52.2	97	45
49	56.2	48	54.5	97	46	55.6	99	46	54.4	97	45
53	56.9	48	55.6	98	46	57.1	100	46	55.5	98	45
57	58.2	47	56.4	97	45	58.0	100	46	56.8	98	44
61	59.5	47	57.9	97	44	59.3	100	45	58.1	98	44
65	59.9	47	58.5	98	44	61.0	102	45	58.6	98	43
69	61.6	46	59.3	96	44	62.1	101	45	58.2	95	43
73	62.8	46	60.2	96	44	62.2	99	45	58.0	92	42
77	63.3	46	61.0	96	44	61.9	98	44	55.4	88	40
81	62.2	45	60.3	97	43	60.4	97	43	51.6	83	40
85	61.1	43	58.6	96	42	58.8	96	41	48.7	80	39
89	60.0	43	58.0	97	39	54.4	91	41	45.8	76	37
93	57.4	40	56.3	98	38	50.9	89	37	43.7	76	36
97	55.7	38	52.7	95	37	47.1	85	35	40.2	72	36
99	56.1	37	53.3	95	34	46.1	82	33	40.1	72	33
101	55.5	35	52.5	95	33	42.8	77	27	39.9	72	30
103	56.1	33	50.7	90	31	41.2	73	25	39.1	70	29
Mean for weeks											
1-13	28.1		28.0	100		28.3	101		28.3	101	
14-52	48.5		47.1	97		48.7	100		47.9	99	
53-103	59.1		56.8	96		54.9	93		50.0	85	



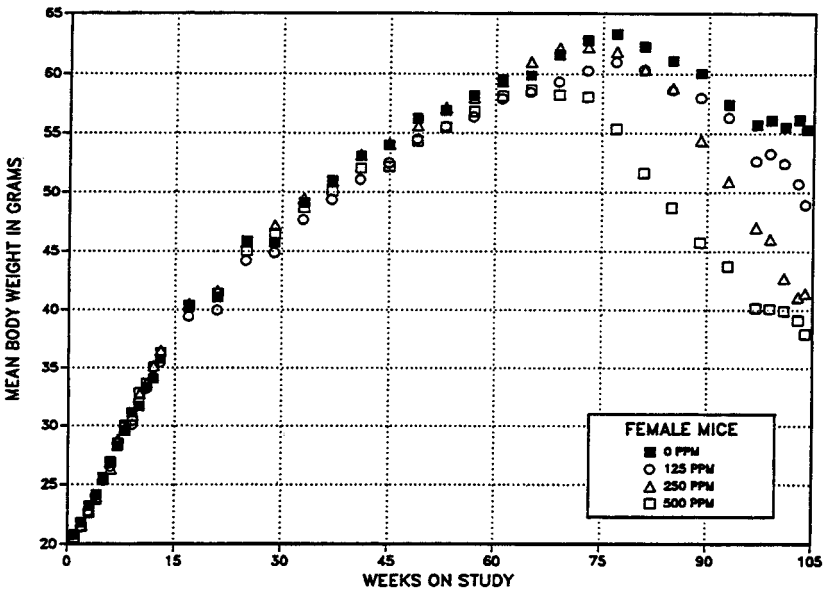


FIGURE 7
Growth Curves for Male and Female Mice Exposed to Pyridine in Drinking Water for 2 Years

Pathology and Statistical Analyses

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

Liver: Hepatocellular neoplasms in male and female mice were clearly related to pyridine exposure. Incidences of hepatocellular adenoma were significantly increased relative to controls in 250 ppm males and females and 1,000 ppm males (Tables 21, D3, and E3). Incidences of hepatocellular carcinoma and hepatoblastoma were significantly increased relative to controls in all exposed groups of males and females except for the incidence of hepatoblastoma in 125 ppm females. Incidences of hepatocellular adenoma, hepatocellular carcinoma, or hepatoblastoma (combined) were significantly increased in all exposed male groups and in 250 and 500 ppm females. The incidences of hepatocellular neoplasms in exposed males and females generally exceeded the historical control ranges (Tables 21, D4, and E4). Incidences of hepatoblastoma in control and exposed males and females exceeded the historical control range. While the control incidence of liver neoplasms in female mice was among the highest historically, almost all neoplasms were adenomas.

Almost every exposed animal that lived one year or more developed one or multiple liver neoplasms, often carcinomas or hepatoblastomas, with many metastasizing to the lung. Hepatocellular neoplasms in exposed mice were similar to those that occur spontaneously. A hepatocellular adenoma was typically a discrete proliferation of hepatocytes that compressed adjacent tissue and had uneven growth patterns resulting in a slightly abnormal architecture (Plate 4). Hepatocellular carcinomas had a distinctly altered structure, cells were often pleomorphic, and the boundary with the adjacent parenchyma was often unclear (Plate 5). Hepatoblastomas had very poorly differentiated cells (frequently basophilic, small, and spindle-shaped) that had markedly altered architectures of solid sheets, rosettes, ribbons, or trabeculae (Plate 6). Hepatoblastomas nearly always were found in the midst of a hepatocellular carcinoma, but unless there was a clearly separate hepatocellular carcinoma, only the diagnosis of hepatoblastoma was made.

Some of the hepatocellular carcinomas and many of the hepatoblastomas had areas of necrosis, and metastatic lesions were noted in the lungs or, less frequently, in the lymph nodes or adjacent abdominal organs (Tables D1 and E1). There were no treatment-related increased incidences of foci of cellular alteration relative to controls (Tables 21, D5, and E5). Foci of cellular alteration were contiguous hepatocytes of less than a lobule up to approximately four lobules; they varied tinctorially from the rest of the liver but tended to merge imperceptibly with the adjacent parenchyma.

Liver neoplasms from control mice, 500 ppm females, and 1,000 ppm males were stained for p53 protein and compared to a control carcinoma from the mammary gland of a p53 positive transgenic mouse. All of the liver sections tested were negative for p53 protein.

Other Organs: Incidences of hematopoietic cell proliferation in the spleen were increased relative to controls in exposed males (0 ppm, 13/49; 250 ppm, 30/50; 500 ppm, 26/47; 1,000 ppm, 23/49; Table D5) and females (0 ppm, 29/49; 125 ppm, 27/50; 250 ppm, 32/48; 500 ppm, 39/49; Table E5) and may have been compensation for destruction of blood cells in the altered vasculature of the hepatic neoplasms and their metastases. Increased incidences of follicular cell hyperplasia in the thyroid gland of exposed males and females were not accompanied by a significant increased incidence of thyroid gland neoplasms relative to controls (males: 8/49, 14/50, 20/49, 12/50; females: 14/50, 21/50, 22/50, 23/50; Tables D1, D5, E1, and E5). An apparent decrease in the incidences of hyaline degeneration in the respiratory epithelium of exposed males and females (males: 20/50, 10/49, 15/49, 2/50; females: 26/50, 16/50, 12/47, 13/50) and increases in incidences of hyaline degeneration in the olfactory epithelium of exposed females (19/50, 27/50, 35/47, 36/50) compared to controls were of unknown biological significance. Hyaline degeneration in the nasal epithelium is an accumulation of eosinophilic material in the cytoplasm and a common alteration in aging mice.

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Male				
Number Examined Microscopically	50	50	49	50
Basophilic Focus[a]	3	1	0	0
Eosinophilic Focus	19	22	18	15
Mixed Cell Focus	4	2	1	1
Hepatocellular Adenoma, Multiple	16	29*	29*	28*
Hepatocellular Adenoma (includes multiple)[b]				
Overall rate[c]	29/50 (58%)	40/50 (80%)	34/49 (69%)	39/50 (78%)
Adjusted rate[d]	63.2%	88.0%	75.7%	84.9%
Terminal rate[e]	24/35 (69%)	27/28 (96%)	27/34 (79%)	31/35 (89%)
First incidence (days)	520	522	513	406
Poly-3 test[f]	P=0.031	P=0.003	P=0.134	P=0.011
Hepatocellular Carcinoma, Multiple	3	19**	26**	18**
Hepatocellular Carcinoma (includes multiple)[g]				
Overall rate	15/50 (30%)	35/50 (70%)	41/49 (84%)	40/50 (80%)
Adjusted rate	32.3%	78.7%	89.9%	85.1%
Terminal rate	9/35 (26%)	23/28 (82%)	32/34 (94%)	28/35 (80%)
First incidence (days)	574	522	513	406
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Hepatoblastoma, Multiple	1	4	6*	2
Hepatoblastoma (includes multiple)[h]				
Overall rate	2/50 (4%)	18/50 (36%)	22/49 (45%)	15/50 (30%)
Adjusted rate	4.5%	41.2%	49.8%	34.4%
Terminal rate	2/35 (6%)	11/28 (39%)	17/34 (50%)	13/35 (37%)
First incidence (days)	722 (T)	549	514	624
Poly-3 test	P=0.005	P<0.001	P<0.001	P<0.001
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma[i]				
Overall rate	38/50 (76%)	47/50 (94%)	46/49 (94%)	47/50 (94%)
Adjusted rate	80.1%	98.9%	98.5%	100.0%
Terminal rate	29/35 (83%)	28/28 (100%)	34/34 (100%)	35/35 (100%)
First incidence (days)	520	522	513	406
Poly-3 test	P<0.001	P=0.002	P=0.003	P<0.001

TABLE 21
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Female (continued)				
Number Examined Microscopically	49	50	50	50
Basophilic Focus	1	0	0	0
Eosinophilic Focus	17	12	14	9
Mixed Cell Focus	5	4	3	0
Hepatocellular Adenoma, Multiple	24	34*	37**	30
Hepatocellular Adenoma (includes multiple)[j]				
Overall rate	37/49 (76%)	39/50 (78%)	43/50 (86%)	34/50 (68%)
Adjusted rate	82.5%	87.9%	97.3%	79.1%
Terminal rate	27/32 (84%)	27/30 (90%)	22/22 (100%)	23/29 (79%)
First incidence (days)	554	419	509	430
Poly-3 test	P=0.372N	P=0.336	P=0.015	P=0.442N
Hepatocellular Carcinoma, Multiple	3	11*	14**	30**
Hepatocellular Carcinoma (includes multiple)[k]				
Overall rate	13/49 (27%)	23/50 (46%)	33/50 (66%)	41/50 (82%)
Adjusted rate	29.8%	55.0%	78.1%	97.1%
Terminal rate	8/32 (25%)	18/30 (60%)	20/22 (91%)	29/29 (100%)
First incidence (days)	476	573	556	479
Poly-3 test	P<0.001	P=0.014	P<0.001	P<0.001
Hepatoblastoma, Multiple	0	0	3	4
Hepatoblastoma (includes multiple)[l]				
Overall rate	1/49 (2%)	2/50 (4%)	9/50 (18%)	16/50 (32%)
Adjusted rate	2.4%	4.9%	21.6%	39.6%
Terminal rate	1/32 (3%)	1/30 (3%)	3/22 (14%)	12/29 (41%)
First incidence (days)	729 (T)	599	564	510
Poly-3 test	P<0.001	P=0.493	P=0.007	P<0.001
Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma[m]				
Overall rate	41/49 (84%)	42/50 (84%)	45/50 (90%)	44/50 (88%)
Adjusted rate	89.9%	94.6%	99.6%	99.5%
Terminal rate	29/32 (91%)	29/30 (97%)	22/22 (100%)	29/29 (100%)
First incidence (days)	476	419	509	430
Poly-3 test	P=0.009	P=0.323	P=0.042	P=0.045

* Significantly different (P 0.05) from the control group by the Poly-3 test
** P 0.01
[a] Number of animals with lesion
[b] Historical incidence for 2-year drinking water studies with untreated control groups (mean ± standard deviation): 179/289 (61.9% ± 9.1%); range, 47%-70%
[c] Number of animals with neoplasm per number of animals with liver examined microscopically
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A lower incidence in an exposure group is indicated by **N**.
[g] Historical incidence: 80/289 (27.7% ± 11.7%); range, 10%-42%
[h] Historical incidence: 9/289 (3.1% ± 5.0%); range, 0%-12%
[i] Historical incidence: 212/289 (73.4% ± 11.7%); range, 53%-81%
[j] Historical incidence: 150/289 (51.9% ± 20.8%); range, 26%-80%
[k] Historical incidence: 55/289 (19.0% ± 13.7%); range, 8%-42%
[l] Historical incidence: 0/289
[m] Historical incidence: 173/289 (59.9% ± 21.3%); range, 32%-82%

GENETIC TOXICOLOGY

Pyridine (100-10,000 µg/plate) was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation enzymes (Haworth *et al.*, 1983; Table F1). Further, no significant increase in mutation frequencies was observed in L5178Y mouse lymphoma cells tested with and without S9 metabolic activation (McGregor *et al.*, 1988; Table F2). In cytogenetic tests with cultured Chinese hamster ovary cells, pyridine did not induce sister chromatid exchanges (Table F3) or chromosomal aberrations (Table F4), with or without S9. At the highest viable dose (1,673 µg/mL) tested for sister chromatid exchange induction in the absence of S9, pyridine induced marked cell cycle delay, and an extended culture time (31 hours) was used to allow sufficient cells to accumulate for analysis.

Pyridine was tested on three separate occasions in two different laboratories for induction of sex-linked recessive lethal mutations in adult male *Drosophila melanogaster* (Valencia *et al.*, 1985; Mason *et al.*, 1992; Foureman *et al.*, 1994; Table F5), and mixed results were obtained. In the first experiment (Valencia *et al.*, 1985), administration of pyridine by injection (7,000 ppm in aqueous 0.7% saline solution) gave negative (P=0.225) results, but feeding (600 or 700 ppm pyridine in aqueous 5% sucrose) produced an increase in recessive lethal mutations that was considered to be equivocal (P=0.043). A second experiment performed in the same laboratory using both injection (500 ppm) and feeding (729 ppm) yielded negative results (Foureman *et al.*, 1994). In the third experiment (Mason *et al.*, 1992) performed in a second laboratory, results of a feeding (500 ppm) experiment were negative (P=0.998), but administration of pyridine by injection (4,300 ppm) induced a significant increase in the frequency of sex-linked recessive lethal mutations (P=0.008). Overall, pyridine was considered to be negative in sex-linked recessive lethal tests when administered by feeding and equivocal when administered by injection. This positive result in the sex-linked recessive lethal test led to the performance of a test for induction of reciprocal translocations in germ cells of treated male *Drosophila melanogaster* (Mason *et al.*, 1992; Table F6); results of this test were negative.

In vivo assays for chromosomal effects were conducted with male mice. No induction of chromosomal aberrations (Table F7) was noted in bone marrow cells at either of two sampling times (400-600 mg/kg pyridine; single injection), and no increase in the frequency of micronucleated polychromatic erythrocytes (Table F8) was noted in bone marrow after intraperitoneal injection of pyridine (up to 500 mg/kg administered three times at 24-hour intervals).

In summary, with the exception of the single positive result obtained in a *Drosophila melanogaster* sex-linked recessive lethal assay, no indication of mutagenic activity was seen with pyridine in a variety of *in vitro* and *in vivo* assays for gene mutation and chromosomal damage.

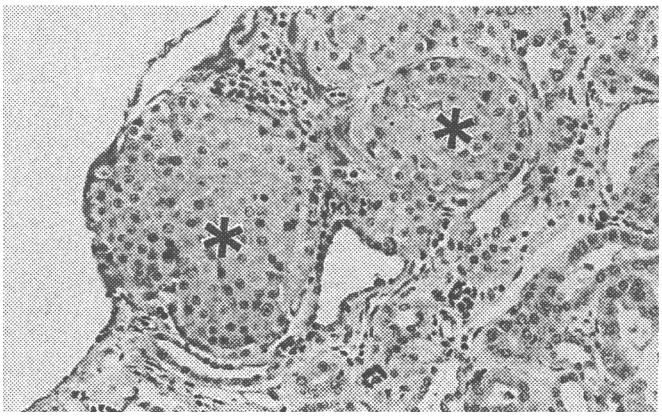


PLATE 1
Kidney from a male F344/N rat exposed to 400 ppm pyridine in drinking water for 2 years. Hyperplasia of the renal tubular epithelium are indicated by asterisks. Note that multiple cross sections of the tubule are distended with epithelial cells. H&E; 66×

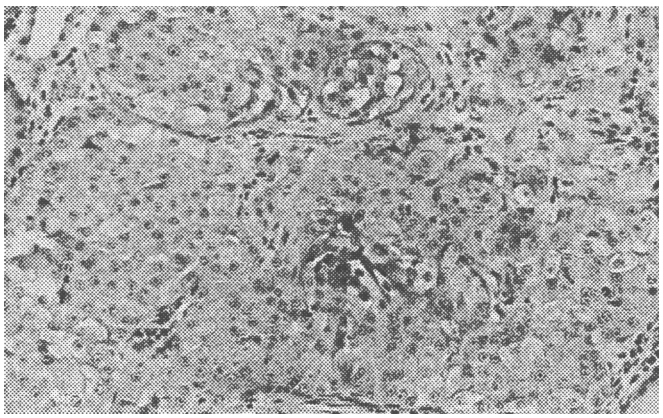


PLATE 2
Kidney from a male F344/N rat exposed to 400 ppm pyridine in drinking water for 2 years. Note the renal tubule adenoma consisting of a larger cluster of cells than a hyperplasia and resulting in a loss of tubular structure. H&E; 66×

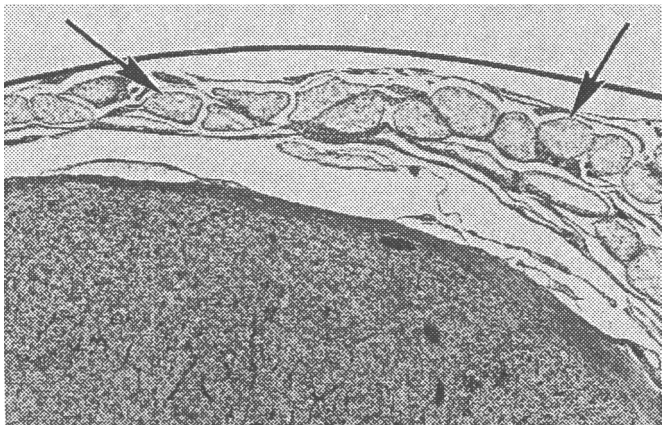


PLATE 3
Testis from a male Wistar rat exposed to 400 ppm pyridine in drinking water for 2 years. A large interstitial cell adenoma compresses degenerate seminiferous tubules (arrows). H&E; 13×

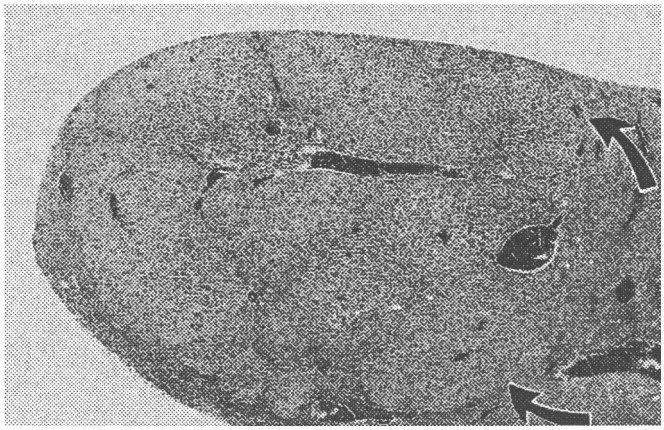


PLATE 4
Liver from a female B6C3F_1 mouse exposed to 250 ppm pyridine in the drinking water for 2 years. A large hepatocellular adenoma compresses (arrows) the parenchyma. H&E; 8×

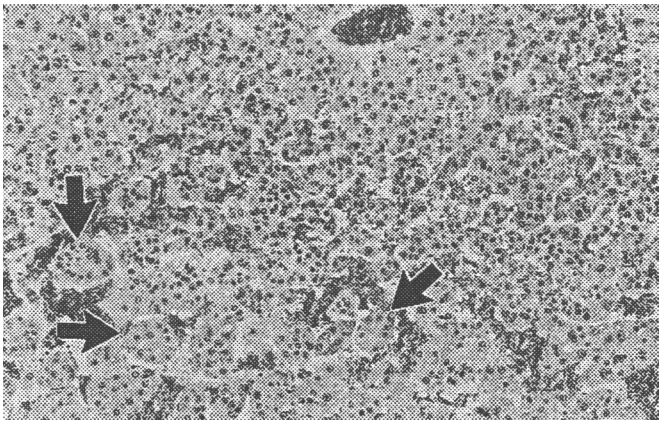


PLATE 5
Liver from a male B6C3F$_1$ mouse exposed to 1,000 ppm pyridine for 2 years. A hepatocellular carcinoma with a trabecular pattern shows clusters of hepatocytes (arrows) rather than the normal lobular architecture. H&E; 33×

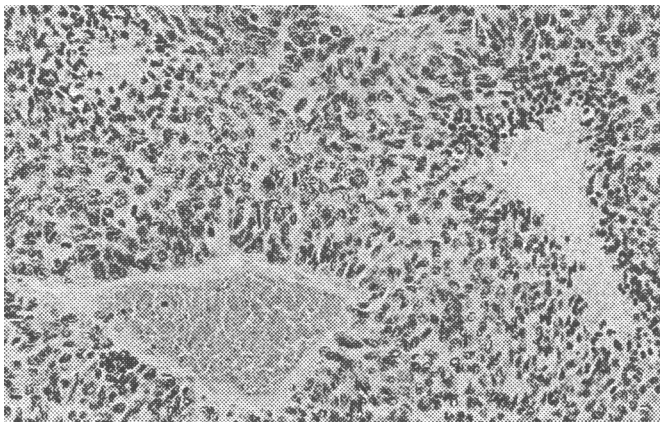


PLATE 6
Liver from a male B6C3F$_1$ mouse exposed to 500 ppm pyridine for 2 years. Note the small spindle-shaped cells of a hepatoblastoma rather than normal polyhedral hepatocytes. H&E; 66×

DISCUSSION AND CONCLUSIONS

Pyridine was nominated by the National Cancer Institute for toxicity and carcinogenicity studies because of its large annual production and the potential for human exposure. No previous 2-year carcinogenesis bioassays for pyridine have been reported in the literature. Pyridine is used in a variety of industrial processes including the production of pesticides and herbicides, and it is found as a natural component in some foods.

The target organs in the 13-week drinking water studies included the liver and kidney in male F344/N and Wistar rats and the liver in female F344/N rats. Decreased water consumption and/or body weight effects were observed in 1,000 ppm mice in the 13-week study, but no target organ lesions were observed. The liver and kidney have previously been reported as target organs in rats administered pyridine in feed at 0.34% to 1.0% for up to 4 months (Baxter, 1948). Liver toxicity was observed in Sprague-Dawley rats administered 50 mg pyridine/kg body weight per day by oral gavage for 13 weeks (Anderson, 1987).

Kidney: In a number of NTP studies with F344/N rats the kidney is the site of a spectrum of lesions. Some lesions may be spontaneous and age-related, particularly chronic, progressive nephropathy. Others result from direct or indirect effects of the test chemical. In 13-week studies small, eosinophilic hyaline droplets are sometimes seen within the cytoplasm of the epithelial cells of the P2 segment of the renal tubule. These protein droplets typically contain a low molecular weight protein (α2u-globulin), which is synthesized under the control of androgens and growth hormones. The α2u-globulin is filtered in the glomerulus; approximately half is reabsorbed by the proximal tubule epithelium and half is excreted in the urine (Neuhaus *et al*., 1981). Normally only small amounts of the reabsorbed protein are visible as hyaline droplets as it is degraded by enzymes in the tubule epithelium. Some chemicals (inducers) reversibly combine with reabsorbed α2u-globulin and make it more resistant to enzymatic degradation, resulting in protein material accumulation in the renal tubule epithelium (Lehman-McKeeman *et al*., 1989). It is theorized that phagosomal accumulation of the proteinaceous material can result in accelerated renal tubule epithelium cell death.

Hyaline droplet nephropathy or α2u-globulin nephropathy are terms used to describe the renal changes associated with α2u-globulin inducers. In addition to accumulation of hyaline droplets, other microscopic changes consistent with hyaline droplet nephropathy include granular cast within tubular lumens of the outer medulla and exacerbated nephropathy. The casts are thought to consist of aggregates of sloughed necrotic cells from the affected P2 segment. Less specific, but generally considered a component of the spectrum of renal changes brought on by α2u-globulin, is an exacerbation of the spontaneous chronic progressive nephropathy. Other findings generally associated with α2u-globulin in 2-year studies include an increase in linear foci of mineralization within the renal medulla and an increase in proliferative lesions (including neoplasms) of the renal tubules. It is theorized that phagolysosomal accumulation of proteinaceous matter leads to an overload phenomenon, resulting in accelerated renal tubule cell death with subsequent regeneration by increased cell replication. Increased cell replication is thought to be lined with eventual development of renal tubule neoplasms (USEPA, 1991).

In male F344/N rats from the 13-week study of pyridine, kidney changes consistent with α2u-globulin inducers were observed in the 1,000 ppm group and to a lesser extent in the 500 ppm group. These changes included a very subtle increase in the amount of hyaline droplets which appeared positive for α2u-globulin by immunohistochemistry and one to three small granular casts in 1,000 and 500 ppm males; at the next lowest exposure concentration (250 ppm) no changes were observed consistent with hyaline droplet nephropathy. In the 2-year studies there was a marginal increase in the incidence of renal tubule adenomas in the 400 ppm male F344/N rats. An extended evaluation of the entire

kidney by step sectioning confirmed a significant exposure-related increase in the incidences of renal tubule adenomas in this group. Slight increases in the incidences of renal tubule hyperplasia were also observed for 400 ppm male F344/N rats and 100 ppm Wistar rats.

Establishing causation between neoplastic outcome and the α2u-globulin response in male rats requires demonstration of similar exposure-response relationships between renal tubule neoplasm incidence and α2u-globulin accumulation (as determined by histopathology and immunohistochemistry), reversible binding of the chemical or its metabolite to α2u-globulin, and sustained cell proliferation in the renal cortex. In studies in which the association between hyaline droplet nephropathy and neoplasm development was clearly demonstrated, the severities of hyaline droplets and granular casts exceeded those observed in the present study. Moreover, the rat renal tubule neoplastic response occurred mainly at an exposure concentration (400 ppm) lower than the concentration at which only subtle lesions characteristic of α2u-globulin inducers were observed (500 ppm). Additionally, six renal tubule neoplasms occurred in the 200 ppm group compared with two in the control group. No evidence of α2u-globulin nephropathy was observed at 250 ppm or below in the 13-week studies. In the F344/N rats in this study of pyridine, there was no significant exacerbation of nephropathy after 2 years, nor were there any significant increases in the incidences of parathyroid gland hyperplasia or fibrous osteodystrophy, two common changes in NTP studies with chemical-exacerbated chronic progressive nephropathy. There were also no liner foci of mineralization within the renal medulla in this study. By contrast to the findings in the F344/N rat, there was evidence (parathyroid gland hyperplasia, fibrous osteodystrophy, and glandular stomach mineralization) that chronic progressive nephropathy was more severe after 2 years in Wistar rats receiving 100 and 200 ppm, although there was no evidence of hyaline droplet nephropathy in male Wistar rats in the 13-week study. All of these considerations combined suggest that the neoplastic response to pyridine in the male F344/N rat kidney was not attributable to α2u-globulin.

There was no evidence for a carcinogenic effect in the kidney of Wistar rats. The same diagnostic criteria and terminology were used in evaluating lesions in the kidney of both strains of rats. The severity of spontaneous nephropathy in control Wistar rats was moderate, whereas that in control male F344/N rats was mild. The results of these studies suggest that the male Wistar rat is not as susceptible as the male F344/N rat to the formation of kidney neoplasms from pyridine exposure. The NTP has not compared the susceptibility of male F344/N rats and male Wistar rats to other kidney carcinogens.

Liver: Liver lesions in F344/N rats were characterized by centrilobular cytomegaly, degeneration, and necrosis; cytoplasmic vacuolization; foci of cellular alteration; fibrosis; and pigmentation in Kupffer's cells and macrophages. Bile duct hyperplasia was observed in all exposed groups of males and females and the incidences were significantly increased in exposed females compared to controls. Periportal fibrosis was a prominent lesion in 400 ppm males. There were no statistically significant increases in the incidences of hepatocellular neoplasms in exposed F344/N or Wistar rats.

The same diagnostic criteria and terminology were applied to the liver lesions in both strains of rats. In general, except for the incidences of centrilobular cytomegaly, which was highest in 400 ppm females, periportal fibrosis, which was highest in 400 ppm male F344/N rats, and cytoplasmic vacuolization, which occurred in control and exposed Wistar rats, treatment-related nonneoplastic liver lesions occurred at higher incidences and with greater severities in Wistar rats than in male or female F344/N rats. These lesions, along with nephropathy, probably contributed to early deaths in Wistar rats. Incidences of fibrosis, extending from the liver capsule downwards into the parenchyma, were significantly increased relative to controls in 200 and 400 ppm Wistar rats but were increased less significantly in 400 ppm male F344/N rats and were not treatment related in females.

Exposure to pyridine was associated with progression of liver neoplasms from benign to malignant in male and female mice. Hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas represent a

biological and morphological continuum in progression of proliferative lesions. It is probable that hepatoblastomas do not represent further progression to a more malignant state but rather are composed of cells that are more primitive. Hepatoblastomas are considered to represent a phenotypic, and possibly genotypic, variant of a malignant liver neoplasm. Because the malignant potential of hepatocellular carcinomas and hepatoblastomas appear similar and hepatoblastomas are generally observed in the hepatocellular neoplasms (mostly carcinomas), it is appropriate to combine the incidences of hepatoblastomas with those of hepatocellular adenoma and carcinoma when interpreting the carcinogenic potential of a chemical. Hepatoblastomas, which are rare, are observed in relatively high numbers only after chemical administration (primarily in mice) and have previously been observed in NTP studies with primidone (NTP, 1999), oxazepam (NTP, 1993a), *o*-nitroanisole (NTP, 1993b), benzofuran (NTP, 1989), ethylene thiourea (NTP, 1992), 1-amino-2,4-dibromoanthraquinone (NTP, 1996), methylphenidate hydrochloride (NTP, 1995), and coumarin (NTP, 1993c).

Pyridine, like primidone (NTP, 1999), phenobarbital (McClain, 1990), and oxazepam (NTP, 1993a, 1998b), induces liver neoplasms in mice but not in rats, even though in rats these chemicals cause a spectrum of toxic liver lesions. The mouse, an animal with a high background rate of liver neoplasms, seems to be particularly sensitive to subsequent development of malignant liver neoplasms after chemical exposure (Drinkwater *et al.*, 1990; Drinkwater, 1994; Bennett *et al.*, 1995; Lee *et al.*, 1995). While there are no studies of the relationship between pyridine exposure and cancer incidence, it is of interest that use of primidone and phenobarbital to treat epilepsy in human (Olsen *et al.*, 1995).

Testis: In the Wistar rat at 2 years, the incidence of interstitial cell adenoma of the testis was increased in the 400 ppm group relative to controls. There was no corresponding increase in interstitial cell hyperplasia. The NTP does not have a historical database for neoplasms in Wistar rats. In one study analyzing neoplasm rates in 1,370 control Wistar rats (from Charles River Laboratories, Kingston, NY, or Hilltop Laboratory Animals, Scottdale, PA, from 1980 to 1990) a control rate of 3.9% (range, 0%-22%) was reported for interstitial cell neoplasms of the testis in animals weighing between 556 and 717 g (Walsh and Poteracki, 1994). The rate for interstitial cell adenomas in Wistar rats exposed to 400 ppm pyridine was only marginally outside this historical range, and inci dences of this neoplasm were not increased relative to controls in the 100 or 200 ppm groups. This was considered to be equivocal evidence for a carcinogenic effect. The mean body weights of the control male Wistar rats in this study were somewhat higher during the second year of the study (reaching a high of 803 g at week 73). Increased body weights have been associated with higher neoplasm rates at some sites in rodents, and this difference, combined with other differences in animal husbandry condition and time of study, may be a factor in the incidences of interstitial cell neoplasms observed in the present study. The spontaneous rate for interstitial cell neoplasms of the testis in F344/N rats is high (about 90%) and often precludes the conclusion of a carcinogenic effect at this site.

Mononuclear Cell Leukemia: Mononuclear cell leukemia is a common neoplasm in F344/N rats. The Wistar rat was added to these studies because it has a low background incidence of mononuclear cell leukemia in comparison to the male F344/N rat, and there was a suggestion from a study by Dieter *et al.* (1989) that pyridine may cause leukemia. However, in these studies, pyridine did not appear to affect the rate for leukemia in male rats. Incidences of mononuclear cell leukemia were increased relative to controls in 200 and 400 ppm F344/N female rats. These incidences were at or just outside the historical control range for this neoplasm, and because there was no supportive evidence for an increase in mononuclear cell leukemia in male rats compared with the incidences of mononuclear cell leukemia in control animals in a concurrent drinking water study at the same laboratory (19/50; NTP, 1998a), the rate observed in the 400 ppm group in this study does not seem to be significant.

Pyridine is metabolized primarily by N-methylation and/or aromatic hydroxylation. Metabolites identified include N-methylpyridinium, 3-hydroxy pyridine, and

N-methyl pyridinium hydroxide. Pyridine is metabolized by cytochromes P2E1 and P4B (CYP2E1 and CYP4B) (Nikula *et al.*, 1995) and enhances the expression of several forms of P_{450}, including CYP2E1, CYP1A1/1A2, and CYP2B1/2B2 in both hepatic and renal tissues (tissues from rat used as the model system) (Kim and Novak, 1990; Kim *et al.*, 1991a; Kim *et al.*, 1993).

Some studies suggest that the induction of cytochrome P_{450}2B enzymes are associated with mouse liver neoplasm formation (Lubet *et al.*, 1989; Rice *et al.*, 1994). Pyridine-induced liver neoplasms from control, 500 ppm male, and 1,000 ppm female mice showed no staining with p53 antibody, a marker that correlates with p53 gene alterations. Chemicals such as phenobarbital, which induces cytochrome P_{450}s in the rodent liver, induce a wide variety of enzyme systems (referred to as pleiotropic response), and it is likely that several effects of the chemical play a role in its liver neoplasm-promoting ability (McClain, 1990). Another nonmutagenic mouse liver carcinogen, methylphenidate, also showed no evidence for p53 protein accumulation in methylphenidate-induced liver neoplasms in the $B6C3F_1$ mouse and similar to pyridine was negative in the p53 (+/-) transgenic mouse model (Tennant *et al.*, 1995, 1999). Tennant *et al.* (1999) also reported that pyridine failed to induce a carcinogenic response in 6 month studies with the TgAC mouse, but Bucher (1998) pointed out that neither the TgAC nor the p53 (+/-) transgenic mouse assays appear responsive to chemicals that induce mouse liver neoplasms in standard 2-year assays.

There is a developing field of study regarding specific genetic changes in mouse and human liver neoplasms. In one series of human hepatoblastomas, p53 alterations were not seen in hepatoblastomas of fetal or mesenchymal origin but did occur in hepatoblastomas classified as small cell (Ruck *et al.*, 1994). Other studies also report a low frequency of p53 mutations in hepatoblastomas (Kar *et al.*, 1993; Kennedy *et al.*, 1994). In contrast, in a study of hepatoblastomas in Japanese patients, p53 mutations were found in nine of 10 cases (Oda *et al.*, 1995). Overexpression of p53 is a rare event in Caucasian patients with hepatocellular carcinoma (Laurent-Puig *et al.*, 1992).

Accumulation of p53 protein has been associated with liver neoplasms caused by viral hepatitis (42%) (Ojanguren *et al.*, 1995; Greenblatt *et al.*, 1997) and in aflatoxin hepatocarcinogenesis (Shen and Ong, 1996). Three studies of liver neoplasms in mice suggest that the p53 gene plays a minimal role in the development of these neoplasms (Kress *et al.*, 1992; Chen *et al.*, 1993; Calvert *et al.*, 1995). Mutations of the neoplasm suppressor gene p53 have been found in hepatocellular carcinomas from patients in many countries (e.g., Japan and Asian countries) where there may be an association between neoplasms and virus infection or aflatoxin exposure. In the United States, p53 mutations are usually not found in hepato cellular carcinomas (Kazachkov *et al.*, 1996), and the etiology of the liver cancer is not known.

Pyridine is negative in most studies for genotoxicity. Pyridine was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation enzymes. Further, no significant increase in mutant frequencies was observed in L5178Y mouse lymphoma cells, tested with and without S9 metabolic activation. In cytogenetic tests with cultured Chinese hamster ovary cells, pyridine did not induce sister chromatid exchanges or chromosomal aberrations, with or without S9. Results were positive for the induction of sex-linked recessive lethal mutations in *Drosophila melanogaster* following injection of pyridine but were negative by the same route of administration for induction of reciprocal translocations in germ cells of *D. melanogaster*. No induction of chromosomal aberrations and no increase in the frequency of micronucleated polychromatic erythrocytes was noted in mouse bone marrow cells after intraperitoneal injection of pyridine.

CONCLUSIONS

Under the conditions of these 2-year drinking water studies, there was *some evidence of carcinogenic activity** of pyridine in male F344/N rats based on increased incidences of renal tubule neoplasms. There was *equivocal evidence of carcinogenic activity* of pyridine in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was *equivocal evidence of carcinogenic activity* in male Wistar rats based on an increased incidence of interstitial cell adenoma of the testis. There was *clear evidence of carcinogenic activity* of pyridine in male and female $B6C3F_1$ mice based on increased incidences of malignant hepatocellular neoplasms.

In F344/N rats, exposure to pyridine resulted in increased incidences of centrilobular cytomegaly and degeneration, cytoplasmic vacuolization, and pigmentation in the liver of males and females; periportal fibrosis, fibrosis, and centrilobular necrosis in the liver of males; and bile duct hyperplasia in females. In male Wistar rats, pyridine exposure resulted in increased incidences of centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and pigmentation in the liver, and secondary to kidney disease, mineralization in the glandular stomach and parathyroid gland hyperplasia.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 13. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 15.

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APPENDIX A
SUMMARY OF LESIONS IN MALE F344/N RATS IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

TABLE A1
Summary of the Incidence of Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine[a]

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	13	15	10
Natural deaths	14	17	10	24
Survivors				
Terminal sacrifice	25	20	25	16
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(48)	(50)	(49)
Lipoma			1 (2%)	
Intestine large, cecum	(49)	(47)	(50)	(49)
Lipoma			1 (2%)	
Intestine small, duodenum	(50)	(47)	(50)	(48)
Intestine small, jejunum	(50)	(47)	(50)	(47)
Carcinoma	1 (2%)			
Intestine small, ileum	(50)	(47)	(50)	(47)
Liver	(50)	(49)	(50)	(50)
Cholangiocarcinoma				1 (2%)
Hepatocellular carcinoma			1 (2%)	
Hepatocellular adenoma	1 (2%)	1 (2%)		2 (4%)
Hepatocellular adenoma, multiple				1 (2%)
Histiocytic sarcoma	1 (2%)			
Mesentery	(11)	(14)	(7)	(8)
Schwannoma benign	1 (9%)			
Oral mucosa	(1)		(2)	
Pharyngeal, squamous cell papilloma	1 (100%)		1 (50%)	
Pancreas	(50)	(48)	(50)	(49)
Acinus, adenoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(49)	(50)	(49)
Squamous cell papilloma			1 (2%)	
Stomach, glandular	(50)	(49)	(50)	(49)
Tongue				(1)
Squamous cell papilloma				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Carcinoma		1 (2%)		
Adrenal medulla	(50)	(49)	(50)	(49)
Pheochromocytoma complex				1 (2%)
Pheochromocytoma benign	11 (22%)	2 (4%)	14 (28%)	4 (8%)
Bilateral, pheochromocytoma benign	6 (12%)	1 (2%)		
Islets, pancreatic	(50)	(48)	(50)	(49)
Adenoma	4 (8%)	2 (4%)	1 (2%)	
Parathyroid gland	(50)	(50)	(50)	(48)

TABLE A1
Summary of the Incidence of Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Endocrine System (continued)				
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	16 (32%)	13 (26%)	12 (24%)	11 (22%)
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(49)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	2 (4%)		3 (6%)	2 (4%)
C-cell, carcinoma		1 (2%)		
Follicular cell, adenoma		2 (4%)		
General Body System				
None				
Genital System				
Epididymis	(49)	(49)	(49)	(48)
Preputial gland	(50)	(47)	(49)	(48)
Adenoma	3 (6%)		7 (14%)	2 (4%)
Carcinoma	5 (10%)	2 (4%)		1 (2%)
Prostate	(50)	(48)	(50)	(49)
Seminal vesicle	(50)	(47)	(50)	(48)
Testes	(49)	(49)	(49)	(48)
Bilateral, interstitial cell, adenoma	33 (67%)	35 (71%)	37 (76%)	40 (83%)
Interstitial cell, adenoma	9 (18%)	8 (16%)	6 (12%)	3 (6%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Melanoma malignant, metastatic, skin			1 (2%)	
Lymph node	(20)	(25)	(20)	(23)
Lymph node, mandibular	(50)	(50)	(50)	(50)
Lymph node, mesenteric	(50)	(47)	(50)	(48)
Spleen	(49)	(48)	(50)	(49)
Thymus	(50)	(49)	(48)	(50)
Thymoma benign				1 (2%)
Integumentary System				
Mammary gland	(49)	(48)	(50)	(49)
Carcinoma		1 (2%)		
Fibroadenoma	4 (8%)	3 (6%)	6 (12%)	4 (8%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma				1 (2%)
Keratoacanthoma	6 (12%)	4 (8%)	1 (2%)	5 (10%)
Keratoacanthoma, multiple			1 (2%)	
Squamous cell papilloma	4 (8%)	1 (2%)	1 (2%)	
Trichoepithelioma		1 (2%)		1 (2%)
Pinna, melanoma malignant			1 (2%)	2 (4%)
Subcutaneous tissue, fibroma	4 (8%)	2 (4%)	4 (8%)	
Subcutaneous tissue, lipoma	1 (2%)		1 (2%)	
Musculoskeletal System				
Skeletal muscle		(1)		

TABLE A1
Summary of the Incidence of Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Nervous System				
Brain	(50)	(50)	(48)	(50)
Oligodendroglioma malignant		1 (2%)		
Spinal cord	(1)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			4 (8%)
Alveolar/bronchiolar carcinoma			2 (4%)	
Carcinoma, metastatic, mammary gland		1 (2%)		
Carcinoma, metastatic, Zymbal's gland		1 (2%)		
Melanoma malignant, metastatic, skin			1 (2%)	
Osteosarcoma, metastatic, nose	1 (2%)			
Nose	(50)	(50)	(49)	(50)
Osteosarcoma	1 (2%)			
Respiratory epithelium, squamous cell carcinoma		1 (2%)		
Trachea	(50)	(50)	(50)	(50)
Special Senses System				
Zymbal's gland	(1)	(1)	(1)	(1)
Carcinoma	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Urinary System				
Kidney	(50)	(48)	(50)	(49)
Mesenchymal tumor malignant		1 (2%)		
Renal tubule, adenoma	1 (2%)		1 (2%)	4 (8%)
Renal tubule, adenoma, multiple			1 (2%)	2 (4%)
Renal tubule, carcinoma		1 (2%)		
Urinary bladder	(50)	(47)	(50)	(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Leukemia mononuclear	29 (58%)	32 (64%)	26 (52%)	27 (54%)
Lymphoma malignant				1 (2%)
Mesothelioma benign	1 (2%)		1 (2%)	
Mesothelioma malignant	1 (2%)	1 (2%)		
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	49	49	49
Total primary neoplasms	151	120	133	123
Total animals with benign neoplasms	47	46	48	49
Total benign neoplasms	112	77	102	89
Total animals with malignant neoplasms	34	40	29	29
Total malignant neoplasms	39	43	31	34
Total animals with metastatic neoplasms	1	2	1	
Total metastatic neoplasms	1	2	2	

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

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	3 0 9	3 0 8	3 0 8	4 0 3	4 0 4	5 0 7	5 0 7	5 0 7	5 0 9	6 0 0	6 0 0	6 0 2	6 0 4	6 0 4	6 0 5	6 0 6	6 0 6	6 0 6	6 0 9	6 0 9	7 0 1	7 1 1	7 1 1	7 1 1	7 1 1
Carcass ID Number	0 2 5	0 1 2	0 3 4	0 4 5	0 2 3	0 4 1	0 4 8	0 1 5	0 1 1	0 1 0	0 0 7	0 3 6	0 0 4	0 3 8	0 4 3	0 1 9	0 4 4	0 0 2	0 0 1	0 2 2	0 4 9	0 0 5	0 1 6	0 1 0	0 1 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																						X			
Histiocytic sarcoma																									
Mesentery			+	+	+						+							+						+	+
Schwannoma benign																									X
Oral mucosa										+															
Pharyngeal, squamous cell papilloma										X															
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign						X														X	X		X		
Bilateral, pheochromocytoma benign																		X						X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X						X				X			
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X		X			X					X					X	X		X			
Pars intermedia, adenoma												X													
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Penis																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Carcinoma		X																							

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

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	
Carcass ID Number	00006	00008	00009	00014	00017	00018	00020	00021	00024	00026	00027	00028	00029	00030	00031	00032	00033	00035	00037	00039	00040	00042	00046	00047	00050	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Histiocytic sarcoma																							X			1
Mesentery	+		+						+																+	11
Schwannoma benign																										1
Oral mucosa																										1
Pharyngeal, squamous cell papilloma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma									X											X						2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth					+			+																		2
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign						X				X					X					X			X	X	X	11
Bilateral, pheochromocytoma benign								X									X		X		X					6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma								X																		4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X	X				X	X	X		X				X	X						X			16
Pars intermedia, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X			X																					2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis											+															1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma										X							X									3
Carcinoma															X					X				X	X	5

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	3 0 9	3 8 8	3 8 8	4 3 4	4 7 3	5 7 1	5 7 4	5 7 9	5 9 5	6 0 2	6 0 4	6 2 5	6 4 0	6 4 4	6 5 6	6 6 7	6 6 7	6 9 2	6 9 5	7 0 1	7 1 5	7 1 8	7 1 8	7 1 9	7 1 9
Carcass ID Number	0 2 5	0 1 2	0 3 4	0 4 5	0 2 3	0 4 1	0 4 8	0 1 5	0 1 1	0 1 0	0 0 7	0 3 6	0 0 4	0 3 8	0 4 3	0 1 9	0 4 4	0 0 2	0 0 1	0 2 2	0 4 9	0 0 5	0 1 6	0 1 0	0 1 3
Genital System (continued)																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Bilateral, interstitial cell, adenoma								X		X	X	X	X		X	X	X			X		X	X	X	X
Interstitial cell, adenoma					X	X	X							X				X	X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node	+				+	+	+			+	+	+	+		+		+		+		+	+	+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Fibroadenoma																						X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma															X										
Squamous cell papilloma																									
Subcutaneous tissue, fibroma												X				X									
Subcutaneous tissue, lipoma																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord																							+		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Osteosarcoma, metastatic, nose												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma												X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland													+												
Carcinoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear	X				X	X		X	X	X	X	X	X		X		X			X	X	X	X	X	
Mesothelioma benign																									
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	
Carcass ID Number	0 0 0 6	0 0 0 8	0 0 0 9	0 1 4	0 1 1 7	0 1 1 8	0 2 2 0	0 2 2 1	0 2 2 4	0 2 2 6	0 2 2 7	0 2 2 8	0 2 2 9	0 3 3 0	0 3 3 1	0 3 3 2	0 3 3 3	0 3 3 5	0 3 3 7	0 3 3 9	0 4 4 0	0 4 4 2	0 4 4 6	0 4 4 7	0 5 5 0	Total Tissues/ Tumors
Genital System (continued)																											
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X		X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X		X	X		33
Interstitial cell, adenoma			X							X		X															9
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																							X				1
Lymph node			+					+						+		+								+			20
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma												X			X	X											4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma		X						X				X				X								X			6
Squamous cell papilloma								X				X							X	X							4
Subcutaneous tissue, fibroma										X	X																4
Subcutaneous tissue, lipoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																X											1
Osteosarcoma, metastatic, nose																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Zymbal's gland																											1
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma			X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																							X				1
Leukemia mononuclear	X	X	X		X	X		X					X	X		X	X			X				X	X		29
Mesothelioma benign																		X									1
Mesothelioma malignant														X													1

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	6 9 8	7 0 0	7 0 1	7 0 8	7 1 8	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	
Carcass ID Number	0 5 9	0 7 0	0 8 3	0 8 2	0 7 5	0 5 1	0 5 4	0 5 5	0 5 7	0 5 8	0 6 1	0 6 3	0 6 4	0 6 5	0 6 8	0 7 6	0 7 8	0 8 0	0 8 4	0 8 5	0 8 6	0 8 8	0 9 2	0 9 3	0 9 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma						X																				1
Mesentery	+	+				+			+						+	+					+			+		14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinus, adenoma																									X	1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth											+															1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma														X												1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign				X																						2
Bilateral, pheochromocytoma benign																									X	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma							X		X																	2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma								X		X		X	X				X			X	X					13
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																			X							1
C-cell, carcinoma																										1
Follicular cell, adenoma													X				X									2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	47
Carcinoma									X			X														2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X		X	X	X		X	35
Interstitial cell, adenoma								X												X						8

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	4 4 4	4 5 5	4 6 6	5 3 8	5 5 3	5 9 8	6 0 4	6 0 4	6 0 7	6 1 8	6 2 0	6 2 5	6 2 8	6 4 1	6 4 2	6 6 4	6 6 5	6 6 5	6 6 6	6 6 6	6 6 6	6 6 7	6 7 3	6 7 7	6 8 2
Carcass ID Number	0 0 9 4	0 0 9 9	0 0 5 6	0 0 7 7	0 0 9 8	0 0 6 9	0 0 7 9	0 0 8 1	0 0 7 2	0 0 8 7	0 1 0 0	0 0 8 9	0 0 7 1	0 0 5 3	0 0 6 2	0 0 9 1	0 0 6 0	0 0 7 4	0 0 5 2	0 0 6 7	0 0 7 3	0 0 9 0	0 0 9 6	0 0 9 5	0 0 6 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+	+	+	+	+	+		+	+	+		+				+		+	+	+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Spleen	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X		
Squamous cell papilloma																									
Trichoepithelioma																									
Subcutaneous tissue, fibroma					X																				X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant		X																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																									
Carcinoma, metastatic, Zymbal's gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, squamous cell carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Mesenchymal tumor malignant																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X	X	X	X		X	X	X	X	X		X	X	X		X	X	X		
Mesothelioma malignant	X																								

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	6 9 8	7 0 0	7 0 1	7 0 8	7 1 8	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	
Carcass ID Number	0 5 9	0 7 0	0 8 3	0 8 2	0 7 5	0 5 1	0 5 4	0 5 5	0 5 7	0 5 8	0 6 1	0 6 3	0 6 4	0 6 5	0 6 8	0 7 6	0 7 8	0 8 0	0 8 4	0 8 5	0 8 6	0 8 8	0 9 2	0 9 3	0 9 7	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+		+	+		+	+		+		+						+					+		25
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma														X												1
Fibroadenoma				X		X																X				3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma					X									X									X			4
Squamous cell papilloma												X														1
Trichoepithelioma																		X								1
Subcutaneous tissue, fibroma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, mammary gland														X												1
Carcinoma, metastatic, Zymbal's gland			X																							1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory epithelium, squamous cell carcinoma				X																						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																					+					1
Zymbal's gland			+																							1
Carcinoma			X																							1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesenchymal tumor malignant																					X					1
Renal tubule, carcinoma																		X								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X			X	X	X	X	X	X	X		X	X								X	X	X		32
Mesothelioma malignant																										1

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	269	486	525	529	534	538	580	585	589	596	609	627	632	640	644	648	648	662	669	673	679	700	700	708	719
Carcass ID Number	11317	13818	11515	14249	12423	14747	11313	13335	10404	10808	14646	15050	14252	13404	10409	13730	13931	12929	12020	14848	11616	11818	12021	11914	13137
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Mesentery														+		+				+	+				
Oral mucosa																+									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma			X																						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign								X			X					X	X			X	X				X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X		X	X					X			X									X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X	X				X																
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X				X		X		X			X	X	X	X	X	X	X	X	X	X	
Interstitial cell, adenoma						X	X		X		X			X											

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	
Carcass ID Number	1 0 1	1 0 2	1 0 3	1 0 5	1 0 6	1 0 7	1 1 0	1 1 1	1 1 2	1 1 9	1 2 2	1 2 4	1 2 5	1 2 6	1 2 7	1 2 8	1 3 2	1 3 5	1 3 6	1 3 9	1 4 0	1 4 1	1 4 3	1 4 4	1 4 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																			X							1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma	X																									1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																		X								1
Mesentery	+					+			+																	7
Oral mucosa																					+					2
Pharyngeal, squamous cell papilloma																					X					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																			X							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth			+																							1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign							X			X			X		X					X		X		X		14
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X													1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X							X		X	X			X										12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X													X										X	3
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X					X				X			X													7
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	37
Interstitial cell, adenoma						X																				6

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	269	486	525	529	534	538	580	585	589	596	609	627	632	640	644	648	648	662	669	673	679	700	700	708	719
Carcass ID Number	11317	13818	11515	14249	12343	14747	11313	13335	10404	10808	14646	15050	14252	13440	10949	13048	13311	12929	12020	14848	11616	11818	12101	11414	13337
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Melanoma malignant, metastatic, skin																									
Lymph node				+	+		+	+	+	+	+	+			+		+		+	+		+		+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma						X								X											X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Keratoacanthoma, multiple																								X	
Squamous cell papilloma																									
Pinna, melanoma malignant																									
Subcutaneous tissue, fibroma							X												X						
Subcutaneous tissue, lipoma					X																				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Melanoma malignant, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland		+																							
Carcinoma		X																							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Renal tubule, adenoma, multiple																								X	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X	X	X		X		X	X	X	X		X	X		X			X
Mesothelioma benign																									

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	
Carcass ID Number	1 0 1	1 0 2	1 0 3	1 0 5	1 0 6	1 0 7	1 1 0	1 1 1	1 1 2	1 1 9	1 2 2	1 2 4	1 2 5	1 2 6	1 2 7	1 2 8	1 3 2	1 3 5	1 3 6	1 3 9	1 4 0	1 4 1	1 4 3	1 4 4	1 4 5	Total Tissues/ Tumors
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Melanoma malignant, metastatic, skin																			X									1
Lymph node								+					+	+								+				+		20
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma														X					X						X			6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma						X																						1
Keratoacanthoma, multiple																												1
Squamous cell papilloma																						X						1
Pinna, melanoma malignant																			X									1
Subcutaneous tissue, fibroma			X												X													4
Subcutaneous tissue, lipoma																												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																												
Brain	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+		48
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma											X	X																2
Melanoma malignant, metastatic, skin																			X									1
Nose	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																												
Zymbal's gland																												1
Carcinoma																												1
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																			X									1
Renal tubule, adenoma, multiple																												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X		X	X					X			X		X	X	X		X	X	X	X			26
Mesothelioma benign																	X											1

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	1 9 4	4 2 8	4 4 4	4 6 5	5 1 5	5 2 0	5 2 3	5 4 3	5 6 2	5 8 4	5 9 8	6 0 1	6 1 6	6 2 2	6 2 7	6 3 4	6 4 4	6 4 7	6 4 7	6 5 1	6 7 0	6 7 2	6 7 5	6 7 6	6 8 1
Carcass ID Number	1 1 5 5	1 7 7	1 6 3	1 9 9	1 7 4	1 9 8	1 6 5	1 7 0	1 6 2	1 9 2	1 9 5	1 9 1	1 5 2	1 5 4	1 8 7	1 5 1	1 6 9	1 5 3	1 8 3	1 5 6	1 8 0	1 7 1	1 6 6	1 8 8	1 6 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Hepatocellular adenoma														X											
Hepatocellular adenoma, multiple																									
Mesentery							+					+			+	+				+					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Squamous cell papilloma																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pheochromocytoma complex																									
Pheochromocytoma benign																							X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X							X		X		X		X		X	X							
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma			X	X	X		X	X		X		X		X		X			X	X	X	X	X	X	X
Interstitial cell, adenoma						X									X		X								

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	6 8 5	6 9 1	6 9 1	6 9 7	6 9 7	7 0 0	7 1 7	7 1 9	7 1 9	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	
Carcass ID Number	1 1 6 8	1 1 7 3	1 1 9 0	1 1 6 1	1 1 7 5	1 1 5 8	1 1 9 4	1 1 7 6	1 1 8 1	1 1 5 7	1 1 5 9	1 1 6 4	1 1 6 7	1 1 7 2	1 1 7 8	1 1 7 9	1 1 8 2	1 1 8 4	1 1 8 5	1 1 8 6	1 1 8 9	1 1 9 3	1 1 9 6	1 1 9 7	2 0 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																						X				1
Hepatocellular adenoma						X																				2
Hepatocellular adenoma, multiple																		X								1
Mesentery			+								+	+														8
Pancreas	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma																							X			1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue	+																									1
Squamous cell papilloma	X																									1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma complex																							X			1
Pheochromocytoma benign												X							X	X						4
Islets, pancreatic	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma							X				X	X	X													11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma										X									X							2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma											X				X											2
Carcinoma																				X						1
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bilateral, interstitial cell, adenoma	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	40
Interstitial cell, adenoma																										3

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	1 9 4	4 2 8	4 4 4	4 6 5	5 1 5	5 2 0	5 2 3	5 4 3	5 6 2	5 8 4	5 9 8	6 0 1	6 1 6	6 2 2	6 2 7	6 3 4	6 4 4	6 4 7	6 4 7	6 5 1	6 7 0	6 7 2	6 7 5	6 7 6	6 8 1
Carcass ID Number	1 1 5 5	1 7 7	1 6 3	1 9 9	1 7 4	1 9 8	1 6 5	1 7 0	1 6 2	1 9 2	1 9 5	1 9 1	1 5 2	1 5 4	1 8 7	1 5 1	1 6 9	1 5 3	1 8 3	1 5 6	1 8 0	1 7 1	1 6 6	1 8 8	1 6 0
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+	+	+		+			+	+	+	+						+		+		+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Fibroadenoma																									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma																					X				X
Trichoepithelioma																									
Pinna, melanoma malignant				X						X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear				+						+															
Zymbal's gland									+																
Carcinoma									X																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																						X			
Renal tubule, adenoma, multiple																	X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X	X	X	X		X	X	X		X	X			X	X			X		X		X	X
Lymphoma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	6 8 5	6 9 1	6 9 1	6 9 7	6 9 7	7 0 0	7 1 7	7 1 9	7 1 9	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	
Carcass ID Number	1 1 6 8	1 1 7 3	1 1 9 0	1 1 6 1	1 1 7 5	1 1 5 8	1 1 9 4	1 1 7 6	1 1 8 1	1 1 5 7	1 1 5 9	1 1 6 4	1 1 6 7	1 1 7 2	1 1 7 8	1 1 7 9	1 1 8 2	1 1 8 4	1 1 8 5	1 1 8 6	1 1 8 9	1 1 9 3	1 1 9 6	1 1 9 7	1 2 0 0	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+			+					+				+		+		+		+		+		23
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymoma benign																					X					1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroadenoma		X				X												X								4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma						X																				1
Keratoacanthoma							X	X													X					5
Trichoepithelioma															X											1
Pinna, melanoma malignant																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X													X						X	X	4
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										2
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Renal tubule, adenoma							X	X																	X	4
Renal tubule, adenoma, multiple																							X			2
Urinary bladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X		X	X		X					X			X		X	X	X	X	X				27
Lymphoma malignant	X																									1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	17/50 (34%)	3/49 (6%)	14/50 (28%)	4/49 (8%)
Adjusted rate[b]	40.4%	7.5%	32.8%	10.6%
Terminal rate[c]	11/25 (44%)	1/20 (5%)	7/25 (28%)	3/16 (19%)
First incidence (days)	571	628	585	675
Poly-3 test[d]	P=0.014N	P<0.001N	P=0.306N	P=0.002N
Adrenal Medulla: Benign or Complex Pheochromocytoma				
Overall rate	17/50 (34%)	3/49 (6%)	14/50 (28%)	5/49 (10%)
Adjusted rate	40.4%	7.5%	32.8%	13.3%
Terminal rate	11/25 (44%)	1/20 (5%)	7/25 (28%)	4/16 (25%)
First incidence (days)	571	628	585	675
Poly-3 test	P=0.030N	P<0.001N	P=0.306N	P=0.005N
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rate	1/50 (2%)	0/48 (0%)	2/50 (4%)	6/49 (12%)
Adjusted rate	2.4%	0.0%	4.9%	15.9%
Terminal rate	1/25 (4%)	0/20 (0%)	1/25 (4%)	2/16 (13%)
First incidence (days)	722 (T)	—[e]	708	644
Poly-3 test	P=0.003	P=0.510N	P=0.498	P=0.042
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections)				
Overall rate	1/50 (2%)	1/48 (2%)	2/50 (4%)	6/49 (12%)
Adjusted rate	2.4%	2.6%	4.9%	15.9%
Terminal rate	1/25 (4%)	1/20 (5%)	1/25 (4%)	2/16 (13%)
First incidence (days)	722 (T)	722 (T)	708	644
Poly-3 test	P=0.008	P=0.750	P=0.498	P=0.042
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	2/50 (4%)	3/48 (6%)	6/50 (12%)	10/49 (20%)
Adjusted rate	4.9%	7.6%	14.5%	26.3%
Terminal rate	2/25 (8%)	2/20 (10%)	3/25 (12%)	5/16 (31%)
First incidence (days)	722 (T)	673	627	644
Poly-3 test	P=0.002	P=0.480	P=0.133	P=0.008
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	2/50 (4%)	4/48 (8%)	6/50 (12%)	10/49 (20%)
Adjusted rate	4.9%	10.2%	14.5%	26.3%
Terminal rate	2/25 (8%)	3/20 (15%)	3/25 (12%)	5/16 (31%)
First incidence (days)	722 (T)	673	627	644
Poly-3 test	P=0.003	P=0.316	P=0.133	P=0.008
Liver: Hepatocellular Adenoma				
Overall rate	1/50 (2%)	1/49 (2%)	0/50 (0%)	3/50 (6%)
Adjusted rate	2.4%	2.5%	0.0%	7.8%
Terminal rate	0/25 (0%)	1/20 (5%)	0/25 (0%)	1/16 (6%)
First incidence (days)	718	722 (T)	—	622
Poly-3 test	P=0.153	P=0.754	P=0.501N	P=0.283
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	1/50 (2%)	1/49 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.4%	2.5%	2.4%	7.8%
Terminal rate	0/25 (0%)	1/20 (5%)	1/25 (4%)	1/16 (6%)
First incidence (days)	718	722 (T)	722 (T)	622
Poly-3 test	P=0.153	P=0.754	P=0.760	P=0.283

TABLE A3
Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	1/50 (2%)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted rate	2.4%	0.0%	0.0%	10.4%
Terminal rate	1/25 (4%)	0/20 (0%)	0/25 (0%)	3/16 (19%)
First incidence (days)	722 (T)	—	—	697
Poly-3 test	P=0.024	P=0.503N	P=0.501N	P=0.157
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted rate	2.4%	0.0%	4.9%	10.4%
Terminal rate	1/25 (4%)	0/20 (0%)	2/25 (8%)	3/16 (19%)
First incidence (days)	722 (T)	—	722 (T)	697
Poly-3 test	P=0.033	P=0.503N	P=0.498	P=0.157
Mammary Gland: Fibroadenoma				
Overall rate	4/50 (8%)	3/50 (6%)	6/50 (12%)	4/50 (8%)
Adjusted rate	9.7%	7.4%	14.4%	10.4%
Terminal rate	3/25 (12%)	2/20 (10%)	3/25 (12%)	1/16 (6%)
First incidence (days)	718	708	538	681
Poly-3 test	P=0.439	P=0.507N	P=0.378	P=0.609
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	6/50 (12%)	4/50 (8%)
Adjusted rate	9.7%	9.9%	14.4%	10.4%
Terminal rate	3/25 (12%)	3/20 (15%)	3/25 (12%)	1/16 (6%)
First incidence (days)	718	708	538	681
Poly-3 test	P=0.487	P=0.637	P=0.378	P=0.609
Pancreatic Islets: Adenoma				
Overall rate	4/50 (8%)	2/48 (4%)	1/50 (2%)	0/49 (0%)
Adjusted rate	9.6%	5.1%	2.4%	0.0%
Terminal rate	1/25 (4%)	2/20 (10%)	1/25 (4%)	0/16 (0%)
First incidence (days)	625	722 (T)	722 (T)	—
Poly-3 test	P=0.033N	P=0.366N	P=0.184N	P=0.075N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	16/50 (32%)	13/50 (26%)	12/50 (24%)	11/50 (22%)
Adjusted rate	36.9%	31.0%	27.0%	26.6%
Terminal rate	9/25 (36%)	7/20 (35%)	5/25 (20%)	3/16 (19%)
First incidence (days)	434	628	269	428
Poly-3 test	P=0.177N	P=0.365N	P=0.221N	P=0.215N
Preputial Gland: Adenoma				
Overall rate	3/50 (6%)	0/47 (0%)	7/49 (14%)	2/48 (4%)
Adjusted rate	7.2%	0.0%	16.7%	5.4%
Terminal rate	2/25 (8%)	0/19 (0%)	4/25 (16%)	2/16 (13%)
First incidence (days)	604	—	529	722 (T)
Poly-3 test	P=0.427	P=0.134N	P=0.158	P=0.556N
Preputial Gland: Carcinoma				
Overall rate	5/50 (10%)	2/47 (4%)	0/49 (0%)	1/48 (2%)
Adjusted rate	11.9%	5.3%	0.0%	2.7%
Terminal rate	4/25 (16%)	2/19 (11%)	0/25 (0%)	1/16 (6%)
First incidence (days)	388	722 (T)	—	722 (T)
Poly-3 test	P=0.046N	P=0.255N	P=0.034N	P=0.133N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Preputial Gland: Adenoma or Carcinoma				
Overall rate	8/50 (16%)	2/47 (4%)	7/49 (14%)	3/48 (6%)
Adjusted rate	18.9%	5.3%	16.7%	8.2%
Terminal rate	6/25 (24%)	2/19 (11%)	4/25 (16%)	3/16 (19%)
First incidence (days)	388	722 (T)	529	722 (T)
Poly-3 test	P=0.212N	P=0.063N	P=0.511N	P=0.146N
Skin: Squamous Cell Papilloma				
Overall rate	4/50 (8%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	9.7%	2.5%	2.4%	0.0%
Terminal rate	4/25 (16%)	1/20 (5%)	1/25 (4%)	0/16 (0%)
First incidence (days)	722 (T)	722 (T)	722 (T)	—
Poly-3 test	P=0.035N	P=0.181N	P=0.179N	P=0.069N
Skin: Keratoacanthoma				
Overall rate	6/50 (12%)	4/50 (8%)	2/50 (4%)	5/50 (10%)
Adjusted rate	14.5%	9.8%	4.9%	12.9%
Terminal rate	5/25 (20%)	2/20 (10%)	1/25 (4%)	1/16 (6%)
First incidence (days)	656	673	708	670
Poly-3 test	P=0.474N	P=0.378N	P=0.134N	P=0.548N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	8/50 (16%)	5/50 (10%)	3/50 (6%)	5/50 (10%)
Adjusted rate	19.3%	12.3%	7.3%	12.9%
Terminal rate	7/25 (28%)	3/20 (15%)	2/25 (8%)	1/16 (6%)
First incidence (days)	656	673	708	670
Poly-3 test	P=0.250N	P=0.282N	P=0.099N	P=0.318N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Trichoepithelioma, or Basal Cell Adenoma				
Overall rate	8/50 (16%)	6/50 (12%)	3/50 (6%)	7/50 (14%)
Adjusted rate	19.3%	14.7%	7.3%	18.1%
Terminal rate	7/25 (28%)	4/20 (20%)	2/25 (8%)	2/16 (13%)
First incidence (days)	656	673	708	670
Poly-3 test	P=0.474N	P=0.396N	P=0.099N	P=0.556N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	4/50 (8%)	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted rate	9.6%	4.8%	9.6%	0.0%
Terminal rate	2/25 (8%)	0/20 (0%)	2/25 (8%)	0/16 (0%)
First incidence (days)	625	553	580	—
Poly-3 test	P=0.092N	P=0.341N	P=0.642	P=0.071N
Testes: Adenoma				
Overall rate	42/49 (86%)	43/49 (88%)	43/49 (88%)	43/48 (90%)
Adjusted rate	93.0%	90.2%	93.2%	95.6%
Terminal rate	23/25 (92%)	18/20 (90%)	24/25 (96%)	16/16 (100%)
First incidence (days)	473	444	529	444
Poly-3 test	P=0.275	P=0.450N	P=0.662	P=0.464
Thyroid Gland (C-cell): Adenoma				
Overall rate	2/50 (4%)	1/50 (2%)	3/50 (6%)	2/49 (4%)
Adjusted rate	4.9%	2.5%	7.3%	5.2%
Terminal rate	2/25 (8%)	1/20 (5%)	3/25 (12%)	2/16 (13%)
First incidence (days)	722 (T)	722 (T)	722 (T)	722 (T)
Poly-3 test	P=0.466	P=0.505N	P=0.497	P=0.668

TABLE A3
Statistical Analysis of Primary Neoplasms in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	2/49 (4%)
Adjusted rate	4.9%	4.9%	7.3%	5.2%
Terminal rate	2/25 (8%)	1/20 (5%)	3/25 (12%)	2/16 (13%)
First incidence (days)	722 (T)	666	722 (T)	722 (T)
Poly-3 test	P=0.531	P=0.691	P=0.497	P=0.668
All Organs: Mononuclear Cell Leukemia				
Overall rate	29/50 (58%)	32/50 (64%)	26/50 (52%)	27/50 (54%)
Adjusted rate	62.7%	67.8%	57.4%	59.7%
Terminal rate	13/25 (52%)	11/20 (55%)	12/25 (48%)	7/16 (44%)
First incidence (days)	309	466	529	444
Poly-3 test	P=0.317N	P=0.378	P=0.381N	P=0.468N
All Organs: Benign Neoplasms				
Overall rate	47/50 (94%)	46/50 (92%)	48/50 (96%)	49/50 (98%)
Adjusted rate	99.2%	93.4%	98.0%	100.0%
Terminal rate	25/25 (100%)	19/20 (95%)	25/25 (100%)	16/16 (100%)
First incidence (days)	434	444	269	428
Poly-3 test	P=0.228	P=0.136N	P=0.712N	P=0.996
All Organs: Malignant Neoplasms				
Overall rate	34/50 (68%)	40/50 (80%)	29/50 (58%)	29/50 (58%)
Adjusted rate	71.8%	81.5%	63.1%	63.9%
Terminal rate	16/25 (64%)	14/20 (70%)	14/25 (56%)	8/16 (50%)
First incidence (days)	309	444	486	444
Poly-3 test	P=0.091N	P=0.182	P=0.243N	P=0.270N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	49/50 (98%)	49/50 (98%)	49/50 (98%)
Adjusted rate	99.7%	98.3%	98.6%	100.0%
Terminal rate	25/25 (100%)	20/20 (100%)	25/25 (100%)	16/16 (100%)
First incidence (days)	309	444	269	428
Poly-3 test	P=0.580	P=0.656N	P=0.760N	P=1.000

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, liver, lung, pancreatic islets, pituitary gland, preputial gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE A4
Historical Incidence of Renal Tubule Neoplasms in Untreated Male F344/N Rats[a]

	Incidence in Controls		
	Adenoma	**Carcinoma**	**Adenoma or Carcinoma**
Overall Historical Incidence			
Total	1/327 (0.3%)	0/327	1/327 (0.3%)
Standard deviation	0.8%		0.8%
Range	0%-2%		0%-2%

[a] Data as of 1 August 1997

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine[a]

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	11	13	15	10
Natural deaths	14	17	10	24
Survivors				
Terminal sacrifice	25	20	25	16
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(48)	(50)	(49)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, acute			1 (2%)	
Inflammation, chronic			1 (2%)	
Parasite metazoan	4 (8%)	4 (8%)	3 (6%)	2 (4%)
Intestine large, rectum	(50)	(48)	(50)	(49)
Edema		1 (2%)		
Parasite metazoan	4 (8%)	2 (4%)		1 (2%)
Intestine large, cecum	(49)	(47)	(50)	(49)
Edema		1 (2%)		
Hyperplasia, lymphoid		1 (2%)		
Inflammation, acute	1 (2%)		1 (2%)	1 (2%)
Inflammation, chronic active		1 (2%)		
Parasite metazoan			1 (2%)	1 (2%)
Ulcer	1 (2%)			
Intestine small, duodenum	(50)	(47)	(50)	(48)
Ectopic pancreas			1 (2%)	
Intestine small, jejunum	(50)	(47)	(50)	(47)
Congestion		1 (2%)		
Intestine small, ileum	(50)	(47)	(50)	(47)
Fibrosis	1 (2%)			
Hyperplasia, lymphoid	6 (12%)	9 (19%)	3 (6%)	4 (9%)
Liver	(50)	(49)	(50)	(50)
Angiectasis		1 (2%)	1 (2%)	1 (2%)
Basophilic focus	12 (24%)	5 (10%)		1 (2%)
Clear cell focus	7 (14%)	1 (2%)	7 (14%)	4 (8%)
Congestion	1 (2%)			
Degeneration, cystic	4 (8%)	12 (24%)	11 (22%)	3 (6%)
Developmental malformation			1 (2%)	1 (2%)
Eosinophilic focus	14 (28%)	23 (47%)	23 (46%)	13 (26%)
Fibrosis	1 (2%)	1 (2%)	1 (2%)	10 (20%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)		
Hepatodiaphragmatic nodule	3 (6%)	1 (2%)		
Mitotic alteration				2 (4%)
Mixed cell focus	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Necrosis	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Pigmentation	4 (8%)	11 (22%)	20 (40%)	25 (50%)
Thrombosis			1 (2%)	
Vacuolization cytoplasmic	4 (8%)	6 (12%)	13 (26%)	17 (34%)
Bile duct, hyperplasia	46 (92%)	43 (88%)	44 (88%)	49 (98%)
Centrilobular, cytomegaly		4 (8%)	8 (16%)	6 (12%)
Centrilobular, degeneration	1 (2%)	3 (6%)	2 (4%)	8 (16%)
Centrilobular, necrosis		3 (6%)		5 (10%)
Periportal, fibrosis			2 (4%)	29 (58%)

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

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Alimentary System (continued)				
Mesentery	(11)	(14)	(7)	(8)
Cyst	1 (9%)			
Hemorrhage			1 (14%)	
Inflammation, acute		1 (7%)		
Fat, necrosis	10 (91%)	13 (93%)	6 (86%)	8 (100%)
Oral mucosa	(1)		(2)	
Pharyngeal, hyperplasia			1 (50%)	
Pancreas	(50)	(48)	(50)	(49)
Atrophy	18 (36%)	15 (31%)	17 (34%)	12 (24%)
Cytoplasmic alteration	2 (4%)			
Hyperplasia	2 (4%)	4 (8%)	2 (4%)	3 (6%)
Inflammation, chronic	1 (2%)		3 (6%)	
Acinus, hyperplasia		1 (2%)		
Artery, inflammation, acute	1 (2%)			
Salivary glands	(50)	(50)	(50)	(50)
Cellular alteration				1 (2%)
Inflammation, chronic active		1 (2%)		
Stomach, forestomach	(50)	(49)	(50)	(49)
Hyperkeratosis				2 (4%)
Inflammation, acute		1 (2%)		1 (2%)
Inflammation, chronic active	2 (4%)			8 (16%)
Ulcer	2 (4%)	10 (20%)	3 (6%)	4 (8%)
Epithelium, hyperplasia, squamous	1 (2%)	7 (14%)	7 (14%)	11 (22%)
Stomach, glandular	(50)	(49)	(50)	(49)
Erosion	15 (30%)	17 (35%)	12 (24%)	12 (24%)
Inflammation, acute				1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)		
Inflammation, chronic active			1 (2%)	1 (2%)
Mineralization		2 (4%)	2 (4%)	8 (16%)
Necrosis				1 (2%)
Ulcer	2 (4%)	5 (10%)	1 (2%)	1 (2%)
Tooth	(2)	(1)	(1)	
Dysplasia		1 (100%)		
Inflammation, acute	1 (50%)			
Inflammation, chronic active	1 (50%)		1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	45 (90%)	43 (86%)	43 (86%)	46 (92%)
Mineralization	1 (2%)		3 (6%)	2 (4%)
Thrombosis	2 (4%)	6 (12%)	3 (6%)	4 (8%)
Coronary artery, inflammation, chronic active		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(49)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)			1 (2%)
Congestion			1 (2%)	
Hyperplasia	8 (16%)	7 (14%)	7 (14%)	2 (4%)
Hypertrophy	1 (2%)			2 (4%)
Vacuolization cytoplasmic	9 (18%)	5 (10%)	9 (18%)	7 (14%)
Adrenal medulla	(50)	(49)	(50)	(49)
Hyperplasia	17 (34%)	22 (45%)	19 (38%)	15 (31%)
Bilateral, hyperplasia	1 (2%)	1 (2%)		1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Endocrine System (continued)				
Islets, pancreatic	(50)	(48)	(50)	(49)
Hyperplasia	5 (10%)	2 (4%)	1 (2%)	1 (2%)
Parathyroid gland	(50)	(50)	(50)	(48)
Hyperplasia		1 (2%)	3 (6%)	3 (6%)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, angiectasis		2 (4%)	2 (4%)	2 (4%)
Pars distalis, cyst	2 (4%)	8 (16%)	3 (6%)	1 (2%)
Pars distalis, degeneration				1 (2%)
Pars distalis, ectasia		1 (2%)		
Pars distalis, hemorrhage	1 (2%)			
Pars distalis, hyperplasia	22 (44%)	16 (32%)	18 (36%)	12 (24%)
Pars distalis, thrombosis		1 (2%)		
Thyroid gland	(50)	(50)	(50)	(49)
Pigmentation		1 (2%)		
Ultimobranchial cyst	1 (2%)	1 (2%)		1 (2%)
C-cell, hyperplasia	7 (14%)	5 (10%)	3 (6%)	3 (6%)
Follicle, dilatation	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Follicular cell, hyperplasia	1 (2%)	5 (10%)	1 (2%)	2 (4%)
General Body System				
None				
Genital System				
Epididymis	(49)	(49)	(49)	(48)
Fibrosis			1 (2%)	
Inflammation, chronic			2 (4%)	
Penis	(1)			
Inflammation, chronic active	1 (100%)			
Preputial gland	(50)	(47)	(49)	(48)
Atrophy	1 (2%)			
Hyperplasia	4 (8%)	3 (6%)	5 (10%)	4 (8%)
Inflammation, acute	2 (4%)			2 (4%)
Inflammation, chronic	17 (34%)	25 (53%)	17 (35%)	23 (48%)
Inflammation, chronic active	5 (10%)	14 (30%)	14 (29%)	5 (10%)
Duct, dilatation		2 (4%)		2 (4%)
Prostate	(50)	(48)	(50)	(49)
Hemorrhage, chronic		1 (2%)		
Hyperplasia, focal	1 (2%)	1 (2%)	4 (8%)	2 (4%)
Inflammation, acute	2 (4%)	2 (4%)		1 (2%)
Inflammation, chronic	2 (4%)	1 (2%)	4 (8%)	3 (6%)
Inflammation, chronic active	31 (62%)	29 (60%)	24 (48%)	22 (45%)
Seminal vesicle	(50)	(47)	(50)	(48)
Dilatation			1 (2%)	
Fibrosis				1 (2%)
Inflammation, acute		1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)			1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Mineralization				1 (2%)
Testes	(49)	(49)	(49)	(48)
Atrophy	2 (4%)			
Necrosis	1 (2%)			
Thrombosis			1 (2%)	
Bilateral, interstitial cell, hyperplasia	3 (6%)	2 (4%)	3 (6%)	1 (2%)
Interstitial cell, hyperplasia	9 (18%)	6 (12%)	6 (12%)	4 (8%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Depletion cellular	2 (4%)	4 (8%)	3 (6%)	1 (2%)
Fibrosis			1 (2%)	1 (2%)
Hemorrhage		1 (2%)		
Lymph node	(20)	(25)	(20)	(23)
Iliac, hyperplasia, lymphoid	1 (5%)	1 (4%)		
Iliac, infiltration cellular, plasma cell	1 (5%)			
Mediastinal, congestion		5 (20%)		4 (17%)
Mediastinal, ectasia			1 (5%)	
Mediastinal, hemorrhage	1 (5%)	1 (4%)	2 (10%)	
Mediastinal, hyperplasia, lymphoid				1 (4%)
Mediastinal, pigmentation			1 (5%)	
Pancreatic, congestion			1 (5%)	2 (9%)
Pancreatic, edema				1 (4%)
Pancreatic, hyperplasia, lymphoid			1 (5%)	
Pancreatic, inflammation, chronic active				1 (4%)
Pancreatic, necrosis			1 (5%)	
Pancreatic, pigmentation			1 (5%)	
Renal, congestion	1 (5%)		1 (5%)	3 (13%)
Renal, edema			1 (5%)	
Renal, fibrosis		1 (4%)		
Renal, hyperplasia, lymphoid			2 (10%)	
Renal, pigmentation			1 (5%)	4 (17%)
Lymph node, mandibular	(50)	(50)	(50)	(50)
Congestion		1 (2%)	1 (2%)	
Ectasia	4 (8%)	3 (6%)	2 (4%)	3 (6%)
Hyperplasia, lymphoid			1 (2%)	
Inflammation, chronic active		1 (2%)		
Lymph node, mesenteric	(50)	(47)	(50)	(48)
Congestion		2 (4%)		1 (2%)
Ectasia	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Fibrosis			2 (4%)	
Hemorrhage		1 (2%)		1 (2%)
Inflammation, acute	1 (2%)			
Necrosis		3 (6%)		
Spleen	(49)	(48)	(50)	(49)
Atrophy			1 (2%)	
Congestion		1 (2%)		1 (2%)
Fibrosis	14 (29%)	11 (23%)	9 (18%)	12 (24%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		1 (2%)
Hyperplasia, focal			1 (2%)	
Necrosis	4 (8%)	2 (4%)	1 (2%)	
Pigmentation				2 (4%)
Thrombosis		1 (2%)		
Thymus	(50)	(49)	(48)	(50)
Cyst	1 (2%)			
Ectopic parathyroid gland				1 (2%)
Fibrosis		1 (2%)		
Hemorrhage		1 (2%)		1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Integumentary System				
Mammary gland	(49)	(48)	(50)	(49)
Concretion		1 (2%)		
Galactocele			1 (2%)	
Hyperplasia	1 (2%)	3 (6%)	2 (4%)	3 (6%)
Duct, dilatation	14 (29%)	16 (33%)	12 (24%)	15 (31%)
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion			2 (4%)	
Hyperkeratosis			1 (2%)	
Hyperplasia, squamous		1 (2%)	1 (2%)	
Inflammation, acute		1 (2%)		
Necrosis			1 (2%)	
Epidermis, degeneration				1 (2%)
Subcutaneous tissue, inflammation, chronic active			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	2 (4%)	1 (2%)	4 (8%)	6 (12%)
Hyperostosis		1 (2%)		
Osteomalacia				1 (2%)
Osteopetrosis	1 (2%)		2 (4%)	
Nervous System				
Brain	(50)	(50)	(48)	(50)
Hemorrhage			1 (2%)	
Hydrocephalus	1 (2%)			
Inflammation, acute				1 (2%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion		1 (2%)		2 (4%)
Hemorrhage			2 (4%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Infiltration cellular, histiocyte	6 (12%)	4 (8%)	9 (18%)	9 (18%)
Inflammation, chronic	8 (16%)	10 (20%)	12 (24%)	9 (18%)
Metaplasia, osseous				1 (2%)
Alveolar epithelium, hyperplasia		3 (6%)		3 (6%)
Nose	(50)	(50)	(49)	(50)
Cyst		1 (2%)	1 (2%)	
Cyst epithelial inclusion				1 (2%)
Inflammation, chronic			1 (2%)	
Inflammation, chronic active	26 (52%)	18 (36%)	21 (43%)	25 (50%)
Polyp inflammatory				1 (2%)
Nasolacrimal duct, cyst			1 (2%)	1 (2%)
Nasolacrimal duct, inflammation, acute	1 (2%)			1 (2%)
Squamous epithelium, nasolacrimal duct, hyperplasia		1 (2%)		
Special Senses System				
Eye		(1)		
Atrophy		1 (100%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Urinary System				
Kidney	(50)	(48)	(50)	(49)
Atrophy			1 (2%)	
Cyst	3 (6%)	3 (6%)	13 (26%)	10 (20%)
Developmental malformation	2 (4%)			
Hydronephrosis	3 (6%)	1 (2%)		2 (4%)
Inflammation, acute				1 (2%)
Nephropathy	47 (94%)	47 (98%)	49 (98%)	49 (100%)
Pigmentation				1 (2%)
Artery, inflammation, acute	1 (2%)			
Artery, inflammation, chronic active	1 (2%)			
Capsule, hemorrhage, chronic		1 (2%)		
Pelvis, inflammation, acute				1 (2%)
Renal tubule, hyperplasia	1 (2%)		4 (8%)	7 (14%)
Urinary bladder	(50)	(47)	(50)	(49)
Hemorrhage		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	4 (8%)		1 (2%)	1 (2%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE F344/N RATS IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

TABLE B1
Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine[a]

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	3	8	7	2
Natural deaths	15	5	14	22
Survivors				
Terminal sacrifice	32	37	29	26
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Schwannoma malignant, metastatic, uterus		1 (2%)		
Intestine large, colon	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Intestine large, cecum	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Intestine small, duodenum	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Carcinoma, metastatic, uterus		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Intestine small, jejunum	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Intestine small, ileum	(50)	(49)	(50)	(50)
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Carcinoma, metastatic, pancreas		1 (2%)		
Carcinoma, metastatic, uterus		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Hepatocellular adenoma	1 (2%)		1 (2%)	
Mesentery	(9)	(11)	(7)	(12)
Carcinoma, metastatic, uterus		1 (9%)		
Fibrous histiocytoma	1 (11%)			
Schwannoma malignant, metastatic, uterus		1 (9%)		
Oral mucosa	(2)	(1)		(2)
Pharyngeal, squamous cell carcinoma	2 (100%)			
Pharyngeal, squamous cell papilloma				1 (50%)
Pancreas	(49)	(50)	(50)	(50)
Carcinoma		2 (4%)		
Carcinoma, metastatic, uterus		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Acinus, adenoma		1 (2%)		1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(50)	(50)
Stomach, glandular	(50)	(50)	(50)	(50)
Carcinoma, metastatic, uterus		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Tongue			(1)	(2)
Squamous cell papilloma				1 (50%)

TABLE B1
Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Adrenal medulla	(50)	(50)	(50)	(49)
Pheochromocytoma benign	2 (4%)		1 (2%)	
Bilateral, pheochromocytoma benign	1 (2%)			
Islets, pancreatic	(49)	(50)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Parathyroid gland	(48)	(50)	(48)	(50)
Pituitary gland	(49)	(50)	(50)	(50)
Pars distalis, adenoma	17 (35%)	12 (24%)	18 (36%)	15 (30%)
Pars distalis, adenoma, multiple	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	3 (6%)	2 (4%)	2 (4%)	
General Body System				
None				
Genital System				
Clitoral gland	(47)	(48)	(50)	(49)
Adenoma	2 (4%)	3 (6%)		1 (2%)
Carcinoma		1 (2%)	1 (2%)	2 (4%)
Bilateral, adenoma			1 (2%)	
Ovary	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Carcinoma, metastatic, pancreas		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Granulosa-theca tumor malignant			1 (2%)	
Uterus	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		
Carcinoma, metastatic, pancreas		1 (2%)		
Polyp stromal	4 (8%)	7 (14%)	9 (18%)	7 (14%)
Polyp stromal, multiple				1 (2%)
Sarcoma stromal	1 (2%)			
Schwannoma malignant, metastatic, uterus		1 (2%)		
Vagina				(1)
Lipoma				1 (100%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Lymph node	(7)	(9)	(15)	(19)
Mediastinal, carcinoma, metastatic, kidney		1 (11%)		
Mediastinal, carcinoma, metastatic, pancreas		1 (11%)		
Mediastinal, fibrous histiocytoma, metastatic, mesentery	1 (14%)			

TABLE B1
Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Hematopoietic System (continued)				
Lymph node, mandibular	(49)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Lymph node, mesenteric	(49)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Carcinoma, metastatic, uterus		1 (2%)		
Fibrous histiocytoma, metastatic, mesentery	1 (2%)			
Spleen	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Carcinoma, metastatic, pancreas		1 (2%)		
Carcinoma, metastatic, uterus		1 (2%)		
Thymus	(50)	(50)	(50)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Carcinoma, metastatic, pancreas		1 (2%)		
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Adenoma	2 (4%)	1 (2%)	1 (2%)	
Carcinoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Fibroadenoma	19 (38%)	15 (30%)	14 (28%)	18 (36%)
Fibroadenoma, multiple	8 (16%)	10 (20%)	6 (12%)	2 (4%)
Sarcoma	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma		1 (2%)		
Keratoacanthoma				1 (2%)
Trichoepithelioma				1 (2%)
Musculoskeletal System				
Skeletal muscle	(2)	(1)		
Carcinoma, metastatic, uterus		1 (100%)		
Abdominal, fibrous histiocytoma, metastatic, mesentery	1 (50%)			
Abdominal, lipoma	1 (50%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant	2 (4%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Carcinoma, metastatic, clitoral gland				1 (2%)
Carcinoma, metastatic, kidney		1 (2%)		
Carcinoma, metastatic, mammary gland			1 (2%)	
Carcinoma, metastatic, pancreas		2 (4%)		
Carcinoma, metastatic, uterus		1 (2%)		
Nose	(50)	(50)	(50)	(50)
Pleura		(1)		
Carcinoma, metastatic, kidney		1 (100%)		
Trachea	(50)	(50)	(50)	(50)

TABLE B1
Summary of the Incidence of Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Special Senses System				
Zymbal's gland		(1)		(1)
Carcinoma		1 (100%)		1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Carcinoma, metastatic, pancreas		1 (2%)		
Transitional epithelium, carcinoma		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	12 (24%)	16 (32%)	22 (44%)	23 (46%)
Lymphoma malignant	1 (2%)			1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	45	42	45	44
Total primary neoplasms	84	78	80	80
Total animals with benign neoplasms	39	34	35	35
Total benign neoplasms	63	54	55	52
Total animals with malignant neoplasms	21	22	23	28
Total malignant neoplasms	21	24	25	28
Total animals with metastatic neoplasms	1	5	1	1
Total metastatic neoplasms	13	36	1	1

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

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

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

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

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	230	231	232	234	235	236	237	238	251	252	253	254	254	241	242	243	244	245	247	248	256	257	258	263	264	265	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery				X																							1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery				X																							1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery				X																							1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery				X																							1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery				X																							1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery				X																							1
Hepatocellular adenoma																					X						1
Mesentery				+								+	+			+					+						9
Fibrous histiocytoma				X																							1
Oral mucosa																											2
Pharyngeal, squamous cell carcinoma																											2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, mesentery				X																							1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery				X																							1
Cardiovascular System																											
Heart	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																						X			X		2
Bilateral, pheochromocytoma benign																											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																						X					1
Fibrous histiocytoma, metastatic, mesentery				X																							1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X															X			X	X	X	X			X		17
Pars distalis, adenoma, multiple																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																						X					3
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																											2

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	3 9 9	4 9 3	5 0 3	5 8 8	5 9 6	6 2 2	6 3 6	6 4 9	6 6 1	6 6 7	6 7 1	6 7 3	6 8 1	6 8 7	6 9 6	7 1 7	7 1 7	7 2 2	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 2 3	2 3 3	2 5 9	2 5 0	2 2 9	2 2 0	2 3 9	2 2 1	2 6 0	2 6 1	2 6 2	2 1 9	2 4 0	2 2 5	2 4 6	2 4 9	2 5 5	2 1 8	2 1 6	2 1 7	2 2 2	2 2 4	2 2 6	2 2 7	2 2 8
Genital System (continued)																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, mesentery																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Sarcoma stromal		X																							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+					+			+	+			+											
Mediastinal, fibrous histiocytoma, metastatic, mesentery																									
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, mesentery																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Carcinoma																									
Fibroadenoma							X		X		X	X						X			X				X
Fibroadenoma, multiple					X									X	X	X						X	X		
Sarcoma															X										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Abdominal, fibrous histiocytoma, metastatic, mesentery																									
Abdominal, lipoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant					X																				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X	X			X					X				X		X
Lymphoma malignant																									

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	230	231	232	234	235	236	237	238	251	252	253	254	241	242	243	244	245	247	248	256	257	258	263	264	265	Total Tissues/ Tumors
Genital System (continued)																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, mesentery				X																						1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X		X											X							X	4
Sarcoma stromal																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+																		+				7
Mediastinal, fibrous histiocytoma, metastatic, mesentery				X																						1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, mesentery				X																						1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											2
Carcinoma	X																									1
Fibroadenoma	X		X			X					X				X	X	X	X		X	X	X	X			19
Fibroadenoma, multiple												X	X													8
Sarcoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle				+				+																		2
Abdominal, fibrous histiocytoma, metastatic, mesentery				X																						1
Abdominal, lipoma								X																		1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant								X																		2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland						+																				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X						X			X		X		X								12
Lymphoma malignant							X																			1

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	
Carcass ID Number	29 1	29 2	29 3	29 4	29 6	29 7	29 8	30 2	30 4	30 5	30 6	30 7	30 8	30 9	31 0	31 3	31 4	71	75	86	87	89	90	95	03	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, uterus																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Carcinoma, metastatic, uterus																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Carcinoma, metastatic, pancreas																										1
Carcinoma, metastatic, uterus																										1
Mesentery											+								+		+			+		11
Carcinoma, metastatic, uterus																										1
Schwannoma malignant, metastatic, uterus																										1
Oral mucosa																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										2
Carcinoma, metastatic, uterus																										1
Acinus, adenoma				X																						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, uterus																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X																X	X		X			X			12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																X										1
C-cell, adenoma																							X			2
General Body System																										
None																										

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	4 8 8	5 3 3	5 4 6	5 7 0	6 1 1	6 4 2	6 5 0	6 6 6	6 6 6	6 8 2	6 9 5	7 1 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 8 0	2 7 7	2 8 4	3 0 0	2 0 8	3 1 2	2 7 8	2 9 9	3 1 5	3 0 1	2 6 7	2 7 4	3 1 1	2 6 6	2 6 8	2 6 9	2 7 0	2 7 2	2 7 3	2 7 6	2 7 9	2 8 1	2 8 2	2 8 3	2 8 5
Genital System																									
Clitoral gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X								X			
Carcinoma													X												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney							X																		
Carcinoma, metastatic, pancreas					X																				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
Carcinoma, metastatic, pancreas					X																				
Polyp stromal															X				X			X	X		
Schwannoma malignant, metastatic, uterus				X																					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney							X																		
Lymph node				+	+		+				+	+					+								
Mediastinal, carcinoma, metastatic, kidney							X																		
Mediastinal, carcinoma, metastatic, pancreas					X																				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney							X																		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas					X																				
Carcinoma, metastatic, uterus	X																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney							X																		
Carcinoma, metastatic, pancreas					X																				
Carcinoma, metastatic, uterus	X																								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney							X																		
Carcinoma, metastatic, pancreas					X																				
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Carcinoma							X																		
Fibroadenoma								X	X	X	X	X	X	X			X							X	X
Fibroadenoma, multiple																			X	X	X	X	X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Carcinoma, metastatic, uterus	X																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	
Carcass ID Number	29 1	29 2	29 3	29 4	29 6	29 7	29 8	30 2	30 4	30 5	30 6	30 7	30 8	30 9	31 0	31 3	31 4	71	75	86	87	89	90	95	30 3	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma						X																				3
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Carcinoma, metastatic, pancreas																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Carcinoma, metastatic, pancreas																										1
Polyp stromal	X															X									X	7
Schwannoma malignant, metastatic, uterus																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Lymph node													+							+			+			9
Mediastinal, carcinoma, metastatic, kidney																										1
Mediastinal, carcinoma, metastatic, pancreas																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Carcinoma, metastatic, uterus																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Carcinoma, metastatic, pancreas																										1
Carcinoma, metastatic, uterus																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, kidney																										1
Carcinoma, metastatic, pancreas																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																					X					2
Fibroadenoma				X														X			X		X	X		15
Fibroadenoma, multiple						X	X						X		X					X						10
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Carcinoma, metastatic, uterus																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	4 8 8	5 3 3	5 4 6	5 7 0	6 1 1	6 4 2	6 5 0	6 6 6	6 6 6	6 8 2	6 9 5	7 1 7	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 8 0	2 7 7	2 8 4	3 0 0	2 8 8	3 1 2	2 7 8	2 9 9	3 1 5	3 0 1	2 6 7	2 7 4	3 1 1	2 6 6	2 6 8	2 6 9	2 7 0	2 7 2	2 7 3	2 7 6	2 7 9	2 8 1	2 8 2	2 8 3	2 8 5
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, kidney							X																		
Carcinoma, metastatic, pancreas			X		X																				
Carcinoma, metastatic, uterus	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura							+																		
Carcinoma, metastatic, kidney							X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Zymbal's gland		+																							
Carcinoma		X																							
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pancreas					X																				
Transitional epithelium, carcinoma							X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X							X	X	X			X		X	X				X	X		X

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	
Carcass ID Number	29 1	29 2	29 3	29 4	29 6	29 7	29 8	30 2	30 4	30 5	30 6	30 7	30 8	30 9	31 0	31 3	31 4	71	75	86	87	89	90	95	03	Total Tissues/ Tumors
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X																	1
Carcinoma, metastatic, kidney																										1
Carcinoma, metastatic, pancreas																										2
Carcinoma, metastatic, uterus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										1
Carcinoma, metastatic, kidney																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Zymbal's gland																										1
Carcinoma																										1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pancreas																										1
Transitional epithelium, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X		X					X								X					X	16

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	4 9 6	5 2 1	5 4 9	5 6 1	5 7 3	5 8 0	5 8 6	6 0 5	6 2 4	6 6 5	6 7 1	6 8 7	6 9 8	6 9 9	7 0 0	7 0 3	7 0 7	7 0 7	7 1 1	7 1 8	7 2 1	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 3 9	3 4 8	3 2 7	3 5 3	3 1 7	3 5 9	3 6 3	3 5 1	3 5 4	3 3 4	3 5 6	3 3 7	3 4 6	3 5 7	3 6 2	3 2 0	3 1 8	3 4 5	3 5 0	3 4 0	3 1 6	3 1 9	3 2 1	3 2 2	3 2 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery	+		+			+							+												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X	X		X		X					X	X		X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X								
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																		X							
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-theca tumor malignant														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal												X					X				X				
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+	+	+	+		+	+				+	+					+	+					
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	32 4	32 5	32 6	32 8	32 9	33 0	33 1	33 2	33 3	33 5	33 6	33 8	34 1	34 2	34 3	34 4	34 7	34 9	35 2	35 5	35 8	36 0	36 1	36 4	36 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																									X	1
Mesentery						+					+											+				7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																							+			1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																X										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X					X							X				X		X	X	X	X	X		X	18
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma															X											2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Bilateral, adenoma																								X		1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-theca tumor malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X		X			X								X			X	X					9
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node														+	+	+		+								15
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	4 9 6	5 2 1	5 4 9	5 6 1	5 7 3	5 8 0	5 8 6	6 0 5	6 2 4	6 6 5	6 7 1	6 8 7	6 9 8	6 9 9	7 0 0	7 0 3	7 0 7	7 0 7	7 1 1	7 1 8	7 2 1	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	3 3 9	3 4 8	3 2 7	3 5 3	3 1 7	3 5 9	3 6 3	3 5 1	3 5 4	3 3 4	3 5 6	3 3 7	3 4 6	3 5 7	3 6 2	3 2 0	3 1 8	3 4 5	3 5 0	3 4 0	3 1 6	3 1 9	3 2 1	3 2 2	3 2 3
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Carcinoma														X											
Fibroadenoma						X					X								X			X		X	
Fibroadenoma, multiple													X				X								X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X										
Carcinoma, metastatic, mammary gland														X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X		X	X	X	X		X			X	X		X			X	X	X			X	X

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	32 4	32 5	32 6	32 8	32 9	33 0	33 1	33 2	33 3	33 5	33 6	33 8	34 1	34 2	34 3	34 4	34 7	34 9	35 2	35 5	35 8	36 0	36 1	36 4	36 5	Total Tissues/ Tumors	
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Adenoma																										1	
Carcinoma																										1	
Fibroadenoma		X	X				X		X		X					X	X		X						X	14	
Fibroadenoma, multiple														X				X		X						6	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Alveolar/bronchiolar adenoma																										1	
Carcinoma, metastatic, mammary gland																										1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Special Senses System																											
Eye											+															1	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear				X		X	X					X		X				X								22	

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	380	457	503	511	583	584	589	603	605	608	616	625	628	634	636	639	641	649	672	673	687	692	705	711	729
Carcass ID Number	394	374	372	367	404	413	378	396	401	382	368	398	399	403	414	393	409	397	391	369	402	405	381	390	366
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery	+					+							+					+	+				+	+	
Oral mucosa																									
Pharyngeal, squamous cell papilloma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue								+																	
Squamous cell papilloma								X																	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma														X					X	X	X	X			X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal			X											X											
Polyp stromal, multiple																							X		
Vagina												+													
Lipoma												X													

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	
Carcass ID Number	370	371	373	376	377	379	380	383	384	385	386	387	388	389	392	395	400	406	407	408	410	411	412	415	375	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+				+							+	+						+							12
Oral mucosa							+						+													2
Pharyngeal, squamous cell papilloma													X													1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma																				X						1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																				+						2
Squamous cell papilloma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X		X	X	X			X	X			X			X			X				15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X						1
Carcinoma										X									X							2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal										X	X			X		X		X								7
Polyp stromal, multiple																										1
Vagina																										1
Lipoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	380	457	503	511	583	588	589	603	605	608	616	625	628	634	636	639	641	649	672	673	687	692	705	711	729
Carcass ID Number	39404	37442	37726	36707	40443	41413	37788	39616	40101	38212	36808	39808	39909	40303	41404	39313	40909	39707	39911	39619	40002	40205	38101	39910	36606
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+	+			+	+	+			+	+	+	+			+	+	+		+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma							X		X										X			X			
Fibroadenoma, multiple												X													
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Trichoepithelioma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X													
Carcinoma, metastatic, clitoral gland																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X	X		X	X	X	X		X	X	X	X	X	X		X		X	X	X	X	
Lymphoma malignant																									

TABLE B2
Individual Animal Tumor Pathology of Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	
Carcass ID Number	37 70	37 71	37 73	37 76	37 77	37 79	38 80	38 83	38 84	38 85	38 86	38 87	38 88	38 89	39 02	39 25	40 00	40 06	40 07	40 08	41 10	41 11	41 12	41 15	37 75	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+									+									+		+					19
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma								X																		1
Fibroadenoma	X		X	X	X		X		X		X	X		X		X				X	X	X		X		18
Fibroadenoma, multiple																	X									2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																									X	1
Trichoepithelioma												X														1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			2
Carcinoma, metastatic, clitoral gland										X																1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye						+	+																			2
Zymbal's gland																								+		1
Carcinoma																								X		1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X	X							X										X					23
Lymphoma malignant													X													1

TABLE B3
Statistical Analysis of Primary Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	3/50 (6%)	0/50 (0%)	1/50 (2%)	0/49 (0%)
Adjusted rate[b]	6.7%	0.0%	2.3%	0.0%
Terminal rate[c]	2/32 (6%)	0/37 (0%)	1/29 (3%)	0/25 (0%)
First incidence (days)	667	—[e]	729 (T)	—
Poly-3 test[d]	P=0.094N	P=0.114N	P=0.311N	P=0.140N
Clitoral Gland: Adenoma				
Overall rate	2/47 (4%)	3/48 (6%)	1/50 (2%)	1/49 (2%)
Adjusted rate	4.7%	6.8%	2.3%	2.5%
Terminal rate	1/32 (3%)	3/36 (8%)	1/29 (3%)	1/25 (4%)
First incidence (days)	622	729 (T)	729 (T)	729 (T)
Poly-3 test	P=0.295N	P=0.521	P=0.487N	P=0.522N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	2/47 (4%)	4/48 (8%)	2/50 (4%)	3/49 (6%)
Adjusted rate	4.7%	9.0%	4.6%	7.6%
Terminal rate	1/32 (3%)	3/36 (8%)	1/29 (3%)	3/25 (12%)
First incidence (days)	622	728	707	729 (T)
Poly-3 test	P=0.483	P=0.359	P=0.680N	P=0.472
Mammary Gland: Fibroadenoma				
Overall rate	27/50 (54%)	25/50 (50%)	20/50 (40%)	20/50 (40%)
Adjusted rate	58.5%	53.7%	44.6%	47.3%
Terminal rate	18/32 (56%)	19/37 (51%)	15/29 (52%)	15/26 (58%)
First incidence (days)	596	666	580	589
Poly-3 test	P=0.139N	P=0.398N	P=0.126N	P=0.193N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	27/50 (54%)	25/50 (50%)	20/50 (40%)	20/50 (40%)
Adjusted rate	58.5%	53.7%	44.6%	47.3%
Terminal rate	18/32 (56%)	19/37 (51%)	15/29 (52%)	15/26 (58%)
First incidence (days)	596	666	580	589
Poly-3 test	P=0.139N	P=0.398N	P=0.126N	P=0.193N
Mammary Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	6.8%	6.5%	4.5%	2.5%
Terminal rate	2/32 (6%)	1/37 (3%)	0/29 (0%)	1/26 (4%)
First incidence (days)	717	650	699	729 (T)
Poly-3 test	P=0.223N	P=0.646N	P=0.503N	P=0.337N
Mammary Gland: Fibroadenoma, Adenoma, or Carcinoma				
Overall rate	27/50 (54%)	26/50 (52%)	21/50 (42%)	21/50 (42%)
Adjusted rate	58.5%	55.5%	46.7%	49.6%
Terminal rate	18/32 (56%)	19/37 (51%)	15/29 (52%)	16/26 (62%)
First incidence (days)	596	650	580	589
Poly-3 test	P=0.191N	P=0.468N	P=0.174N	P=0.262N
Pancreas: Adenoma or Carcinoma				
Overall rate	0/49 (0%)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	0.0%	6.4%	0.0%	2.5%
Terminal rate	0/32 (0%)	1/37 (3%)	0/29 (0%)	1/26 (4%)
First incidence (days)	—	546	—	729 (T)
Poly-3 test	P=0.609	P=0.131	—[f]	P=0.486

TABLE B3
Statistical Analysis of Primary Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	18/49 (37%)	12/50 (24%)	18/50 (36%)	15/50 (30%)
Adjusted rate	39.9%	25.8%	40.4%	35.8%
Terminal rate	10/31 (32%)	8/37 (22%)	13/29 (45%)	10/26 (39%)
First incidence (days)	588	642	671	634
Poly-3 test	P=0.509	P=0.110N	P=0.565	P=0.431N
Thyroid Gland (C-cell): Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.7%	6.5%	4.6%	0.0%
Terminal rate	1/32 (3%)	2/37 (5%)	1/29 (3%)	0/26 (0%)
First incidence (days)	687	695	707	—
Poly-3 test	P=0.087N	P=0.649N	P=0.506N	P=0.135N
Uterus: Stromal Polyp				
Overall rate	4/50 (8%)	7/50 (14%)	9/50 (18%)	8/50 (16%)
Adjusted rate	9.0%	15.3%	20.4%	19.1%
Terminal rate	4/32 (13%)	7/37 (19%)	6/29 (21%)	5/26 (19%)
First incidence (days)	729 (T)	729 (T)	687	503
Poly-3 test	P=0.125	P=0.278	P=0.111	P=0.147
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	5/50 (10%)	7/50 (14%)	9/50 (18%)	8/50 (16%)
Adjusted rate	11.1%	15.3%	20.4%	19.1%
Terminal rate	4/32 (13%)	7/37 (19%)	6/29 (21%)	5/26 (19%)
First incidence (days)	493	729 (T)	687	503
Poly-3 test	P=0.177	P=0.390	P=0.180	P=0.227
All Organs: Mononuclear Cell Leukemia				
Overall rate	12/50 (24%)	16/50 (32%)	22/50 (44%)	23/50 (46%)
Adjusted rate	26.5%	34.3%	45.4%	48.7%
Terminal rate	8/32 (25%)	12/37 (32%)	8/29 (28%)	5/26 (19%)
First incidence (days)	636	546	496	380
Poly-3 test	P=0.013	P=0.279	P=0.043	P=0.020
All Organs: Benign Neoplasms				
Overall rate	39/50 (78%)	34/50 (68%)	35/50 (70%)	35/50 (70%)
Adjusted rate	81.6%	72.5%	77.1%	78.6%
Terminal rate	24/32 (75%)	27/37 (73%)	25/29 (86%)	23/26 (89%)
First incidence (days)	588	642	580	503
Poly-3 test	P=0.511N	P=0.203N	P=0.385N	P=0.459N
All Organs: Malignant Neoplasms				
Overall rate	21/50 (42%)	23/50 (46%)	23/50 (46%)	28/50 (56%)
Adjusted rate	44.3%	46.7%	47.4%	59.3%
Terminal rate	13/32 (41%)	13/37 (35%)	8/29 (28%)	10/26 (39%)
First incidence (days)	399	488	496	380
Poly-3 test	P=0.077	P=0.486	P=0.459	P=0.100

TABLE B3
Statistical Analysis of Primary Neoplasms in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	43/50 (86%)	45/50 (90%)	44/50 (88%)
Adjusted rate	91.2%	86.0%	91.7%	91.0%
Terminal rate	28/32 (88%)	30/37 (81%)	26/29 (90%)	23/26 (89%)
First incidence (days)	399	488	496	380
Poly-3 test	P=0.452	P=0.307N	P=0.613	P=0.627N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, clitoral gland, pancreas, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B4
Historical Incidence of Leukemias in Untreated Female F344/N Rats[a]

	Incidence in Controls
Overall Historical Incidence	
Total	102/330 (30.9%)
Standard deviation	10.0%
Range	16%-44%

[a] Data as of 1 August 1997; includes data for lymphocytic, monocytic, mononuclear cell, and undifferentiated leukemias

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine[a]

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	3	8	7	2
Natural deaths	15	5	14	22
Survivors				
Terminal sacrifice	32	37	29	26
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)	
Parasite metazoan	3 (6%)	3 (6%)	3 (6%)	1 (2%)
Intestine large, rectum	(50)	(50)	(50)	(50)
Parasite metazoan	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Intestine large, cecum	(50)	(50)	(50)	(50)
Inflammation, chronic				1 (2%)
Inflammation, chronic active			1 (2%)	
Parasite metazoan			1 (2%)	
Ulcer		1 (2%)		
Intestine small, duodenum	(50)	(50)	(50)	(50)
Ectopic pancreas	1 (2%)			
Inflammation, chronic active			1 (2%)	
Intestine small, ileum	(50)	(49)	(50)	(50)
Hyperplasia, lymphoid	3 (6%)	2 (4%)	2 (4%)	5 (10%)
Inflammation, chronic active				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Basophilic focus	38 (76%)	28 (56%)	11 (22%)	
Clear cell focus	4 (8%)	9 (18%)	11 (22%)	16 (32%)
Congestion	4 (8%)	1 (2%)	3 (6%)	2 (4%)
Developmental malformation	1 (2%)	2 (4%)	1 (2%)	
Eosinophilic focus	19 (38%)	24 (48%)	22 (44%)	15 (30%)
Fibrosis	1 (2%)	1 (2%)		
Hematopoietic cell proliferation		1 (2%)	1 (2%)	2 (4%)
Hemorrhage		1 (2%)	1 (2%)	
Hepatodiaphragmatic nodule	9 (18%)	8 (16%)	3 (6%)	3 (6%)
Inflammation, chronic active	9 (18%)	1 (2%)	2 (4%)	4 (8%)
Mitotic alteration	1 (2%)			1 (2%)
Mixed cell focus	2 (4%)	4 (8%)	1 (2%)	5 (10%)
Necrosis	6 (12%)	1 (2%)	1 (2%)	
Pigmentation	6 (12%)	2 (4%)	6 (12%)	17 (34%)
Tension lipidosis	3 (6%)	1 (2%)		
Vacuolization cytoplasmic	10 (20%)	7 (14%)	9 (18%)	18 (36%)
Bile duct, hyperplasia	20 (40%)	29 (58%)	34 (68%)	29 (58%)
Capsule, inflammation, chronic				2 (4%)
Centrilobular, cytomegaly		1 (2%)	4 (8%)	20 (40%)
Centrilobular, degeneration	1 (2%)	2 (4%)	2 (4%)	7 (14%)
Centrilobular, necrosis	1 (2%)	2 (4%)	1 (2%)	

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

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Alimentary System (continued)				
Mesentery	(9)	(11)	(7)	(12)
Ectopic spleen			1 (14%)	
Inflammation				1 (8%)
Fat, necrosis	8 (89%)	9 (82%)	6 (86%)	11 (92%)
Oral mucosa	(2)	(1)		(2)
Pharyngeal, hyperplasia				1 (50%)
Pharyngeal, inflammation, acute		1 (100%)		
Pancreas	(49)	(50)	(50)	(50)
Atrophy	22 (45%)	14 (28%)	13 (26%)	14 (28%)
Cytoplasmic alteration	1 (2%)			
Ectopic liver		2 (4%)	2 (4%)	3 (6%)
Hyperplasia		3 (6%)	2 (4%)	
Inflammation, chronic			1 (2%)	2 (4%)
Salivary glands	(50)	(50)	(50)	(50)
Atrophy		2 (4%)	3 (6%)	1 (2%)
Cytoplasmic alteration		1 (2%)		1 (2%)
Inflammation, chronic		2 (4%)		
Stomach, forestomach	(50)	(50)	(50)	(50)
Fibrosis			1 (2%)	
Hyperkeratosis	1 (2%)			
Inflammation, acute	1 (2%)		1 (2%)	
Inflammation, chronic			1 (2%)	1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Ulcer	3 (6%)	3 (6%)	4 (8%)	4 (8%)
Epithelium, hyperplasia, squamous	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Stomach, glandular	(50)	(50)	(50)	(50)
Erosion	6 (12%)	9 (18%)	9 (18%)	7 (14%)
Inflammation, chronic				1 (2%)
Inflammation, chronic active	1 (2%)			
Mineralization			2 (4%)	
Ulcer	1 (2%)	1 (2%)	3 (6%)	
Tongue			(1)	(2)
Epithelium, hyperplasia			1 (100%)	1 (50%)
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Cardiomyopathy	42 (86%)	43 (86%)	43 (86%)	36 (72%)
Inflammation, chronic active	1 (2%)			
Mineralization	1 (2%)			
Thrombosis			2 (4%)	1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)			
Atrophy			1 (2%)	
Congestion		1 (2%)		1 (2%)
Cyst		1 (2%)		1 (2%)
Hematopoietic cell proliferation	1 (2%)			
Hemorrhage	1 (2%)			
Hyperplasia	11 (22%)	12 (24%)	9 (18%)	6 (12%)
Vacuolization cytoplasmic	6 (12%)	8 (16%)	6 (12%)	3 (6%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Endocrine System (continued)				
Adrenal medulla	(50)	(50)	(50)	(49)
Hyperplasia	5 (10%)	7 (14%)	8 (16%)	2 (4%)
Necrosis		1 (2%)		
Islets, pancreatic	(49)	(50)	(50)	(50)
Hyperplasia			1 (2%)	1 (2%)
Parathyroid gland	(48)	(50)	(48)	(50)
Hyperplasia	1 (2%)			
Pituitary gland	(49)	(50)	(50)	(50)
Pigmentation			1 (2%)	
Pars distalis, angiectasis	11 (22%)	9 (18%)	12 (24%)	4 (8%)
Pars distalis, cyst	16 (33%)	18 (36%)	20 (40%)	8 (16%)
Pars distalis, ectasia		1 (2%)		
Pars distalis, hemorrhage	1 (2%)			
Pars distalis, hyperplasia	22 (45%)	29 (58%)	21 (42%)	18 (36%)
Pars intermedia, hyperplasia	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
Ultimobranchial cyst		3 (6%)		1 (2%)
C-cell, hyperplasia	16 (32%)	17 (34%)	13 (26%)	10 (20%)
Follicular cell, hyperplasia	1 (2%)			
General Body System				
None				
Genital System				
Clitoral gland	(47)	(48)	(50)	(49)
Hyperplasia	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Inflammation, acute	1 (2%)	2 (4%)		
Inflammation, chronic	3 (6%)	1 (2%)	5 (10%)	2 (4%)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Vacuolization cytoplasmic				1 (2%)
Bilateral, inflammation, acute			1 (2%)	
Duct, ectasia	3 (6%)	5 (10%)	4 (8%)	2 (4%)
Ovary	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Cyst	3 (6%)	7 (14%)	4 (8%)	2 (4%)
Hyperplasia		1 (2%)		
Inflammation, chronic	1 (2%)			1 (2%)
Pigmentation			1 (2%)	
Bilateral, cyst		1 (2%)		2 (4%)
Uterus	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Cyst		1 (2%)		1 (2%)
Developmental malformation			1 (2%)	
Dilatation		1 (2%)	1 (2%)	2 (4%)
Hemorrhage		1 (2%)		1 (2%)
Hyperplasia				1 (2%)
Hyperplasia, cystic	6 (12%)		5 (10%)	7 (14%)
Inflammation, acute				1 (2%)
Inflammation, chronic		1 (2%)		1 (2%)
Inflammation, chronic active		1 (2%)		
Metaplasia, squamous			1 (2%)	
Necrosis	1 (2%)			1 (2%)
Cervix, hypertrophy			1 (2%)	
Cervix, inflammation, chronic				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Depletion cellular	1 (2%)		2 (4%)	2 (4%)
Fibrosis	1 (2%)	1 (2%)		
Hyperplasia	3 (6%)	4 (8%)		1 (2%)
Hyperplasia, reticulum cell		1 (2%)		
Necrosis			1 (2%)	
Erythroid cell, hyperplasia			1 (2%)	
Myeloid cell, hyperplasia		1 (2%)		
Lymph node	(7)	(9)	(15)	(19)
Iliac, congestion	2 (29%)			
Iliac, ectasia				2 (11%)
Mediastinal, congestion	3 (43%)	1 (11%)	4 (27%)	1 (5%)
Mediastinal, hyperplasia, lymphoid			1 (7%)	
Mediastinal, pigmentation	1 (14%)			1 (5%)
Pancreatic, congestion			1 (7%)	
Pancreatic, pigmentation		1 (11%)		
Renal, congestion	1 (14%)	1 (11%)	1 (7%)	
Renal, ectasia		1 (11%)		1 (5%)
Renal, hyperplasia, lymphoid				1 (5%)
Lymph node, mandibular	(49)	(50)	(50)	(50)
Atrophy	1 (2%)			
Congestion		1 (2%)	1 (2%)	
Ectasia	3 (6%)	4 (8%)	9 (18%)	2 (4%)
Edema				1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		1 (2%)
Hyperplasia, plasma cell	1 (2%)			
Infiltration cellular, plasma cell		1 (2%)		
Necrosis			1 (2%)	
Lymph node, mesenteric	(49)	(50)	(50)	(50)
Congestion	2 (4%)		3 (6%)	
Ectasia			4 (8%)	
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid		2 (4%)		2 (4%)
Inflammation, acute				1 (2%)
Inflammation, chronic				1 (2%)
Spleen	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Congestion	1 (2%)		2 (4%)	
Fibrosis	2 (4%)	3 (6%)	3 (6%)	4 (8%)
Hematopoietic cell proliferation	2 (4%)	4 (8%)		2 (4%)
Hemorrhage		2 (4%)		
Metaplasia, osseous		1 (2%)		
Necrosis		1 (2%)	2 (4%)	1 (2%)
Pigmentation				1 (2%)
Capsule, inflammation, chronic				1 (2%)
Thymus	(50)	(50)	(50)	(50)
Congestion			1 (2%)	
Cyst			1 (2%)	
Ectopic parathyroid gland	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Fibrosis		1 (2%)		
Inflammation, acute	1 (2%)			
Inflammation, chronic				1 (2%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocele	3 (6%)	5 (10%)	1 (2%)	
Hyperplasia	5 (10%)	2 (4%)	6 (12%)	5 (10%)
Inflammation, chronic active			1 (2%)	
Duct, dilatation	13 (26%)	9 (18%)	13 (26%)	13 (26%)
Skin	(50)	(50)	(50)	(50)
Hyperkeratosis			2 (4%)	
Hyperplasia, squamous	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute	1 (2%)			1 (2%)
Inflammation, chronic	1 (2%)			
Inflammation, chronic active	2 (4%)	1 (2%)		1 (2%)
Subcutaneous tissue, fibrosis		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteopetrosis	9 (18%)	12 (24%)	10 (20%)	5 (10%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)		2 (4%)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion	1 (2%)			
Hemorrhage				1 (2%)
Infiltration cellular, histiocyte	13 (26%)	10 (20%)	9 (18%)	11 (22%)
Inflammation, chronic	9 (18%)	8 (16%)	6 (12%)	8 (16%)
Bronchiole, alveolus, hyperplasia			1 (2%)	
Nose	(50)	(50)	(50)	(50)
Congestion			1 (2%)	
Cyst	1 (2%)	1 (2%)		
Hemorrhage				1 (2%)
Inflammation, chronic	2 (4%)		3 (6%)	
Inflammation, chronic active	15 (30%)	15 (30%)	16 (32%)	19 (38%)
Nasolacrimal duct, cyst		2 (4%)		
Nasolacrimal duct, inflammation, chronic active	1 (2%)		1 (2%)	
Respiratory epithelium, hyperplasia				1 (2%)
Special Senses System				
Eye			(1)	(2)
Hemorrhage			1 (100%)	2 (100%)
Harderian gland	(1)			
Inflammation, chronic	1 (100%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Accumulation, hyaline droplet				1 (2%)
Congestion	2 (4%)		1 (2%)	
Cyst			1 (2%)	
Hydronephrosis		2 (4%)		
Inflammation, acute				1 (2%)
Mineralization	3 (6%)		4 (8%)	6 (12%)
Nephropathy	41 (82%)	42 (84%)	35 (70%)	37 (74%)
Pigmentation			2 (4%)	1 (2%)
Renal tubule, hyperplasia				1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Inflammation, chronic		3 (6%)	1 (2%)	2 (4%)

APPENDIX C
SUMMARY OF LESIONS IN MALE WISTAR RATS IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

TABLE C1
Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine[a]

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	2	9	9	10
Natural deaths	26	27	30	33
Survivors				
Terminal sacrifice	22	14	11	7
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(32)	(37)	(29)	(27)
Carcinoma	1 (3%)			
Intestine small, duodenum	(39)	(44)	(42)	(42)
Carcinoma		1 (2%)		
Intestine small, jejunum	(37)	(36)	(34)	(35)
Carcinoma	1 (3%)	2 (6%)		
Intestine small, ileum	(28)	(32)	(28)	(31)
Liver	(50)	(50)	(50)	(50)
Cholangiocarcinoma	1 (2%)			2 (4%)
Hepatocellular adenoma	2 (4%)		1 (2%)	
Histiocytic sarcoma				1 (2%)
Oral mucosa	(5)	(1)	(1)	
Squamous cell carcinoma	1 (20%)			
Pancreas	(46)	(50)	(50)	(49)
Carcinoma		1 (2%)		
Acinus, adenoma	6 (13%)	7 (14%)	8 (16%)	7 (14%)
Acinus, adenoma, multiple	8 (17%)	4 (8%)	4 (8%)	
Acinus, carcinoma	2 (4%)		2 (4%)	
Acinus, carcinoma, multiple	2 (4%)		1 (2%)	
Stomach, forestomach	(49)	(50)	(50)	(49)
Fibrosarcoma			1 (2%)	
Squamous cell papilloma				1 (2%)
Stomach, glandular	(49)	(50)	(48)	(48)
Fibrosarcoma, metastatic, stomach, forestomach			1 (2%)	
Tongue			(1)	
Squamous cell carcinoma			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocardium, schwannoma benign	2 (4%)	2 (4%)		1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma		1 (2%)		
Carcinoma				1 (2%)
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Pheochromocytoma benign	5 (10%)	4 (8%)	1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Endocrine System (continued)				
Islets, pancreatic	(47)	(50)	(49)	(49)
Adenoma	8 (17%)		3 (6%)	
Carcinoma		1 (2%)		1 (2%)
Parathyroid gland	(48)	(47)	(48)	(47)
Adenoma	1 (2%)			
Pituitary gland	(49)	(49)	(50)	(50)
Pars distalis, adenoma	15 (31%)	16 (33%)	12 (24%)	13 (26%)
Pars distalis, adenoma, multiple	1 (2%)	1 (2%)		
Pars intermedia, adenoma	1 (2%)			1 (2%)
Thyroid gland	(49)	(50)	(48)	(49)
Bilateral, follicular cell, adenoma			1 (2%)	
C-cell, adenoma	4 (8%)	2 (4%)		3 (6%)
Follicular cell, adenoma			4 (8%)	
Follicular cell, carcinoma	3 (6%)	3 (6%)	1 (2%)	
General Body System				
Tissue NOS		(1)		
Hemangiosarcoma		1 (100%)		
Genital System				
Epididymis	(50)	(49)	(49)	(50)
Preputial gland	(50)	(48)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	1 (2%)
Prostate	(50)	(49)	(50)	(50)
Adenoma	3 (6%)	1 (2%)	1 (2%)	
Schwannoma malignant				1 (2%)
Seminal vesicle	(49)	(49)	(50)	(49)
Testes	(50)	(49)	(49)	(50)
Bilateral, interstitial cell, adenoma	3 (6%)	1 (2%)	1 (2%)	5 (10%)
Interstitial cell, adenoma	2 (4%)	5 (10%)	3 (6%)	7 (14%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Lymph node	(31)	(44)	(38)	(32)
Iliac, hemangiosarcoma		1 (2%)		
Pancreatic, histiocytic sarcoma				1 (3%)
Lymph node, mandibular	(48)	(49)	(47)	(48)
Histiocytic sarcoma				1 (2%)
Lymph node, mesenteric	(46)	(50)	(50)	(50)
Hemangioma				1 (2%)
Hemangiosarcoma		1 (2%)	1 (2%)	
Histiocytic sarcoma				1 (2%)
Spleen	(49)	(50)	(49)	(49)
Hemangiosarcoma		1 (2%)		
Thymus	(48)	(49)	(49)	(50)
Thymoma benign	1 (2%)		2 (4%)	
Thymoma malignant	1 (2%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Integumentary System				
Mammary gland	(48)	(46)	(44)	(46)
Carcinoma			1 (2%)	
Fibroadenoma	1 (2%)	1 (2%)		1 (2%)
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma		1 (2%)		
Basal cell carcinoma				1 (2%)
Carcinoma, metastatic, Zymbal's gland			1 (2%)	
Fibroma			2 (4%)	
Keratoacanthoma	7 (14%)	3 (6%)	2 (4%)	1 (2%)
Squamous cell carcinoma		1 (2%)		
Squamous cell papilloma	2 (4%)	1 (2%)	1 (2%)	
Sebaceous gland, adenoma			1 (2%)	
Subcutaneous tissue, fibroma	5 (10%)	6 (12%)		1 (2%)
Subcutaneous tissue, fibroma, multiple				1 (2%)
Subcutaneous tissue, fibrosarcoma			1 (2%)	1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, osteoma	1 (2%)			
Joint, sarcoma				1 (2%)
Skeletal muscle	(1)		(2)	
Fibroma			1 (50%)	
Lipoma	1 (100%)		1 (50%)	
Nervous System				
Brain	(50)	(49)	(50)	(50)
Astrocytoma malignant	1 (2%)	1 (2%)	1 (2%)	
Hemangioma	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma			1 (2%)	
Carcinoma, metastatic, Zymbal's gland			1 (2%)	1 (2%)
Fibrosarcoma, metastatic, skin				1 (2%)
Histiocytic sarcoma				1 (2%)
Nose	(50)	(50)	(50)	(50)
Chondroma				1 (2%)
Squamous cell carcinoma, metastatic, oral mucosa	1 (2%)			
Special Senses System				
Zymbal's gland	(1)		(2)	(3)
Carcinoma	1 (100%)		2 (100%)	3 (100%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Histiocytic sarcoma				1 (2%)
Lipoma	1 (2%)			
Renal tubule, adenoma	1 (2%)	4 (8%)	1 (2%)	2 (4%)
Renal tubule, adenoma, multiple	1 (2%)	1 (2%)		
Renal tubule, carcinoma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	1 (2%)	1 (2%)	2 (4%)	
Lymphoma malignant		2 (4%)		1 (2%)
Mesothelioma malignant			1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]	43	38	32	39
Total primary neoplasms	101	79	68	62
Total animals with benign neoplasms	40	37	29	33
Total benign neoplasms	84	61	51	47
Total animals with malignant neoplasms	17	14	12	13
Total malignant neoplasms	17	18	17	15
Total animals with metastatic neoplasms	1		3	2
Total metastatic neoplasms	1		4	2

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

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	2 8 3	4 6 8	5 3 6	5 5 7	5 5 9	5 7 2	5 7 6	5 8 7	5 8 9	5 9 2	5 9 8	6 0 1	6 1 6	6 1 8	6 2 4	6 3 9	6 4 4	6 4 4	6 5 4	6 6 0	6 7 4	6 7 6	6 8 1	6 9 5	7 0 1
Carcass ID Number	0 3 6	0 1 3	0 5 0	0 0 3	0 4 7	0 4 1	0 3 1	0 4 3	0 0 1	0 3 8	0 2 8	0 1 4	0 2 4	0 3 2	0 4 6	0 3 0	0 2 3	0 4 8	0 0 5	0 2 7	0 4 4	0 0 7	0 3 9	0 3 5	0 2 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	A	A	A	+	+	A	+	+	+	A	A	+	+	A	A	A	A	+	+	+	+	A	+
Intestine large, rectum	A	+	+	A	+	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	A	A	A	A	+	A	+	A	+	A	A	+	A	A	A	A	A	+	+	+	+	A	+
Carcinoma																									
Intestine small, duodenum	A	+	+	A	A	+	+	A	+	+	+	A	A	+	+	+	A	A	+	+	+	+	+	A	+
Intestine small, jejunum	A	+	+	A	A	+	+	+	+	+	+	A	A	A	+	A	A	A	+	+	+	+	+	A	+
Carcinoma																									
Intestine small, ileum	A	+	+	A	A	A	+	A	A	A	A	A	A	A	+	A	A	A	A	A	A	+	A	A	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Hepatocellular adenoma																			X						
Mesentery		+										+												+	+
Oral mucosa									+										+						+
Squamous cell carcinoma									X																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+		+
Acinus, adenoma																									
Acinus, adenoma, multiple									X																
Acinus, carcinoma																									
Acinus, carcinoma, multiple																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Stomach, forestomach	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel		+		+	+		+					+		+										+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocardium, schwannoma benign																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant								X																	
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenoma															X						X				
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X			X								X					X			X	X	X		
Pars distalis, adenoma, multiple																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
Follicular cell, carcinoma																					X				

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

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	7 0 5	7 0 7	7 1 7	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	
Carcass ID Number	0 2 5	0 2 1	0 1 9	0 0 2	0 0 4	0 0 6	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 5	0 1 6	0 1 7	0 1 8	0 2 0	0 2 2	0 2 9	0 3 3	0 3 4	0 3 7	0 4 0	0 4 2	0 4 5	0 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Intestine large, rectum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, cecum	A	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Carcinoma																			X							1
Intestine small, duodenum	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, jejunum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Carcinoma								X																		1
Intestine small, ileum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	28
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																X										1
Hepatocellular adenoma															X											2
Mesentery		+	+																					+		7
Oral mucosa							+					+														5
Squamous cell carcinoma																										1
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Acinus, adenoma						X						X		X		X				X		X				6
Acinus, adenoma, multiple					X		X		X		X		X								X		X			8
Acinus, carcinoma							X																		X	2
Acinus, carcinoma, multiple															X								X			2
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																+				+						2
Cardiovascular System																										
Blood vessel			+																							8
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocardium, schwannoma benign																		X							X	2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign							X	X		X							X				X					5
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma			X			X	X				X					X		X							8
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma														X												1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma					X	X	X		X	X				X				X			X					15
Pars distalis, adenoma, multiple																				X						1
Pars intermedia, adenoma												X														1
Thyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma					X												X						X			4
Follicular cell, carcinoma	X																			X						3

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	2 8 3	4 6 8	5 3 6	5 5 7	5 5 9	5 7 2	5 7 6	5 8 7	5 8 9	5 9 2	5 9 8	6 0 1	6 1 6	6 1 8	6 2 4	6 3 9	6 4 4	6 4 4	6 5 4	6 6 0	6 7 4	6 7 6	6 8 1	6 9 5	7 0 1
Carcass ID Number	0 3 6	0 1 3	0 5 0	0 0 3	0 4 7	0 4 1	0 3 1	0 4 3	0 0 1	0 3 8	0 2 8	0 1 4	0 2 4	0 3 2	0 4 6	0 3 0	0 2 3	0 4 8	0 0 5	0 2 7	0 4 4	0 0 7	0 3 9	0 3 5	0 2 6
General Body System																									
None																									
Genital System																									
Coagulating gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																									
Interstitial cell, adenoma										X															
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+		+		+		+	+		+	+	+			+			+	+		+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	M	+	A	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+		M	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign																									
Thymoma malignant															X										
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma											X												X		
Squamous cell papilloma							X																		
Subcutaneous tissue, fibroma						X																			X
Subcutaneous tissue, sarcoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, osteoma												X													
Skeletal muscle																									
Lipoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																						X			
Hemangioma																									
Peripheral nerve																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, oral mucosa									X																
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	7 0 5	7 0 7	7 1 7	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	
Carcass ID Number	0 2 5	0 2 1	0 1 9	0 0 2	0 0 4	0 0 6	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 5	0 1 6	0 1 7	0 1 8	0 2 0	0 2 2	0 2 9	0 3 3	0 3 4	0 3 7	0 4 0	0 4 2	0 4 5	0 4 9	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma														X												1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma				X									X						X							3
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X				X				X																3
Interstitial cell, adenoma																									X	2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+		+	+	+		+				+	+			+	+	+	+			+		+	+	+	31
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymoma benign						X																				1
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Fibroadenoma																X										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma			X									X	X			X					X					7
Squamous cell papilloma					X																					2
Subcutaneous tissue, fibroma				X								X				X										5
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, osteoma																										1
Skeletal muscle														+												1
Lipoma														X												1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Hemangioma	X																									1
Peripheral nerve											+															1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, oral mucosa																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	283	468	536	557	559	572	776	787	889	892	998	601	616	618	624	639	644	644	645	660	674	676	681	695	701
Carcass ID Number	036	113	150	003	047	411	311	043	401	038	288	114	244	232	346	430	323	488	405	027	444	407	039	335	266
Special Senses System																									
Ear		+																							
Harderian gland																									
Zymbal's gland																				+					
Carcinoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Renal tubule, adenoma																									X
Renal tubule, adenoma, multiple							X																		
Urinary bladder	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	705	707	717	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	
Carcass ID Number	025	021	019	022	004	006	008	009	010	011	012	015	016	017	018	020	022	029	033	034	037	040	042	045	049	Total Tissues/ Tumors	
Special Senses System																											
Ear																										1	
Harderian gland											+															1	
Zymbal's gland																										1	
Carcinoma																										1	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Lipoma																				X						1	
Renal tubule, adenoma																										1	
Renal tubule, adenoma, multiple																										1	
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Leukemia mononuclear														X												1	

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	336	352	372	445	470	479	486	506	536	541	549	552	561	573	581	593	595	610	611	634	638	639	642	647	649
Carcass ID Number	00880	00882	00863	00737	00796	00881	00858	01000	00878	00853	00992	00998	00881	00660	00979	00765	00870	00885	00772	00764	00557	00554	00552	00799	00551
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	A	A	+	A	+	+	+	+	+	A
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	A	+	A	+	+	+	+	+	A
Intestine large, cecum	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	A	A	+	A	+	+	A	+	+	A
Intestine small, duodenum	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+
Carcinoma																									
Intestine small, jejunum	+	+	+	A	A	A	+	+	+	+	A	+	+	A	+	A	+	+	A	A	+	+	+	+	+
Carcinoma																									
Intestine small, ileum	+	A	+	A	A	A	+	+	+	+	+	A	+	A	+	A	A	+	A	A	+	A	+	A	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery														+											
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																					X				
Acinus, adenoma			X					X			X							X				X		
Acinus, adenoma, multiple				X																	X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel		+		+		+	+	+	+	+	+		+					+	+	+		+	+			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocardium, schwannoma benign																X									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign							X																		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																					X				
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X					X				X		X		X				
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma															X										
Follicular cell, carcinoma																X									X
General Body System																									
Tissue NOS																									
Hemangiosarcoma																									
Genital System																									
Coagulating gland	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	651	660	668	679	682	690	697	698	710	714	716	722	722	722	722	722	722	722	722	722	722	722	722	722	722	
Carcass ID Number	00559	00666	00691	00993	00884	00555	00995	00887	00883	00771	00667	00556	00661	00662	00668	00669	00673	00774	00775	00776	00886	00889	00890	00994	00997	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	A	+	+	+	A	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine large, rectum	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, cecum	A	A	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma								X																		1
Intestine small, jejunum	A	+	+	+	A	A	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Carcinoma																	X								X	2
Intestine small, ileum	A	+	+	+	A	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																										1
Oral mucosa																						+				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Acinus, adenoma												X	X													7
Acinus, adenoma, multiple																X								X		4
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth														+									+			2
Cardiovascular System																										
Blood vessel	+		+	+		+	+			+	+										+				+	23
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocardium, schwannoma benign																								X		2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant								X																		1
Pheochromocytoma benign		X												X						X						4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X			X	X	X	X	X	X		X											X	X	X	16
Pars distalis, adenoma, multiple															X											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma													X													2
Follicular cell, carcinoma												X														3
General Body System																										
Tissue NOS		+																								1
Hemangiosarcoma		X																								1
Genital System																										
Coagulating gland	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	42
Epididymis	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Penis						+																				1
Preputial gland	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	336	352	372	445	470	479	486	506	536	541	549	552	561	573	581	593	595	610	611	634	638	639	642	647	649
Carcass ID Number	00800	00802	00863	00877	00896	00981	01058	01100	00878	00953	00992	00998	00888	00960	00979	00965	00970	00985	00972	00964	00957	00954	00952	00991	00951
Genital System (continued)																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma																									
Interstitial cell, adenoma							X															X			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Iliac, hemangiosarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma								X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma																						X			
Squamous cell carcinoma																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma												X								X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Peripheral nerve								+		+													+		
Spinal cord								+		+													+		
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																		X				X			
Renal tubule, adenoma, multiple																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
Lymphoma malignant																						X			

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 100 ppm

Number of Days on Study	651	660	668	679	682	690	697	698	710	711	716	722	722	722	722	722	722	722	722	722	722	722	722	722	722	
Carcass ID Number	00559	00606	00691	00993	00884	00555	00995	00887	00883	00771	00667	00556	00661	00662	00668	00669	00673	00774	00775	00776	00886	00889	00890	00994	00997	Total Tissues/ Tumors
Genital System (continued)																										
Prostate	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																X										1
Seminal vesicle	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma																		X								1
Interstitial cell, adenoma		X										X									X					5
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+		44
Iliac, hemangiosarcoma																						X				1
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																							X			1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma		X																								1
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibroadenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																						X				1
Keratoacanthoma																	X			X						3
Squamous cell carcinoma														X												1
Squamous cell papilloma																					X					1
Subcutaneous tissue, fibroma													X	X	X					X						6
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma malignant																				X						1
Peripheral nerve				+																						4
Spinal cord				+																						4
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma							X																X			4
Renal tubule, adenoma, multiple				X																						1
Urinary bladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Lymphoma malignant														X												2

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	345	404	447	473	479	481	486	487	494	500	501	510	515	520	548	561	575	588	608	622	628	630	631	632	645
Carcass ID Number	11313	11414	12949	14499	14977	14444	10067	10363	13232	13030	13419	13311	13217	12908	12024	13737	13338	11515	12323	14212	14245	14646	14406	15050
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	A	+	+	+	A	+	+	A	A	+	+	A	A	+	+	A	A	+
Intestine large, rectum	+	+	+	+	+	+	A	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	A	+
Intestine large, cecum	+	+	+	+	+	+	A	A	+	+	+	A	+	+	A	A	+	A	A	A	+	+	A	A	A
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	A	+	A	+	+	A	+	+
Intestine small, jejunum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	A	A	A	A	A	A	A	+	A	A	+
Intestine small, ileum	+	+	A	+	+	+	A	A	+	+	+	A	+	+	A	A	A	+	A	A	A	A	A	A	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Mesentery																									
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma							X					X							X					X	
Acinus, adenoma, multiple																						X			
Acinus, carcinoma																									
Acinus, carcinoma, multiple																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Fibrosarcoma, metastatic, stomach, forestomach																									
Tongue																									
Squamous cell carcinoma																									
Tooth	+																							+	
Cardiovascular System																									
Blood vessel	+						+			+	+	+							+	+	+	+			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant						X																			
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+
Adenoma												X													
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X				X											X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Bilateral, follicular cell, adenoma																									
Follicular cell, adenoma																						X			
Follicular cell, carcinoma																									X
General Body System																									
None																									
Genital System																									
Coagulating gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	650	660	664	744	745	682	683	688	700	704	704	705	713	721	722	722	722	722	722	722	722	722	722	722	722	
Carcass ID Number	10 01	11 41	14 48	11 18	14 43	12 20	10 09	14 42	11 11	12 12	13 35	13 36	12 28	12 21	10 02	10 04	10 05	11 10	11 16	11 17	12 25	12 26	13 34	13 39	14 40	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	A	A	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Intestine large, rectum	A	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Intestine large, cecum	A	A	A	A	A	A	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+		29
Intestine small, duodenum	+	+	+	+	A	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	A	+	A	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Intestine small, ileum	A	+	A	A	A	A	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	28
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma															X											1
Mesentery							+									+										2
Oral mucosa									+																	1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma	X											X		X		X										8
Acinus, adenoma, multiple															X					X	X					4
Acinus, carcinoma																X						X				2
Acinus, carcinoma, multiple															X											1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma							X																			1
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibrosarcoma, metastatic, stomach, forestomach							X																			1
Tongue											+															1
Squamous cell carcinoma											X															1
Tooth											+										+					4
Cardiovascular System																										
Blood vessel			+		+									+												12
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign														X												1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X				X																				3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma				X	X	X				X						X					X		X	X		12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bilateral, follicular cell, adenoma				X																						1
Follicular cell, adenoma			X						X							X										4
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Coagulating gland	M	M	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	45
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	345	404	447	473	479	481	486	487	494	500	501	510	515	520	548	561	575	588	608	622	628	630	631	632	645
Carcass ID Number	11113	11144	11299	12449	14497	14441	14007	10363	13232	13030	13019	13311	12717	10828	12024	13737	13338	13815	11523	12343	11212	14545	14466	14061	15050
Genital System (continued)																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Bilateral, interstitial cell, adenoma																									
Interstitial cell, adenoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+		+		+	+	+	+	+	+	+	+	+	+	+	+		+		+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign															X										
Integumentary System																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland									X																
Fibroma																									
Keratoacanthoma																									
Squamous cell papilloma															X										
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									+
Fibroma																									X
Lipoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Peripheral nerve											+														
Spinal cord											+														
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, Zymbal's gland									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear													+												
Eye									+																
Harderian gland	+										+														+
Lacrimal gland									+																
Zymbal's gland									+																
Carcinoma									X																

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	650	660	664	674	675	682	683	688	700	704	704	705	713	721	722	722	722	722	722	722	722	722	722	722	722	
Carcass ID Number	10001	10411	10448	10418	10443	10420	10409	10422	10411	10212	10435	10436	10428	10421	10202	10204	10205	10110	10116	10117	10225	10226	10234	10239	10240	Total Tissues/ Tumors
Genital System (continued)																										
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, interstitial cell, adenoma					X																					1
Interstitial cell, adenoma		X									X				X											3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+	+	+			+	+	+		+	+	+	+	+	+		+	+	+			+	+	38
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X														1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma benign	X																									2
Integumentary System																										
Mammary gland	M	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Carcinoma					X																					1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland																										1
Fibroma							X											X								2
Keratoacanthoma												X				X										2
Squamous cell papilloma																										1
Sebaceous gland, adenoma																	X									1
Subcutaneous tissue, fibrosarcoma				X																						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																					+					2
Fibroma																										1
Lipoma																					X					1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant							X																			1
Peripheral nerve														+												2
Spinal cord														+												2
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma											X															1
Carcinoma, metastatic, Zymbal's gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Eye																										1
Harderian gland																								+		4
Lacrimal gland																										1
Zymbal's gland							+																			2
Carcinoma							X																			2

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	3 5 4	4 0 4	4 4 7	4 7 3	4 7 9	4 8 1	4 8 6	4 8 7	4 9 4	5 0 0	5 0 1	5 1 0	5 1 5	5 2 0	5 4 8	5 6 1	5 7 5	5 8 8	6 0 8	6 2 2	6 2 8	6 3 0	6 3 1	6 3 2	6 4 5
Carcass ID Number	1 1 3	1 1 4	1 2 9	1 4 9	1 4 7	1 4 4	1 0 7	1 0 3	1 3 2	1 3 0	1 3 9	1 3 1	1 2 7	1 0 8	1 2 4	1 3 7	1 3 3	1 3 8	1 1 5	1 2 3	1 1 2	1 4 5	1 4 6	1 0 6	1 5 0
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesothelioma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 200 ppm

Number of Days on Study	650	600	644	744	755	822	833	888	700	704	704	705	713	721	722	722	722	722	722	722	722	722	722	722	722	
Carcass ID Number	101	141	448	118	143	220	209	242	111	212	235	236	228	221	202	204	205	210	216	217	225	226	234	239	240	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung											X															1
Renal tubule, adenoma														X												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X									X													2
Mesothelioma malignant															X											1

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	0 9 4	4 4 3	4 5 0	4 6 3	4 6 4	4 6 6	4 6 7	4 6 8	4 8 3	4 8 6	4 8 9	4 9 3	4 9 9	5 1 1	5 3 1	5 3 2	5 3 9	5 4 5	5 5 0	5 5 2	5 5 3	5 5 3	5 5 6	5 6 2	5 6 8
Carcass ID Number	1 8 0	1 5 8	1 6 1	1 8 9	1 9 9	1 8 3	1 7 1	1 7 9	1 9 2	1 6 6	1 7 8	1 8 6	1 6 4	1 7 6	1 7 0	1 6 9	1 5 4	1 8 1	1 6 5	1 8 2	1 8 8	1 9 5	1 8 4	1 9 7	1 7 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	A	+	A	+	+	+	+	A	+	+	+	+	A	+	+	A	+	A	+	+	A	+	A
Intestine large, rectum	+	A	A	+	A	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	+	A	+	+	+	+	A	+	+	+	A	A	+	A	A	+	A	+	A	A	+	A
Intestine small, duodenum	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	A	+	+	+	+	A
Intestine small, ileum	+	A	A	+	A	+	+	A	+	+	A	+	+	+	A	+	+	A	+	+	+	A	+	+	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																				X		X			
Histiocytic sarcoma																	X								
Mesentery				+																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																		X	X						X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Squamous cell papilloma															X										
Stomach, glandular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel										+			+												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocardium, schwannoma benign																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma									X					X		X						X			
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
General Body System																									
None																									
Genital System																									
Coagulating gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma															X										
Interstitial cell, adenoma					X						X	X	X												

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	5 7 4	5 8 0	5 8 2	5 8 7	5 9 5	6 0 6	6 1 6	6 2 7	6 2 9	6 3 1	6 5 8	6 6 0	6 7 4	6 8 2	6 8 3	6 8 5	6 8 7	7 0 9	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	
Carcass ID Number	2 0 0	1 9 3	1 9 4	1 5 2	1 5 7	1 5 9	1 7 7	1 9 6	1 8 5	1 7 5	1 9 0	1 9 1	1 6 2	1 6 3	1 8 7	1 6 8	1 7 4	1 5 1	1 5 3	1 5 5	1 5 6	1 6 0	1 6 7	1 7 3	1 9 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	A	+	A	+	+	A	+	+	+	+	+	A	A	+	A	A	A	+	+	+	+	+	+	+	33
Intestine large, rectum	+	+	+	A	+	+	+	+	+	+	+	+	A	A	+	A	+	A	+	+	+	+	+	+	+	40
Intestine large, cecum	+	A	+	A	+	A	A	+	A	+	A	+	A	A	+	A	A	A	+	+	+	+	+	+	+	27
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	A	A	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	A	+	A	+	+	A	+	A	+	+	+	A	A	+	A	A	A	+	+	+	+	+	+	+	35
Intestine small, ileum	+	A	+	A	+	A	A	+	A	+	+	+	A	A	+	A	A	A	+	+	+	+	+	+	+	31
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																										2
Histiocytic sarcoma																										1
Mesentery										+																2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma											X								X		X	X				7
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth								+										+				+				3
Cardiovascular System																										
Blood vessel						+																				3
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocardium, schwannoma benign																		X								1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																		X								1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma										X																1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma					X		X	X		X	X	X	X										X		X	13
Pars intermedia, adenoma																	X									1
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma	X								X														X			3
General Body System																										
None																										
Genital System																										
Coagulating gland	+	+	+	+	+	+	A	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	45
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant													X													1
Seminal vesicle	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma				X														X					X	X		5
Interstitial cell, adenoma		X						X																	X	7

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	0 9 4	4 4 3	4 5 0	4 6 3	4 6 4	4 6 6	4 6 7	4 6 8	4 8 3	4 8 6	4 8 9	4 9 3	4 9 9	5 1 1	5 3 1	5 3 2	5 3 9	5 4 5	5 5 0	5 5 2	5 5 3	5 5 3	5 5 6	5 6 2	5 6 8
Carcass ID Number	1 8 0	1 5 8	1 6 1	1 8 9	1 9 9	1 8 3	1 7 1	1 7 9	1 9 2	1 6 6	1 7 8	1 8 6	1 6 4	1 7 6	1 7 0	1 6 9	1 5 4	1 8 1	1 6 5	1 8 2	1 8 8	1 9 5	1 8 4	1 9 7	1 7 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Lymph node	+			+	+	+	+	+		+	+	+	+	+	+		+	+	+	+	+	+			+
Pancreatic, histiocytic sarcoma																	X								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Histiocytic sarcoma																	X								
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Histiocytic sarcoma																	X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Joint, sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve					+											+									
Spinal cord																+									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																									
Fibrosarcoma, metastatic, skin																									
Histiocytic sarcoma																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondroma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																+									
Harderian gland																									
Zymbal's gland						+																			
Carcinoma						X																			

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	5 7 4	5 8 0	5 8 2	5 8 7	5 9 5	6 0 6	6 1 6	6 2 7	6 2 9	6 3 1	6 5 8	6 6 0	6 7 4	6 8 2	6 8 3	6 8 5	6 8 7	7 0 9	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	
Carcass ID Number	2 0 0	1 9 3	1 9 4	1 5 2	1 5 7	1 5 9	1 7 7	1 9 6	1 8 5	1 7 5	1 9 0	1 9 1	1 6 2	1 6 3	1 8 7	1 6 8	1 7 4	1 5 1	1 5 3	1 5 5	1 5 6	1 6 0	1 6 7	1 7 3	1 9 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node	+	+					+				+	+	+		+	+	+			+	+		+		+	32
Pancreatic, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma										X																1
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Fibroadenoma										X																1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																				X						1
Keratoacanthoma																	X									1
Subcutaneous tissue, fibroma																					X					1
Subcutaneous tissue, fibroma, multiple																						X				1
Subcutaneous tissue, fibrosarcoma																		X								1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Joint, sarcoma																						X				1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve			+							+												+				5
Spinal cord			+							+												+				4
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, Zymbal's gland															X											1
Fibrosarcoma, metastatic, skin																		X								1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chondroma		X																								1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																										1
Harderian gland															+											1
Zymbal's gland															+		+									3
Carcinoma															X		X									3

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	0 9 4	4 4 3	4 5 0	4 6 3	4 6 4	4 6 6	4 6 7	4 6 8	4 8 3	4 8 6	4 8 9	4 9 3	4 9 9	5 1 1	5 3 1	5 3 2	5 3 9	5 4 5	5 5 0	5 5 2	5 5 3	5 5 3	5 5 6	5 6 2	5 6 8
Carcass ID Number	1 8 0	1 5 8	1 6 1	1 8 9	1 9 9	1 8 3	1 7 1	1 7 9	1 9 2	1 6 6	1 7 8	1 8 6	1 6 4	1 7 6	1 7 0	1 6 9	1 5 4	1 8 1	1 6 5	1 8 2	1 8 8	1 9 5	1 8 4	1 9 7	1 7 2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Renal tubule, adenoma																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	A	+	+	A
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Lymphoma malignant						X																			

TABLE C2
Individual Animal Tumor Pathology of Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine: 400 ppm

Number of Days on Study	574	580	582	587	595	606	616	627	629	631	658	660	674	682	683	685	687	709	722	722	722	722	722	722	722	
Carcass ID Number	20000	19303	19404	15202	15577	15599	17706	19616	18505	17509	19090	19901	16202	16303	18807	16808	17404	15101	15533	15555	15606	16060	16707	17303	19908	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Renal tubule, adenoma						X									X											2
Renal tubule, carcinoma																X										1
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	44
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant																										1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	5/50 (10%)	4/50 (8%)	1/50 (2%)	0/50 (0%)
Adjusted rate[b]	12.5%	11.1%	3.0%	0.0%
Terminal rate[c]	5/22 (23%)	2/14 (14%)	0/11 (0%)	0/7 (0%)
First incidence (days)	722 (T)	486	721	—[e]
Poly-3 test[d]	P=0.022N	P=0.568N	P=0.144N	P=0.073N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	6/50 (12%)	5/50 (10%)	2/50 (4%)	1/50 (2%)
Adjusted rate	14.8%	13.8%	5.8%	3.5%
Terminal rate	5/22 (23%)	2/14 (14%)	0/11 (0%)	0/7 (0%)
First incidence (days)	587	486	481	553
Poly-3 test	P=0.055N	P=0.582N	P=0.189N	P=0.133N
Small Intestine (Duodenum, Jejunum): Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	2.5%	8.5%	0.0%	0.0%
Terminal rate	1/22 (5%)	2/14 (14%)	0/11 (0%)	0/7 (0%)
First incidence (days)	722 (T)	698	—	—
Poly-3 test	P=0.221N	P=0.259	P=0.534N	P=0.569N
Kidney (Renal Tubule): Adenoma (Single Sections)				
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	2/50 (4%)
Adjusted rate	4.9%	13.9%	3.0%	7.0%
Terminal rate	0/22 (0%)	1/14 (7%)	0/11 (0%)	0/7 (0%)
First incidence (days)	576	610	721	606
Poly-3 test	P=0.531N	P=0.167	P=0.564N	P=0.562
Kidney (Renal Tubule): Adenoma or Carcinoma (Single Sections)				
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	3/50 (6%)
Adjusted rate	4.9%	13.9%	3.0%	10.4%
Terminal rate	0/22 (0%)	1/14 (7%)	0/11 (0%)	0/7 (0%)
First incidence (days)	576	610	721	606
Poly-3 test	P=0.420	P=0.167	P=0.564N	P=0.348
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	3/50 (6%)	6/50 (12%)	5/50 (10%)	4/50 (8%)
Adjusted rate	7.4%	16.5%	14.4%	13.6%
Terminal rate	1/22 (5%)	1/14 (7%)	2/11 (18%)	0/7 (0%)
First incidence (days)	576	610	520	550
Poly-3 test	P=0.288	P=0.187	P=0.271	P=0.328
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	3/50 (6%)	6/50 (12%)	6/50 (12%)	4/50 (8%)
Adjusted rate	7.4%	16.5%	17.2%	13.6%
Terminal rate	1/22 (5%)	1/14 (7%)	2/11 (18%)	0/7 (0%)
First incidence (days)	576	610	520	550
Poly-3 test	P=0.258	P=0.187	P=0.167	P=0.328
Pancreas: Adenoma				
Overall rate	14/46 (30%)	11/50 (22%)	12/50 (24%)	7/49 (14%)
Adjusted rate	37.4%	28.3%	32.9%	23.7%
Terminal rate	13/22 (59%)	4/14 (29%)	4/11 (36%)	3/7 (43%)
First incidence (days)	589	372	486	545
Poly-3 test	P=0.176N	P=0.267N	P=0.433N	P=0.168N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Pancreas: Carcinoma				
Overall rate	4/46 (9%)	1/50 (2%)	3/50 (6%)	0/49 (0%)
Adjusted rate	10.8%	2.8%	8.9%	0.0%
Terminal rate	4/22 (18%)	0/14 (0%)	3/11 (27%)	0/7 (0%)
First incidence (days)	722 (T)	638	722 (T)	—
Poly-3 test	P=0.107N	P=0.190N	P=0.550N	P=0.105N
Pancreas: Adenoma or Carcinoma				
Overall rate	16/46 (35%)	11/50 (22%)	13/50 (26%)	7/49 (14%)
Adjusted rate	42.7%	28.3%	35.6%	23.7%
Terminal rate	15/22 (68%)	4/14 (29%)	5/11 (45%)	3/7 (43%)
First incidence (days)	589	372	486	545
Poly-3 test	P=0.098N	P=0.131N	P=0.343N	P=0.077N
Pancreatic Islets: Adenoma				
Overall rate	8/47 (17%)	0/50 (0%)	3/49 (6%)	0/49 (0%)
Adjusted rate	20.8%	0.0%	8.8%	0.0%
Terminal rate	5/22 (23%)	0/14 (0%)	0/11 (0%)	0/7 (0%)
First incidence (days)	624	—	510	—
Poly-3 test	P=0.005N	P=0.005N	P=0.134N	P=0.014N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	8/47 (17%)	1/50 (2%)	3/49 (6%)	1/49 (2%)
Adjusted rate	20.8%	2.8%	8.8%	3.6%
Terminal rate	5/22 (23%)	0/14 (0%)	0/11 (0%)	0/7 (0%)
First incidence (days)	624	638	510	631
Poly-3 test	P=0.025N	P=0.020N	P=0.134N	P=0.048N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	16/49 (33%)	17/49 (35%)	12/50 (24%)	13/50 (26%)
Adjusted rate	38.2%	45.7%	33.1%	39.7%
Terminal rate	9/22 (41%)	5/14 (36%)	4/11 (36%)	2/7 (29%)
First incidence (days)	468	506	494	483
Poly-3 test	P=0.480N	P=0.324	P=0.404N	P=0.545
Prostate Gland: Adenoma				
Overall rate	3/50 (6%)	1/49 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	7.5%	2.9%	3.0%	0.0%
Terminal rate	3/22 (14%)	1/14 (7%)	1/11 (9%)	0/7 (0%)
First incidence (days)	722 (T)	722 (T)	722 (T)	—
Poly-3 test	P=0.097N	P=0.363N	P=0.368N	P=0.195N
Skin: Keratoacanthoma				
Overall rate	7/50 (14%)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted rate	17.2%	8.5%	5.9%	3.5%
Terminal rate	4/22 (18%)	2/14 (14%)	1/11 (9%)	0/7 (0%)
First incidence (days)	598	639	705	687
Poly-3 test	P=0.035N	P=0.216N	P=0.128N	P=0.090N
Skin: Squamous Cell Papilloma or Keratoacanthoma				
Overall rate	9/50 (18%)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted rate	21.8%	11.3%	8.7%	3.5%
Terminal rate	5/22 (23%)	3/14 (21%)	1/11 (9%)	0/7 (0%)
First incidence (days)	576	639	548	687
Poly-3 test	P=0.014N	P=0.177N	P=0.106N	P=0.038N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	9/50 (18%)	5/50 (10%)	3/50 (6%)	1/50 (2%)
Adjusted rate	21.8%	14.1%	8.7%	3.5%
Terminal rate	5/22 (23%)	4/14 (29%)	1/11 (9%)	0/7 (0%)
First incidence (days)	576	639	548	687
Poly-3 test	P=0.013N	P=0.282N	P=0.106N	P=0.038N
Skin: Squamous Cell Papilloma, Keratoacanthoma, Basal Cell Adenoma, Basal Cell Carcinoma, or Squamous Cell Carcinoma				
Overall rate	9/50 (18%)	6/50 (12%)	3/50 (6%)	2/50 (4%)
Adjusted rate	21.8%	17.0%	8.7%	7.1%
Terminal rate	5/22 (23%)	5/14 (36%)	1/11 (9%)	1/7 (14%)
First incidence (days)	576	639	548	687
Poly-3 test	P=0.036N	P=0.401N	P=0.106N	P=0.096N
Skin: Fibroma				
Overall rate	5/50 (10%)	6/50 (12%)	2/50 (4%)	2/50 (4%)
Adjusted rate	12.3%	16.7%	5.9%	7.1%
Terminal rate	3/22 (14%)	4/14 (29%)	1/11 (9%)	2/7 (29%)
First incidence (days)	572	552	683	722 (T)
Poly-3 test	P=0.198N	P=0.412	P=0.294N	P=0.388N
Skin: Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	6/50 (12%)	6/50 (12%)	3/50 (6%)	3/50 (6%)
Adjusted rate	14.6%	16.7%	8.8%	10.7%
Terminal rate	3/22 (14%)	4/14 (29%)	1/11 (9%)	2/7 (29%)
First incidence (days)	572	552	674	709
Poly-3 test	P=0.282N	P=0.527	P=0.338N	P=0.453N
Testes: Adenoma				
Overall rate	5/50 (10%)	6/49 (12%)	4/49 (8%)	12/50 (24%)
Adjusted rate	12.3%	16.9%	11.9%	36.6%
Terminal rate	3/22 (14%)	3/14 (21%)	1/11 (9%)	3/7 (43%)
First incidence (days)	592	486	660	464
Poly-3 test	P=0.008	P=0.404	P=0.618N	P=0.012
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/49 (8%)	2/50 (4%)	0/48 (0%)	3/49 (6%)
Adjusted rate	10.2%	5.6%	0.0%	10.6%
Terminal rate	3/22 (14%)	1/14 (7%)	0/11 (0%)	1/7 (14%)
First incidence (days)	701	581	—	574
Poly-3 test	P=0.483N	P=0.382N	P=0.085N	P=0.634
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	0/49 (0%)	0/50 (0%)	5/48 (10%)	0/49 (0%)
Adjusted rate	0.0%	0.0%	14.9%	0.0%
Terminal rate	0/22 (0%)	0/14 (0%)	1/11 (9%)	0/7 (0%)
First incidence (days)	—	—	630	—
Poly-3 test	P=0.220	—[f]	P=0.019	—
Thyroid Gland (Follicular Cell): Carcinoma				
Overall rate	3/49 (6%)	3/50 (6%)	1/48 (2%)	0/49 (0%)
Adjusted rate	7.6%	8.4%	3.0%	0.0%
Terminal rate	1/22 (5%)	1/14 (7%)	0/11 (0%)	0/7 (0%)
First incidence (days)	674	593	645	—
Poly-3 test	P=0.093N	P=0.618	P=0.370N	P=0.196N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	3/49 (6%)	3/50 (6%)	6/48 (13%)	0/49 (0%)
Adjusted rate	7.6%	8.4%	17.7%	0.0%
Terminal rate	1/22 (5%)	1/14 (7%)	1/11 (9%)	0/7 (0%)
First incidence (days)	674	593	630	—
Poly-3 test	P=0.355N	P=0.618	P=0.168	P=0.196N
Zymbal's Gland: Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.5%	0.0%	5.8%	10.3%
Terminal rate	0/22 (0%)	0/14 (0%)	0/11 (0%)	0/7 (0%)
First incidence (days)	660	—	494	466
Poly-3 test	P=0.063	P=0.528N	P=0.447	P=0.200
All Organs: Hemangiosarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted rate	0.0%	8.5%	3.0%	0.0%
Terminal rate	0/22 (0%)	2/14 (14%)	0/11 (0%)	0/7 (0%)
First incidence (days)	—	660	705	—
Poly-3 test	P=0.519N	P=0.096	P=0.466	—
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted rate	2.5%	8.5%	3.0%	3.5%
Terminal rate	0/22 (0%)	2/14 (14%)	0/11 (0%)	0/7 (0%)
First incidence (days)	705	660	705	631
Poly-3 test	P=0.573N	P=0.259	P=0.722	P=0.678
All Organs: Benign Neoplasms				
Overall rate	40/50 (80%)	37/50 (74%)	29/50 (58%)	33/50 (66%)
Adjusted rate	86.7%	84.4%	72.4%	81.9%
Terminal rate	21/22 (96%)	13/14 (93%)	8/11 (73%)	6/7 (86%)
First incidence (days)	468	372	486	464
Poly-3 test	P=0.214N	P=0.497N	P=0.055N	P=0.353N
All Organs: Malignant Neoplasms				
Overall rate	17/50 (34%)	14/50 (28%)	12/50 (24%)	13/50 (26%)
Adjusted rate	40.2%	37.5%	33.2%	40.5%
Terminal rate	9/22 (41%)	7/14 (50%)	3/11 (27%)	2/7 (29%)
First incidence (days)	587	552	481	466
Poly-3 test	P=0.513N	P=0.496N	P=0.341N	P=0.584
All Organs: Benign or Malignant Neoplasms				
Overall rate	43/50 (86%)	38/50 (76%)	32/50 (64%)	39/50 (78%)
Adjusted rate	91.2%	86.1%	78.4%	90.9%
Terminal rate	21/22 (96%)	13/14 (93%)	9/11 (82%)	7/7 (100%)
First incidence (days)	468	372	481	464
Poly-3 test	P=0.534N	P=0.306N	P=0.050N	P=0.656N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, pancreas, pancreatic islets, pituitary gland, prostate gland, testis, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine[a]

	0 ppm	100 ppm	200 ppm	400 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	2	9	9	10
Natural deaths	26	27	30	33
Survivors				
Terminal sacrifice	22	14	11	7
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Foreign body			1 (2%)	1 (2%)
Inflammation, acute				1 (2%)
Ulcer				1 (2%)
Muscularis, degeneration				1 (2%)
Intestine large, colon	(35)	(39)	(36)	(33)
Mineralization			1 (3%)	1 (3%)
Parasite metazoan			1 (3%)	
Intestine large, rectum	(42)	(42)	(41)	(40)
Hemorrhage	1 (2%)			
Mineralization		1 (2%)		
Parasite metazoan				1 (3%)
Ulcer				1 (3%)
Intestine large, cecum	(32)	(37)	(29)	(27)
Congestion			1 (3%)	
Edema		1 (3%)		
Hemorrhage	1 (3%)	2 (5%)	1 (3%)	
Inflammation, acute		2 (5%)	2 (7%)	1 (4%)
Inflammation, chronic			1 (3%)	1 (4%)
Ulcer		2 (5%)		2 (7%)
Artery, mineralization		1 (3%)		
Intestine small, jejunum	(37)	(36)	(34)	(35)
Inflammation, chronic				1 (3%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	5 (10%)	9 (18%)	2 (4%)	
Basophilic focus				2 (4%)
Cholangiofibrosis				1 (2%)
Clear cell focus	15 (30%)	7 (14%)	8 (16%)	8 (16%)
Congestion	19 (38%)	12 (24%)	6 (12%)	17 (34%)
Degeneration, cystic	7 (14%)	13 (26%)	9 (18%)	5 (10%)
Eosinophilic focus	14 (28%)	12 (24%)	4 (8%)	2 (4%)
Fibrosis	1 (2%)	5 (10%)	26 (52%)	31 (62%)
Hemorrhage	1 (2%)	1 (2%)	5 (10%)	3 (6%)
Hepatodiaphragmatic nodule	2 (4%)	1 (2%)	2 (4%)	
Hypertrophy			1 (2%)	
Infarct			1 (2%)	
Infiltration cellular, histiocyte		1 (2%)	2 (4%)	
Inflammation, acute	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Mineralization		1 (2%)	3 (6%)	3 (6%)
Mixed cell focus	1 (2%)		1 (2%)	1 (2%)
Necrosis	6 (12%)	7 (14%)	6 (12%)	2 (4%)

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

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Alimentary System (continued)				
Liver (continued)	(50)	(50)	(50)	(50)
Pigmentation	6 (12%)	15 (30%)	34 (68%)	42 (84%)
Regeneration				2 (4%)
Tension lipidosis			1 (2%)	
Thrombosis			1 (2%)	
Vacuolization cytoplasmic	18 (36%)	18 (36%)	12 (24%)	15 (30%)
Artery, mineralization		1 (2%)		
Bile duct, cyst			2 (4%)	3 (6%)
Bile duct, dilatation		2 (4%)		
Bile duct, hyperplasia	31 (62%)	33 (66%)	30 (60%)	27 (54%)
Centrilobular, cytomegaly		1 (2%)	1 (2%)	1 (2%)
Centrilobular, degeneration	1 (2%)	15 (30%)	25 (50%)	33 (66%)
Centrilobular, hypertrophy		1 (2%)		
Centrilobular, necrosis	5 (10%)	6 (12%)	4 (8%)	23 (46%)
Hepatocyte, atrophy	2 (4%)		1 (2%)	1 (2%)
Oval cell, hyperplasia	1 (2%)			
Periportal, fibrosis			5 (10%)	7 (14%)
Sinusoid, congestion	1 (2%)			
Mesentery	(7)	(1)	(2)	(2)
Mineralization	1 (14%)			
Artery, inflammation	5 (71%)	1 (100%)		1 (50%)
Artery, mineralization	2 (29%)			
Fat, necrosis	1 (14%)			1 (50%)
Vein, thrombosis			2 (100%)	
Oral mucosa	(5)	(1)	(1)	
Hyperplasia, squamous		1 (100%)	1 (100%)	
Inflammation, suppurative	3 (60%)			
Pancreas	(46)	(50)	(50)	(49)
Atrophy	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Basophilic focus	1 (2%)			
Edema			1 (2%)	
Fibrosis			1 (2%)	
Hemorrhage		1 (2%)		
Hyperplasia	18 (39%)	18 (36%)	8 (16%)	8 (16%)
Necrosis	1 (2%)			
Acinus, hyperplasia	1 (2%)		1 (2%)	
Artery, inflammation	3 (7%)	5 (10%)	3 (6%)	
Artery, mineralization	2 (4%)	6 (12%)	1 (2%)	
Duct, hyperplasia	1 (2%)	1 (2%)	1 (2%)	
Salivary glands	(48)	(49)	(47)	(48)
Atrophy				1 (2%)
Inflammation, acute		1 (2%)		
Artery, mineralization	2 (4%)	3 (6%)		
Duct, cyst	1 (2%)		1 (2%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Alimentary System (continued)				
Stomach, forestomach	(49)	(50)	(50)	(49)
Cyst			1 (2%)	2 (4%)
Erosion	1 (2%)			
Fibrosis				1 (2%)
Foreign body			1 (2%)	2 (4%)
Hemorrhage			1 (2%)	
Hyperplasia, squamous	2 (4%)	13 (26%)	11 (22%)	10 (20%)
Inflammation, acute	1 (2%)			
Inflammation, chronic			1 (2%)	1 (2%)
Inflammation, chronic active				1 (2%)
Mineralization	3 (6%)	5 (10%)	3 (6%)	1 (2%)
Ulcer	2 (4%)	4 (8%)	3 (6%)	4 (8%)
Ulcer, chronic	1 (2%)			
Stomach, glandular	(49)	(50)	(48)	(48)
Erosion	3 (6%)	3 (6%)	2 (4%)	4 (8%)
Fibrosis		1 (2%)		
Hemorrhage			2 (4%)	
Hyperplasia	1 (2%)		1 (2%)	
Inflammation, chronic active			1 (2%)	
Mineralization	8 (16%)	25 (50%)	16 (33%)	6 (13%)
Ulcer			1 (2%)	
Artery, mineralization			1 (2%)	1 (2%)
Serosa, edema		1 (2%)		
Tooth	(2)	(2)	(4)	(3)
Peridontal tissue, inflammation, chronic				1 (33%)
Peridontal tissue, inflammation, chronic active	1 (50%)			1 (33%)
Peridontal tissue, inflammation, granulomatous		1 (50%)		
Peridontal tissue, inflammation, suppurative	1 (50%)	1 (50%)	4 (100%)	1 (33%)
Cardiovascular System				
Blood vessel	(8)	(23)	(12)	(3)
Mineralization	6 (75%)	6 (26%)	1 (8%)	
Aorta, mineralization	7 (88%)	21 (91%)	10 (83%)	3 (100%)
Pulmonary artery, degeneration		1 (4%)		
Pulmonary artery, mineralization	3 (38%)	3 (13%)	5 (42%)	2 (67%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	49 (98%)	49 (98%)	49 (98%)	47 (94%)
Inflammation, chronic	1 (2%)			
Mineralization	6 (12%)	17 (34%)	12 (24%)	3 (6%)
Thrombosis	1 (2%)		1 (2%)	
Artery, inflammation		1 (2%)		
Artery, inflammation, acute				1 (2%)
Artery, mineralization	4 (8%)	15 (30%)	9 (18%)	2 (4%)
Artery, thrombosis	1 (2%)			
Atrium, dilatation			1 (2%)	1 (2%)
Atrium, thrombosis	4 (8%)	2 (4%)	5 (10%)	3 (6%)
Valve, inflammation				1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Accessory adrenal cortical nodule	1 (2%)			
Angiectasis	1 (2%)		1 (2%)	
Congestion		2 (4%)		1 (2%)
Degeneration		2 (4%)		
Hemorrhage	3 (6%)			
Hyperplasia	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hypertrophy	2 (4%)	2 (4%)	2 (4%)	
Mineralization		1 (2%)		
Necrosis				2 (4%)
Thrombosis		1 (2%)		1 (2%)
Vacuolization cytoplasmic	17 (34%)	13 (26%)	12 (24%)	7 (14%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	3 (6%)	4 (8%)	2 (4%)	1 (2%)
Islets, pancreatic	(47)	(50)	(49)	(49)
Hyperplasia	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Parathyroid gland	(48)	(47)	(48)	(47)
Hyperplasia	16 (33%)	32 (68%)	29 (60%)	12 (26%)
Inflammation, chronic	1 (2%)			
Pituitary gland	(49)	(49)	(50)	(50)
Angiectasis				1 (2%)
Congestion				2 (4%)
Cyst	17 (35%)	13 (27%)	18 (36%)	11 (22%)
Hemorrhage			1 (2%)	1 (2%)
Hyperplasia	13 (27%)	10 (20%)	7 (14%)	3 (6%)
Hypertrophy				1 (2%)
Pars distalis, hyperplasia	2 (4%)	1 (2%)		
Thyroid gland	(49)	(50)	(48)	(49)
Inflammation, granulomatous			1 (2%)	
C-cell, hyperplasia		1 (2%)	1 (2%)	
Follicle, cyst	2 (4%)	4 (8%)	5 (10%)	1 (2%)
Follicular cell, hyperplasia		2 (4%)	1 (2%)	
General Body System				
None				
Genital System				
Coagulating gland	(48)	(42)	(45)	(45)
Inflammation, acute		1 (2%)	1 (2%)	
Inflammation, chronic				1 (2%)
Inflammation, chronic active	1 (2%)			
Artery, mineralization		1 (2%)		
Epididymis	(50)	(49)	(49)	(50)
Arteriole, mineralization	1 (2%)			
Artery, inflammation				1 (2%)
Epithelium, hyperplasia				1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Genital System (continued)				
Preputial gland	(50)	(48)	(50)	(50)
Atrophy			1 (2%)	
Hyperplasia, squamous				1 (2%)
Inflammation, chronic	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)	
Inflammation, suppurative	12 (24%)	9 (19%)	10 (20%)	3 (6%)
Duct, cyst	49 (98%)	43 (90%)	46 (92%)	48 (96%)
Prostate	(50)	(49)	(50)	(50)
Fibrosis			2 (4%)	1 (2%)
Hemorrhage	1 (2%)		1 (2%)	
Hyperplasia	4 (8%)	4 (8%)	1 (2%)	2 (4%)
Inflammation, acute	4 (8%)	1 (2%)		
Inflammation, chronic	3 (6%)	4 (8%)	5 (10%)	2 (4%)
Inflammation, chronic active	5 (10%)	5 (10%)	2 (4%)	2 (4%)
Artery, mineralization	1 (2%)			
Seminal vesicle	(49)	(49)	(50)	(49)
Cyst		1 (2%)		
Hyperplasia		1 (2%)		
Inflammation, chronic		1 (2%)		
Inflammation, chronic active			1 (2%)	
Artery, mineralization		1 (2%)		
Testes	(50)	(49)	(49)	(50)
Atrophy	20 (40%)	20 (41%)	18 (37%)	9 (18%)
Congestion				1 (2%)
Inflammation, granulomatous			1 (2%)	1 (2%)
Mineralization	6 (12%)	2 (4%)	9 (18%)	4 (8%)
Artery, inflammation	24 (48%)	24 (49%)	14 (29%)	11 (22%)
Artery, mineralization		3 (6%)	2 (4%)	
Interstitial cell, hyperplasia	3 (6%)	4 (8%)	7 (14%)	7 (14%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		1 (2%)
Erythroid cell, hyperplasia		1 (2%)		
Myeloid cell, hyperplasia	2 (4%)	1 (2%)	1 (2%)	
Lymph node	(31)	(44)	(38)	(32)
Ectasia	2 (6%)	1 (2%)		
Hemorrhage	2 (6%)	1 (2%)		
Hyperplasia, plasma cell	2 (6%)			
Iliac, ectasia	5 (16%)	3 (7%)	3 (8%)	1 (3%)
Iliac, hemorrhage	1 (3%)	2 (5%)	2 (5%)	3 (9%)
Iliac, hyperplasia, lymphoid		1 (2%)	2 (5%)	1 (3%)
Iliac, hyperplasia, plasma cell		4 (9%)	2 (5%)	2 (6%)
Inguinal, atrophy	1 (3%)			
Inguinal, ectasia	1 (3%)		1 (3%)	
Inguinal, hemorrhage		1 (2%)	1 (3%)	1 (3%)
Inguinal, hyperplasia, lymphoid			1 (3%)	
Inguinal, infiltration cellular, histiocyte			1 (3%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Hematopoietic System (continued)				
Lymph node (continued)	(31)	(44)	(38)	(32)
Mediastinal, atrophy		1 (2%)		
Mediastinal, congestion	1 (3%)	3 (7%)	2 (5%)	1 (3%)
Mediastinal, ectasia	6 (19%)	12 (27%)	9 (24%)	6 (19%)
Mediastinal, hemorrhage	8 (26%)	15 (34%)	10 (26%)	9 (28%)
Mediastinal, hyperplasia, lymphoid				1 (3%)
Mediastinal, hyperplasia, plasma cell		2 (5%)	1 (3%)	1 (3%)
Pancreatic, ectasia	2 (6%)	5 (11%)		1 (3%)
Pancreatic, hemorrhage	4 (13%)	5 (11%)	4 (11%)	7 (22%)
Pancreatic, hyperplasia, lymphoid	2 (6%)	1 (2%)		4 (13%)
Pancreatic, hyperplasia, plasma cell	1 (3%)		2 (5%)	2 (6%)
Pancreatic, pigmentation			1 (3%)	
Renal, ectasia	15 (48%)	20 (45%)	16 (42%)	10 (31%)
Renal, fibrosis		2 (5%)		
Renal, hemorrhage	10 (32%)	17 (39%)	19 (50%)	12 (38%)
Renal, hyperplasia, lymphoid			1 (3%)	2 (6%)
Renal, hyperplasia, plasma cell		1 (2%)	6 (16%)	2 (6%)
Renal, pigmentation			3 (8%)	
Lymph node, mandibular	(48)	(49)	(47)	(48)
Congestion		5 (10%)	1 (2%)	4 (8%)
Ectasia	15 (31%)	8 (16%)	10 (21%)	10 (21%)
Hemorrhage	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)		1 (2%)
Hyperplasia, plasma cell	4 (8%)	8 (16%)	6 (13%)	4 (8%)
Lymph node, mesenteric	(46)	(50)	(50)	(50)
Atrophy		6 (12%)	1 (2%)	2 (4%)
Ectasia	5 (11%)	6 (12%)	6 (12%)	5 (10%)
Hemorrhage	12 (26%)	14 (28%)	12 (24%)	12 (24%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)	5 (10%)
Hyperplasia, plasma cell		2 (4%)		1 (2%)
Spleen	(49)	(50)	(49)	(49)
Angiectasis	1 (2%)			
Atrophy	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Congestion	1 (2%)		1 (2%)	
Fibrosis		1 (2%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	1 (2%)	2 (4%)		2 (4%)
Hyperplasia, lymphoid	1 (2%)			
Necrosis	1 (2%)			
Artery, mineralization	1 (2%)	1 (2%)		
Thymus	(48)	(49)	(49)	(50)
Atrophy	15 (31%)	29 (59%)	28 (57%)	24 (48%)
Cyst	5 (10%)	6 (12%)	4 (8%)	6 (12%)
Ectopic parathyroid gland	3 (6%)	5 (10%)	1 (2%)	1 (2%)
Ectopic thyroid	1 (2%)			
Fibrosis			1 (2%)	
Hemorrhage	8 (17%)	6 (12%)	8 (16%)	14 (28%)
Hyperplasia, lymphoid	1 (2%)			
Hyperplasia, squamous				2 (4%)
Artery, mineralization		1 (2%)		
Epithelial cell, hyperplasia			1 (2%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Integumentary System				
Mammary gland	(48)	(46)	(44)	(46)
Cyst		2 (4%)		1 (2%)
Hyperplasia	4 (8%)		2 (5%)	4 (9%)
Artery, mineralization	3 (6%)	5 (11%)		
Duct, dilatation	6 (13%)	7 (15%)	5 (11%)	4 (9%)
Skin	(50)	(50)	(50)	(50)
Cyst	1 (2%)	2 (4%)	1 (2%)	
Hyperkeratosis	1 (2%)			
Hyperplasia, squamous		2 (4%)	1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)	2 (4%)		1 (2%)
Inflammation, suppurative		1 (2%)		1 (2%)
Ulcer	1 (2%)	1 (2%)		2 (4%)
Hair follicle, cyst	1 (2%)			1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy	10 (20%)	21 (42%)	16 (32%)	6 (12%)
Inflammation, chronic active		1 (2%)		
Osteosclerosis			1 (2%)	
Cartilage, degeneration				1 (2%)
Cranium, fibrous osteodystrophy	10 (20%)	15 (30%)	13 (26%)	2 (4%)
Joint, arthrosis				1 (2%)
Joint, fibrosis				1 (2%)
Joint, inflammation, chronic			1 (2%)	1 (2%)
Mandible, hyperplasia				1 (2%)
Metacarpal, inflammation, chronic active				1 (2%)
Metatarsal, hyperplasia			1 (2%)	
Metatarsal, inflammation, chronic active				1 (2%)
Periosteum, hyperplasia				1 (2%)
Rib, callus		1 (2%)		
Vertebra, fibrous osteodystrophy		4 (8%)	2 (4%)	
Vertebra, inflammation, chronic				1 (2%)
Nervous System				
Brain	(50)	(49)	(50)	(50)
Degeneration		1 (2%)		
Hemorrhage	1 (2%)	1 (2%)		
Hydrocephalus	1 (2%)	1 (2%)		
Peripheral nerve	(1)	(4)	(2)	(5)
Degeneration	1 (100%)			
Mineralization		2 (50%)	2 (100%)	
Radicular neuropathy		4 (100%)	1 (50%)	2 (40%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion		4 (8%)	2 (4%)	4 (8%)
Edema		2 (4%)		
Hemorrhage	2 (4%)	1 (2%)	10 (20%)	7 (14%)
Inflammation, acute	1 (2%)	3 (6%)		
Inflammation, chronic	1 (2%)		1 (2%)	
Inflammation, granulomatous	4 (8%)	1 (2%)	5 (10%)	2 (4%)
Mineralization		1 (2%)		
Necrosis	1 (2%)		1 (2%)	
Alveolar epithelium, hyperplasia	1 (2%)		2 (4%)	
Alveolar epithelium, hypertrophy		1 (2%)		
Alveolus, infiltration cellular, histiocyte	8 (16%)	5 (10%)	4 (8%)	
Alveolus, mineralization	2 (4%)			
Artery, mineralization	2 (4%)	3 (6%)		
Bronchus, inflammation, acute	1 (2%)			
Bronchus, mineralization	1 (2%)			
Interstitium, fibrosis	4 (8%)	6 (12%)	4 (8%)	1 (2%)
Interstitium, inflammation, chronic		2 (4%)		
Nose	(50)	(50)	(50)	(50)
Cyst	1 (2%)			
Erosion	1 (2%)			
Foreign body	11 (22%)	4 (8%)	6 (12%)	1 (2%)
Hemorrhage	3 (6%)		1 (2%)	
Hyperplasia, squamous	1 (2%)			
Inflammation, acute	7 (14%)	7 (14%)	4 (8%)	2 (4%)
Inflammation, chronic	7 (14%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic active	4 (8%)	6 (12%)	5 (10%)	6 (12%)
Metaplasia, squamous		1 (2%)	1 (2%)	2 (4%)
Thrombosis			1 (2%)	
Ulcer			2 (4%)	
Artery, thrombosis				1 (2%)
Olfactory epithelium, hyperplasia	1 (2%)			
Olfactory epithelium, metaplasia			1 (2%)	
Respiratory epithelium, hyperplasia	20 (40%)	9 (18%)	12 (24%)	15 (30%)
Respiratory epithelium, metaplasia		1 (2%)		
Respiratory epithelium, metaplasia, squamous			1 (2%)	
Trachea	(50)	(50)	(50)	(50)
Cyst		1 (2%)		
Foreign body			1 (2%)	
Inflammation, acute		1 (2%)		
Inflammation, chronic active				1 (2%)
Special Senses System				
Eye			(1)	
Cornea, ulcer			1 (100%)	
Harderian gland	(1)		(4)	(1)
Inflammation, chronic				1 (100%)
Lacrimal gland			(1)	
Atrophy			1 (100%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

	0 ppm	100 ppm	200 ppm	400 ppm
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Congestion	4 (8%)			2 (4%)
Cyst	21 (42%)	31 (62%)	19 (38%)	16 (32%)
Hydronephrosis	19 (38%)	20 (40%)	30 (60%)	15 (30%)
Inflammation, acute		2 (4%)		1 (2%)
Mineralization	8 (16%)	17 (34%)	8 (16%)	5 (10%)
Nephropathy	50 (100%)	50 (100%)	50 (100%)	50 (100%)
Artery, mineralization	5 (10%)	8 (16%)	3 (6%)	
Renal tubule, accumulation, hyaline droplet			1 (2%)	1 (2%)
Renal tubule, hyperplasia	6 (12%)	17 (34%)	8 (16%)	5 (10%)
Vein, thrombosis		2 (4%)	1 (2%)	3 (6%)
Urinary bladder	(47)	(49)	(47)	(44)
Dilatation			1 (2%)	
Edema		1 (2%)		
Hemorrhage			1 (2%)	
Inflammation, acute		1 (2%)		
Inflammation, chronic	1 (2%)			
Inflammation, chronic active			1 (2%)	
Ulcer		1 (2%)		
Artery, mineralization			1 (2%)	
Transitional epithelium, hyperplasia	1 (2%)	3 (6%)	1 (2%)	

APPENDIX D
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	2	1	1	3
Moribund	2	3	3	1
Natural deaths	11	18	11	11
Survivors				
Other			1	
Terminal sacrifice	35	28	34	35
Animals examined microscopically	50	50	49	50
Alimentary System				
Intestine small, duodenum	(43)	(44)	(43)	(44)
Intestine small, jejunum	(40)	(46)	(42)	(44)
Carcinoma				1 (2%)
Histiocytic sarcoma			1 (2%)	
Liver	(50)	(50)	(49)	(50)
Hemangioma		1 (2%)		
Hemangiosarcoma	1 (2%)			
Hemangiosarcoma, multiple		2 (4%)		
Hepatoblastoma	1 (2%)	14 (28%)	16 (33%)	13 (26%)
Hepatoblastoma, multiple	1 (2%)	4 (8%)	6 (12%)	2 (4%)
Hepatocellular carcinoma	12 (24%)	16 (32%)	15 (31%)	22 (44%)
Hepatocellular carcinoma, multiple	3 (6%)	19 (38%)	26 (53%)	18 (36%)
Hepatocellular adenoma	13 (26%)	11 (22%)	5 (10%)	11 (22%)
Hepatocellular adenoma, multiple	16 (32%)	29 (58%)	29 (59%)	28 (56%)
Hepatocholangiocarcinoma, multiple		1 (2%)		
Histiocytic sarcoma	1 (2%)	2 (4%)		
Mast cell tumor malignant, metastatic, skin			1 (2%)	
Sarcoma, metastatic, mesentery		1 (2%)		
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Mesentery	(2)	(7)	(6)	(4)
Hepatocholangiocarcinoma, metastatic, liver		1 (14%)		
Histiocytic sarcoma		1 (14%)		
Sarcoma		1 (14%)	1 (17%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (25%)
Pancreas	(49)	(50)	(48)	(50)
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Stomach, forestomach	(49)	(50)	(48)	(49)
Squamous cell papilloma	1 (2%)			
Stomach, glandular	(49)	(50)	(48)	(47)
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Cardiovascular System				
Heart	(50)	(50)	(49)	(50)

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Endocrine System				
Adrenal cortex	(49)	(49)	(49)	(49)
Adenoma	1 (2%)			1 (2%)
Sarcoma, metastatic, mesentery		1 (2%)		
Capsule, adenoma	2 (4%)			
Capsule, sarcoma, metastatic, mesentery			1 (2%)	
Capsule, squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Adrenal medulla	(48)	(48)	(49)	(49)
Pheochromocytoma benign		1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Islets, pancreatic	(49)	(50)	(48)	(50)
Adenoma		1 (2%)	2 (4%)	1 (2%)
Thyroid gland	(49)	(50)	(49)	(50)
Follicular cell, adenoma	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Follicular cell, adenoma, multiple			1 (2%)	
General Body System				
Peritoneum				(1)
Squamous cell carcinoma, metastatic, uncertain primary site				1 (100%)
Tissue NOS		(1)		
Thoracic, hemangiosarcoma			1 (100%)	
Genital System				
Coagulating gland		(1)		
Sarcoma, metastatic, mesentery		1 (100%)		
Epididymis	(50)	(50)	(49)	(50)
Sarcoma		1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)	1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Preputial gland	(50)	(50)	(49)	(49)
Sarcoma, metastatic, mesentery			1 (2%)	
Prostate	(50)	(48)	(48)	(49)
Sarcoma, metastatic, mesentery			1 (2%)	
Seminal vesicle	(49)	(49)	(49)	(50)
Sarcoma, metastatic, mesentery		1 (2%)	1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Testes	(50)	(50)	(49)	(50)
Sarcoma, metastatic, mesentery		1 (2%)	1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Hemangiosarcoma		1 (2%)		
Hemangiosarcoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (2%)	1 (2%)		
Mast cell tumor malignant, metastatic, skin			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Hematopoietic System (continued)				
Lymph node	(2)	(4)	(4)	(2)
Mediastinal, hepatocholangiocarcinoma, metastatic, liver		1 (25%)		
Mediastinal, sarcoma, metastatic, mesentery		1 (25%)	1 (25%)	
Mediastinal, squamous cell carcinoma, metastatic, uncertain primary site				1 (50%)
Lymph node, mandibular	(48)	(47)	(48)	(50)
Mast cell tumor malignant, metastatic, skin			1 (2%)	
Squamous cell carcinoma, metastatic, skin	1 (2%)			
Lymph node, mesenteric	(43)	(47)	(44)	(50)
Hemangioma		1 (2%)	1 (2%)	
Histiocytic sarcoma		1 (2%)	1 (2%)	
Sarcoma, metastatic, mesentery			1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Spleen	(49)	(50)	(47)	(49)
Hemangiosarcoma	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Hemangiosarcoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Mast cell tumor malignant, metastatic, skin			1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Thymus	(46)	(46)	(39)	(47)
Hepatocellular carcinoma, metastatic, liver		1 (2%)		
Sarcoma, metastatic, mesentery			1 (3%)	
Integumentary System				
Skin	(49)	(50)	(48)	(50)
Squamous cell carcinoma	1 (2%)			
Subcutaneous tissue, basal cell adenoma				1 (2%)
Subcutaneous tissue, hemangioma		1 (2%)		1 (2%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, histiocytic sarcoma		1 (2%)		
Subcutaneous tissue, mast cell tumor malignant			1 (2%)	
Musculoskeletal System				
Skeletal muscle		(3)	(2)	(1)
Hepatoblastoma, metastatic, liver		1 (33%)		
Sarcoma, metastatic, mesentery		1 (33%)	1 (50%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (100%)
Nervous System				
Brain	(50)	(50)	(49)	(50)
Histiocytic sarcoma		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Respiratory System				
Lung	(49)	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	10 (20%)	5 (10%)	7 (14%)	6 (12%)
Alveolar/bronchiolar adenoma, multiple	2 (4%)		1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Hemangiosarcoma, metastatic, liver		1 (2%)		
Hepatoblastoma, metastatic, liver		4 (8%)	7 (14%)	3 (6%)
Hepatocellular carcinoma, metastatic, liver	7 (14%)	7 (14%)	11 (22%)	13 (26%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma		1 (2%)		
Mediastinum, hepatocellular carcinoma, metastatic, liver		1 (2%)		
Mediastinum, hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Nose	(50)	(49)	(49)	(50)
Special Senses System				
Harderian gland	(5)			(1)
Adenoma	3 (60%)			1 (100%)
Carcinoma	2 (40%)			
Urinary System				
Kidney	(49)	(50)	(48)	(50)
Hemangiosarcoma, metastatic, tissue NOS			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Mast cell tumor malignant, metastatic, skin			1 (2%)	
Sarcoma, metastatic, mesentery			1 (2%)	
Renal tubule, adenoma		1 (2%)	1 (2%)	
Urinary bladder	(48)	(49)	(44)	(50)
Hemangioma			1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Transitional epithelium, papilloma	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)	2 (4%)	1 (2%)	
Lymphoma malignant	3 (6%)	3 (6%)	3 (6%)	1 (2%)
Mesothelioma malignant			1 (2%)	1 (2%)

TABLE D1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	43	49	48	47
Total primary neoplasms	79	122	122	114
Total animals with benign neoplasms	35	42	36	39
Total benign neoplasms	51	53	49	54
Total animals with malignant neoplasms	22	46	47	42
Total malignant neoplasms	28	69	73	60
Total animals with metastatic neoplasms	8	12	19	14
Total metastatic neoplasms	8	30	35	30
Total animals with malignant neoplasms of uncertain primary site				1

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

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	1 1 8	5 2 0	5 4 2	5 7 4	5 9 8	6 2 1	6 3 3	6 3 7	6 3 9	6 5 3	6 6 3	6 7 0	6 7 2	7 0 6	7 1 4	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2
Carcass ID Number	0 1 2	0 3 7	0 4 0	0 2 5	0 3 2	0 0 5	0 1 7	0 4 3	0 0 1	0 3 0	0 2 7	0 2 1	0 2 3	0 2 4	0 3 4	1 1 1	1 1 3	1 1 4	1 1 5	1 1 6	1 1 8	1 1 9	1 2 0	2 2 2	2 2 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	A	A	+	A	A	+	A	+	+	+	+	+	M	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	+	+	+	A	+	A	M	A	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	A	+	A	A	A	A	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	+	A	+	A	A	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma														X											
Hepatoblastoma																									
Hepatoblastoma, multiple																									
Hepatocellular carcinoma				X	X		X						X		X										
Hepatocellular carcinoma, multiple								X														X	X		
Hepatocellular adenoma		X				X							X		X	X						X			
Hepatocellular adenoma, multiple														X			X			X	X				X
Histiocytic sarcoma										X															
Mesentery																									
Oral mucosa											+														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Tongue																									
Tooth		+	+	+	+	+	+		+	+	+	+	+	+			+	+	+		+		+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Capsule, adenoma					X																				
Adrenal medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	M	+	+	+	M	+	+	+	+	+	A	M	+	M	M	M	+	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	I	A	+	+	+	+	+	+	+	M	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																	X						X		
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	
Carcass ID Number	0 2 8	0 2 9	0 4 1	0 4 2	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	0 0 2	0 0 3	0 0 4	0 0 6	0 0 7	0 0 8	0 0 9	0 1 0	0 1 3	0 3 3	0 3 5	0 3 6	0 3 8	0 3 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatoblastoma										X																1
Hepatoblastoma, multiple																									X	1
Hepatocellular carcinoma			X		X	X	X	X	X														X			12
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma	X												X	X	X	X		X				X				13
Hepatocellular adenoma, multiple			X		X	X			X		X	X					X		X	X				X	X	16
Histiocytic sarcoma																										1
Mesentery				+			+																			2
Oral mucosa																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																							X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																									+	1
Tooth	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	42
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X																					1
Capsule, adenoma															X											2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	M	M	+	+	+	+	M	M	+	M	+	M	+	+	+	+	M	+	+	+	+	M	+	M	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										2
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	72 2	72 2	72 2	72 2	72 2	72 2	72 2	72 2	72 2	72 2	72 2	72 2	72 3	72 3	72 3	72 3	72 3	72 3	72 3	72 3	72 3	72 3	72 3	72 3	72 3	72 3	
Carcass ID Number	00 28	00 29	00 41	00 42	00 44	00 45	00 46	00 47	00 48	00 49	00 50	00 51	00 02	00 03	00 04	00 06	00 07	00 08	00 09	00 10	00 11	00 33	00 35	00 36	00 38	00 39	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Lymph node																											2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic, skin																											1
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma						X																					1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																											
Mammary gland	M	+	M	M	M	M	M	M	M	M	M	M	+	M	+	M	M	M	M	M	M	M	M	M	M	M	5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																											1
Subcutaneous tissue, hemangiosarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma									X		X						X										10
Alveolar/bronchiolar adenoma, multiple		X													X												2
Alveolar/bronchiolar carcinoma																											1
Hepatocellular carcinoma, metastatic, liver					X		X																	X			7
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																											
Eye																										+	1
Harderian gland																		+						+		+	5
Adenoma																								X			3
Carcinoma																		X								X	2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Transitional epithelium, papilloma																											1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Lymphoma malignant			X																			X					3

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

Number of Days on Study	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	723	723	723	
Carcass ID Number	00555	00556	00558	00600	00604	00655	00666	00671	00672	00673	00676	00682	00683	00684	00686	00690	00691	00692	00693	00698	00699	01000	00887	00955	00966	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	33
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma						X																				1
Hemangiosarcoma, multiple																										2
Hepatoblastoma	X		X			X			X					X		X						X				14
Hepatoblastoma, multiple										X								X								4
Hepatocellular carcinoma		X				X					X	X	X		X	X				X	X			X		16
Hepatocellular carcinoma, multiple			X	X	X		X			X				X			X		X			X			X	19
Hepatocellular adenoma	X				X					X			X			X							X			11
Hepatocellular adenoma, multiple		X	X	X		X	X	X	X		X	X		X	X		X	X	X	X	X	X			X	29
Hepatocholangiocarcinoma, multiple																										1
Histiocytic sarcoma																										2
Sarcoma, metastatic, mesentery																										1
Mesentery											+			+										+		7
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth								+					+	+						+		+		+		10
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, mesentery																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																		X								1
Sarcoma, metastatic, mesentery																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Parathyroid gland	M	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	M	M	M	+	+	+	+	M	M	35
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma		X																								2
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

Number of Days on Study	0 0 8	2 3 7	5 2 2	5 3 2	5 4 6	5 4 9	5 6 1	5 8 7	5 9 1	5 9 5	6 0 8	6 3 8	6 4 5	6 5 0	6 7 4	6 7 6	6 7 7	6 8 0	6 9 2	6 9 6	7 0 2	7 1 5	7 2 2	7 2 2	7 2 2
Carcass ID Number	0 7 8	0 7 0	0 6 3	0 6 9	0 9 4	0 8 9	0 7 5	0 7 7	0 9 7	0 8 1	0 5 2	0 5 9	0 8 8	0 7 4	0 8 0	0 5 7	0 6 8	0 6 7	0 6 1	0 7 9	0 6 2	0 8 5	0 5 1	0 5 3	0 5 4
Genital System																									
Coagulating gland							+																		
Sarcoma, metastatic, mesentery							X																		
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma																									
Sarcoma, metastatic, mesentery							X																		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery							X																		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery							X																		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Hemangiosarcoma, metastatic, liver														X											
Histiocytic sarcoma												X													
Lymph node							+			+								+						+	
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																		X							
Mediastinal, sarcoma, metastatic, mesentery							X																		
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																						X			
Histiocytic sarcoma		X																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																					
Hemangiosarcoma, metastatic, liver														X											
Histiocytic sarcoma		X																							
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	I	+	+	+	+	+	I	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																						X			
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	+	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangioma																		X							
Subcutaneous tissue, histiocytic sarcoma												X													
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+														+				+
Hepatoblastoma, metastatic, liver																									X
Sarcoma, metastatic, mesentery							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Peripheral nerve																					+				
Spinal cord																					+				

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

Number of Days on Study	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 3	7 2 3	7 2 3	
Carcass ID Number	0 0 5 5	0 0 5 6	0 0 5 8	0 0 6 0	0 0 6 4	0 0 6 5	0 0 6 6	0 0 7 1	0 0 7 2	0 0 7 3	0 0 7 6	0 0 8 2	0 0 8 3	0 0 8 4	0 0 8 6	0 0 9 0	0 0 9 1	0 0 9 2	0 0 9 3	0 0 9 8	0 0 9 9	0 1 0 0	0 0 8 7	0 0 9 5	0 0 9 6	Total Tissues/ Tumors
Genital System																											
Coagulating gland																											1
Sarcoma, metastatic, mesentery																											1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma														X													1
Sarcoma, metastatic, mesentery																											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, mesentery																											1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, mesentery																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																											1
Hemangiosarcoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Lymph node																											4
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																											1
Mediastinal, sarcoma, metastatic, mesentery																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+		47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		47
Hemangioma																											1
Histiocytic sarcoma																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma									X																X		3
Hemangiosarcoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		46
Hepatocellular carcinoma, metastatic, liver																											1
Integumentary System																											
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M		3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Subcutaneous tissue, hemangioma																											1
Subcutaneous tissue, histiocytic sarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Skeletal muscle																											3
Hepatoblastoma, metastatic, liver																											1
Sarcoma, metastatic, mesentery																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																											1
Peripheral nerve																											1
Spinal cord																											1

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

Number of Days on Study	0 0 8	2 3 7	5 2 2	5 3 2	5 4 6	5 4 9	5 6 1	5 8 7	5 9 1	5 9 5	6 0 8	6 3 8	6 4 5	6 5 0	6 7 4	6 7 6	6 7 7	6 8 0	6 9 2	6 9 6	7 0 2	7 1 5	7 2 2	7 2 2	7 2 2
Carcass ID Number	0 7 8	0 7 0	0 6 3	0 6 9	0 9 4	0 8 9	0 7 5	0 7 7	0 9 7	0 8 1	0 5 2	0 5 9	0 8 8	0 7 4	0 8 0	0 5 7	0 6 8	0 6 7	0 6 1	0 7 9	0 6 2	0 8 5	0 5 1	0 5 3	0 5 4
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X																		X		
Alveolar/bronchiolar carcinoma																									
Hemangiosarcoma, metastatic, liver														X											
Hepatoblastoma, metastatic, liver											X							X							X
Hepatocellular carcinoma, metastatic, liver														X	X					X		X		X	
Hepatocholangiocarcinoma, metastatic, liver																		X							
Histiocytic sarcoma		X																							
Mediastinum, hepatocellular carcinoma, metastatic, liver																						X			
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																		X							
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma												X													
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X										X													
Lymphoma malignant										X					X			X							

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

Number of Days on Study	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	723	723	723	
Carcass ID Number	05 5	05 6	05 8	06 0	06 4	06 5	06 6	07 1	07 2	07 3	07 6	08 2	08 3	08 4	08 6	09 0	09 1	09 2	09 3	09 8	09 9	10 0	08 7	09 5	09 6	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X		X						X													5
Alveolar/bronchiolar carcinoma																						X		X		2
Hemangiosarcoma, metastatic, liver																										1
Hepatoblastoma, metastatic, liver						X																				4
Hepatocellular carcinoma, metastatic, liver		X														X										7
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Mediastinum, hepatocellular carcinoma, metastatic, liver																									1	
Mediastinum, hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Renal tubule, adenoma		X																								1
Urinary bladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant																										3

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	0 2 5 5 5 5 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7
	0 2 1 1 2 8 2 3 3 4 4 5 6 6 0 2 2 2 2 2 2 2 2 2
	3 6 3 4 6 6 3 0 7 2 3 7 1 4 8 2 2 2 2 2 2 2 2 2
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	2 2 0 1 2 2 0 2 3 3 4 1 3 0 0 0 0 0 0 1 1 1 1 1
	4 0 1 6 6 7 3 5 6 1 8 5 7 5 4 2 6 7 8 0 1 2 3 4
Alimentary System	
Esophagus	+ +
Gallbladder	+ + A + A M A + + M A A A M + + + + + M + + + +
Intestine large, colon	+ + + + A A + + + + A + + + + + + + + + + + + +
Intestine large, rectum	+ + + + + + + + + + A M + + + + + + + + + + + +
Intestine large, cecum	+ + A + + A + + + M A + A A A + + + + + + + + +
Intestine small, duodenum	+ + A + A A + + + + A + A A + + + + + + + + + +
Intestine small, jejunum	+ + A + A + + + + A A + A A + + + + + + + + + +
Histiocytic sarcoma	
Intestine small, ileum	+ + + + A A + + + + A + A A A + + + + + + + + +
Liver	+ +
Hepatoblastoma	X X X X X X X X
Hepatoblastoma, multiple	X X X X X
Hepatocellular carcinoma	X X X X X X X X X X X
Hepatocellular carcinoma, multiple	X X X X X X X X X X
Hepatocellular adenoma	X X X X
Hepatocellular adenoma, multiple	X X X X X X X X X X X X
Mast cell tumor malignant, metastatic, skin	
Mesentery	+ + + + +
Sarcoma	X
Pancreas	+ + + + + + + + + + A + + + + + + + + + + + + +
Salivary glands	+ +
Stomach, forestomach	+ + + + + + + + + + A + + + + + + + + + + + + +
Stomach, glandular	+ + + + + + + + + + A + + + + + + + + + + + + +
Tooth	
Cardiovascular System	
Blood vessel	M M +
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Capsule, sarcoma, metastatic, mesentery	X
Adrenal medulla	+ +
Islets, pancreatic	+ + + + + + + + + + A + + + + + + + + + + + + +
Adenoma	X X
Parathyroid gland	+ + + + + + M + + + + + + + M + + + + + + M + + M
Pituitary gland	+ + + + + + M + + + I + + + + + + + + + + + + +
Thyroid gland	+ +
Follicular cell, adenoma	
Follicular cell, adenoma, multiple	
General Body System	
Tissue NOS	+
Thoracic, hemangiosarcoma	X

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	
Carcass ID Number	11 17	11 18	11 19	12 21	12 22	12 23	12 28	12 29	13 30	13 32	13 33	13 34	13 35	13 38	13 39	14 40	14 41	14 42	14 43	14 44	14 45	14 46	14 47	14 49	15 50	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	M	+	M	M	+	M	M	+	+	+	+	M	A	M	+	+	+	+	+	+	+	+	+	+	M	30
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	42
Histiocytic sarcoma																							X			1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatoblastoma	X			X							X	X				X	X		X		X	X			16
Hepatoblastoma, multiple						X	X																			6
Hepatocellular carcinoma	X						X									X		X		X		X			X	15
Hepatocellular carcinoma, multiple		X	X		X	X		X	X	X	X	X	X	X	X		X		X		X		X	X			26
Hepatocellular adenoma		X				X																				5
Hepatocellular adenoma, multiple				X	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	29
Mast cell tumor malignant, metastatic, skin																					X					1
Mesentery										+								+								6
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth				+																						1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, sarcoma, metastatic, mesentery																									1	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										2
Parathyroid gland	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	+	40
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma												X														1
Follicular cell, adenoma, multiple																					X					1
General Body System																										
Tissue NOS																										1
Thoracic, hemangiosarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	0 0 3	2 2 6	5 1 3	5 1 4	5 2 6	5 8 6	6 2 3	6 3 0	6 3 7	6 4 2	6 4 3	6 5 7	6 6 1	6 6 4	7 0 8	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2
Carcass ID Number	1 2 4	1 2 0	1 0 1	1 1 6	1 2 6	1 2 7	1 0 3	1 2 5	1 3 6	1 3 1	1 4 8	1 1 5	1 3 7	1 0 5	1 0 4	1 0 2	1 0 6	1 0 7	1 0 8	1 1 0	1 1 1	1 1 2	1 1 3	1 1 4
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery									X															
Penis		+																						
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery									X															
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+
Sarcoma, metastatic, mesentery									X															
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery									X															
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery									X															
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, skin																								
Lymph node									+			+								+				
Mediastinal, sarcoma, metastatic, mesentery									X															
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, skin																								
Lymph node, mesenteric	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																							X	
Histiocytic sarcoma																								
Sarcoma, metastatic, mesentery									X															
Spleen	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Mast cell tumor malignant, metastatic, skin																								
Thymus	+	+	+	+	+	+	M	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, mesentery									X															
Integumentary System																								
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, mast cell tumor malignant																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+	+															
Sarcoma, metastatic, mesentery									X															
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve								+																
Spinal cord								+																

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	
Carcass ID Number	11 17	11 18	11 19	12 21	12 22	12 23	12 28	12 29	13 30	13 32	13 33	13 34	13 35	13 38	13 39	14 40	14 41	14 42	14 43	14 44	14 45	14 46	14 47	14 49	15 50	Total Tissues/ Tumors		
Genital System																												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Sarcoma, metastatic, mesentery																										1		
Penis																										1		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Sarcoma, metastatic, mesentery																										1		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48		
Sarcoma, metastatic, mesentery																										1		
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Sarcoma, metastatic, mesentery																										1		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Sarcoma, metastatic, mesentery																										1		
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Mast cell tumor malignant, metastatic, skin																					X					1		
Lymph node									+																	4		
Mediastinal, sarcoma, metastatic, mesentery																										1		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48		
Mast cell tumor malignant, metastatic, skin																					X					1		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	44		
Hemangioma																										1		
Histiocytic sarcoma																							X			1		
Sarcoma, metastatic, mesentery																										1		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47		
Hemangiosarcoma																									X	1		
Mast cell tumor malignant, metastatic, skin																					X					1		
Thymus	+	+	+	M	+	+	M	M	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	39		
Sarcoma, metastatic, mesentery																										1		
Integumentary System																												
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M			
Skin	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48		
Subcutaneous tissue, mast cell tumor malignant																					X					1		
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Skeletal muscle																										2		
Sarcoma, metastatic, mesentery																										1		
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Peripheral nerve																										1		
Spinal cord																										1		

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	0 0 3	2 2 6	5 1 3	5 1 4	5 2 6	5 8 6	6 2 3	6 3 0	6 3 7	6 4 2	6 4 3	6 5 7	6 6 1	6 6 4	7 0 8	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2
Carcass ID Number	1 2 4	1 2 0	1 0 1	1 1 6	1 2 6	1 2 7	1 0 3	1 2 5	1 3 6	1 3 1	1 4 8	1 1 5	1 3 7	1 0 5	1 0 4	1 0 2	1 0 6	1 0 7	1 0 8	1 1 0	1 1 1	1 1 2	1 1 3	1 1 4
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X					X									X					
Alveolar/bronchiolar adenoma, multiple																								
Alveolar/bronchiolar carcinoma																								
Hepatoblastoma, metastatic, liver					X															X	X		X	
Hepatocellular carcinoma, metastatic, liver							X			X													X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
None																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, tissue NOS								X																
Mast cell tumor malignant, metastatic, skin																								
Sarcoma, metastatic, mesentery									X															
Renal tubule, adenoma																						X		
Urinary bladder	+	+	A	+	A	+	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								X
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Lymphoma malignant		X																		X				
Mesothelioma malignant																								

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	
Carcass ID Number	11717	11718	11719	12021	12022	12023	12028	12029	13030	13032	13033	13034	13035	13038	13039	14040	14041	14042	14043	14044	14045	14046	14047	14049	14050	Total Tissues/ Tumors	
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Alveolar/bronchiolar adenoma						X									X				X					X		7	
Alveolar/bronchiolar adenoma, multiple		X																								1	
Alveolar/bronchiolar carcinoma								X																		1	
Hepatoblastoma, metastatic, liver						X															X	X				7	
Hepatocellular carcinoma, metastatic, liver		X	X					X		X				X		X			X				X			11	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Special Senses System																												
None																												
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Hemangiosarcoma, metastatic, tissue NOS																										1	
Mast cell tumor malignant, metastatic, skin																					X					1	
Sarcoma, metastatic, mesentery																										1	
Renal tubule, adenoma																										1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	44	
Hemangioma																										1	
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Histiocytic sarcoma																							X			1	
Lymphoma malignant									X																	3	
Mesothelioma malignant										X																1	

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

Number of Days on Study	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 2	7 2 3	7 2 3	7 2 3	7 2 3	7 2 3	
Carcass ID Number	1 7 2	1 7 6	1 7 7	1 7 8	1 7 9	1 8 0	1 8 1	1 8 2	1 8 3	1 8 5	1 8 6	1 8 7	1 8 9	1 9 0	1 9 1	1 9 2	1 9 5	1 9 7	1 9 9	2 0 0	1 6 2	1 6 7	1 6 9	1 9 3	1 9 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	M	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	36
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma			X		X						X			X	X	X	X		X						X	13
Hepatoblastoma, multiple																										2
Hepatocellular carcinoma		X	X		X		X	X	X			X				X							X	X		22
Hepatocellular carcinoma, multiple						X				X	X		X		X			X	X		X				X	X	18
Hepatocellular adenoma				X								X	X					X			X				X		11
Hepatocellular adenoma, multiple	X	X	X			X	X		X		X			X	X	X	X		X	X		X				X	28
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Mesentery				+																						4
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Tooth	+													+												3
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Capsule, squamous cell carcinoma, metastatic, uncertain primary site																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Parathyroid gland	M	+	M	M	+	+	M	+	+	M	M	+	M	+	+	M	M	+	+	+	+	+	M	M	+	31
Pituitary gland	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma				X																						2
General Body System																										
Peritoneum																										1
Squamous cell carcinoma, metastatic, uncertain primary site																										1

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

Number of Days on Study	0 0 0 4 4 5 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7
	0 0 5 0 3 9 2 3 4 6 7 8 8 9 0 2 2 2 2 2 2 2 2 2 2
	3 9 9 6 2 4 4 9 9 5 2 0 6 9 9 2 2 2 2 2 2 2 2 2 2
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	5 7 6 7 7 7 9 6 7 5 8 8 9 5 5 8 5 5 5 5 5 6 6 6 6
	6 0 8 3 5 1 4 6 4 7 8 8 4 3 4 1 2 5 8 9 0 1 3 4 5
Genital System	
Epididymis	+ +
Squamous cell carcinoma, metastatic, uncertain primary site	X
Preputial gland	+ + + + + + + + + + + + M + + + + + + + + + + + +
Prostate	+ + + + + + + + + + + + M + + + + + + + + + + + +
Seminal vesicle	+ +
Squamous cell carcinoma, metastatic, uncertain primary site	X
Testes	+ +
Squamous cell carcinoma, metastatic, uncertain primary site	X
Hematopoietic System	
Bone marrow	+ +
Lymph node	+
Mediastinal, squamous cell carcinoma, metastatic, uncertain primary site	X
Lymph node, mandibular	+ +
Lymph node, mesenteric	+ +
Squamous cell carcinoma, metastatic, uncertain primary site	X
Spleen	+ + + + + + + M + + + + + + + + + + + + + + + + +
Hemangiosarcoma	X
Squamous cell carcinoma, metastatic, uncertain primary site	X
Thymus	+ + + + + M + + + + + + + + + M + + + + + + + + +
Integumentary System	
Mammary gland	M M M M M M M M M M M M M M M M M M M M M M M M M
Skin	+ +
Subcutaneous tissue, basal cell adenoma	
Subcutaneous tissue, hemangioma	X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Squamous cell carcinoma, metastatic, uncertain primary site	X
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X
Alveolar/bronchiolar adenoma, multiple	X
Alveolar/bronchiolar carcinoma	
Hepatoblastoma, metastatic, liver	X X
Hepatocellular carcinoma, metastatic, liver	X X X X X X X X X
Nose	+ +
Trachea	+ +

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

Number of Days on Study	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	723	723	723	723	723	
Carcass ID Number	17 2	17 6	17 7	17 8	17 9	18 0	18 1	18 2	18 3	18 5	18 6	18 7	18 9	19 0	19 1	19 2	19 5	19 7	19 9	20 0	16 2	16 7	16 9	19 3	19 6	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																									+	2
Mediastinal, squamous cell carcinoma, metastatic, uncertain primary site																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, basal cell adenoma				X																						1
Subcutaneous tissue, hemangioma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X											X							X	X					6
Alveolar/bronchiolar adenoma, multiple																								X		2
Alveolar/bronchiolar carcinoma													X													1
Hepatoblastoma, metastatic, liver																	X									3
Hepatocellular carcinoma, metastatic, liver			X		X			X								X						X				13
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

Number of Days on Study	0 0 0 4 4 5 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7
	0 0 5 0 3 9 2 3 4 6 7 8 8 9 0 2 2 2 2 2 2 2 2 2 2
	3 9 9 6 2 4 4 9 9 5 2 0 6 9 9 2 2 2 2 2 2 2 2 2 2
Carcass ID Number	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
	5 7 6 7 7 7 9 6 7 5 8 9 5 5 8 1 2 5 8 9 0 1 3 4 5
	6 0 8 3 5 1 4 6 4 7 8 8 4 3 4 1 2 5 8 9 0 1 3 4 5
Special Senses System	
Eye	+
Harderian gland	+
Adenoma	X
Urinary System	
Kidney	+ +
Urinary bladder	+ +
Squamous cell carcinoma, metastatic, uncertain primary site	X
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant	X
Mesothelioma malignant	X

TABLE D2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Drinking Water Study of Pyridine: 1,000 ppm

Number of Days on Study	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	722	723	723	723	723	723	
Carcass ID Number	11772	11776	11777	11778	11779	11880	11881	11882	11883	11885	11886	11887	11889	11890	11891	11892	11895	11897	11899	12000	11662	11667	11669	11693	11696	Total Tissues/ Tumors
Special Senses System																										
Eye																										1
Harderian gland																										1
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, uncertain primary site																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										1
Mesothelioma malignant																										1

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Adrenal Cortex: Adenoma				
Overall rate[a]	3/49 (6%)	0/49 (0%)	0/49 (0%)	1/49 (2%)
Adjusted rate[b]	6.8%	0.0%	0.0%	2.4%
Terminal rate[c]	2/35 (6%)	0/27 (0%)	0/34 (0%)	1/34 (3%)
First incidence (days)	598	—[e]	—	722 (T)
Poly-3 test[d]	P=0.234N	P=0.134N	P=0.126N	P=0.321N
Harderian Gland: Adenoma				
Overall rate	3/50 (6%)	0/50 (0%)	0/49 (0%)	1/50 (2%)
Adjusted rate	6.7%	0.0%	0.0%	2.3%
Terminal rate	1/35 (3%)	0/28 (0%)	0/34 (0%)	1/35 (3%)
First incidence (days)	633	—	—	722 (T)
Poly-3 test	P=0.235N	P=0.133N	P=0.130N	P=0.320N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	0/50 (0%)	0/49 (0%)	1/50 (2%)
Adjusted rate	11.1%	0.0%	0.0%	2.3%
Terminal rate	3/35 (9%)	0/28 (0%)	0/34 (0%)	1/35 (3%)
First incidence (days)	633	—	—	722 (T)
Poly-3 test	P=0.052N	P=0.038N	P=0.036N	P=0.111N
Liver: Hepatocellular Adenoma				
Overall rate	29/50 (58%)	40/50 (80%)	34/49 (69%)	39/50 (78%)
Adjusted rate	63.2%	88.0%	75.7%	84.9%
Terminal rate	24/35 (69%)	27/28 (96%)	27/34 (79%)	31/35 (89%)
First incidence (days)	520	522	513	406
Poly-3 test	P=0.031	P=0.003	P=0.134	P=0.011
Liver: Hepatocellular Carcinoma				
Overall rate	15/50 (30%)	35/50 (70%)	41/49 (84%)	40/50 (80%)
Adjusted rate	32.3%	78.7%	89.9%	85.1%
Terminal rate	9/35 (26%)	23/28 (82%)	32/34 (94%)	28/35 (80%)
First incidence (days)	574	522	513	406
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	37/50 (74%)	45/50 (90%)	45/49 (92%)	47/50 (94%)
Adjusted rate	78.0%	96.5%	96.8%	100.0%
Terminal rate	28/35 (80%)	28/28 (100%)	34/34 (100%)	35/35 (100%)
First incidence (days)	520	522	513	406
Poly-3 test	P<0.001	P=0.004	P=0.004	P<0.001
Liver: Hepatoblastoma				
Overall rate	2/50 (4%)	18/50 (36%)	22/49 (45%)	15/50 (30%)
Adjusted rate	4.5%	41.2%	49.8%	34.4%
Terminal rate	2/35 (6%)	11/28 (39%)	17/34 (50%)	13/35 (37%)
First incidence (days)	722 (T)	549	514	624
Poly-3 test	P=0.005	P<0.001	P<0.001	P<0.001
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	17/50 (34%)	42/50 (84%)	45/49 (92%)	42/50 (84%)
Adjusted rate	36.7%	91.3%	96.8%	89.4%
Terminal rate	11/35 (31%)	26/28 (93%)	34/34 (100%)	30/35 (86%)
First incidence (days)	574	522	513	406
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	38/50 (76%)	47/50 (94%)	46/49 (94%)	47/50 (94%)
Adjusted rate	80.1%	98.9%	98.5%	100.0%
Terminal rate	29/35 (83%)	28/28 (100%)	34/34 (100%)	35/35 (100%)
First incidence (days)	520	522	513	406
Poly-3 test	P<0.001	P=0.002	P=0.003	P<0.001
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	12/49 (24%)	5/50 (10%)	8/49 (16%)	8/50 (16%)
Adjusted rate	27.0%	11.9%	18.5%	18.3%
Terminal rate	9/35 (26%)	4/28 (14%)	6/34 (18%)	6/35 (17%)
First incidence (days)	520	546	526	639
Poly-3 test	P=0.303N	P=0.065N	P=0.245N	P=0.239N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	13/49 (27%)	7/50 (14%)	9/49 (18%)	8/50 (16%)
Adjusted rate	29.1%	16.6%	20.8%	18.3%
Terminal rate	9/35 (26%)	6/28 (21%)	7/34 (21%)	6/35 (17%)
First incidence (days)	520	546	526	639
Poly-3 test	P=0.197N	P=0.130N	P=0.258N	P=0.174N
Spleen: Hemangiosarcoma				
Overall rate	1/49 (2%)	3/50 (6%)	1/47 (2%)	1/49 (2%)
Adjusted rate	2.3%	7.1%	2.4%	2.4%
Terminal rate	1/35 (3%)	2/28 (7%)	1/34 (3%)	1/35 (3%)
First incidence (days)	722 (T)	532	722 (T)	722 (T)
Poly-3 test	P=0.459N	P=0.292	P=0.748	P=0.755
All Organs: Hemangioma				
Overall rate	0/50 (0%)	3/50 (6%)	2/49 (4%)	1/50 (2%)
Adjusted rate	0.0%	7.2%	4.7%	2.3%
Terminal rate	0/35 (0%)	1/28 (4%)	2/34 (6%)	1/35 (3%)
First incidence (days)	—	680	722 (T)	722 (T)
Poly-3 test	P=0.536	P=0.107	P=0.225	P=0.493
All Organs: Hemangiosarcoma				
Overall rate	2/50 (4%)	4/50 (8%)	2/49 (4%)	1/50 (2%)
Adjusted rate	4.5%	9.4%	4.7%	2.3%
Terminal rate	1/35 (3%)	2/28 (7%)	1/34 (3%)	1/35 (3%)
First incidence (days)	706	532	630	722 (T)
Poly-3 test	P=0.276N	P=0.313	P=0.678	P=0.512N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	7/50 (14%)	4/49 (8%)	1/50 (2%)
Adjusted rate	4.5%	16.4%	9.4%	2.3%
Terminal rate	1/35 (3%)	3/28 (11%)	3/34 (9%)	1/35 (3%)
First incidence (days)	706	532	630	722 (T)
Poly-3 test	P=0.215N	P=0.067	P=0.316	P=0.512N
All Organs: Malignant Lymphoma				
Overall rate	3/50 (6%)	3/50 (6%)	3/49 (6%)	1/50 (2%)
Adjusted rate	6.6%	7.1%	6.9%	2.3%
Terminal rate	2/35 (6%)	0/28 (0%)	2/34 (6%)	1/35 (3%)
First incidence (days)	542	595	226	722 (T)
Poly-3 test	P=0.233N	P=0.632	P=0.643	P=0.322N

TABLE D3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
All Organs: Benign Neoplasms				
Overall rate	35/50 (70%)	42/50 (84%)	36/49 (73%)	39/50 (78%)
Adjusted rate	74.7%	91.2%	79.1%	84.9%
Terminal rate	27/35 (77%)	27/28 (96%)	28/34 (82%)	31/35 (89%)
First incidence (days)	520	522	513	406
Poly-3 test	P=0.275	P=0.023	P=0.398	P=0.157
All Organs: Malignant Neoplasms				
Overall rate	22/50 (44%)	46/50 (92%)	47/49 (96%)	42/50 (84%)
Adjusted rate	46.5%	94.8%	98.4%	89.4%
Terminal rate	13/35 (37%)	26/28 (93%)	34/34 (100%)	30/35 (86%)
First incidence (days)	542	237	226	406
Poly-3 test	P<0.001	P<0.001	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	43/50 (86%)	49/50 (98%)	48/49 (98%)	47/50 (94%)
Adjusted rate	88.7%	100.0%	100.0%	100.0%
Terminal rate	31/35 (89%)	28/28 (100%)	34/34 (100%)	35/35 (100%)
First incidence (days)	520	237	226	406
Poly-3 test	P=0.009	P=0.018	P=0.019	P=0.021

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, liver, lung, and spleen; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE D4
Historical Incidence of Liver Neoplasms in Untreated Male B6C3F$_1$ Mice[a]

	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Overall Historical Incidence				
Total	179/289 (61.9%)	80/289 (27.7%)	9/289 (3.1%)	212/289 (73.4%)
Standard deviation	9.1%	11.7%	5.0%	11.7%
Range	47%-70%	10%-42%	0%-12%	53%-81%

[a] Data as of 1 August 1997

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	2	1	1	3
Moribund	2	3	3	1
Natural deaths	11	18	11	11
Survivors				
Other			1	
Terminal sacrifice	35	28	34	35
Animals examined microscopically	50	50	49	50
Alimentary System				
Gallbladder	(43)	(33)	(30)	(36)
Hyperplasia				1 (3%)
Infiltration cellular, lymphocyte	1 (2%)			
Ulcer				1 (3%)
Intestine large, colon	(48)	(48)	(46)	(50)
Inflammation, chronic active	1 (2%)			
Intestine large, cecum	(47)	(44)	(42)	(45)
Lymphoid tissue, hyperplasia			2 (5%)	1 (2%)
Lymphoid tissue, necrosis			1 (2%)	
Intestine small, jejunum	(40)	(46)	(42)	(44)
Peyer's patch, hyperplasia, lymphoid	1 (3%)	1 (2%)	3 (7%)	1 (2%)
Liver	(50)	(50)	(49)	(50)
Angiectasis	1 (2%)	1 (2%)		
Basophilic focus	3 (6%)	1 (2%)		
Clear cell focus	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Cyst			1 (2%)	
Eosinophilic focus	19 (38%)	22 (44%)	18 (37%)	15 (30%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	
Hemorrhage	1 (2%)			
Infiltration cellular, mixed cell	1 (2%)	1 (2%)		1 (2%)
Mixed cell focus	4 (8%)	2 (4%)	1 (2%)	1 (2%)
Necrosis	3 (6%)	5 (10%)	7 (14%)	6 (12%)
Vacuolization cytoplasmic, diffuse	2 (4%)	1 (2%)		
Centrilobular, congestion	1 (2%)			
Centrilobular, hypertrophy				1 (2%)
Centrilobular, vacuolization cytoplasmic	1 (2%)	2 (4%)		6 (12%)
Periportal, vacuolization cytoplasmic	1 (2%)			2 (4%)
Mesentery	(2)	(7)	(6)	(4)
Fat, necrosis	2 (100%)	3 (43%)	1 (17%)	2 (50%)
Oral mucosa	(1)			
Ulcer	1 (100%)			
Pancreas	(49)	(50)	(48)	(50)
Acinus, atrophy	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Acinus, cytoplasmic alteration			1 (2%)	1 (2%)
Duct, cyst			1 (2%)	1 (2%)
Salivary glands	(48)	(50)	(49)	(50)
Infiltration cellular, lymphocyte	31 (65%)	33 (66%)	26 (53%)	34 (68%)
Stomach, forestomach	(49)	(50)	(48)	(49)
Inflammation, chronic				1 (2%)
Inflammation, chronic active	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Ulcer				1 (2%)
Epithelium, hyperplasia		1 (2%)	2 (4%)	2 (4%)

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Alimentary System (continued)				
Stomach, glandular	(49)	(50)	(48)	(47)
Necrosis	2 (4%)	2 (4%)	4 (8%)	1 (2%)
Glands, dysplasia			2 (4%)	
Tooth	(42)	(10)	(1)	(3)
Developmental malformation	42 (100%)	10 (100%)	1 (100%)	3 (100%)
Cardiovascular System				
Blood vessel	(50)	(49)	(47)	(49)
Aorta, thrombosis	1 (2%)			
Heart	(50)	(50)	(49)	(50)
Cardiomyopathy			1 (2%)	
Mineralization		3 (6%)		
Thrombosis				1 (2%)
Artery, inflammation, chronic active	2 (4%)			
Myocardium, hypertrophy	1 (2%)			
Endocrine System				
Adrenal cortex	(49)	(49)	(49)	(49)
Cytoplasmic alteration	18 (37%)	13 (27%)	9 (18%)	11 (22%)
Hyperplasia	2 (4%)	1 (2%)	2 (4%)	
Vacuolization cytoplasmic	2 (4%)			1 (2%)
Capsule, hyperplasia	42 (86%)	29 (59%)	30 (61%)	29 (59%)
Islets, pancreatic	(49)	(50)	(48)	(50)
Hyperplasia		5 (10%)	2 (4%)	
Parathyroid gland	(31)	(35)	(40)	(31)
Cyst	1 (3%)	1 (3%)		
Pituitary gland	(46)	(47)	(45)	(49)
Cyst	1 (2%)	1 (2%)		
Pars distalis, hyperplasia			1 (2%)	
Thyroid gland	(49)	(50)	(49)	(50)
Infiltration cellular, lymphocyte		1 (2%)		
Follicle, cyst	1 (2%)			
Follicular cell, hyperplasia	8 (16%)	14 (28%)	20 (41%)	12 (24%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(49)	(50)
Angiectasis		1 (2%)		
Infiltration cellular, lymphocyte	1 (2%)	4 (8%)	4 (8%)	4 (8%)
Inflammation, granulomatous	1 (2%)	1 (2%)		3 (6%)
Penis			(1)	
Inflammation, chronic active			1 (100%)	
Preputial gland	(50)	(50)	(49)	(49)
Atrophy	48 (96%)	45 (90%)	47 (96%)	42 (86%)
Cyst	29 (58%)	25 (50%)	32 (65%)	28 (57%)
Inflammation, chronic	18 (36%)	18 (36%)	13 (27%)	12 (24%)
Inflammation, chronic active	4 (8%)	6 (12%)	3 (6%)	6 (12%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Genital System (continued)				
Prostate	(50)	(48)	(48)	(49)
Cyst	1 (2%)			
Hyperplasia	1 (2%)			1 (2%)
Inflammation, chronic	7 (14%)	3 (6%)	10 (21%)	8 (16%)
Inflammation, chronic active	1 (2%)			1 (2%)
Testes	(50)	(50)	(49)	(50)
Atrophy	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Mineralization	1 (2%)			
Interstitial cell, hyperplasia	1 (2%)			
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Atrophy	2 (4%)			
Erythroid cell, hyperplasia		1 (2%)		
Myeloid cell, hyperplasia	1 (2%)	1 (2%)		1 (2%)
Lymph node	(2)	(4)	(4)	(2)
Iliac, hyperplasia, lymphoid	1 (50%)			
Mediastinal, congestion	1 (50%)			
Pancreatic, hyperplasia, lymphoid		1 (25%)		
Renal, hemorrhage			2 (50%)	1 (50%)
Renal, necrosis			1 (25%)	
Lymph node, mandibular	(48)	(47)	(48)	(50)
Hyperplasia, lymphoid	3 (6%)		1 (2%)	1 (2%)
Hyperplasia, plasma cell	2 (4%)			
Necrosis			1 (2%)	
Lymph node, mesenteric	(43)	(47)	(44)	(50)
Angiectasis		2 (4%)		
Atrophy				1 (2%)
Hematopoietic cell proliferation	2 (5%)	3 (6%)	6 (14%)	1 (2%)
Hemorrhage	13 (30%)	10 (21%)	10 (23%)	12 (24%)
Hyperplasia, histiocytic	2 (5%)		1 (2%)	
Hyperplasia, lymphoid	1 (2%)	5 (11%)	3 (7%)	4 (8%)
Hyperplasia, plasma cell	1 (2%)	1 (2%)		
Necrosis			1 (2%)	
Spleen	(49)	(50)	(47)	(49)
Atrophy		2 (4%)	3 (6%)	
Hematopoietic cell proliferation	13 (27%)	30 (60%)	26 (55%)	23 (47%)
Hyperplasia, lymphoid		1 (2%)	1 (2%)	1 (2%)
Necrosis			1 (2%)	
Thymus	(46)	(46)	(39)	(47)
Atrophy	26 (57%)	21 (46%)	16 (41%)	16 (34%)
Cyst		1 (2%)		
Necrosis			1 (3%)	1 (2%)
Integumentary System				
Skin	(49)	(50)	(48)	(50)
Inflammation, chronic active	1 (2%)			
Ulcer	1 (2%)			
Subcutaneous tissue, edema	1 (2%)	1 (2%)		
Subcutaneous tissue, inflammation, acute		1 (2%)		
Subcutaneous tissue, inflammation, chronic active	1 (2%)	1 (2%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	250 ppm	500 ppm	1,000 ppm
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(49)	(50)
Hemorrhage		1 (2%)		
Inflammation, chronic active	1 (2%)			
Mineralization	41 (82%)	27 (54%)	30 (61%)	35 (70%)
Peripheral nerve		(1)	(1)	
Sciatic, degeneration		1 (100%)		
Respiratory System				
Lung	(49)	(50)	(49)	(50)
Congestion	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hemorrhage		1 (2%)		
Infiltration cellular, lymphocyte		4 (8%)	2 (4%)	
Alveolar epithelium, hyperplasia	4 (8%)	8 (16%)	1 (2%)	2 (4%)
Alveolus, infiltration cellular, histiocyte	1 (2%)	2 (4%)	4 (8%)	1 (2%)
Nose	(50)	(49)	(49)	(50)
Foreign body	1 (2%)			
Olfactory epithelium, degeneration, hyaline	15 (30%)	31 (63%)	35 (71%)	7 (14%)
Olfactory epithelium, glands, hyperplasia	1 (2%)			
Respiratory epithelium, degeneration, hyaline	20 (40%)	10 (20%)	15 (31%)	2 (4%)
Respiratory epithelium, hyperplasia	20 (40%)	22 (45%)	11 (22%)	15 (30%)
Respiratory epithelium, inflammation, chronic active	2 (4%)	1 (2%)		1 (2%)
Special Senses System				
Eye	(1)			(1)
Cataract	1 (100%)			
Cornea, inflammation, chronic	1 (100%)			
Cornea, inflammation, chronic active				1 (100%)
Urinary System				
Kidney	(49)	(50)	(48)	(50)
Atrophy				1 (2%)
Cyst	4 (8%)	2 (4%)	4 (8%)	
Fibrosis		1 (2%)		
Hydronephrosis	1 (2%)			
Infarct	2 (4%)	1 (2%)	2 (4%)	6 (12%)
Infiltration cellular, lymphocyte	3 (6%)	1 (2%)	2 (4%)	6 (12%)
Inflammation, chronic active	2 (4%)			
Mineralization	2 (4%)	3 (6%)		
Nephropathy	34 (69%)	27 (54%)	25 (52%)	32 (64%)
Artery, inflammation, chronic	1 (2%)			
Artery, inflammation, chronic active	1 (2%)			
Renal tubule, accumulation, hyaline droplet		1 (2%)		
Renal tubule, dilatation		1 (2%)	2 (4%)	5 (10%)
Renal tubule, hyperplasia	3 (6%)		1 (2%)	1 (2%)
Renal tubule, pigmentation		5 (10%)	3 (6%)	2 (4%)
Urinary bladder	(48)	(49)	(44)	(50)
Infiltration cellular, lymphocyte	8 (17%)	7 (14%)	9 (20%)	8 (16%)

APPENDIX E
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DRINKING WATER STUDY OF PYRIDINE

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine[a]

	0 ppm	125 ppm	250 ppm	500 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	3	6	4	5
Moribund	3	2	3	5
Natural deaths	12	12	21	11
Survivors				
Terminal sacrifice	32	30	22	29
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(50)	(50)	(50)
Gallbladder	(37)	(40)	(33)	(34)
Intestine large, rectum	(44)	(48)	(47)	(47)
Intestine large, cecum	(44)	(49)	(40)	(45)
Leiomyosarcoma				1 (2%)
Intestine small, jejunum	(42)	(47)	(38)	(43)
Intestine small, ileum	(43)	(48)	(37)	(41)
Carcinoma				1 (2%)
Liver	(49)	(50)	(50)	(50)
Hemangioma				1 (2%)
Hepatoblastoma	1 (2%)	2 (4%)	6 (12%)	12 (24%)
Hepatoblastoma, multiple			3 (6%)	4 (8%)
Hepatocellular carcinoma	10 (20%)	12 (24%)	19 (38%)	11 (22%)
Hepatocellular carcinoma, multiple	3 (6%)	11 (22%)	14 (28%)	30 (60%)
Hepatocellular adenoma	13 (27%)	5 (10%)	6 (12%)	4 (8%)
Hepatocellular adenoma, multiple	24 (49%)	34 (68%)	37 (74%)	30 (60%)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Sarcoma, metastatic, skin	1 (2%)			
Mesentery	(17)	(18)	(13)	(13)
Hepatoblastoma, metastatic, liver			1 (8%)	1 (8%)
Histiocytic sarcoma		2 (11%)		
Lipoma		1 (6%)		
Sarcoma		2 (11%)		
Pancreas	(49)	(49)	(47)	(48)
Histiocytic sarcoma		2 (4%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Salivary glands	(50)	(50)	(49)	(50)
Schwannoma malignant, metastatic, skin		1 (2%)		
Stomach, forestomach	(49)	(49)	(49)	(49)
Squamous cell papilloma		1 (2%)		
Stomach, glandular	(48)	(49)	(48)	(49)
Cardiovascular System				
Blood vessel	(48)	(47)	(47)	(47)
Aorta, histiocytic sarcoma		1 (2%)		
Heart	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Sarcoma, metastatic, skin			1 (2%)	

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Endocrine System				
Adrenal cortex	(49)	(50)	(48)	(50)
Carcinoma, multiple	1 (2%)			
Histiocytic sarcoma	1 (2%)	1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Capsule, adenoma	1 (2%)			
Islets, pancreatic	(49)	(50)	(47)	(49)
Adenoma	1 (2%)	2 (4%)		
Pituitary gland	(47)	(44)	(42)	(46)
Pars distalis, adenoma	8 (17%)	9 (20%)	6 (14%)	2 (4%)
Thyroid gland	(50)	(50)	(50)	(50)
Follicular cell, adenoma	3 (6%)	2 (4%)	3 (6%)	3 (6%)
General Body System				
Peritoneum			(2)	
Hepatoblastoma, metastatic, liver			1 (50%)	
Tissue NOS			(2)	
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (50%)	
Hepatoblastoma, metastatic, liver			1 (50%)	
Genital System				
Clitoral gland	(47)	(48)	(48)	(45)
Ovary	(47)	(49)	(46)	(49)
Cystadenoma	4 (9%)	3 (6%)	1 (2%)	
Granulosa cell tumor benign	1 (2%)		1 (2%)	
Hemangioma				1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Oviduct		(1)		
Schwannoma malignant, metastatic, skin		1 (100%)		
Uterus	(48)	(50)	(47)	(50)
Adenoma	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Polyp stromal	2 (4%)	1 (2%)		
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Lymph node	(10)	(10)	(7)	(7)
Iliac, histiocytic sarcoma	1 (10%)	1 (10%)		
Iliac, rhabdomyosarcoma, metastatic, skeletal muscle		1 (10%)		
Mediastinal, sarcoma, metastatic, mesentery		1 (10%)		
Mediastinal, sarcoma, metastatic, skin	1 (10%)			
Pancreatic, hepatoblastoma, metastatic, liver			1 (14%)	
Pancreatic, sarcoma, metastatic, mesentery		1 (10%)		
Lymph node, mandibular	(48)	(50)	(49)	(47)
Histiocytic sarcoma	2 (4%)	1 (2%)		
Sarcoma, metastatic, skin			1 (2%)	
Schwannoma malignant, metastatic, skin		1 (2%)		

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Hematopoietic System (continued)				
Lymph node, mesenteric	(48)	(47)	(43)	(45)
Hemangioma				1 (2%)
Hepatoblastoma, metastatic, liver			1 (2%)	1 (2%)
Histiocytic sarcoma	1 (2%)	2 (4%)		
Spleen	(49)	(50)	(48)	(49)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Thymus	(45)	(44)	(46)	(39)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Integumentary System				
Skin	(49)	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)		
Subcutaneous tissue, hemangioma			1 (2%)	
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, sarcoma	2 (4%)	2 (4%)	3 (6%)	4 (8%)
Subcutaneous tissue, schwannoma malignant	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Musculoskeletal System				
Skeletal muscle		(1)	(1)	(1)
Hepatoblastoma, metastatic, liver			1 (100%)	
Rhabdomyosarcoma		1 (100%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	3 (6%)		3 (6%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	2 (4%)	3 (6%)
Carcinoma, metastatic, harderian gland	1 (2%)			
Hepatoblastoma, metastatic, liver			1 (2%)	3 (6%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)		6 (12%)	10 (20%)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Rhabdomyosarcoma, metastatic, skeletal muscle		1 (2%)		
Sarcoma, metastatic, mesentery		1 (2%)		
Sarcoma, metastatic, skin			2 (4%)	
Schwannoma malignant, metastatic, skin		1 (2%)		
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)	
Mediastinum, sarcoma, metastatic, skin			1 (2%)	
Mediastinum, schwannoma malignant, metastatic, skin		1 (2%)		
Nose	(50)	(50)	(47)	(50)
Sarcoma				1 (2%)
Sarcoma, metastatic, skin	1 (2%)			
Trachea	(50)	(50)	(50)	(50)

TABLE E1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Special Senses System				
Harderian gland	(1)	(1)		(1)
Adenoma		1 (100%)		
Carcinoma	1 (100%)			1 (100%)
Urinary System				
Kidney	(49)	(50)	(49)	(49)
Histiocytic sarcoma	1 (2%)	1 (2%)		
Schwannoma malignant, metastatic, skin		1 (2%)		
Urinary bladder	(45)	(49)	(44)	(43)
Histiocytic sarcoma		1 (2%)		
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	2 (4%)		
Leukemia granulocytic		1 (2%)		
Lymphoma malignant	6 (12%)	7 (14%)	4 (8%)	6 (12%)
Mesothelioma malignant				2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	47	45	45	45
Total primary neoplasms	90	105	108	122
Total animals with benign neoplasms	40	41	43	36
Total benign neoplasms	61	63	55	45
Total animals with malignant neoplasms	26	30	40	44
Total malignant neoplasms	29	42	53	77
Total animals with metastatic neoplasms	5	3	10	12
Total metastatic neoplasms	6	14	21	15

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

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

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

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

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	22 5	22 9	23 1	23 2	23 3	23 4	23 6	23 7	23 8	23 9	24 0	24 1	24 2	24 3	24 6	24 9	25 1	25 2	25 4	25 5	25 9	26 0	26 1	26 2	26 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	37
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatoblastoma								X																		1
Hepatocellular carcinoma			X			X	X	X																X		10
Hepatocellular carcinoma, multiple														X						X						3
Hepatocellular adenoma					X				X				X			X			X		X		X		X	13
Hepatocellular adenoma, multiple	X	X	X	X			X	X		X	X	X		X				X		X		X		X		24
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin																	X									1
Mesentery	+	+						+				+	+	+	+											17
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth																			+					+		2
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, multiple																										1
Histiocytic sarcoma																										1
Capsule, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	M	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	M	+	31
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma				X	X							X							X	X		X		X		8
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma			X																		X					3
General Body System																										
None																										

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	0 6 4	1 5 1	3 7 5	4 7 6	5 5 4	5 6 5	5 6 8	6 2 5	6 4 4	6 4 4	6 6 2	6 7 0	6 8 7	6 9 1	6 9 7	7 1 1	7 1 4	7 1 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 6 4	2 2 7	2 5 8	2 3 5	2 3 0	2 4 8	2 4 4	2 2 6	2 5 0	2 5 3	2 1 7	2 2 8	2 4 5	2 4 7	2 5 6	2 2 4	2 5 7	2 6 3	2 1 6	2 1 8	2 1 9	2 2 0	2 2 1	2 2 2	2 2 3
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Cystadenoma																									
Granulosa cell tumor benign																			X						
Histiocytic sarcoma			X																						
Uterus	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenoma																									
Polyp stromal		X																X							
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Lymph node				+			+	+		+					+	+							+		
Iliac, histiocytic sarcoma								X																	
Mediastinal, sarcoma, metastatic, skin																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X					X																	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Spleen	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, sarcoma																									
Subcutaneous tissue, schwannoma malignant																					X				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve			+																						
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma											X														
Carcinoma, metastatic, harderian gland																									
Hepatocellular carcinoma, metastatic, liver				X						X															
Histiocytic sarcoma			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Carcinoma																									

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	22 5	22 9	23 1	23 2	23 3	23 4	23 6	23 7	23 8	23 9	24 0	24 1	24 2	24 3	24 6	24 9	25 1	25 2	25 4	25 5	25 9	26 0	26 1	26 2	26 5	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	I	+	+	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma										X				X									X		X	4
Granulosa cell tumor benign																										1
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma					X																					1
Polyp stromal																										2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node										+		+													+	10
Iliac, histiocytic sarcoma																										1
Mediastinal, sarcoma, metastatic, skin										X																1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma									X																	1
Subcutaneous tissue, sarcoma										X							X									2
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																				X						1
Alveolar/bronchiolar adenoma, multiple												X														1
Alveolar/bronchiolar carcinoma				X																						2
Carcinoma, metastatic, harderian gland											X															1
Hepatocellular carcinoma, metastatic, liver																										2
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin																	X									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland											+															1
Carcinoma											X															1

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	064	151	375	476	554	565	568	625	644	644	662	670	687	691	697	711	714	719	729	729	729	729	729	729	729
Carcass ID Number	264	227	258	235	230	248	244	226	250	253	217	228	245	247	256	224	257	263	216	218	219	220	221	222	223
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Urinary bladder	+	+	+	+	+	A	+	+	+	A	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X					X																	
Lymphoma malignant													X		X	X	X						X		

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 0 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	225	229	231	232	233	234	236	237	238	239	240	241	242	243	246	249	251	252	254	255	259	260	261	262	265	Total Tissues/ Tumors		
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49		
Histiocytic sarcoma																										1		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45		
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50		
Histiocytic sarcoma																										2		
Lymphoma malignant													X													6		

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

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

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	27 6	27 8	28 0	28 3	28 5	28 6	28 7	28 8	29 0	29 2	29 3	29 6	29 8	29 9	30 0	30 2	30 3	30 4	30 8	30 9	31 0	31 2	31 3	31 4	31 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma																										2
Hepatocellular carcinoma		X		X		X							X				X			X			X	X		12
Hepatocellular carcinoma, multiple			X								X			X	X				X		X				X	11
Hepatocellular adenoma																					X					5
Hepatocellular adenoma, multiple	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X		X		X		34
Histiocytic sarcoma																					X					1
Mesentery		+					+		+						+				+		+	+		+	+	18
Histiocytic sarcoma																					X			X		2
Lipoma																										1
Sarcoma																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																					X			X		2
Sarcoma, metastatic, mesentery																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, skin																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma									X																	1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Aorta, histiocytic sarcoma																					X					1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																					X					1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																					X					1
Sarcoma, metastatic, mesentery																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X									2
Parathyroid gland	M	+	M	+	M	+	+	+	M	+	+	M	M	M	+	+	+	+	+	+	+	M	+	M	M	29
Pituitary gland	M	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	44
Pars distalis, adenoma					X						X						X		X						X	9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma					X																					2
General Body System																										
None																										

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

Number of Days on Study	0 0 0 1 3 4 5 5 5 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 0 1 2 7 7 1 5 7 9 0 0 4 4 7 7 8 9 1 1 2 2 2 2 2 2 4 6 0 2 2 9 5 3 9 5 8 2 9 4 7 0 6 1 3 4 9 9 9 9 9
Carcass ID Number	2 2 2 3 2 3 2 2 2 2 2 3 2 2 2 2 2 2 3 2 2 2 2 2 7 8 7 0 8 1 9 8 6 7 9 0 7 9 9 8 6 0 7 0 6 6 7 7 7 0 4 9 5 1 1 5 9 9 7 1 1 1 4 7 2 8 6 5 7 6 7 2 3 4
Genital System	
Clitoral gland	+ + + + + + M + + + + + + + + + + + + + + + + + +
Ovary	+ +
Cystadenoma	X X
Histiocytic sarcoma	
Sarcoma, metastatic, mesentery	X
Oviduct	+
Schwannoma malignant, metastatic, skin	X
Uterus	+ +
Histiocytic sarcoma	
Polyp stromal	
Hematopoietic System	
Bone marrow	+ +
Histiocytic sarcoma	
Lymph node	+ + + + + +
Iliac, histiocytic sarcoma	
Iliac, rhabdomyosarcoma, metastatic, skeletal muscle	X
Mediastinal, sarcoma, metastatic, mesentery	X
Pancreatic, sarcoma, metastatic, mesentery	X
Lymph node, mandibular	+ +
Histiocytic sarcoma	
Schwannoma malignant, metastatic, skin	X
Lymph node, mesenteric	+ + + + + + + + + + + + + + M + + + + + + + M + + +
Histiocytic sarcoma	
Spleen	+ +
Histiocytic sarcoma	
Thymus	+ + + + + + + + M + + M + M + + + + + M + + + + +
Histiocytic sarcoma	
Integumentary System	
Mammary gland	+ +
Skin	+ +
Squamous cell papilloma	
Subcutaneous tissue, sarcoma	X X
Subcutaneous tissue, schwannoma malignant	X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Rhabdomyosarcoma	X
Nervous System	
Brain	+ +

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	27 6	27 8	28 0	28 3	28 5	28 6	28 7	28 8	29 0	29 2	29 3	29 6	29 8	29 9	30 0	30 2	30 3	30 4	30 8	30 9	31 0	31 2	31 3	31 4	31 5	Total Tissues/ Tumors	
Genital System																											
Clitoral gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49	
Cystadenoma								X																		3	
Histiocytic sarcoma																					X					1	
Sarcoma, metastatic, mesentery																										1	
Oviduct																										1	
Schwannoma malignant, metastatic, skin																										1	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																					X					1	
Polyp stromal															X											1	
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																					X					1	
Lymph node							+										+				+					10	
Iliac, histiocytic sarcoma																					X					1	
Iliac, rhabdomyosarcoma, metastatic, skeletal muscle																										1	
Mediastinal, sarcoma, metastatic, mesentery																										1	
Pancreatic, sarcoma, metastatic, mesentery																										1	
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																					X					1	
Schwannoma malignant, metastatic, skin																										1	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	47	
Histiocytic sarcoma																					X			X		2	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																					X					1	
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	44	
Histiocytic sarcoma																					X					1	
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Squamous cell papilloma		X																								1	
Subcutaneous tissue, sarcoma																										2	
Subcutaneous tissue, schwannoma malignant																										1	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Skeletal muscle																										1	
Rhabdomyosarcoma																										1	
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

Number of Days on Study	0 0 0 1 3 4 5 5 5 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 0 1 2 7 7 1 5 7 9 0 0 4 4 7 7 8 9 1 1 2 2 2 2 2 2 4 6 0 2 2 9 5 3 9 5 8 2 9 4 7 0 6 1 3 4 9 9 9 9 9
Carcass ID Number	2 2 2 3 2 3 2 2 2 2 2 3 2 2 2 2 2 3 2 3 2 2 2 2 2 7 8 7 0 8 1 9 8 6 7 9 0 7 9 9 8 6 0 7 0 6 6 7 7 7 0 4 9 5 1 1 5 9 9 7 1 1 1 4 7 2 8 6 5 7 6 7 2 3 4
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	X X
Alveolar/bronchiolar carcinoma	
Histiocytic sarcoma	
Rhabdomyosarcoma, metastatic, skeletal muscle	X
Sarcoma, metastatic, mesentery	X
Schwannoma malignant, metastatic, skin	X
Mediastinum, schwannoma malignant, metastatic, skin	X
Nose	+ +
Trachea	+ +
Special Senses System	
Harderian gland	
Adenoma	
Urinary System	
Kidney	+ +
Histiocytic sarcoma	
Schwannoma malignant, metastatic, skin	X
Urinary bladder	A +
Histiocytic sarcoma	
Systemic Lesions	
Multiple organs	+ +
Histiocytic sarcoma	
Leukemia granulocytic	X
Lymphoma malignant	X X X X

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 125 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	27 6	27 8	28 0	28 3	28 5	28 6	28 7	28 8	29 0	29 2	29 3	29 6	29 8	29 9	30 0	30 2	30 3	30 4	30 8	30 9	31 0	31 2	31 3	31 4	31 5	Total Tissues/ Tumors	
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Alveolar/bronchiolar adenoma						X																				3	
Alveolar/bronchiolar carcinoma																							X			1	
Histiocytic sarcoma																					X					1	
Rhabdomyosarcoma, metastatic, skeletal muscle																										1	
Sarcoma, metastatic, mesentery																										1	
Schwannoma malignant, metastatic, skin																										1	
Mediastinum, schwannoma malignant, metastatic, skin																										1	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Special Senses System																											
Harderian gland									+																	1	
Adenoma									X																	1	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																					X					1	
Schwannoma malignant, metastatic, skin																										1	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Histiocytic sarcoma																					X					1	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																					X			X		2	
Leukemia granulocytic																										1	
Lymphoma malignant			X				X										X									7	

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

Number of Days on Study	0 0 0 1 4 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 0 3 4 7 1 0 5 6 8 2 3 3 4 4 5 7 8 9 9 9 9 0 0 0 1 3 3 0 5 7 9 6 4 3 4 2 3 2 8 9 8 4 2 6 7 9 0 0 8 2
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 2 3 1 1 6 5 4 6 5 5 5 4 2 3 5 4 6 2 4 2 2 3 2 4 4 5 9 7 6 8 0 4 2 5 2 5 8 0 4 7 7 4 7 5 4 4 6 3 1 9
Alimentary System	
Esophagus	+ +
Gallbladder	A A A + A A A A A M + + + A + + A + A A A + A A +
Intestine large, colon	+ A + + + + + + + + + + + A + + + + + + + + + + +
Intestine large, rectum	A A + + + + + + + + + + + A + + + + + + + + + + +
Intestine large, cecum	A A + + + + + A + + + A + A + A + + + A A + A A +
Intestine small, duodenum	A A A + + M + A + + A + + A A + A + + A + + A + +
Intestine small, jejunum	A A A + A + + A + + + + + A A + A A + + A A + M + +
Intestine small, ileum	A A A + A + + A + + A A + A A + A + + A A + A + +
Liver	+ +
Hepatoblastoma	X X X X X
Hepatoblastoma, multiple	X
Hepatocellular carcinoma	X X X X X X X X
Hepatocellular carcinoma, multiple	X X
Hepatocellular adenoma	X X X
Hepatocellular adenoma, multiple	X X X X X X X X X X X X X X X X X X X X X
Mesentery	+ + + + + +
Hepatoblastoma, metastatic, liver	X
Pancreas	+ A + + + + + + + + + + + A + + + + + A + + + + +
Salivary glands	+ M +
Stomach, forestomach	+ + + + + + + + + + + + + A + + + + + + + + + + +
Stomach, glandular	+ A + + + + + + + + + + + A + + + + + + + + + + +
Cardiovascular System	
Blood vessel	M M + + + + + + + + + + + + A + + + + + + + + + + +
Heart	+ +
Sarcoma, metastatic, skin	X
Endocrine System	
Adrenal cortex	+ + + + + + + + + + + M + A + + + + + + + + + + +
Adrenal medulla	+ + + + + + + + + + + M M A + + + + + + + + A M +
Islets, pancreatic	+ A + + + + + + + + + + + + A + + + + + A + + + + +
Parathyroid gland	+ M + M + + M + A + M + M + M + + M + M M + + M M
Pituitary gland	+ I M + + + + + + I M I + + + + + + + + + + M M +
Pars distalis, adenoma	X
Thyroid gland	+ +
Follicular cell, adenoma	
General Body System	
Peritoneum	+ +
Hepatoblastoma, metastatic, liver	X
Tissue NOS	+
Alveolar/bronchiolar carcinoma, metastatic, lung	
Hepatoblastoma, metastatic, liver	X
Genital System	
Clitoral gland	+ M +
Ovary	+ + + + + + M + + + + + + + A + + + + + A + + + +
Cystadenoma	
Granulosa cell tumor benign	X
Uterus	+ A + + + + + + + + + + + + A + + + + + A + + + +

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

Number of Days on Study	722	723	727	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	361	363	232	137	119	121	225	228	230	231	232	233	235	239	240	244	246	249	250	251	253	256	258	262	263	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	33
Intestine large, colon	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma																								X		6
Hepatoblastoma, multiple						X																			X	3
Hepatocellular carcinoma				X					X		X			X	X	X				X	X			X	X	19
Hepatocellular carcinoma, multiple		X	X		X	X	X	X		X		X	X						X			X	X			14
Hepatocellular adenoma												X	X							X						6
Hepatocellular adenoma, multiple	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X		X	X	X	X	X	37
Mesentery			+		M	+		+	+	+	+					+							+			13
Hepatoblastoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid gland	+	M	+	+	+	M	+	M	M	M	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	30
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Pars distalis, adenoma				X				X					X				X		X							6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma				X																		X			X	3
General Body System																										
Peritoneum																										2
Hepatoblastoma, metastatic, liver																										1
Tissue NOS			+																							2
Alveolar/bronchiolar carcinoma, metastatic, lung			X																							1
Hepatoblastoma, metastatic, liver																										1
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Cystadenoma											X															1
Granulosa cell tumor benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

Number of Days on Study	0 0 0 1 4 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 7 7 7 7 0 3 4 7 1 0 5 6 8 2 3 3 4 4 5 7 8 9 9 9 9 0 0 0 1 3 3 0 5 7 9 6 4 3 4 2 3 2 8 9 8 4 2 6 7 9 0 0 8 2
Carcass ID Number	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 2 3 1 1 6 5 4 6 5 5 5 4 2 3 5 4 6 2 4 2 2 3 2 4 4 5 9 7 6 8 0 4 2 5 2 5 8 0 4 7 7 4 7 5 2 4 6 6 3 1 9
Hematopoietic System	
Bone marrow	+ + + + A +
Lymph node	+ + + + +
Pancreatic, hepatoblastoma, metastatic, liver	X
Lymph node, mandibular	+ M +
Sarcoma, metastatic, skin	X
Lymph node, mesenteric	M A + + + + + + + + + A + + A + M + + + A + + + + +
Hepatoblastoma, metastatic, liver	X
Spleen	+ + + + + + + + + + + + + A + + + + + A + + + + +
Thymus	+ M + + + + + + + + + + + M + M + + + + + + + + +
Alveolar/bronchiolar carcinoma, metastatic, lung	
Integumentary System	
Mammary gland	+ + + + + + + + + + + + + A + + + + + + + + + + +
Skin	+ +
Subcutaneous tissue, hemangioma	
Subcutaneous tissue, hemangiosarcoma	
Subcutaneous tissue, sarcoma	X X X
Subcutaneous tissue, schwannoma malignant	X
Musculoskeletal System	
Bone	+ +
Skeletal muscle	+
Hepatoblastoma, metastatic, liver	X
Nervous System	
Brain	+ +
Respiratory System	
Lung	+ +
Alveolar/bronchiolar carcinoma	
Hepatoblastoma, metastatic, liver	X
Hepatocellular carcinoma, metastatic, liver	X X
Sarcoma, metastatic, skin	X X
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung	
Mediastinum, sarcoma, metastatic, skin	X
Nose	+ A + + + + + + A + + + + + + A + + + + + + + + + +
Trachea	+ +
Special Senses System	
None	
Urinary System	
Kidney	+ A +
Urinary bladder	+ A + + M + + + A + + + + + + A + + + + + A A + + + +
Systemic Lesions	
Multiple organs	+ +
Lymphoma malignant	X X X X X

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 250 ppm

Number of Days on Study	722	723	727	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	361	338	323	317	319	321	325	328	330	331	332	333	335	339	340	344	346	349	350	351	353	356	358	362	363	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node																					+				+	7
Pancreatic, hepatoblastoma, metastatic, liver																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, skin																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	43
Hepatoblastoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Alveolar/bronchiolar carcinoma, metastatic, lung			X																							1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangioma				X																						1
Subcutaneous tissue, hemangiosarcoma		X																								1
Subcutaneous tissue, sarcoma																										3
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Hepatoblastoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma			X			X																				2
Hepatoblastoma, metastatic, liver																										1
Hepatocellular carcinoma, metastatic, liver										X		X								X		X				6
Sarcoma, metastatic, skin																										2
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			X																						1	
Mediastinum, sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
None																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										4

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	0112	0144	0155	1188	2899	3696	4430	4709	5101	5226	5271	5595	6155	6266	6627	6880	6806	6900	7000	7003	7299	7299	7299	7299
Carcass ID Number	4133	4105	3995	4006	3991	3771	4014	3999	3994	3977	4015	3988	3984	3998	4002	4044	3972	3893	3974	4009	3666	3667	3668	3669
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	A	+	+	+	+	+	A	A	A	A	M	M	A	M	A	+	M
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	A	A	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	A	+	A	+	+	+	+	+
Leiomyosarcoma																									
Intestine small, duodenum	A	+	+	+	+	+	+	+	A	+	+	+	+	+	A	A	A	A	+	A	A	+	+	+	+
Intestine small, jejunum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	M	+	A	A	A	+	+	+	+
Intestine small, ileum	A	+	+	A	+	+	+	+	+	+	+	+	+	+	A	A	A	A	A	A	A	+	+	+	+
Carcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma													X												
Hepatoblastoma									X		X		X			X						X	X	X	
Hepatoblastoma, multiple																									
Hepatocellular carcinoma								X		X				X						X		X	X		
Hepatocellular carcinoma, multiple												X	X		X	X	X	X	X		X			X	X
Hepatocellular adenoma									X						X							X		X	
Hepatocellular adenoma, multiple							X			X	X	X	X	X					X	X	X				
Mesentery										+			+		+	+					+				
Hepatoblastoma, metastatic, liver																X									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Cardiovascular System																									
Blood vessel	M	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	M	M	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																							X		X
General Body System																									
None																									
Genital System																									
Clitoral gland	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Hemangioma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	37 0	37 3	37 5	37 6	37 8	37 9	38 0	38 1	38 2	38 3	38 5	38 7	38 9	39 0	39 2	39 6	39 7	40 0	40 1	40 3	40 7	40 8	41 0	41 1	41 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	34
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leiomyosarcoma						X																				1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Carcinoma																				X						1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hepatoblastoma	X									X									X	X			X			12
Hepatoblastoma, multiple								X	X		X						X									4
Hepatocellular carcinoma				X		X							X		X									X		11
Hepatocellular carcinoma, multiple	X	X	X		X		X	X	X	X	X	X		X		X	X	X	X	X	X	X	X		X	30
Hepatocellular adenoma																										4
Hepatocellular adenoma, multiple	X	X		X	X	X	X	X		X	X	X		X	X	X	X	X		X	X	X	X	X	X	30
Mesentery		+	+						+	+	+					+	+							+		13
Hepatoblastoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Blood vessel	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	+	+	+	M	+	+	+	+	+	M	M	M	+	M	+	M	M	+	+	+	+	+	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Pars distalis, adenoma	X																						X			2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma										X																3
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	M	+	+	+	+	+	+	45
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma					X																					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	0 1 2	0 1 4	0 1 5	1 8 8	2 9 9	3 6 6	4 3 0	4 7 9	5 1 0	5 2 6	5 7 1	5 9 5	6 1 5	6 2 6	6 7 7	6 8 0	6 8 6	6 9 0	6 9 0	7 0 0	7 0 3	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	4 1 3	4 0 5	3 9 5	4 0 6	3 9 1	3 7 1	4 1 4	3 9 9	3 9 4	3 7 7	4 1 5	3 8 8	3 8 4	3 9 8	4 0 2	4 0 4	3 7 2	3 8 6	3 9 3	3 7 4	4 0 9	3 6 6	3 6 7	3 6 8	3 6 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node									+				+												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+
Lymph node, mesenteric	M	M	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+
Hemangioma																									
Hepatoblastoma, metastatic, liver																X									
Spleen	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	M	M	A	M	M	+	I	+	I
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma					X			X											X						
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma												X			X						X				
Hepatoblastoma, metastatic, liver																						X			
Hepatocellular carcinoma, metastatic, liver																X		X		X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma								X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland																									
Carcinoma																									
Urinary System																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	A	A	A	A	A	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant									X																
Mesothelioma malignant													X		X										

TABLE E2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Drinking Water Study of Pyridine: 500 ppm

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	370	373	375	376	378	379	380	381	382	383	385	387	389	390	392	396	397	400	401	403	407	408	410	411	412	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+											+		+					+	+			7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hemangioma											X															1
Hepatoblastoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	39
Integumentary System																										
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma					X																					4
Subcutaneous tissue, schwannoma malignant																								X		1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X			X																						3
Alveolar/bronchiolar carcinoma																										3
Hepatoblastoma, metastatic, liver																	X						X			3
Hepatocellular carcinoma, metastatic, liver	X	X												X					X	X			X		X	10
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland					+																					1
Carcinoma					X																					1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant		X													X		X					X	X			6
Mesothelioma malignant																										2

TABLE E3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Liver: Hepatocellular Adenoma				
Overall rate[a]	37/49 (76%)	39/50 (78%)	43/50 (86%)	34/50 (68%)
Adjusted rate[b]	82.5%	87.9%	97.3%	79.1%
Terminal rate[c]	27/32 (84%)	27/30 (90%)	22/22 (100%)	23/29 (79%)
First incidence (days)	554	419	509	430
Poly-3 test[d]	P=0.372N	P=0.336	P=0.015	P=0.442N
Liver: Hepatocellular Carcinoma				
Overall rate	13/49 (27%)	23/50 (46%)	33/50 (66%)	41/50 (82%)
Adjusted rate	29.8%	55.0%	78.1%	97.1%
Terminal rate	8/32 (25%)	18/30 (60%)	20/22 (91%)	29/29 (100%)
First incidence (days)	476	573	556	479
Poly-3 test	P<0.001	P=0.014	P<0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	41/49 (84%)	42/50 (84%)	44/50 (88%)	44/50 (88%)
Adjusted rate	89.9%	94.6%	98.4%	99.5%
Terminal rate	29/32 (91%)	29/30 (97%)	22/22 (100%)	29/29 (100%)
First incidence (days)	476	419	509	430
Poly-3 test	P=0.011	P=0.323	P=0.081	P=0.045
Liver: Hepatoblastoma				
Overall rate	1/49 (2%)	2/50 (4%)	9/50 (18%)	16/50 (32%)
Adjusted rate	2.4%	4.9%	21.6%	39.6%
Terminal rate	1/32 (3%)	1/30 (3%)	3/22 (14%)	12/29 (41%)
First incidence (days)	729 (T)	599	564	510
Poly-3 test	P<0.001	P=0.493	P=0.007	P<0.001
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	13/49 (27%)	23/50 (46%)	36/50 (72%)	43/50 (86%)
Adjusted rate	29.8%	55.0%	82.8%	99.0%
Terminal rate	8/32 (25%)	18/30 (60%)	20/22 (91%)	29/29 (100%)
First incidence (days)	476	573	556	479
Poly-3 test	P<0.001	P=0.014	P<0.001	P<0.001
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	41/49 (84%)	42/50 (84%)	45/50 (90%)	44/50 (88%)
Adjusted rate	89.9%	94.6%	99.6%	99.5%
Terminal rate	29/32 (91%)	29/30 (97%)	22/22 (100%)	29/29 (100%)
First incidence (days)	476	419	509	430
Poly-3 test	P=0.009	P=0.323	P=0.042	P=0.045
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	3/50 (6%)	0/50 (0%)	3/50 (6%)
Adjusted rate	4.7%	7.2%	0.0%	7.8%
Terminal rate	2/32 (6%)	1/30 (3%)	0/22 (0%)	2/29 (7%)
First incidence (days)	729 (T)	555	—[e]	703
Poly-3 test	P=0.463	P=0.486	P=0.254N	P=0.455
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted rate	4.7%	2.5%	5.0%	7.6%
Terminal rate	1/32 (3%)	1/30 (3%)	1/22 (5%)	0/29 (0%)
First incidence (days)	662	729 (T)	727	595
Poly-3 test	P=0.287	P=0.521N	P=0.665	P=0.460

TABLE E3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	2/50 (4%)	5/50 (10%)
Adjusted rate	9.3%	9.6%	5.0%	12.7%
Terminal rate	3/32 (9%)	2/30 (7%)	1/22 (5%)	2/29 (7%)
First incidence (days)	662	555	727	595
Poly-3 test	P=0.399	P=0.624	P=0.374N	P=0.445
Ovary: Cystadenoma				
Overall rate	4/47 (9%)	3/49 (6%)	1/46 (2%)	0/49 (0%)
Adjusted rate	9.9%	7.6%	2.7%	0.0%
Terminal rate	4/32 (13%)	2/29 (7%)	1/21 (5%)	0/29 (0%)
First incidence (days)	729 (T)	696	729 (T)	—
Poly-3 test	P=0.029N	P=0.513N	P=0.210N	P=0.069N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	8/47 (17%)	9/44 (20%)	6/42 (14%)	2/46 (4%)
Adjusted rate	19.7%	25.0%	17.1%	5.7%
Terminal rate	8/31 (26%)	6/26 (23%)	5/21 (24%)	2/27 (7%)
First incidence (days)	729 (T)	608	700	729 (T)
Poly-3 test	P=0.041N	P=0.391	P=0.502N	P=0.071N
Skin (Subcutaneous Tissue): Sarcoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted rate	4.7%	4.9%	7.4%	9.9%
Terminal rate	2/32 (6%)	1/30 (3%)	0/22 (0%)	1/29 (3%)
First incidence (days)	729 (T)	573	556	299
Poly-3 test	P=0.197	P=0.679	P=0.477	P=0.311
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted rate	7.0%	4.9%	7.6%	7.8%
Terminal rate	3/32 (9%)	1/30 (3%)	3/22 (14%)	3/29 (10%)
First incidence (days)	729 (T)	674	729 (T)	729 (T)
Poly-3 test	P=0.472	P=0.522N	P=0.628	P=0.615
All Organs: Hemangioma				
Overall rate	0/50 (0%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	2.5%	7.7%
Terminal rate	0/32 (0%)	0/30 (0%)	1/22 (5%)	2/29 (7%)
First incidence (days)	—	—	729 (T)	615
Poly-3 test	P=0.017	—[f]	P=0.485	P=0.103
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	5.0%	7.7%
Terminal rate	0/32 (0%)	0/30 (0%)	1/22 (5%)	2/29 (7%)
First incidence (days)	—	—	723	615
Poly-3 test	P=0.022	—	P=0.221	P=0.103
All Organs: Malignant Lymphoma				
Overall rate	6/50 (12%)	7/50 (14%)	4/50 (8%)	6/50 (12%)
Adjusted rate	13.9%	17.1%	9.8%	15.3%
Terminal rate	2/32 (6%)	5/30 (17%)	0/22 (0%)	5/29 (17%)
First incidence (days)	687	599	624	510
Poly-3 test	P=0.546N	P=0.460	P=0.407N	P=0.554

TABLE E3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
All Organs: Benign Neoplasms				
Overall rate	40/50 (80%)	41/50 (82%)	43/50 (86%)	36/50 (72%)
Adjusted rate	85.5%	91.5%	97.3%	83.7%
Terminal rate	28/32 (88%)	28/30 (93%)	22/22 (100%)	25/29 (86%)
First incidence (days)	151	419	509	430
Poly-3 test	P=0.445N	P=0.275	P=0.035	P=0.527N
All Organs: Malignant Neoplasms				
Overall rate	26/50 (52%)	30/50 (60%)	40/50 (80%)	44/50 (88%)
Adjusted rate	56.0%	69.7%	90.1%	99.2%
Terminal rate	14/32 (44%)	20/30 (67%)	20/22 (91%)	29/29 (100%)
First incidence (days)	375	573	556	299
Poly-3 test	P<0.001	P=0.128	P<0.001	P<0.001
All Organs: Benign or Malignant Neoplasms				
Overall rate	47/50 (94%)	45/50 (90%)	45/50 (90%)	45/50 (90%)
Adjusted rate	96.5%	99.7%	99.6%	99.7%
Terminal rate	31/32 (97%)	30/30 (100%)	22/22 (100%)	29/29 (100%)
First incidence (days)	151	419	509	299
Poly-3 test	P=0.174	P=0.348	P=0.366	P=0.347

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE E4
Historical Incidence of Liver Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

	Incidence in Controls			
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatoblastoma	Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma
Overall Historical Incidence				
Total	150/289 (51.9%)	55/289 (19.0%)	0/289	173/289 (59.9%)
Standard deviation	20.8%	13.7%		21.3%
Range	26%-80%	8%-42%		32%-82%

[a] Data as of 1 August 1997

TABLE E5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine[a]

	0 ppm	125 ppm	250 ppm	500 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental deaths	3	6	4	5
Moribund	3	2	3	5
Natural deaths	12	12	21	11
Survivors				
Terminal sacrifice	32	30	22	29
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(37)	(40)	(33)	(34)
Hyperplasia				1 (3%)
Intestine large, rectum	(44)	(48)	(47)	(47)
Artery, necrosis				1 (2%)
Intestine large, cecum	(44)	(49)	(40)	(45)
Edema			1 (3%)	
Intestine small, jejunum	(42)	(47)	(38)	(43)
Peyer's patch, hyperplasia, lymphoid	1 (2%)			
Intestine small, ileum	(43)	(48)	(37)	(41)
Peyer's patch, hyperplasia, lymphoid		1 (2%)		
Liver	(49)	(50)	(50)	(50)
Basophilic focus	1 (2%)			
Clear cell focus	1 (2%)	5 (10%)	1 (2%)	2 (4%)
Cyst			1 (2%)	
Eosinophilic focus	17 (35%)	12 (24%)	14 (28%)	9 (18%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)			
Infiltration cellular, lymphocyte	4 (8%)			
Mixed cell focus	5 (10%)	4 (8%)	3 (6%)	
Necrosis	5 (10%)	2 (4%)	5 (10%)	7 (14%)
Vacuolization cytoplasmic, diffuse	1 (2%)			1 (2%)
Centrilobular, congestion				1 (2%)
Centrilobular, degeneration			1 (2%)	1 (2%)
Midzonal, vacuolization cytoplasmic			1 (2%)	
Periportal, vacuolization cytoplasmic		2 (4%)	1 (2%)	
Mesentery	(17)	(18)	(13)	(13)
Infiltration cellular, lymphocyte	1 (6%)			
Inflammation, chronic active	2 (12%)			
Fat, necrosis	12 (71%)	13 (72%)	11 (85%)	9 (69%)
Pancreas	(49)	(49)	(47)	(48)
Infiltration cellular, lymphocyte	1 (2%)	1 (2%)		
Inflammation, chronic active	1 (2%)			2 (4%)
Acinus, atrophy		2 (4%)	1 (2%)	2 (4%)
Artery, inflammation, chronic			1 (2%)	
Duct, cyst		1 (2%)	2 (4%)	2 (4%)
Salivary glands	(50)	(50)	(49)	(50)
Infiltration cellular, lymphocyte	33 (66%)	35 (70%)	36 (73%)	29 (58%)
Stomach, forestomach	(49)	(49)	(49)	(49)
Ulcer	1 (2%)			
Epithelium, hyperplasia	1 (2%)			
Stomach, glandular	(48)	(49)	(48)	(49)
Necrosis	3 (6%)	3 (6%)	4 (8%)	3 (6%)
Tooth	(2)			
Developmental malformation	2 (100%)			

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

TABLE E5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Cardiovascular System				
Blood vessel	(48)	(47)	(47)	(47)
Aorta, inflammation, chronic active	1 (2%)			
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	1 (2%)			
Inflammation, chronic active	1 (2%)			
Mineralization			1 (2%)	
Atrium, thrombosis				1 (2%)
Endocrine System				
Adrenal cortex	(49)	(50)	(48)	(50)
Cytoplasmic alteration	2 (4%)			2 (4%)
Hematopoietic cell proliferation		1 (2%)	1 (2%)	
Hemorrhage	1 (2%)			2 (4%)
Hyperplasia	1 (2%)			
Capsule, hyperplasia	41 (84%)	35 (70%)	39 (81%)	37 (74%)
Adrenal medulla	(49)	(49)	(45)	(49)
Hyperplasia	1 (2%)	2 (4%)		
Islets, pancreatic	(49)	(50)	(47)	(49)
Hyperplasia			2 (4%)	3 (6%)
Parathyroid gland	(31)	(29)	(30)	(36)
Infiltration cellular, lymphocyte				1 (3%)
Pituitary gland	(47)	(44)	(42)	(46)
Hemorrhage				1 (2%)
Pars distalis, angiectasis		1 (2%)		1 (2%)
Pars distalis, hyperplasia	5 (11%)	4 (9%)	6 (14%)	8 (17%)
Pars intermedia, hyperplasia	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
Infiltration cellular, lymphocyte		3 (6%)		3 (6%)
C-cell, hyperplasia	1 (2%)			
Follicle, cyst	4 (8%)		1 (2%)	
Follicular cell, hyperplasia	14 (28%)	21 (42%)	22 (44%)	23 (46%)
General Body System				
Peritoneum			(2)	
Inflammation, chronic active			1 (50%)	
Genital System				
Clitoral gland	(47)	(48)	(48)	(45)
Atrophy	45 (96%)	43 (90%)	45 (94%)	43 (96%)
Cyst	3 (6%)			
Inflammation, chronic	2 (4%)	2 (4%)	1 (2%)	4 (9%)
Inflammation, chronic active	2 (4%)		3 (6%)	
Pigmentation	2 (4%)		1 (2%)	3 (7%)
Ovary	(47)	(49)	(46)	(49)
Angiectasis		1 (2%)		
Cyst	14 (30%)	9 (18%)	11 (24%)	11 (22%)
Periovarian tissue, hyperplasia, lymphoid		1 (2%)		
Uterus	(48)	(50)	(47)	(50)
Congestion	1 (2%)			
Cyst	3 (6%)	3 (6%)	5 (11%)	2 (4%)
Hyperplasia, cystic	44 (92%)	43 (86%)	38 (81%)	39 (78%)
Inflammation, chronic active	1 (2%)			1 (2%)
Pigmentation				1 (2%)

TABLE E5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Atrophy	1 (2%)	1 (2%)		
Myeloid cell, hyperplasia	1 (2%)			2 (4%)
Lymph node	(10)	(10)	(7)	(7)
Iliac, hemorrhage	1 (10%)			
Iliac, hyperplasia, lymphoid	3 (30%)		2 (29%)	
Iliac, inflammation, chronic active				1 (14%)
Iliac, pigmentation	1 (10%)			
Inguinal, hyperplasia, lymphoid			1 (14%)	
Mediastinal, hemorrhage	1 (10%)		1 (14%)	
Mediastinal, hyperplasia, plasma cell		1 (10%)		
Mediastinal, inflammation, chronic active	1 (10%)			
Mediastinal, pigmentation			1 (14%)	
Renal, hemorrhage			1 (14%)	
Renal, hyperplasia, lymphoid	1 (10%)			
Lymph node, mandibular	(48)	(50)	(49)	(47)
Hemorrhage	3 (6%)		1 (2%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)	2 (4%)		
Lymph node, mesenteric	(48)	(47)	(43)	(45)
Angiectasis			1 (2%)	2 (4%)
Ectasia		1 (2%)		
Hematopoietic cell proliferation	1 (2%)			1 (2%)
Hemorrhage	4 (8%)	2 (4%)	3 (7%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		
Artery, necrosis				1 (2%)
Spleen	(49)	(50)	(48)	(49)
Atrophy		1 (2%)	1 (2%)	
Hematopoietic cell proliferation	29 (59%)	27 (54%)	32 (67%)	39 (80%)
Hemorrhage		1 (2%)	1 (2%)	
Hyperplasia, lymphoid	2 (4%)	5 (10%)	4 (8%)	2 (4%)
Inflammation, chronic active	1 (2%)			
Pigmentation	1 (2%)			1 (2%)
Thymus	(45)	(44)	(46)	(39)
Atrophy	11 (24%)	11 (25%)	13 (28%)	10 (26%)
Ectopic parathyroid gland	1 (2%)		2 (4%)	
Hyperplasia, lymphoid	1 (2%)		1 (2%)	
Inflammation, acute	1 (2%)			
Necrosis	2 (4%)	4 (9%)	3 (7%)	3 (8%)
Integumentary System				
Mammary gland	(47)	(50)	(49)	(48)
Hyperplasia	2 (4%)	1 (2%)		
Skin	(49)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, necrosis		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fibrous osteodystrophy		5 (10%)	2 (4%)	
Hyperostosis	1 (2%)			

TABLE E5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Drinking Water Study of Pyridine

	0 ppm	125 ppm	250 ppm	500 ppm
Nervous System				
Brain	(50)	(50)	(50)	(50)
Cyst epithelial inclusion				1 (2%)
Hemorrhage	1 (2%)	1 (2%)		
Infiltration cellular, histiocyte		1 (2%)		
Mineralization	25 (50%)	27 (54%)	18 (36%)	19 (38%)
Meninges, inflammation, chronic active	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion		2 (4%)	4 (8%)	3 (6%)
Hemorrhage	1 (2%)			1 (2%)
Infiltration cellular, lymphocyte	4 (8%)	2 (4%)		1 (2%)
Inflammation, chronic active	1 (2%)			
Alveolar epithelium, hyperplasia	5 (10%)	3 (6%)	1 (2%)	
Alveolus, infiltration cellular, histiocyte	2 (4%)			2 (4%)
Nose	(50)	(50)	(47)	(50)
Foreign body	1 (2%)			
Olfactory epithelium, degeneration, hyaline	19 (38%)	27 (54%)	35 (74%)	36 (72%)
Olfactory epithelium, inflammation, chronic active				1 (2%)
Olfactory epithelium, necrosis		1 (2%)		
Respiratory epithelium, degeneration, hyaline	26 (52%)	16 (32%)	12 (26%)	13 (26%)
Respiratory epithelium, hyperplasia	12 (24%)	8 (16%)	12 (26%)	4 (8%)
Respiratory epithelium, inflammation, chronic active	3 (6%)			1 (2%)
Respiratory epithelium, necrosis		1 (2%)		
Special Senses System				
None				
Urinary System				
Kidney	(49)	(50)	(49)	(49)
Infarct	1 (2%)	2 (4%)	1 (2%)	
Infiltration cellular, plasma cell				1 (2%)
Infiltration cellular, lymphocyte	4 (8%)	2 (4%)	5 (10%)	2 (4%)
Nephropathy	5 (10%)	10 (20%)	7 (14%)	8 (16%)
Glomerulus, amyloid deposition			1 (2%)	
Renal tubule, dilatation		1 (2%)	2 (4%)	2 (4%)
Renal tubule, pigmentation			3 (6%)	2 (4%)
Renal tubule, regeneration		1 (2%)		1 (2%)
Urinary bladder	(45)	(49)	(44)	(43)
Infiltration cellular, lymphocyte	16 (36%)	16 (33%)	17 (39%)	22 (51%)

APPENDIX F
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Haworth *et al.* (1983). Pyridine was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37E C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37E C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of pyridine; 10,000 µg/plate was selected as the high dose. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants that is not dose-related, is not reproducible, or is not of sufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by McGregor *et al.* (1988). Pyridine was supplied as a coded aliquot by Radian Corporation. The high dose of pyridine did not exceed 5,000 µg/mL in the absence of toxicity. L5178Y mouse lymphoma cells were maintained at 37E C as suspension cultures in supplemented Fischer's medium; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring cells resistant to trifluorothymidine (TFT), subcultures were exposed to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day; to medium containing thymidine, hypoxanthine, and glycine for 1 day; and to normal medium for 3 to 5 days. For cloning, the horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with pyridine continued for 4 hours, at which time the medium plus pyridine was removed, and the cells were resuspended in 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, cells were plated in medium and soft agar supplemented with TFT for selection of TFT-resistant cells, and cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37E C in 5% CO_2 for 10 to 12 days. The test was initially performed without S9. Because a clearly positive response was not obtained, the test was repeated using freshly prepared S9 from the livers of Aroclor 1254-induced male 344 rats.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented by Caspary *et al.* (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant (P# 0.05) for pyridine to be considered positive, i.e., capable of inducing TFT resistance. A single significant response led to a "questionable" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Pyridine was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of pyridine; the high dose was limited by toxicity or, in the absence of toxicity, 5,000 µg/mL was selected as the high dose. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

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

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P<0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with pyridine for 11.5 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with pyridine and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 11.5 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test.

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

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant (P#0.05) difference for one dose point and a significant trend (P#0.015) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose

resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

DROSOPHILA MELANOGASTER TEST PROTOCOLS

The assays for induction sex-linked recessive lethal (SLRL) mutations and chromosomal reciprocal translocations (RTs) were performed with adult flies as described by Valencia *et al.* (1985) and Mason *et al.* (1992). Pyridine was supplied as a coded aliquot by Radian Corporation.

Sex-Linked Recessive Lethal Mutation Test: Pyridine was assayed in the SLRL test by feeding for 3 days to adult Canton-S wild-type males no more than 24 hours old at the beginning of treatment. Because no clearly positive response was obtained in the feeding experiments, it was retested by injection into adult males.

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

Toxicity tests were performed to set concentrations of pyridine at a level that would induce 30% mortality after 72 hours of feeding or 24 hours after injection, while keeping induced sterility at an acceptable level. Canton-S males were allowed to feed for 72 hours on a solution of pyridine in 5% sucrose. In the injection experiments, 24- to 72-hour old Canton-S males were treated with a solution of pyridine dissolved in saline and allowed to recover for 24 hours. A concurrent saline control group was also included. In the adult exposures, treated males were mated to three *Basc* females for 3 days and were given fresh females at 2-day intervals to produce three matings of 3, 2, and 2 days (in each case, sample sperm from successive matings were treated at successively earlier postmeiotic stages). F_1 heterozygous females were mated with their siblings and then placed in individual vials. F_1 daughters from the same parental male were kept together to identify clusters. (A cluster occurs when a number of mutants from a given male result from a single spontaneous premeiotic mutation event and is identified when the number of mutants from that male exceeds the number predicted by a Poisson distribution.) If a cluster was identified, all data from the male in question were discarded. Presumptive lethal mutations were identified as vials containing fewer than 5% of the expected number of wild-type males after 17 days; these were retested to confirm the response.

SLRL data were analyzed by simultaneous comparison with the concurrent and historical controls (Mason *et al.*, 1992) using a normal approximation to the binomial test (Margolin *et al.*, 1983). A test result was considered positive if the P value was less or equal to 0.01 and the mutation frequency in the tested group was greater than 0.10% or if the P value was less than or equal to 0.05 and the frequency in the treatment group was greater than 0.15%. A test was considered to be inconclusive if the P value was between 0.05 and 0.01 but the frequency in the treatment group was between 0.10% and 0.15% or if the P value was between 0.10 and 0.05 but the frequency in the treatment group was greater than 0.10%. A test was considered negative if the P value was greater than or equal to 0.10 or if the frequency in the treatment group was less than 0.10%.

Reciprocal Translocation Test: Because one of the injection experiments (Mason *et al.*, 1992) produced a positive result in the SLRL test, pyridine was assayed for induction of RTs using the same exposure method. The treatment regimen was essentially the same as that for the SLRL test, except that Canton-S males were mated *en masse* to marker (*bw;st* or *bw;e*) females. The females were transferred to fresh medium every 3 to 4 days for a period of about 3 weeks to produce a total of six broods. The results of the SLRL test were used to determine the germ cell stages most likely to be affected by pyridine. F_1 heterozygous males were backcrossed

individually to *bw;st* females, and the F_2 progeny were screened for pseudolinkage, which results from the induction of a translocation in a germ cell of the parental male. Flies suspected of carrying RTs were retested to confirm the findings. The translocation data were analyzed according to the conditional binomial response test of Kastenbaum and Bowman (1970).

MOUSE BONE MARROW CYTOGENETIC TEST PROTOCOLS

Chromosomal Aberrations Test: A dose range-finding study was performed in the absence of adequate toxicity information from the literature, and the highest dose was limited by toxicity. Pyridine was tested for induction of Abs in mouse bone marrow by two different protocols. The first protocol used a standard harvest time of 17 hours, and the second protocol used a delayed harvest time of 36 hours.

Male B6C3F_1 mice (10 animals per dose group) were injected intraperitoneally with pyridine dissolved in phosphate-buffered saline (PBS) (injection volume=0.4 mL.). Solvent control mice received equivalent injections of PBS alone. The positive control was mitomycin C. The mice were subcutaneously implanted with a BrdU tablet (McFee *et al.*, 1983) 18 hours before the scheduled harvest. (For the standard protocol, this required BrdU implantation to precede injection with pyridine by 1 hour). The use of BrdU allowed selection of the appropriate cell population for scoring. (Abs induced by chemical administration are present in maximum number at the first metaphase following treatment; they decline in number during subsequent nuclear divisions due to cell death.) Two hours before sacrifice, the mice received an intraperitoneal injection of colchicine in saline. The animals were killed 17 or 36 hours after pyridine injection (18 hours after BrdU dosing). One or both femurs were removed, and the marrow was flushed out with PBS (pH 7.0). Cells were treated with a hypotonic salt solution, fixed, and dropped onto chilled slides. After a 24-hour drying period, the slides were stained and scored.

Fifty first-division metaphase cells were scored from each of eight animals per group. Responses were evaluated as the percentage of aberrant metaphase cells, excluding gaps. The data were analyzed by a trend test (Margolin *et al.*, 1986).

Micronucleus Test: Preliminary range-finding studies were performed. Factors affecting dose selection included chemical solubility and toxicity and the extent of cell cycle delay induced by pyridine exposure. The standard three-exposure protocol is described in detail by Shelby *et al.* (1993). Male B6C3F_1 mice were injected intraperitoneally three times at 24-hour intervals with pyridine dissolved in PBS; the total dosing volume was 0.4 mL. Solvent control animals were injected with 0.4 mL of PBS only. The positive control animals received injections of cyclophosphamide. The animals were killed 24 hours after the third injection, and blood smears were prepared from bone marrow cells obtained from the femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells in each of five animals per dose group. In addition, the percentage of PCEs among the total erythrocyte population in the bone marrow was scored for each dose group as a measure of toxicity.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among PCEs was analyzed by a statistical software package that tested for increasing trend over dose groups using a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single dose group is less than or equal to 0.025 divided by the number of dose groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials

(as noted above). Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitude of those effects.

RESULTS

Pyridine (100-10,000 µg/plate) was not mutagenic in *S. typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation enzymes (Haworth *et al.*, 1983; Table F1). Further, no significant increase in mutant frequencies was observed in L5178Y mouse lymphoma cells, tested with and without S9 metabolic activation (McGregor *et al.*, 1988; Table F2). In cytogenetic tests with cultured CHO cells, pyridine did not induce SCEs (Table F3) or Abs (Table F4), with or without S9. At the highest viable dose (1,673 µg/mL) tested for SCE induction in the absence of S9, pyridine induced marked cell cycle delay, and an extended culture time (31 hours) was used to allow sufficient cells to accumulate for analysis.

Pyridine was tested on three separate occasions in two different laboratories for induction of SLRL mutations in adult male *D. melanogaster* (Valencia *et al.*, 1985; Mason *et al.*, 1992; Foureman *et al.*, 1994; Table F5), and mixed results were obtained. In the first experiment (Valencia *et al.*, 1985), administration of pyridine by injection (7,000 ppm in aqueous 0.7% saline solution) gave negative (P=0.225) results, but feeding (600 and 700 ppm pyridine in aqueous 5% sucrose) produced an increase in recessive lethal mutations that was considered to be equivocal (P=0.043). A second experiment performed in the same laboratory using both injection (500 ppm) and feeding (729 ppm) yielded negative results (Foureman *et al.*, 1994). In the third experiment (Mason *et al.*, 1992) performed in a second laboratory, results of a feeding (500 ppm) experiment were negative (P=0.998), but administration of pyridine by injection (4,300 ppm) induced a significant increase in the frequency of SLRL mutations (P=0.008). Overall, pyridine was considered to be negative in SLRL tests when administered by feeding and equivocal when administered by injection. This positive result in the SLRL test led to the performance of a test for induction of RTs in germ cells of treated male *D. melanogaster* (Mason *et al.*, 1992; Table F6); results of this test were negative.

In vivo assays for chromosomal effects were conducted with male mice. No induction of Abs (Table F7) was noted in bone marrow cells at either of two sampling times (400-600 mg/kg pyridine; single injection), and no increase in the frequency of micronucleated PCEs (Table F8) was noted in bone marrow after intraperitoneal injection of pyridine (up to 500 mg/kg administered three times at 24-hour intervals).

In summary, with the exception of the single positive result obtained in a *D. melanogaster* SLRL assay, no indication of mutagenic activity was seen with pyridine in a variety of *in vitro* and *in vivo* assays for gene mutation and chromosomal damage.

TABLE F1
Mutagenicity of Pyridine in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/plate[b]					
		−S9		+10% hamster S9		+10% rat S9	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	115 ± 8.3	105 ± 3.5	116 ± 9.8	107 ± 14.4	113 ± 2.4	105 ± 8.0
	100	106 ± 6.4	113 ± 1.5	116 ± 5.4	131 ± 10.5	119 ± 6.4	107 ± 17.0
	333.3	93 ± 3.6	114 ± 5.5	103 ± 1.7	131 ± 8.6	129 ± 3.1	112 ± 15.1
	1,000	96 ± 5.2	114 ± 16.5	94 ± 2.3	115 ± 5.8	127 ± 1.3	117 ± 3.0
	3,333.3	93 ± 0.0	105 ± 4.6	121 ± 6.9	135 ± 12.2	122 ± 8.3	114 ± 3.9
	10,000	96 ± 10.7	117 ± 8.4	94 ± 2.8	148 ± 4.8	112 ± 8.1	119 ± 10.7
Trial summary		Negative	Negative	Negative	Equivocal	Negative	Negative
Positive control[c]		483 ± 7.2	416 ± 11.3	1,119 ± 119.8	2,115 ± 14.6	1,075 ± 30.0	549 ± 71.3
TA1535	0	31 ± 0.7	21 ± 5.6	12 ± 2.3	12 ± 1.9	11 ± 1.8	14 ± 0.9
	100	34 ± 1.3	21 ± 4.8	9 ± 1.5	13 ± 2.3	14 ± 0.6	15 ± 3.7
	333.3	29 ± 5.6	18 ± 1.2	11 ± 2.1	11 ± 2.3	12 ± 1.3	12 ± 0.6
	1,000	27 ± 4.0	18 ± 1.5	10 ± 2.5	12 ± 1.8	14 ± 2.3	11 ± 1.2
	3,333.3	32 ± 3.8	17 ± 2.0	14 ± 1.9	11 ± 1.8	11 ± 1.7	12 ± 0.9
	10,000	33 ± 7.1	17 ± 4.0	14 ± 5.3	14 ± 1.2	13 ± 4.1	15 ± 1.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		412 ± 9.4	346 ± 14.4	257 ± 13.8	266 ± 9.5	314 ± 14.9	167 ± 4.9
TA1537	0	9 ± 1.3	5 ± 1.5	18 ± 3.5	10 ± 0.7	23 ± 2.1	6 ± 1.0
	100	13 ± 5.7	6 ± 1.2	20 ± 1.9	7 ± 0.6	20 ± 1.0	7 ± 0.7
	333.3	9 ± 0.6	6 ± 0.9	18 ± 4.9	8 ± 2.3	17 ± 2.2	4 ± 1.5
	1,000	14 ± 1.2	7 ± 1.0	18 ± 3.8	10 ± 2.2	22 ± 3.0	6 ± 1.0
	3,333.3	10 ± 3.0	5 ± 0.3	20 ± 4.7	9 ± 1.7	17 ± 2.7	5 ± 0.6
	10,000	14 ± 0.3	6 ± 0.9	17 ± 4.2	5 ± 1.8	18 ± 1.2	6 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		329 ± 159.1	847 ± 54.3	459 ± 52.4	411 ± 10.3	495 ± 52.6	239 ± 24.6
TA98	0	35 ± 4.7	37 ± 3.5	49 ± 5.6	35 ± 2.3	31 ± 5.2	34 ± 3.2
	100	35 ± 4.9	33 ± 3.5	45 ± 2.0	39 ± 0.3	41 ± 2.4	40 ± 0.3
	333.3	35 ± 2.3	31 ± 5.9	39 ± 5.7	40 ± 0.9	36 ± 3.2	32 ± 5.1
	1,000	33 ± 4.9	29 ± 2.3	46 ± 7.5	37 ± 2.6	34 ± 1.5	38 ± 0.3
	3,333.3	25 ± 0.7	29 ± 3.4	50 ± 14.2	30 ± 4.7	33 ± 3.5	28 ± 1.8
	10,000	22 ± 3.5	27 ± 3.8	43 ± 6.4	43 ± 7.8	30 ± 5.6	26 ± 5.6
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		691 ± 10.1	671 ± 57.5	570 ± 57.5	1,271 ± 7.8	574 ± 22.3	365 ± 22.9

[a] Study was performed at SRI International. The detailed protocol and these data are presented by Haworth *et al.* (1983). 0 µg/plate was the solvent control.
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE F2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Pyridine[a]

Compound	Concentration (µg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction
!S9						
Trial 1						
Medium[c]		112	102	95	28	
		99	106	86	29	
		108	103	100	31	
		101	89	92	31	30
Methyl methanesulfonate[d]	15	43	26	239	186	
		49	26	195	133	160*
Pyridine	625	89	100	99	37	
		105	102	95	30	34
	1,250	73	88	47	21	
		86	101	80	31	26
	2,500	94	69	81	29	
		78	71	56	24	26
	5,000	82	70	60	24	
		88	77	113	43	34
Trial 2						
Medium		76	98	89	39	
		99	102	136	46	
		84	97	122	49	
		65	102	120	62	49
Methyl methanesulfonate	15	27	23	440	550	
		24	20	473	671	610*
Pyridine	1,000	82	101	160	65	
		58	90	106	61	63
	2,000	74	77	154	69	
		68	78	167	81	75
	3,000	78	68	182	78	
		71	76	161	76	77*
	4,000	47	68	97	68	
		55	76	154	94	81*
	5,000	48	57	138	97	
		69	66	151	73	85*
Trial 3						
Medium		98	100	60	20	
		108	110	67	21	
		71	84	70	33	
		102	106	85	28	25
Methyl methanesulfonate	15	25	14	126	166	
		23	13	103	151	159*
Pyridine	2,000	90	87	68	25	
		79	85	53	22	24
	3,000	116	85	89	26	
		90	79	64	24	25
	4,000	72	75	86	40	
		88	79	145	55	47*
	5,000	82	70	73	30	
		89	67	79	30	30

TABLE F2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Pyridine

Compound	Concentration (µg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9						
Trial 1						
Medium		90	90	126	47	
		79	104	124	53	
		83	102	137	55	
		74	105	141	64	55
Methylcholanthrene[d]	2.5	50	18	820	552	
		43	20	726	561	556*
Pyridine	1,000	82	88	133	54	
		89	96	152	57	56
	2,000	94	77	230	82	
		77	99	123	53	68
	3,000	77	86	204	89	
		89	80	140	52	71
	4,000	100	70	167	55	
		78	79	147	63	59
	5,000	95	81	158	55	
		98	73	207	70	63
Trial 2						
Solvent control		85	101	111	43	
		91	108	138	50	
		100	93	188	62	
		105	98	159	50	52
Methylcholanthrene	2.5	54	24	686	421	
		58	28	791	451	436*
Pyridine	2,000	86	104	95	37	
		87	108	119	46	41
	3,000	78	101	87	37	
		79	105	117	49	43
	4,000	80	97	94	39	
		84	91	107	42	41
	5,000	109	78	101	31	
		109	84	115	35	33

* Positive response (P#0.05) versus the solvent control
[a] Study was performed at Inveresk Research International. The detailed protocol and these data are presented by McGregor *et al*. (1988).
[b] Mutant fraction=mutant cells/10^6 clonable cells
[c] Solvent control
[d] Positive control

TABLE F3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Pyridine[a]

Compound	Concentration (µg/mL)	Total Cells Scored	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
!S9								
Summary: Negative								
Distilled water[c]		50	1,049	415	0.39	8.3	26.0	
		50	1,049	424	0.40	8.5	31.0[e]	
Mitomycin-C[d]	0.001	50	1,049	665	0.63	13.3	26.0	56.84
	0.004	10	208	201	0.96	20.1	26.0	139.08
Pyridine	167	50	1,043	407	0.39	8.1	26.0	!3.46
	502	50	1,049	437	0.41	8.7	26.0	3.07
	1,673	50	1,050	434	0.41	8.7	31.0	2.26
	5,020	0						
					P=0.273[f]			
+S9								
Summary: Negative								
Distilled water		50	1,050	389	0.37	7.8	26.0	
Cyclophosphamide[d]	0.125	50	1,051	598	0.56	12.0	26.0	53.58
	0.5	10	207	186	0.89	18.6	26.0	142.54
Pyridine	502	50	1,048	416	0.39	8.3	26.0	7.14
	1,673	50	1,051	421	0.40	8.4	26.0	8.12
	5,020	50	1,051	388	0.36	7.8	26.0	!0.35
					P=0.494			

[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented by Galloway *et al.* (1987). SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Solvent control
[d] Positive control
[e] Due to cell cycle delay, harvest time was extended to maximize the number of second-division metaphase cells available for analysis.
[f] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

TABLE F4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Pyridine[a]

Compound	Concentration (µg/mL)	Total Cells Scored	Number of Aberrations	Aberrations/ Cell	Cells with Aberrations (%)
!S9					
Harvest time: 13.5 hours					
Summary: Negative					
Distilled water[b]		200	2	0.01	1.0
Mitomycin-C[c]	0.4	25	37	1.48	76.0
Pyridine	503	200	0	0.00	0.0
	1,081	200	0	0.00	0.0
	2,325	200	2	0.01	1.0
					P=0.450[d]
+S9					
Harvest time: 13.5 hours					
Summary: Negative					
Distilled water		200	2	0.01	1.0
Cyclophosphamide[c]	20	25	42	1.68	48.0
Pyridine	1,081	200	1	0.01	0.5
	2,325	200	1	0.01	0.5
	5,000	200	3	0.02	1.5
					P=0.305

[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented by Galloway *et al*. (1987).
[b] Solvent control
[c] Positive control
[d] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

TABLE F5
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Pyridine[a]

Route of Exposure	Dose (ppm)	Incidence of Death (%)	Incidence of Sterility (%)	No. of Lethals/No. of X Chromosomes Tested			Total[b]
				Mating 1	Mating 2	Mating 3	
Study performed at Brown University[c]							
Feed	600	5	0	0/1,116	1/1,123	1/1,136	2/3,375 (0.06%)
	0			0/1,214	1/1,128	0/1,050	1/3,392 (0.03%)
	700	20	2	4/1,027	1/1,069	0/1,082	5/3,178 (0.16%)
	0			0/1,114	1/1,142	0/1,105	1/3,361 (0.03%)
	Combined data set (600 ppm and 700 ppm trials):			4/2,143	2/2,192	1/2,218	7/6,553 (0.11%)
				0/2,328	2/2,270	0/2,155	2/6,753 (0.03%)
							P=0.043[d]
Injection	7,000	5	0	1/1,770	1/2,281	3/2,039	5/6,090 (0.08%)
	0			1/2,170	2/2,750	0/1,379	3/6,299 (0.05%)
							P=0.225
Feed	729	22	0	1/1,724	0/2,664	1/1,121	2/5,509 (0.04%)
	0			0/1,902	1/2,541	6/1,413	7/5,856 (0.12%)
							P=0.943
Injection	500	4	0	4/1,916	1/2,006	2/1,944	7/5,866 (0.12%)
	0			2/1,908	1/1,933	0/1,921	3/5,762 (0.05%)
							P=0.108
Study performed at University of Wisconsin, Madison[e]							
Feed	500	12	1	1/2,063	0/1,989	0/1,666	1/5,718 (0.02%)
	0			3/1,947	5/1,726	2/1,438	10/5,111 (0.20%)
							P=0.998
Injection	4,300	26	9	7/1,854	1/1,731	1/1,608	9/5,193 (0.17%)
	0			3/4,163	2/3,949	1/3,285	6/11,397 (0.05%)
							P=0.008

[a] The mean mutant frequency from 518 negative control experiments is 0.074% (Mason *et al.*, 1992).
[b] Total number of lethal mutations/total number of X chromosomes tested for three mating trials
[c] The detailed protocol and these data are presented by Valencia *et al.* (1985) (first two exposures) and Foureman (1994) (last 2 exposures).
[d] Data from the 600 ppm and 700 ppm trials were combined to provide and adequate sample size for statistical analysis. The P value was generated from the combined data set.
[e] The detailed protocol and these data are presented by Mason *et al.* (1992).

TABLE F6
Induction of Reciprocal Translocations in *Drosophila melanogaster* by Pyridine[a]

Route of Exposure	Dose (ppm)	Translocations/Total F_1 Tested 1	2	3	4	5	6	No. of Tests	Total No. of Translocations	Total Translocations (%)
Injection	4,300	0/1,483	0/1,413	0/1,243	0/819	0/254	0/11	5,223	0	0
Historical control		0/27,245	0/31,611	0/22,410	2/23,623	0/10,506	0/768	116,163	2	0.002

[a] Study was performed at University of Wisconsin, Madison. The detailed protocol and these data are presented by Mason *et al.* (1992). Results were not significant at the 5% level (Kastenbaum and Bowman, 1970).

TABLE F7
Induction of Chromosomal Aberrations in Mouse Bone Marrow Cells by Pyridine[a]

Compound	Dose (mg/kg)	Total Cells Scored	Total Aberrations (!gaps)	Cells with Aberrations[b] (%)
Trial 1				
Sample time: 17 hours				
Phosphate-buffered saline[c]		400	2	0.50 ± 0.33
Mitomycin-C[d]	1	400	11	2.25 ± 0.45
	2	400	48	9.50 ± 1.76
Pyridine	400	400	2	0.50 ± 0.50
	500	400	8	1.75 ± 0.59
	600	400	2	0.50 ± 0.33
				P=0.222[e]
Trial 2				
Sample time: 36 hours				
Phosphate-buffered saline		400	6	1.50 ± 0.63
Mitomycin-C	1	400	14	3.00 ± 0.85
	2	400	68	6.25 ± 2.31
Pyridine	400	400	3	0.75 ± 0.53
	500	400	6	1.50 ± 0.82
	600	400	0	0.00 ± 0.00
				P=0.948

[a] Study was performed at Environmental Health Research and Testing, Inc. Fifty first-division metaphase cells were scored from each of eight mice per group. The detailed protocol and these data are presented by McFee (1989).
[b] Mean ± standard error
[c] Solvent control
[d] Positive control
[e] Significance tested by the one-tailed trend test; significant at P#0.05 (Margolin *et al*., 1986)

TABLE F8
Induction of Micronuclei in Bone Marrow Polychromatic Erythrocytes of Mice Treated with Pyridine by Intraperitoneal Injection[a]

Compound	Dose (mg/kg)	Number of Mice with Erythrocytes Scored	Micronucleated PCEs/ 1,000 PCEs[b]	PCEs[b] (%)
Phosphate-buffered saline[c]		5	1.60 ± 0.51	52.52 ± 4.30
Cyclophosphamide[d]	15	5	11.50 ± 0.91	52.46 ± 1.71
Pyridine	31.25	5	1.40 ± 0.29	52.22 ± 1.11
	62.5	5	1.60 ± 0.43	53.04 ± 3.89
	125	5	1.10 ± 0.51	51.40 ± 3.66
	250	5	1.10 ± 0.37	51.22 ± 1.61
	500	5	1.20 ± 0.25	48.02 ± 1.88
			P=0.811[e]	

[a] Study was performed at Environmental Health Research and Testing, Inc. The detailed protocol and these data are presented by Shelby *et al*. (1993).
[b] Mean ± standard error
[c] Solvent control
[d] Positive control
[e] Significance of micronucleated PCEs/1,000 PCEs tested by the one-tailed trend test; significant at P#0.025 (ILS, 1990)

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine[a]

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male						
Hematology						
n						
Day 5	10	9	10	10	10	10
Day 20	10	10	10	10	10	9
Week 13	10	10	10	10	10	10
Automated hematocrit (%)						
Day 5	46.8 ± 0.3	47.3 ± 0.5	48.1 ± 0.4*	47.9 ± 0.5*	47.9 ± 0.5	49.6 ± 0.4**
Day 20	49.6 ± 0.4	50.4 ± 0.3	48.2 ± 0.6	47.9 ± 0.3**	47.8 ± 0.4**	45.0 ± 0.4**
Week 13	46.9 ± 0.5	46.4 ± 0.3	46.8 ± 0.2	46.1 ± 0.3	45.9 ± 0.3	44.4 ± 0.7**
Manual hematocrit (%)						
Day 5	44.2 ± 0.3	44.7 ± 0.6	45.2 ± 0.3*	45.4 ± 0.5	45.5 ± 0.6	46.5 ± 0.5**
Day 20	48.0 ± 0.3	49.1 ± 0.6	46.6 ± 0.5	46.3 ± 0.5	46.5 ± 0.5*	43.3 ± 0.5**
Week 13	45.7 ± 0.5	44.8 ± 0.4	45.6 ± 0.4	44.7 ± 0.2	44.3 ± 0.4*	42.7 ± 0.7**
Hemoglobin (g/dL)						
Day 5	15.3 ± 0.1	15.4 ± 0.1	15.6 ± 0.1	15.7 ± 0.1	15.8 ± 0.1**	16.0 ± 0.2**
Day 20	16.3 ± 0.2	16.6 ± 0.1	15.7 ± 0.2	15.6 ± 0.1**	15.7 ± 0.1*	14.8 ± 0.2**
Week 13	15.4 ± 0.2	15.2 ± 0.1	15.3 ± 0.1	15.0 ± 0.2	14.9 ± 0.1*	14.3 ± 0.2**
Erythrocytes (10^6/µL)						
Day 5	8.40 ± 0.07	8.41 ± 0.13	8.54 ± 0.08	8.54 ± 0.07	8.58 ± 0.10	8.79 ± 0.08**
Day 20	8.92 ± 0.07	9.07 ± 0.07	8.62 ± 0.11	8.62 ± 0.07*	8.66 ± 0.10	8.27 ± 0.13**
Week 13	9.09 ± 0.11	9.00 ± 0.07	9.12 ± 0.05	8.88 ± 0.07	8.87 ± 0.09	8.52 ± 0.20*
Reticulocytes (10^6/µL)						
Day 5	0.18 ± 0.03	0.26 ± 0.05	0.20 ± 0.01	0.15 ± 0.02	0.15 ± 0.01	0.15 ± 0.01
Day 20	0.18 ± 0.02	0.17 ± 0.02	0.18 ± 0.01	0.20 ± 0.01	0.19 ± 0.02	0.16 ± 0.01
Week 13	0.17 ± 0.01	0.18 ± 0.02	0.19 ± 0.02	0.19 ± 0.02	0.19 ± 0.01	0.19 ± 0.02
Nucleated erythrocytes (10^3/µL)						
Day 5	0.01 ± 0.01	0.04 ± 0.02	0.00 ± 0.00	0.02 ± 0.02	0.04 ± 0.02	0.00 ± 0.00
Day 20	0.00 ± 0.00	0.03 ± 0.02	0.01 ± 0.01	0.05 ± 0.02*	0.02 ± 0.01	0.03 ± 0.02
Week 13	0.02 ± 0.01	0.04 ± 0.02	0.03 ± 0.02	0.01 ± 0.01	0.01 ± 0.01	0.06 ± 0.02
Mean cell volume (fL)						
Day 5	55.8 ± 0.3	56.3 ± 0.4	56.4 ± 0.3	56.2 ± 0.3	55.9 ± 0.3	56.6 ± 0.2
Day 20	55.5 ± 0.2	55.5 ± 0.4	55.8 ± 0.3	55.5 ± 0.3	55.3 ± 0.4	54.6 ± 0.5
Week 13	51.6 ± 0.2	51.5 ± 0.2	51.4 ± 0.2	52.0 ± 0.3	51.8 ± 0.5	52.3 ± 0.7
Mean cell hemoglobin (pg)						
Day 5	18.3 ± 0.1	18.3 ± 0.1	18.3 ± 0.1	18.3 ± 0.1	18.5 ± 0.1	18.2 ± 0.1
Day 20	18.3 ± 0.1	18.3 ± 0.1	18.3 ± 0.1	18.1 ± 0.1	18.1 ± 0.1	17.9 ± 0.1*
Week 13	17.0 ± 0.1	16.9 ± 0.1	16.8 ± 0.1	16.8 ± 0.1	16.8 ± 0.2	16.9 ± 0.2
Mean cell hemoglobin concentration (g/dL)						
Day 5	32.8 ± 0.2	32.4 ± 0.1	32.5 ± 0.1	32.7 ± 0.1	33.1 ± 0.2	32.3 ± 0.2
Day 20	32.8 ± 0.2	33.0 ± 0.2	32.6 ± 0.2	32.7 ± 0.2	32.8 ± 0.2	32.9 ± 0.2
Week 13	32.8 ± 0.1	32.9 ± 0.1	32.7 ± 0.1	32.4 ± 0.2	32.5 ± 0.1*	32.3 ± 0.1**
Platelets (10^3/µL)						
Day 5	908.7 ± 26.6	973.1 ± 33.9	957.3 ± 23.1	924.4 ± 27.9	880.7 ± 21.4	937.0 ± 19.9
Day 20	856.9 ± 12.1	902.3 ± 31.3	880.4 ± 22.8	917.8 ± 15.1*	1,065.7 ± 39.8**	949.0 ± 28.2**
Week 13	731.0 ± 26.3	711.2 ± 12.1	732.3 ± 15.5	760.1 ± 15.5	791.8 ± 42.0*	869.5 ± 65.4*
Leukocytes (10^3/µL)						
Day 5	10.82 ± 0.44	11.72 ± 0.45	11.25 ± 0.43	10.36 ± 0.40	10.19 ± 0.45	10.82 ± 0.42
Day 20	9.31 ± 0.42	11.48 ± 0.49*	8.83 ± 0.22	9.32 ± 0.34	9.62 ± 0.51	9.42 ± 0.49
Week 13	9.46 ± 0.43	10.24 ± 0.31	9.93 ± 0.50	9.96 ± 0.37	10.24 ± 0.49	11.26 ± 0.56
Segmented neutrophils (10^3/µL)						
Day 5	1.84 ± 0.14	1.66 ± 0.13	1.47 ± 0.16	1.60 ± 0.13	1.45 ± 0.13	1.77 ± 0.23
Day 20	1.45 ± 0.15	1.68 ± 0.17	1.08 ± 0.13	1.28 ± 0.10	1.54 ± 0.22	1.00 ± 0.09
Week 13	2.01 ± 0.20	1.84 ± 0.14	1.64 ± 0.21	1.78 ± 0.23	1.90 ± 0.16	2.16 ± 0.29

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male (continued)						
Hematology (continued)						
n						
Day 5	10	9	10	10	10	10
Day 20	10	10	10	10	10	9
Week 13	10	10	10	10	10	10
Lymphocytes (10^3/μL)						
Day 5	8.84 ± 0.39	9.95 ± 0.44	9.73 ± 0.46	8.61 ± 0.36	8.66 ± 0.39	9.02 ± 0.34
Day 20	7.80 ± 0.32	9.73 ± 0.49*	7.68 ± 0.27	8.00 ± 0.37	7.99 ± 0.48	8.32 ± 0.45
Week 13	7.40 ± 0.37	8.37 ± 0.28	8.25 ± 0.48	8.15 ± 0.41	8.27 ± 0.51	9.03 ± 0.44*
Monocytes (10^3/μL)						
Day 5	0.11 ± 0.04	0.05 ± 0.02	0.05 ± 0.02	0.09 ± 0.04	0.05 ± 0.02	0.01 ± 0.01
Day 20	0.05 ± 0.02	0.03 ± 0.02	0.04 ± 0.02	0.01 ± 0.01	0.03 ± 0.01	0.06 ± 0.02
Week 13	0.02 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.03 ± 0.02	0.05 ± 0.04
Basophils (10^3/μL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 20	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 13	0.000 ± 0.000	0.011 ± 0.011	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)						
Day 5	0.02 ± 0.01	0.06 ± 0.03	0.01 ± 0.01	0.06 ± 0.03	0.03 ± 0.02	0.03 ± 0.02
Day 20	0.01 ± 0.01	0.04 ± 0.02	0.04 ± 0.01	0.03 ± 0.02	0.06 ± 0.02	0.04 ± 0.02
Week 13	0.02 ± 0.02	0.01 ± 0.01	0.02 ± 0.01	0.02 ± 0.02	0.05 ± 0.02	0.02 ± 0.01
Clinical Chemistry						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	9
Week 13	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 5	23.1 ± 0.7	24.1 ± 0.8	25.5 ± 0.7	25.9 ± 0.9	24.1 ± 0.8	23.8 ± 0.8
Day 20	24.3 ± 0.6	22.8 ± 0.6	23.9 ± 0.5	24.8 ± 0.4	23.2 ± 0.5	25.0 ± 0.5
Week 13	25.1 ± 0.4	23.1 ± 0.7	23.9 ± 0.6	23.9 ± 0.7	25.0 ± 1.0	25.3 ± 1.1
Creatinine (mg/dL)						
Day 5	0.49 ± 0.01	0.51 ± 0.02	0.53 ± 0.02	0.49 ± 0.01	0.51 ± 0.01	0.50 ± 0.01
Day 20	0.61 ± 0.03	0.56 ± 0.03	0.59 ± 0.02	0.60 ± 0.02	0.60 ± 0.03	0.61 ± 0.02
Week 13	0.59 ± 0.02	0.55 ± 0.03	0.60 ± 0.03	0.60 ± 0.04	0.59 ± 0.03	0.64 ± 0.03
Total protein (g/dL)						
Day 5	6.3 ± 0.1	6.4 ± 0.1	6.6 ± 0.1	6.5 ± 0.1	6.4 ± 0.1	6.3 ± 0.1
Day 20	6.8 ± 0.1	7.0 ± 0.1	7.1 ± 0.1	7.1 ± 0.1	7.1 ± 0.1	7.1 ± 0.1
Week 13	6.4 ± 0.1	6.5 ± 0.1	6.8 ± 0.1*	6.9 ± 0.1**	7.1 ± 0.1**	6.8 ± 0.1**
Albumin (g/dL)						
Day 5	3.5 ± 0.1	3.6 ± 0.1	3.8 ± 0.1*	3.7 ± 0.1*	3.6 ± 0.1	3.6 ± 0.1
Day 20	3.8 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	4.1 ± 0.1**	3.9 ± 0.1
Week 13	3.5 ± 0.1	3.6 ± 0.1	3.9 ± 0.1**	3.8 ± 0.0**	4.0 ± 0.0**	3.9 ± 0.1**
Alanine aminotransferase (IU/L)						
Day 5	42 ± 2	46 ± 1	51 ± 1**	47 ± 1	60 ± 11	46 ± 1
Day 20	53 ± 3	44 ± 3	40 ± 1*	39 ± 2**	49 ± 6	54 ± 6
Week 13	60 ± 2	56 ± 4	52 ± 5	44 ± 2*	50 ± 3	583 ± 268
Alkaline phosphatase (IU/L)						
Day 5	441 ± 15	468 ± 8	454 ± 16	423 ± 9	465 ± 10	456 ± 10
Day 20	411 ± 11	302 ± 12**	385 ± 14**	320 ± 14**	275 ± 21**	331 ± 10**
Week 13	236 ± 6	219 ± 4	223 ± 6	203 ± 3*	176 ± 8**	278 ± 25

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male (continued)						
Clinical Chemistry (continued)						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	9
Week 13	10	10	10	10	10	10
Creatine kinase (U/L)						
Day 5	275 ± 63	260 ± 66	262 ± 43	183 ± 17	244 ± 33[b]	193 ± 21
Day 20	169 ± 14[b]	241 ± 31[b]	167 ± 14	198 ± 20	180 ± 20	171 ± 28
Week 13	234 ± 62	243 ± 63	223 ± 58	202 ± 56	339 ± 115	161 ± 32[b]
Sorbitol dehydrogenase (IU/L)						
Day 5	8 ± 0	9 ± 0	10 ± 1*	9 ± 1	27 ± 17	11 ± 0**
Day 20	10 ± 0	8 ± 0	10 ± 1	10 ± 1	39 ± 13	23 ± 7
Week 13	12 ± 1	11 ± 1	10 ± 1	10 ± 1	12 ± 1	395 ± 217
Bile acids (μmol/L)						
Day 5	33.5 ± 4.0	34.7 ± 3.5	38.6 ± 7.5	26.6 ± 1.7	45.9 ± 7.3	40.6 ± 5.1
Day 20	28.3 ± 3.2	40.3 ± 3.7*	26.6 ± 3.7	30.3 ± 2.7	61.0 ± 6.1**	59.6 ± 7.6**
Week 13	30.5 ± 4.7	29.5 ± 4.2	26.0 ± 3.9	40.3 ± 7.7	62.1 ± 12.9*	150.0 ± 19.7**
Female						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	10
Week 13	10	10	10	10	10	8
Hematology						
Automated hematocrit (%)						
Day 5	48.4 ± 0.5	48.9 ± 0.5	50.3 ± 0.6	48.6 ± 0.6	50.7 ± 0.7	50.5 ± 1.0
Day 20	48.2 ± 0.4	47.4 ± 0.5	47.8 ± 0.3	47.0 ± 0.5	45.5 ± 0.6**	48.2 ± 1.0
Week 13	46.5 ± 0.3	45.4 ± 0.3*	45.5 ± 0.3*	43.5 ± 0.5**	43.1 ± 0.3**	43.8 ± 0.4**
Manual hematocrit (%)						
Day 5	44.9 ± 0.7	45.5 ± 0.4	46.9 ± 0.4	45.5 ± 0.6	46.9 ± 0.5	47.0 ± 0.9
Day 20	46.7 ± 0.3	45.8 ± 0.6	46.3 ± 0.2	45.5 ± 0.4	44.4 ± 0.6*	47.4 ± 0.9
Week 13	44.8 ± 0.3	44.0 ± 0.3	44.0 ± 0.4	41.3 ± 0.8**	40.9 ± 0.4**	41.5 ± 0.5**
Hemoglobin (g/dL)						
Day 5	16.0 ± 0.1	16.0 ± 0.2	16.4 ± 0.1	15.9 ± 0.2	16.6 ± 0.2	16.5 ± 0.3
Day 20	16.6 ± 0.2	16.3 ± 0.1	16.3 ± 0.1	15.8 ± 0.1**	15.6 ± 0.2**	16.2 ± 0.3**
Week 13	15.8 ± 0.1	15.3 ± 0.1**	15.2 ± 0.1**	14.4 ± 0.2**	14.2 ± 0.1**	14.3 ± 0.1**
Erythrocytes (10^6/μL)						
Day 5	7.96 ± 0.07	7.97 ± 0.11	8.19 ± 0.11	7.86 ± 0.09	8.30 ± 0.11	8.18 ± 0.21
Day 20	8.25 ± 0.09	8.06 ± 0.08	8.14 ± 0.07	7.92 ± 0.10	7.85 ± 0.09	8.43 ± 0.18
Week 13	8.66 ± 0.06	8.43 ± 0.04**	8.40 ± 0.11*	7.94 ± 0.11**	7.93 ± 0.10**	8.17 ± 0.11**
Reticulocytes (10^6/μL)						
Day 5	0.18 ± 0.02	0.17 ± 0.01	0.18 ± 0.02	0.13 ± 0.01	0.19 ± 0.02	0.16 ± 0.01
Day 20	0.16 ± 0.01	0.16 ± 0.02	0.16 ± 0.01	0.18 ± 0.01	0.17 ± 0.02	0.17 ± 0.01
Week 13	0.15 ± 0.01	0.15 ± 0.01	0.15 ± 0.01	0.15 ± 0.01	0.15 ± 0.01	0.17 ± 0.01
Nucleated erythrocytes (10^3/μL)						
Day 5	0.03 ± 0.03	0.05 ± 0.02	0.04 ± 0.03	0.06 ± 0.02	0.04 ± 0.02	0.04 ± 0.03
Day 20	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01
Week 13	0.00 ± 0.00	0.00 ± 0.00	0.03 ± 0.01	0.03 ± 0.02	0.01 ± 0.01	0.00 ± 0.00

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Female (continued)						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	10
Week 13	10	10	10	10	10	8
Hematology (continued)						
Mean cell volume (fL)						
Day 5	60.9 ± 0.4	61.6 ± 0.5	61.6 ± 0.3	61.7 ± 0.4	61.3 ± 0.3	61.7 ± 0.7
Day 20	58.4 ± 0.4	58.7 ± 0.3	58.7 ± 0.3	59.4 ± 0.5	58.0 ± 0.3	57.3 ± 0.4
Week 13	53.7 ± 0.2	54.0 ± 0.1	54.2 ± 0.6	54.2 ± 0.2	54.4 ± 0.4	53.6 ± 0.3
Mean cell hemoglobin (pg)						
Day 5	20.1 ± 0.2	20.1 ± 0.2	20.1 ± 0.2	20.2 ± 0.2	20.0 ± 0.1	20.2 ± 0.2[b]
Day 20	20.1 ± 0.1	20.2 ± 0.1	20.0 ± 0.1	19.9 ± 0.1	19.8 ± 0.1	19.3 ± 0.1**
Week 13	18.2 ± 0.1	18.1 ± 0.1	18.2 ± 0.2	18.2 ± 0.2	18.0 ± 0.2**	17.5 ± 0.2**
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.1 ± 0.2	32.7 ± 0.1	32.7 ± 0.3	32.7 ± 0.3	32.7 ± 0.2	32.7 ± 0.2
Day 20	34.4 ± 0.2	34.4 ± 0.2	34.0 ± 0.2	33.7 ± 0.2	34.2 ± 0.3	33.7 ± 0.2*
Week 13	34.0 ± 0.1	33.7 ± 0.2	33.5 ± 0.1*	33.1 ± 0.2**	33.0 ± 0.1**	32.7 ± 0.2**
Platelets (10^3/µL)						
Day 5	941.7 ± 30.3	885.4 ± 26.5	971.4 ± 26.3	906.8 ± 11.8[b]	863.3 ± 21.2	857.5 ± 61.5
Day 20	930.8 ± 22.3	885.0 ± 28.0	884.6 ± 44.3	982.5 ± 23.9	919.7 ± 16.9	812.6 ± 61.7
Week 13	721.5 ± 17.2	741.0 ± 9.5	729.4 ± 32.6	738.5 ± 38.4	759.2 ± 36.4	751.3 ± 45.7
Leukocytes (10^3/µL)						
Day 5	10.19 ± 0.41	9.35 ± 0.34	8.84 ± 0.35	8.67 ± 0.26	8.97 ± 0.50	8.36 ± 0.56*
Day 20	9.54 ± 0.29	9.60 ± 0.34	9.15 ± 0.42	9.41 ± 0.32	9.05 ± 0.35	8.95 ± 0.43
Week 13	8.01 ± 0.32	8.38 ± 0.18	8.35 ± 0.23	7.93 ± 0.47	8.89 ± 0.28	8.70 ± 0.49
Segmented neutrophils (10^3/µL)						
Day 5	1.18 ± 0.18	1.48 ± 0.22	1.17 ± 0.13	0.98 ± 0.12	1.20 ± 0.23	1.15 ± 0.17
Day 20	1.31 ± 0.14	1.49 ± 0.19	1.32 ± 0.13	1.44 ± 0.17	1.41 ± 0.17	1.87 ± 0.25
Week 13	1.55 ± 0.15	1.48 ± 0.18	1.42 ± 0.09	1.39 ± 0.14	1.62 ± 0.19	1.27 ± 0.16
Lymphocytes (10^3/µL)						
Day 5	8.89 ± 0.42	7.81 ± 0.43	7.61 ± 0.41	7.64 ± 0.28	7.93 ± 0.52	7.14 ± 0.62
Day 20	8.18 ± 0.32	8.06 ± 0.42	7.75 ± 0.46	7.82 ± 0.26	7.54 ± 0.36	6.99 ± 0.48
Week 13	6.41 ± 0.23	6.87 ± 0.23	6.86 ± 0.24	6.42 ± 0.41	7.20 ± 0.28	7.40 ± 0.48
Monocytes (10^3/µL)						
Day 5	0.11 ± 0.04	0.03 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.01	0.03 ± 0.01
Day 20	0.05 ± 0.02	0.04 ± 0.03	0.04 ± 0.02	0.11 ± 0.03	0.08 ± 0.04	0.07 ± 0.04
Week 13	0.04 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.04 ± 0.02	0.04 ± 0.02	0.01 ± 0.01
Basophils (10^3/µL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 20	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 13	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/µL)						
Day 5	0.01 ± 0.01	0.03 ± 0.02	0.03 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.05 ± 0.03
Day 20	0.01 ± 0.01	0.01 ± 0.01	0.04 ± 0.03	0.04 ± 0.02	0.02 ± 0.01	0.03 ± 0.02
Week 13	0.02 ± 0.01	0.03 ± 0.01	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.01	0.03 ± 0.02

TABLE G1
Hematology and Clinical Chemistry Data for F344/N Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Female (continued)						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	10
Week 13	10	10	10	10	10	8
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 5	20.9 ± 1.0	21.2 ± 2.0	20.6 ± 0.8	20.3 ± 1.0	24.0 ± 1.0	22.9 ± 0.7
Day 20	21.5 ± 0.7	22.0 ± 1.3	22.1 ± 1.1	22.6 ± 0.6	22.0 ± 0.6	25.9 ± 1.4
Week 13	21.0 ± 0.8	20.4 ± 0.8	21.5 ± 1.2	18.3 ± 0.6	19.8 ± 0.7	23.4 ± 1.3
Creatinine (mg/dL)						
Day 5	0.55 ± 0.02	0.55 ± 0.03	0.51 ± 0.01	0.52 ± 0.03	0.58 ± 0.01	0.56 ± 0.02
Day 20	0.58 ± 0.02	0.56 ± 0.03	0.61 ± 0.02	0.56 ± 0.03	0.57 ± 0.02	0.59 ± 0.02[b]
Week 13	0.62 ± 0.02	0.60 ± 0.01	0.63 ± 0.03	0.61 ± 0.02	0.60 ± 0.03	0.61 ± 0.05
Total protein (g/dL)						
Day 5	6.0 ± 0.1	6.2 ± 0.1	6.7 ± 0.0**	6.2 ± 0.1	6.5 ± 0.1**	6.0 ± 0.1
Day 20	6.4 ± 0.1	6.6 ± 0.1	6.5 ± 0.1	6.8 ± 0.1*	6.9 ± 0.1**	6.8 ± 0.1**
Week 13	6.8 ± 0.1	6.6 ± 0.1	6.7 ± 0.1	6.8 ± 0.1	7.0 ± 0.1	6.7 ± 0.1
Albumin (g/dL)						
Day 5	3.7 ± 0.0	3.7 ± 0.1	4.0 ± 0.1**	3.7 ± 0.1	3.9 ± 0.1*	3.8 ± 0.1
Day 20	3.5 ± 0.1	3.6 ± 0.1	3.7 ± 0.1	3.8 ± 0.1**	4.1 ± 0.1**	4.0 ± 0.1**
Week 13	3.9 ± 0.1	3.9 ± 0.0	4.0 ± 0.1	4.0 ± 0.1	4.0 ± 0.1	4.0 ± 0.1
Alanine aminotransferase (IU/L)						
Day 5	36 ± 1	34 ± 1	33 ± 1	35 ± 2	45 ± 5	432 ± 294
Day 20	35 ± 1	33 ± 2	30 ± 1	28 ± 1*	29 ± 2*	1,295 ± 1,133
Week 13	40 ± 1	31 ± 2**	33 ± 2*	30 ± 1**	30 ± 1**	141 ± 72
Alkaline phosphatase (IU/L)						
Day 5	419 ± 7	375 ± 11*	367 ± 7**	368 ± 8**	405 ± 10	410 ± 12
Day 20	357 ± 8	328 ± 5**	315 ± 7**	287 ± 3**	283 ± 6**	314 ± 18**
Week 13	210 ± 5	193 ± 5	176 ± 4**	162 ± 7**	168 ± 5**	209 ± 17**
Creatine kinase (IU/L)						
Day 5	195 ± 28	230 ± 43	257 ± 22	207 ± 21[b]	300 ± 27**	288 ± 39*
Day 20	266 ± 74	222 ± 53	208 ± 45	175 ± 38	143 ± 9	144 ± 15[b]
Week 13	169 ± 23	119 ± 19	187 ± 42	210 ± 40	159 ± 20	240 ± 70
Sorbitol dehydrogenase (IU/L)						
Day 5	8 ± 1	7 ± 0	6 ± 1	7 ± 0	39 ± 20	111 ± 91
Day 20	8 ± 1	9 ± 1	10 ± 0	10 ± 0	17 ± 6**	383 ± 162**[b]
Week 13	8 ± 0	9 ± 0	8 ± 1	9 ± 1	10 ± 1	289 ± 204**
Bile acids (μmol/L)						
Day 5	32.3 ± 3.4	28.3 ± 5.1	20.9 ± 2.8	43.0 ± 5.9	39.3 ± 11.2	69.2 ± 25.7
Day 20	34.1 ± 3.9	37.0 ± 5.9	41.1 ± 6.1	40.0 ± 8.9	55.0 ± 4.9*	202.0 ± 114.1**
Week 13	47.3 ± 9.8	39.5 ± 4.9	38.0 ± 5.6	38.9 ± 4.6	54.5 ± 7.9	87.3 ± 21.8

* Significantly different (P#0.05) from the control group by Dunn's or Shirley's test
** P#0.01
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9

TABLE G2
Hematology and Clinical Chemistry Data for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine[a]

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Hematology						
n						
Day 5	10	10	10	10	10	10
Day 20	10	9	9	9	10	10
Week 13	10	10	10	10	9	10
Automated hematocrit (%)						
Day 5	40.7 ± 0.4	40.1 ± 0.7	41.0 ± 0.5	41.5 ± 0.6	45.6 ± 0.7**	45.0 ± 1.0**
Day 20	43.0 ± 0.5	43.0 ± 0.7	42.6 ± 0.8	43.1 ± 0.5	42.9 ± 0.3	44.2 ± 0.9
Week 13	45.0 ± 0.5	45.3 ± 0.7	45.4 ± 0.3	46.2 ± 0.7	46.0 ± 0.3	44.6 ± 0.7
Manual hematocrit (%)						
Day 5	39.3 ± 0.4	38.6 ± 0.9	39.8 ± 0.5	40.1 ± 0.7	44.2 ± 0.8**	43.4 ± 1.0**
Day 20	41.3 ± 0.6	42.7 ± 0.7	41.8 ± 0.8	42.2 ± 0.5	41.3 ± 0.4	43.5 ± 1.0
Week 13	43.5 ± 0.6	44.0 ± 0.6	44.2 ± 0.2	44.7 ± 0.6	44.4 ± 0.4	43.4 ± 0.6
Hemoglobin (g/dL)						
Day 5	13.3 ± 0.1	13.1 ± 0.2	13.5 ± 0.2	13.7 ± 0.2	15.1 ± 0.2**	14.8 ± 0.3**
Day 20	14.3 ± 0.2	14.2 ± 0.2	14.0 ± 0.2	14.1 ± 0.2	14.0 ± 0.1	14.6 ± 0.3
Week 13	15.1 ± 0.2	15.2 ± 0.2	15.2 ± 0.1	15.5 ± 0.1	15.3 ± 0.1	14.8 ± 0.2
Erythrocytes (10^6/µL)						
Day 5	6.43 ± 0.07	6.35 ± 0.10	6.43 ± 0.09	6.62 ± 0.08	7.34 ± 0.16**	7.13 ± 0.17**
Day 20	6.99 ± 0.12	6.94 ± 0.10	6.90 ± 0.12	7.04 ± 0.10	7.07 ± 0.09	7.36 ± 0.13
Week 13	8.52 ± 0.14	8.59 ± 0.17	8.71 ± 0.12	8.61 ± 0.14	8.64 ± 0.12	8.42 ± 0.10
Reticulocytes (10^6/µL)						
Day 5	0.27 ± 0.02	0.29 ± 0.03	0.29 ± 0.02	0.32 ± 0.02	0.27 ± 0.02	0.26 ± 0.02
Day 20	0.21 ± 0.01	0.21 ± 0.01	0.18 ± 0.01	0.19 ± 0.01	0.22 ± 0.02	0.23 ± 0.01
Week 13	0.13 ± 0.01	0.15 ± 0.01	0.14 ± 0.01	0.16 ± 0.01	0.18 ± 0.02	0.15 ± 0.01
Nucleated erythrocytes (10^3/µL)						
Day 5	0.06 ± 0.02	0.02 ± 0.01	0.04 ± 0.02	0.01 ± 0.01*	0.02 ± 0.01	0.02 ± 0.01
Day 20	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.01	0.03 ± 0.02	0.03 ± 0.02	0.01 ± 0.01
Week 13	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.03 ± 0.02	0.04 ± 0.02
Mean cell volume (fL)						
Day 5	63.5 ± 0.6	63.2 ± 0.7	63.9 ± 0.7	62.6 ± 0.6	62.2 ± 0.5	63.2 ± 0.7
Day 20	61.7 ± 0.7	62.1 ± 0.9	61.8 ± 0.7	61.4 ± 0.6	60.7 ± 0.4	60.2 ± 0.5
Week 13	52.9 ± 0.6	52.9 ± 0.5	52.4 ± 0.5	53.8 ± 0.6	53.3 ± 0.7	53.2 ± 0.5
Mean cell hemoglobin (pg)						
Day 5	20.8 ± 0.2	20.7 ± 0.2	21.0 ± 0.2	20.6 ± 0.2	20.6 ± 0.2	20.8 ± 0.2
Day 20	20.4 ± 0.2	20.5 ± 0.2	20.4 ± 0.2	20.1 ± 0.2	19.8 ± 0.2	19.8 ± 0.2*
Week 13	17.7 ± 0.3	17.7 ± 0.2	17.5 ± 0.2	18.0 ± 0.2	17.7 ± 0.2	17.6 ± 0.2
Mean cell hemoglobin concentration (g/dL)						
Day 5	32.8 ± 0.1	32.7 ± 0.1	32.9 ± 0.2	32.9 ± 0.2	33.1 ± 0.2	32.9 ± 0.1
Day 20	33.2 ± 0.2	33.1 ± 0.3	33.0 ± 0.2	32.8 ± 0.2	32.7 ± 0.1	33.0 ± 0.1
Week 13	33.5 ± 0.2	33.6 ± 0.1	33.5 ± 0.2	33.5 ± 0.2	33.3 ± 0.2	33.3 ± 0.1
Platelets (10^3/µL)						
Day 5	1,356.5 ± 55.6	1,361.6 ± 46.8	1,398.8 ± 66.0	1,297.1 ± 70.9	1,364.3 ± 50.5	1,421.5 ± 75.1
Day 20	1,227.3 ± 39.0	1,227.0 ± 49.9	1,225.9 ± 46.1	1,177.4 ± 67.6	1,207.3 ± 52.1	1,258.0 ± 78.4
Week 13	1,055.2 ± 89.2	993.1 ± 57.2	1,012.2 ± 53.8	1,040.8 ± 55.8	1,232.1 ± 62.4	1,047.6 ± 72.7
Leukocytes (10^3/µL)						
Day 5	9.82 ± 0.56	11.44 ± 0.45	9.11 ± 0.94	9.29 ± 0.61	8.98 ± 0.32	9.05 ± 0.84
Day 20	10.09 ± 0.61	12.41 ± 0.53	10.14 ± 0.87	9.52 ± 0.35	10.16 ± 0.78	11.15 ± 0.92
Week 13	9.81 ± 0.77	10.67 ± 0.88	9.89 ± 0.61	10.45 ± 0.43	11.38 ± 0.47	10.81 ± 0.87
Segmented neutrophils (10^3/µL)						
Day 5	1.34 ± 0.17	1.98 ± 0.27	1.39 ± 0.21	1.47 ± 0.20	1.52 ± 0.14	1.26 ± 0.16
Day 20	1.46 ± 0.19	1.84 ± 0.24	1.54 ± 0.14	1.29 ± 0.17	1.55 ± 0.15	2.02 ± 0.34
Week 13	1.66 ± 0.17	1.52 ± 0.16	1.55 ± 0.21	1.71 ± 0.14	2.08 ± 0.19	1.67 ± 0.21

TABLE G2
Hematology and Clinical Chemistry Data for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Hematology (continued)						
n						
Day 5	10	10	10	10	10	10
Day 20	10	9	9	9	10	10
Week 13	10	10	10	10	9	10
Lymphocytes (10^3/μL)						
Day 5	8.41 ± 0.49	9.32 ± 0.35	7.64 ± 0.78	7.70 ± 0.51	7.38 ± 0.34	7.69 ± 0.86
Day 20	8.52 ± 0.60	10.48 ± 0.62	8.51 ± 0.80	8.13 ± 0.37	8.50 ± 0.66	9.01 ± 0.74
Week 13	8.06 ± 0.72	9.06 ± 0.79	8.24 ± 0.70	8.63 ± 0.42	9.19 ± 0.50	9.05 ± 0.81
Monocytes (10^3/μL)						
Day 5	0.04 ± 0.02	0.08 ± 0.03	0.05 ± 0.03	0.09 ± 0.03	0.03 ± 0.01	0.04 ± 0.02
Day 20	0.08 ± 0.03	0.08 ± 0.03	0.07 ± 0.02	0.07 ± 0.02	0.05 ± 0.02	0.09 ± 0.02
Week 13	0.03 ± 0.02	0.05 ± 0.03	0.03 ± 0.02	0.03 ± 0.02	0.06 ± 0.03	0.07 ± 0.02
Basophils (10^3/μL)						
Day 5	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 20	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 13	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/μL)						
Day 5	0.03 ± 0.02	0.06 ± 0.03	0.03 ± 0.02	0.03 ± 0.03	0.05 ± 0.02	0.06 ± 0.03
Day 20	0.03 ± 0.02	0.01 ± 0.01	0.03 ± 0.02	0.03 ± 0.02	0.06 ± 0.03	0.04 ± 0.02
Week 13	0.06 ± 0.02	0.05 ± 0.02	0.07 ± 0.03	0.09 ± 0.04	0.05 ± 0.03	0.02 ± 0.01
Clinical Chemistry						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	10
Week 13	10	10	10	10	9	10
Urea nitrogen (mg/dL)						
Day 5	19.9 ± 0.8	19.4 ± 0.6	18.4 ± 1.0	18.9 ± 1.0	23.1 ± 1.1*	25.2 ± 1.3**
Day 20	23.3 ± 0.9	24.5 ± 0.5	22.7 ± 0.6	25.6 ± 1.0	25.8 ± 0.6*	28.0 ± 1.1**
Week 13	28.1 ± 0.8	27.5 ± 0.9	27.0 ± 1.0	26.8 ± 1.7	31.2 ± 1.8	29.7 ± 2.3
Creatinine (mg/dL)						
Day 5	0.50 ± 0.03	0.52 ± 0.02	0.46 ± 0.02	0.48 ± 0.02	0.53 ± 0.03	0.52 ± 0.01
Day 20	0.54 ± 0.02	0.53 ± 0.02	0.54 ± 0.02	0.53 ± 0.05	0.57 ± 0.02	0.57 ± 0.04
Week 13	0.62 ± 0.04	0.68 ± 0.02	0.68 ± 0.02	0.72 ± 0.03	0.74 ± 0.04	0.67 ± 0.03
Total protein (g/dL)						
Day 5	5.9 ± 0.1	5.8 ± 0.1	5.8 ± 0.1	5.9 ± 0.1	5.8 ± 0.1	6.1 ± 0.2
Day 20	6.5 ± 0.1	6.7 ± 0.1	6.4 ± 0.1	6.8 ± 0.1	6.7 ± 0.1	6.7 ± 0.1
Week 13	6.6 ± 0.1	6.7 ± 0.1	6.7 ± 0.1	7.0 ± 0.1	6.9 ± 0.1	6.6 ± 0.1
Albumin (g/dL)						
Day 5	3.0 ± 0.0	3.2 ± 0.1	3.1 ± 0.0	3.2 ± 0.1	3.2 ± 0.1	3.3 ± 0.1*
Day 20	3.3 ± 0.1	3.4 ± 0.1	3.3 ± 0.1	3.5 ± 0.0	3.4 ± 0.1	3.4 ± 0.1
Week 13	3.6 ± 0.1	3.8 ± 0.1	3.8 ± 0.1	3.9 ± 0.1*	3.8 ± 0.1	3.8 ± 0.1
Alanine aminotransferase (IU/L)						
Day 5	52 ± 2	53 ± 2	52 ± 2	53 ± 4	117 ± 30**	134 ± 74
Day 20	48 ± 2	43 ± 1	45 ± 2	45 ± 2	45 ± 2	299 ± 162
Week 13	54 ± 2	51 ± 4	50 ± 3	47 ± 3	146 ± 51	62 ± 11
Alkaline phosphatase (IU/L)						
Day 5	339 ± 13	343 ± 19	327 ± 20	303 ± 26	339 ± 29	378 ± 30
Day 20	294 ± 11	281 ± 21	268 ± 16	229 ± 16*	262 ± 19	288 ± 30
Week 13	179 ± 7	189 ± 8	160 ± 7	157 ± 6*	168 ± 18	143 ± 11*

TABLE G2
Hematology and Clinical Chemistry Data for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Clinical Chemistry (continued)						
n						
Day 5	10	10	10	10	10	10
Day 20	10	10	10	10	10	10
Week 13	10	10	10	10	9	10
Creatine kinase (U/L)						
Day 5	242 ± 23	211 ± 22	280 ± 31	255 ± 21	306 ± 35	291 ± 51
Day 20	223 ± 42	322 ± 69	345 ± 80	298 ± 56	333 ± 91	362 ± 99
Week 13	274 ± 65	454 ± 136	290 ± 45	272 ± 58	331 ± 64	309 ± 56
Sorbitol dehydrogenase (IU/L)						
Day 5	8 ± 1	8 ± 1	7 ± 1	7 ± 0	615 ± 179**	370 ± 289**
Day 20	7 ± 0	7 ± 1	7 ± 1	8 ± 1	9 ± 1	1,075 ± 605**
Week 13	7 ± 0	8 ± 1	7 ± 1	9 ± 1	253 ± 94**	49 ± 29**
Bile acids (µmol/L)						
Day 5	100.0 ± 14.8	77.4 ± 8.4	118.5 ± 12.6	119.1 ± 16.9	235.0 ± 44.4**	191.3 ± 27.9**
Day 20	70.2 ± 8.1	76.0 ± 8.4	98.0 ± 14.9	159.1 ± 41.2*	111.5 ± 23.3	172.4 ± 37.9*
Week 13	75.5 ± 13.9	66.7 ± 6.7	67.4 ± 6.3	64.1 ± 8.1	117.8 ± 24.9	116.3 ± 20.2

* Significantly different (P#0.05) from the control group by Dunn's or Shirley's test
** P#0.01
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

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

TABLE H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for F344/N Rats in the 13-Week Drinking Water Study of Pyridine[a]

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	335 ± 9	334 ± 7	337 ± 6	334 ± 7	316 ± 5	287 ± 5**
Heart						
Absolute	1.145 ± 0.034	1.187 ± 0.049	1.140 ± 0.038	1.140 ± 0.029	1.129 ± 0.059	1.159 ± 0.037
Relative	3.42 ± 0.08	3.56 ± 0.13	3.38 ± 0.08	3.42 ± 0.08	3.57 ± 0.17	4.04 ± 0.12**
R. Kidney						
Absolute	1.352 ± 0.037	1.333 ± 0.039	1.345 ± 0.032	1.398 ± 0.040	1.381 ± 0.026	1.396 ± 0.037
Relative	4.04 ± 0.05	3.99 ± 0.06	3.99 ± 0.05	4.18 ± 0.08	4.38 ± 0.08**	4.87 ± 0.08**
Liver						
Absolute	14.384 ± 0.601	14.901 ± 0.579	15.415 ± 0.429	16.091 ± 0.541*	16.535 ± 0.295*	15.512 ± 0.500*
Relative	42.81 ± 0.99	44.52 ± 0.77	45.75 ± 0.76*	48.07 ± 0.81**	52.41 ± 0.99**	54.06 ± 1.27**
Lung						
Absolute	1.837 ± 0.061	1.782 ± 0.048	1.791 ± 0.050	1.844 ± 0.077	1.747 ± 0.051	1.558 ± 0.053**
Relative	5.49 ± 0.16	5.36 ± 0.17	5.33 ± 0.17	5.51 ± 0.18	5.55 ± 0.20	5.43 ± 0.16
R. Testis						
Absolute	1.502 ± 0.026	1.474 ± 0.020	1.486 ± 0.025	1.502 ± 0.019	1.516 ± 0.013	1.437 ± 0.019
Relative	4.51 ± 0.15	4.43 ± 0.10	4.42 ± 0.08	4.50 ± 0.05	4.81 ± 0.07*	5.02 ± 0.08**
Thymus						
Absolute	0.320 ± 0.022	0.363 ± 0.031	0.352 ± 0.020	0.350 ± 0.018	0.362 ± 0.026	0.294 ± 0.023
Relative	0.95 ± 0.06	1.08 ± 0.07	1.04 ± 0.05	1.05 ± 0.04	1.15 ± 0.08	1.03 ± 0.08
Female						
n	10	10	10	10	10	8
Necropsy body wt	198 ± 3	196 ± 4	195 ± 2	197 ± 4	185 ± 2**	180 ± 3**
Heart						
Absolute	0.807 ± 0.033	0.752 ± 0.027	0.797 ± 0.030	0.786 ± 0.033	0.806 ± 0.029	0.767 ± 0.054
Relative	4.07 ± 0.16	3.83 ± 0.11	4.10 ± 0.17	3.99 ± 0.15	4.37 ± 0.18	4.26 ± 0.30
R. Kidney						
Absolute	0.752 ± 0.017	0.731 ± 0.018	0.741 ± 0.008	0.795 ± 0.012	0.774 ± 0.019	0.739 ± 0.024
Relative	3.80 ± 0.09	3.74 ± 0.10	3.81 ± 0.06	4.04 ± 0.05	4.19 ± 0.11**	4.10 ± 0.10*
Liver						
Absolute	6.866 ± 0.135	7.305 ± 0.133	7.874 ± 0.212**	8.732 ± 0.244**	9.391 ± 0.152**	9.619 ± 0.293**
Relative	34.68 ± 0.53	37.32 ± 0.76	40.46 ± 1.23**	44.30 ± 0.82**	50.80 ± 0.75**	53.44 ± 1.79**
Lung						
Absolute	1.277 ± 0.049	1.230 ± 0.048	1.253 ± 0.070	1.289 ± 0.059	1.290 ± 0.034	1.173 ± 0.022
Relative	6.46 ± 0.27	6.26 ± 0.15	6.45 ± 0.40	6.53 ± 0.22	6.98 ± 0.16	6.51 ± 0.07
Thymus						
Absolute	0.265 ± 0.011	0.295 ± 0.013	0.280 ± 0.008	0.305 ± 0.037	0.313 ± 0.034	0.252 ± 0.011
Relative	1.34 ± 0.06	1.50 ± 0.06	1.44 ± 0.04	1.54 ± 0.18	1.70 ± 0.19	1.39 ± 0.05

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

TABLE H2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine[a]

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
n	10	10	10	10	9	10
Necropsy body wt	490 ± 10	457 ± 12	469 ± 6	445 ± 17*	428 ± 8**	405 ± 15**
Heart						
Absolute	1.679 ± 0.043	1.730 ± 0.088	1.780 ± 0.051	1.712 ± 0.090	1.560 ± 0.081	1.513 ± 0.071
Relative	3.44 ± 0.09	3.78 ± 0.14	3.80 ± 0.13	3.84 ± 0.10	3.63 ± 0.13	3.74 ± 0.12
R. Kidney						
Absolute	1.948 ± 0.069	1.924 ± 0.061	2.004 ± 0.046	2.085 ± 0.079	2.041 ± 0.115	1.998 ± 0.114
Relative	3.98 ± 0.11	4.21 ± 0.09	4.27 ± 0.10	4.70 ± 0.13**	4.76 ± 0.21**	4.92 ± 0.19**
Liver						
Absolute	20.949 ± 0.624	21.152 ± 0.840	21.528 ± 0.608	21.706 ± 0.945	22.662 ± 1.098	21.367 ± 1.160
Relative	42.79 ± 0.98	46.33 ± 1.47	45.90 ± 1.25	48.78 ± 0.97**	52.77 ± 1.68**	52.60 ± 1.65**
Lung						
Absolute	2.534 ± 0.090	2.366 ± 0.129	2.429 ± 0.098	2.217 ± 0.104	2.133 ± 0.134	2.213 ± 0.111
Relative	5.22 ± 0.28	5.16 ± 0.20	5.20 ± 0.25	5.00 ± 0.19	4.97 ± 0.25	5.46 ± 0.19
R. Testis						
Absolute	1.737 ± 0.046	1.632 ± 0.074	1.843 ± 0.039	1.731 ± 0.051	1.939 ± 0.181	1.823 ± 0.085
Relative	3.56 ± 0.14	3.59 ± 0.17	3.93 ± 0.09	3.92 ± 0.12	4.50 ± 0.34**	4.52 ± 0.18**
Thymus						
Absolute	0.479 ± 0.039	0.501 ± 0.035	0.458 ± 0.026	0.499 ± 0.036	0.423 ± 0.029	0.507 ± 0.061
Relative	0.98 ± 0.08	1.11 ± 0.09	0.98 ± 0.06	1.12 ± 0.07	0.99 ± 0.06	1.23 ± 0.12

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

TABLE H3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Drinking Water Study of Pyridine[a]

	0 ppm	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male						
n	10	10	10	10	10	10
Necropsy body wt	38.9 ± 0.8	37.6 ± 1.1	38.8 ± 0.9	39.6 ± 1.2	38.8 ± 0.8	36.9 ± 0.7
Heart						
Absolute	0.199 ± 0.008	0.193 ± 0.010	0.211 ± 0.013	0.203 ± 0.010	0.188 ± 0.006	0.193 ± 0.008
Relative	5.12 ± 0.17	5.15 ± 0.26	5.41 ± 0.28	5.11 ± 0.19	4.85 ± 0.14	5.25 ± 0.19
R. Kidney						
Absolute	0.304 ± 0.007	0.291 ± 0.010	0.302 ± 0.016	0.293 ± 0.011	0.254 ± 0.009*	0.274 ± 0.008*
Relative	7.85 ± 0.24	7.76 ± 0.16	7.80 ± 0.43	7.41 ± 0.23	6.57 ± 0.26**	7.44 ± 0.24
Liver						
Absolute	1.855 ± 0.044	1.878 ± 0.048	2.058 ± 0.057*	2.177 ± 0.083**	2.264 ± 0.066**	2.249 ± 0.067**
Relative	47.81 ± 1.21	50.16 ± 1.06	53.08 ± 1.19**	54.85 ± 0.76**	58.36 ± 1.23**	60.96 ± 1.01**
Lung						
Absolute	0.281 ± 0.020	0.267 ± 0.017	0.293 ± 0.022	0.274 ± 0.018[b]	0.288 ± 0.017	0.269 ± 0.008
Relative	7.31 ± 0.66	7.13 ± 0.44	7.54 ± 0.48	6.85 ± 0.41[b]	7.46 ± 0.47	7.36 ± 0.33
R. Testis						
Absolute	0.125 ± 0.003	0.125 ± 0.004	0.127 ± 0.004	0.129 ± 0.004	0.123 ± 0.002	0.117 ± 0.004
Relative	3.22 ± 0.10	3.34 ± 0.07	3.27 ± 0.12	3.27 ± 0.10	3.18 ± 0.06	3.18 ± 0.12
Thymus						
Absolute	0.057 ± 0.007	0.059 ± 0.005	0.065 ± 0.007	0.057 ± 0.009	0.055 ± 0.005	0.047 ± 0.006
Relative	1.46 ± 0.17	1.59 ± 0.16	1.65 ± 0.17	1.42 ± 0.18	1.42 ± 0.13	1.28 ± 0.14
Female						
n	10	10	10	9	10	10
Necropsy body wt	33.0 ± 1.1	37.1 ± 1.1	33.9 ± 0.9	34.0 ± 1.1	32.9 ± 0.9	29.4 ± 0.9*
Heart						
Absolute	0.146 ± 0.007	0.157 ± 0.006	0.139 ± 0.003	0.134 ± 0.006	0.141 ± 0.006	0.129 ± 0.003*
Relative	4.45 ± 0.24	4.27 ± 0.21	4.13 ± 0.17	3.93 ± 0.10	4.28 ± 0.14	4.40 ± 0.12
R. Kidney						
Absolute	0.199 ± 0.006	0.219 ± 0.004	0.193 ± 0.010	0.203 ± 0.007	0.206 ± 0.004	0.204 ± 0.005
Relative	6.07 ± 0.14	5.94 ± 0.14	5.73 ± 0.32	5.97 ± 0.12	6.28 ± 0.14	6.98 ± 0.19**
Liver						
Absolute	1.513 ± 0.039	1.766 ± 0.039*	1.630 ± 0.044	1.743 ± 0.081*	1.836 ± 0.059**	1.609 ± 0.071
Relative	46.04 ± 1.09	47.80 ± 0.84	48.29 ± 1.67	51.04 ± 1.20**	55.71 ± 0.81**	54.69 ± 1.58**
Lung						
Absolute	0.263 ± 0.016	0.268 ± 0.015	0.224 ± 0.008	0.233 ± 0.009	0.252 ± 0.012	0.231 ± 0.012
Relative	7.98 ± 0.44	7.25 ± 0.41	6.60 ± 0.24*	6.90 ± 0.35	7.66 ± 0.32	7.91 ± 0.46
Thymus						
Absolute	0.062 ± 0.005	0.068 ± 0.004	0.060 ± 0.005	0.065 ± 0.005	0.056 ± 0.003	0.055 ± 0.003
Relative	1.87 ± 0.12	1.85 ± 0.12	1.78 ± 0.13	1.91 ± 0.15	1.72 ± 0.12	1.89 ± 0.10

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

APPENDIX I
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE I1
Summary of Reproductive Tissue Evaluations for Male F344/N Rats in the 13-Week Drinking Water Study of Pyridine[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	339 ± 9	334 ± 7	316 ± 5*	287 ± 5**
L. cauda epididymis	0.1834 ± 0.0057	0.1866 ± 0.0040	0.1939 ± 0.0039	0.1785 ± 0.0042
L. epididymis	0.4590 ± 0.0105	0.4529 ± 0.0037	0.4723 ± 0.0030	0.4201 ± 0.0068**
L. testis	1.5272 ± 0.0165	1.5036 ± 0.0181	1.5726 ± 0.0150	1.4368 ± 0.0125**
Spermatid measurements				
Spermatid heads (10^7/g testis)	11.29 ± 0.72[b]	10.86 ± 0.41[b]	10.87 ± 0.35	11.36 ± 0.37
Spermatid heads (10^7/testis)	17.29 ± 1.17[b]	16.31 ± 0.60[b]	17.07 ± 0.49	16.33 ± 0.58
Spermatid count (mean/10^{14} mL suspension)	86.47 ± 5.84[b]	81.53 ± 3.01[b]	85.33 ± 2.44	81.63 ± 2.88
Epididymal spermatozoal measurements				
Motility (%)	98.89 ± 0.19	98.96 ± 0.16	99.00 ± 0.13	98.87 ± 0.15
Concentration (10^6/g cauda epididymal tissue)	748 ± 34	733 ± 24	683 ± 18	714 ± 36

* Significantly different (P#0.05) from the control group by Williams' test
** Significantly different (P#0.01) from the control group by Williams' test (body weights) or Dunnett's test (epididymal and testis weights)
[a] Data are presented as mean ± standard error. Differences from the control group are not significant by Dunnett's test (caudal weight) or Dunn's test (spermatid and epididymal spermatozoal measurements).
[b] n=9

TABLE I2
Summary of Estrous Cycle Characterization for Female F344/N Rats in the 13-Week Drinking Water Study of Pyridine[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
n	10	10	10	8
Necropsy body wt (g)	198 ± 3	197 ± 4	185 ± 2**	180 ± 3**
Estrous cycle length (days)	5.00 ± 0.00[b]	5.00 ± 0.00	5.30 ± 0.30	6.08 ± 0.30**[c]
Estrous stages (% of cycle)				
Diestrus	42.5	45.8	40.8	54.2
Proestrus	13.3	16.7	16.7	12.5
Estrus	25.0	19.2	23.3	19.8
Metestrus	19.2	18.3	19.2	13.5

** Significantly different (P#0.01) from the control group by Williams' test (body weights) or Shirley's test (estrous cycle length)
[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. By multivariate analysis of variance, exposed females do not differ significantly from the control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.
[c] Estrous cycle was longer than 12 days or unclear in 2 of 8 animals.

TABLE I3
Summary of Reproductive Tissue Evaluations for Male Mice in the 13-Week Drinking Water Study of Pyridine[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
n	10	10	10	10
Weights (g)				
Necropsy body wt	38.9 ± 0.8	39.6 ± 1.2	38.8 ± 0.8	36.9 ± 0.7
L. cauda epididymis	0.0170 ± 0.0011	0.0166 ± 0.0006	0.0170 ± 0.0008	0.0155 ± 0.0008
L. epididymis	0.0453 ± 0.0018	0.0480 ± 0.0016	0.0449 ± 0.0017	0.0446 ± 0.0019
L. testis	0.1174 ± 0.0036	0.1181 ± 0.0034	0.1169 ± 0.0033	0.1088 ± 0.0044
Spermatid measurements				
Spermatid heads (10^7/g testis)	15.81 ± 0.62	13.37 ± 0.56	15.53 ± 1.05	14.73 ± 1.10
Spermatid heads (10^7/testis)	1.85 ± 0.09	1.57 ± 0.05*	1.80 ± 0.11	1.61 ± 0.14
Spermatid count (mean/10^{14} mL suspension)	57.90 ± 2.69	49.00 ± 1.69*	56.28 ± 3.37	50.45 ± 4.26
Epididymal spermatozoal measurements				
Motility (%)	99.31 ± 0.13	98.58 ± 0.12**	98.16 ± 0.26**	97.21 ± 0.42**
Concentration (10^6/g cauda epididymal tissue)	1,630 ± 126	1,432 ± 57	1,360 ± 54	1,461 ± 72

* Significantly different (P#0.05) from the control group by Dunn's test
** Significantly different (P#0.01) from the control group by Shirley's test
[a] Data are presented as mean ± standard error. Differences from the control group are not significant by Dunnett's test (body and tissue weights) or Dunn's test (spermatid heads per gram testis and epididymal spermatozoal concentration).

TABLE I4
Summary of Estrous Cycle Characterization for Female Mice in the 13-Week Drinking Water Study of Pyridine[a]

	0 ppm	250 ppm	500 ppm	1,000 ppm
n	10	9	10	10
Necropsy body wt (g)	33.0 ± 1.1	34.0 ± 1.1	32.9 ± 0.9	29.4 ± 0.9*
Estrous cycle length (days)	4.72 ± 0.55[b]	4.50 ± 0.16[c]	4.72 ± 0.22[b]	4.28 ± 0.15[b]
Estrous stages (% of cycle)				
Diestrus	36.7	35.2	31.7	31.7
Proestrus	20.0	13.9	17.5	20.0
Estrus	25.0	35.2	35.8	27.5
Metestrus	18.3	15.7	15.0	20.8

* Significantly different (P#0.05) from the control group by Dunnett's test
[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the control group for estrous cycle length are not significant by Dunn's test. By multivariate analysis of variance, exposed females do not differ significantly from the control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.
[c] Estrous cycle was longer than 12 days or unclear in 1 of 9 animals.

APPENDIX J
DETERMINATIONS OF PYRIDINE IN PLASMA

TABLE J1
Plasma Concentrations of Pyridine in F344/N Rats in the 13-Week Drinking Water Study of Pyridine[a]

	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
Male					
n	10[b]	10[c]	9[d]	9	10
Concentration (µg/mL)	0.045 ± 0.016	0.018 ± 0.007	0.084 ± 0.022	4.760 ± 1.334	38.140 ± 4.173
Female					
n	10[e]	10[e]	10	10	8
Concentration (µg/mL)	0.057 ± 0.014	0.075 ± 0.019	2.851 ± 0.602	14.810 ± 1.682	28.351 ± 5.070

[a] Mean ± standard error; the minimum detection limit (MDL) was calculated to be 0.009 µg/mL. A value of 0 was used for samples with a concentration below the MDL.
[b] Three samples were less than the MDL.
[c] Five samples were less than the MDL.
[d] One sample was less than the MDL.
[e] Two samples were less than the MDL.

TABLE J2
Plasma Concentrations of Pyridine in Male Wistar Rats in the 13-Week Drinking Water Study of Pyridine[a]

	50 ppm	100 ppm	250 ppm	500 ppm	1,000 ppm
n	10[b]	9[c]	9[d]	9	9
Concentration (µg/mL)	0.153 ± 0.096	0.043 ± 0.010	2.811 ± 1.406	8.278 ± 1.716	22.602 ± 5.798

[a] Mean ± standard error; the minimum detection limit (MDL) was calculated to be 0.009 µg/mL. A value of 0 was used for samples with a concentration below the MDL.
[b] Five samples were less than the MDL.
[c] Two samples were less than the MDL.
[d] One sample was less than the MDL.

APPENDIX K
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF PYRIDINE

Pyridine was obtained from Aldrich Chemical Company (Milwaukee, WI) in one lot (00103BV), which was used during the 13-week and 2-year studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the pyridine studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a clear colorless liquid, was identified as pyridine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra (*Sadtler Standard Spectra*) of pyridine. The infrared and nuclear magnetic spectra are presented in Figures K1 and K2.

The purity of lot 00103BV was determined by elemental analyses, Karl Fischer water analysis, functional group titration, and gas chromatography. For amine group titration, the sample was dissolved in glacial acetic acid, then titrated with 0.1 N perchloric acid in glacial acetic acid to a potentiometric endpoint. The titration was monitored with a combination mV/pH electrode filled with aqueous 3 M potassium chloride. Gas chromatography was performed using a flame ionization detector. Two systems were used:

A) 10% Carbowax 20M-TPA on 80/100 Chromosorb W AW glass column, with an isothermal oven temperature of 93E C, an oven temperature program of 60E C for 6 minutes, then 60E to 220E C at 10E C per minute, and a nitrogen carrier gas at a flow rate of 70 mL/minute, and

B) DB-5 Capillary fused silica column, with an oven temperature program of 50E C for 5 minutes, then 50E to 250E C at 10E C per minute, and a helium carrier gas at a flow rate of 5 mL/minute.

Elemental analyses for hydrogen and nitrogen were in agreement with the theoretical values for pyridine; results for carbon were slightly low. Karl Fischer water analysis indicated 0.049% ± 0.003% water. Functional group titration indicated a purity of 99.8% ± 0.6%. Gas chromatography using systems A and B indicated one major peak and no impurities with an area greater than or equal to 0.1% relative to the major peak area. Concomitant analyses of lot 00103BV with lot 18400080202, a previously analyzed lot that was not used in the current studies, were performed with gas chromatography by system A but with an isothermal oven temperature of 95E C and with *n*-butanol as an internal standard. Results indicated a purity of 99.9% ± 0.7% for lot 00103BV relative to lot 18400080202. The overall purity of lot 00103BV was determined to be greater than 99%.

The analytical chemistry laboratory conducted bulk stability studies on lot 18400080202 with gas chromatography. A flame ionization detector was used with a 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport glass column, a nitrogen carrier gas at a flow rate of 70 mL/minute, an oven temperature of 50E C, and a 0.4% ethyl acetate internal standard. Samples stored for 2 weeks at 25E or 60E C showed some decomposition. To ensure stability, the bulk chemical was stored at 1E to 7E C (13-week studies) or 2E to 8E C (2-year studies) in amber glass bottles in the dark. Stability was monitored during the studies using gas chromatography. No degradation of the bulk chemical was detected.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared as needed by mixing pyridine with deionized water (Table K1). Formulations were stored in Teflon®-capped amber glass bottles (13-week studies) or glass carboys (2-year studies) at room temperature in the dark for up to 3 weeks.

Stability studies of a 0.01 mg/mL formulation were performed by the analytical chemistry laboratory using high-performance liquid chromatography with a Waters µBondapak C18 column, ultraviolet (254 nm) detection, a solvent system of 0.005 M triethanolamine in water:methanol (30:70) with the pH adjusted to 7.0 with 10% phosphoric acid, and a flow rate of 1 mL/minute. The stability of the dose formulation was confirmed for at least 3 weeks when stored in the dark at room temperature. Solutions stored at room temperature exposed to air and light were also stable for 96 hours. In an earlier study by the analytical chemistry laboratory, the stability of a 19.64 mg/mL formulation was tested by gas chromatography using flame ionization detection, a 10% Carbowax 20 M/2% KOH on 80/100 mesh Chromosorb W AW silenized glass column, a nitrogen carrier gas at 25 mL/minute, and an oven temperature of 80E C. Stability was confirmed for 7 days at room temperature.

Periodic analyses of the dose formulations of pyridine were conducted at the study laboratory and the analytical chemistry laboratory using HPLC. For the 13-week studies, dose formulations were analyzed after preparation at the beginning, midpoint, and end of the studies (Table K2). During the 2-year studies, dose formulations were analyzed approximately every 6 to 10 weeks (Table K3). All 45 dose formulations analyzed and used during the 13-week studies were within 10% of the target concentration; 44 of 45 animal room samples were within 10% of the target concentration. Results of periodic referee analyses performed by the analytical chemistry laboratory during the 13-week studies agreed with the results obtained by the study laboratory (Table K4). During the 2-year studies, 191 of 192 of the dose formulations analyzed were within 10% of the target concentration. One formulation was 47% less than the target concentration; because records indicated that the proper amounts of pyridine and deionized water were used, it is possible that the wrong dose formulation was sampled for analysis. This dose formulation was remixed, and the remix was found to be within 10% of the target concentration. All 69 animal room samples were within 10% of the target concentration.

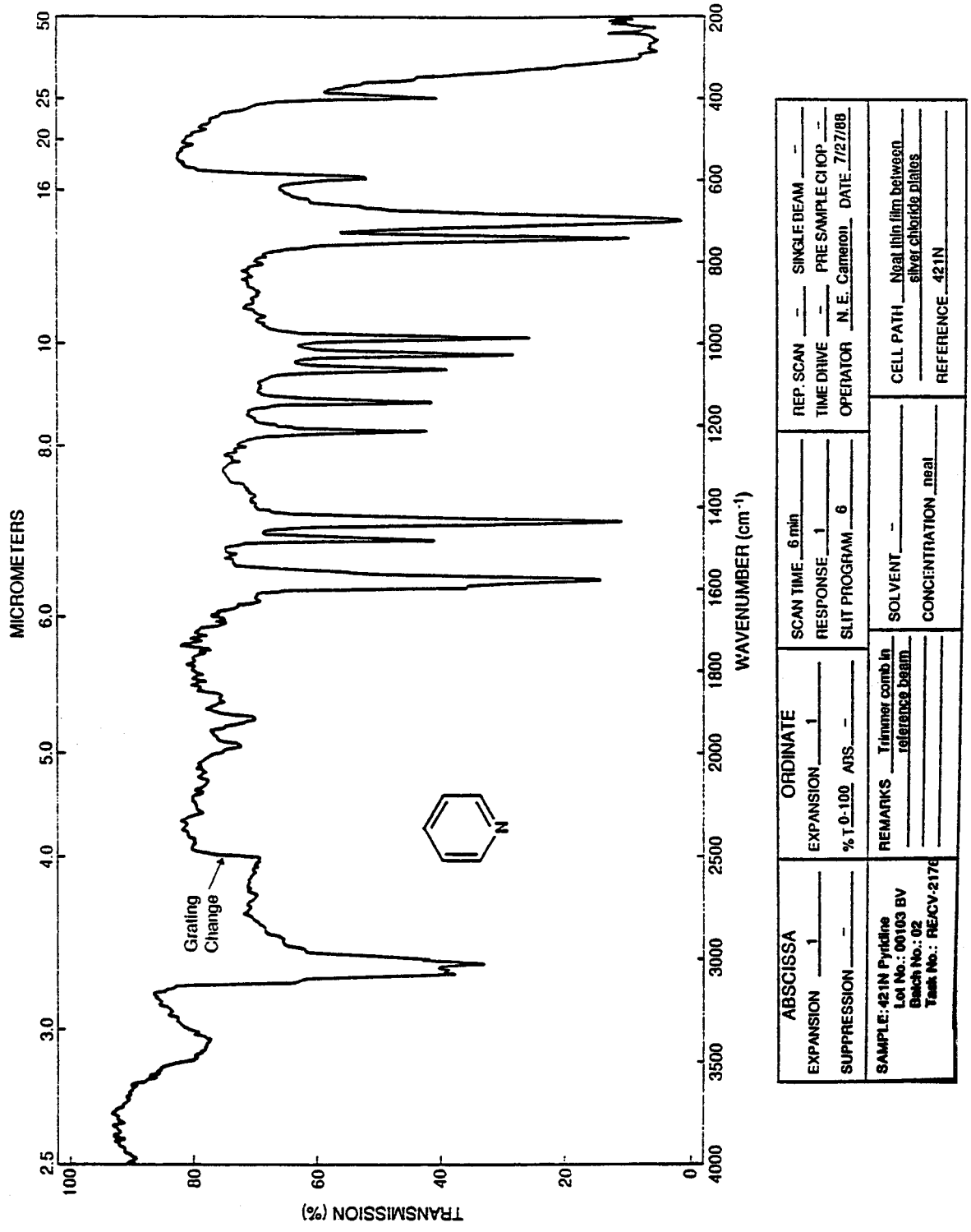

FIGURE K1
Infrared Absorption Spectrum of Pyridine

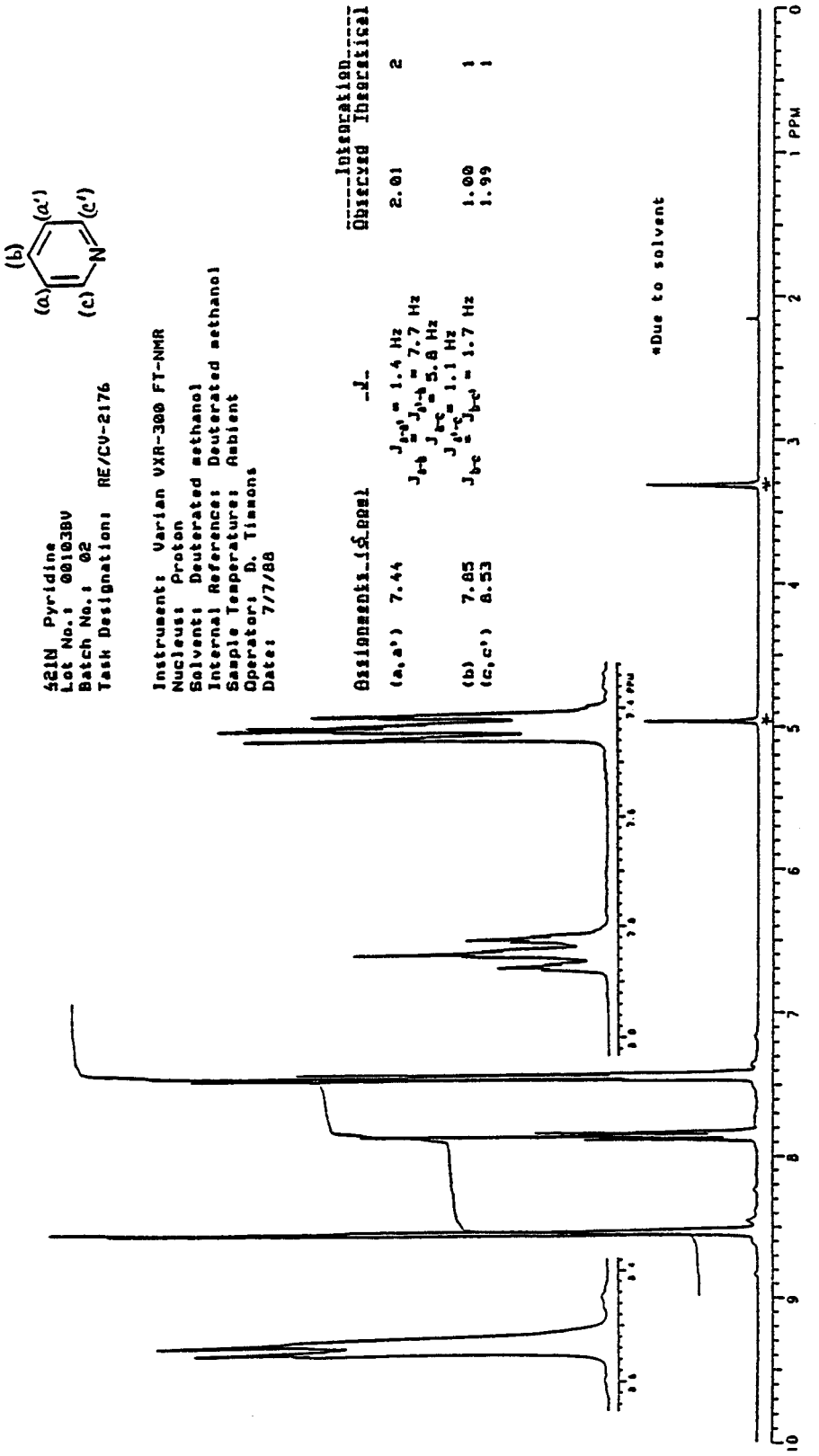

FIGURE K2
Nuclear Magnetic Resonance Spectrum of Pyridine

TABLE K1
Preparation and Storage of Dose Formulations in the Drinking Water Studies of Pyridine

13-Week Studies	2-Year Studies
Preparation	
Dose formulations were prepared as needed by combining weighed amounts of pyridine at room temperature and deionized water, then diluting to volume with additional water and mixing.	Same as 13-week studies
Chemical Lot Number	
00103BV	00103BV
Maximum Storage Time	
3 weeks	3 weeks
Storage Conditions	
Stored in sealed Teflon®-capped, amber glass bottles at room temperature in the dark	Stored in sealed glass carboys at room temperature in the dark
Study Laboratory	
TSI Mason Research Institute (Worcester, MA)	TSI Mason Laboratories (Worcester, MA)
Referee Laboratory	
Midwest Research Institute (Kansas City, MO)	None performed

TABLE K2
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 13-Week Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	Difference from Target (%)
F344/N Rats				
11 January 1990	11 January 1990	0.05	0.048	!4
		0.10	0.097	!3
		0.25	0.235	!6
		0.50	0.492	!2
		1.00	0.989	!1
	26 January 1990[c]	0.05	0.044	!12
		0.10	0.096	!4
		0.25	0.246	!2
		0.50	0.487	!3
		1.00	0.973	!3
1 March 1990	1 March 1990	0.05	0.051	+2
		0.10	0.100	0
		0.25	0.249	0
		0.50	0.501	0
		1.00	0.973	!3
	13 March 1990[c]	0.05	0.053	+6
		0.10	0.100	0
		0.25	0.241	!4
		0.50	0.504	+1
		1.00	0.966	!3
12 April 1990	16 April 1990	0.05	0.050	0
		0.10	0.098	!2
		0.25	0.249	0
		0.50	0.502	0
		1.00	0.996	0
	25 April 1990[c]	0.05	0.050	0
		0.10	0.097	!3
		0.25	0.249	0
		0.50	0.506	+1
		1.00	0.993	!1
Wistar Rats				
15 February 1990	16 February 1990	0.05	0.050	0
		0.10	0.100	0
		0.25	0.254	+2
		0.50	0.507	+1
		1.00	1.005	+1
	2 March 1990[c]	0.05	0.050	0
		0.10	0.099	!1
		0.25	0.249	0
		0.50	0.493	!1
		1.00	0.998	0

TABLE K2
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 13-Week Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Wistar Rats (continued)				
5 April 1990	5 April 1990	0.05	0.051	+2
		0.10	0.101	+1
		0.25	0.250	0
		0.50	0.500	0
		1.00	0.999	0
	16 April 1990[c]	0.05	0.049	!2
		0.10	0.097	!3
		0.25	0.248	!1
		0.50	0.494	!1
		1.00	0.996	0
17 May 1990	17 May 1990	0.05	0.048	!4
		0.10	0.099	!1
		0.25	0.248	!1
		0.50	0.494	!1
		1.00	1.006	+1
	25 May 1990[c]	0.05	0.050	0
		0.10	0.098	!2
		0.25	0.246	!2
		0.50	0.495	!1
		1.00	0.997	0
Mice				
7 December 1989	7 December 1989	0.05	0.049	!2
		0.10	0.097	!3
		0.25	0.242	!3
		0.50	0.483	!3
		1.00	0.966	!3
	27 December 1989[c]	0.05	0.051	+2
		0.10	0.099	!1
		0.25	0.246	!2
		0.50	0.504	+1
		1.00	0.986	!1
25 January 1990	26 January 1990	0.05	0.052	+4
		0.10	0.097	!3
		0.25	0.246	!2
		0.50	0.487	!3
		1.00	0.981	!2
	13 February 1990[c]	0.05	0.049	!2
		0.10	0.097	!3
		0.25	0.240	!4
		0.50	0.489	!2
		1.00	0.973	!3

TABLE K2
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 13-Week Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
1 March 1990	1 March 1990	0.05	0.051	+2
		0.10	0.100	0
		0.25	0.249	0
		0.50	0.501	0
		1.00	0.973	!3
	13 March 1990[c]	0.05	0.052	+4
		0.10	0.096	!4
		0.25	0.239	!4
		0.50	0.494	!1
		1.00	0.952	!5

[a] 0.05 mg/mL=50 ppm; 0.10 mg/mL=100 ppm; 0.25 mg/mL=250 ppm; 0.50 mg/mL=500 ppm; 1.00 mg/mL=1,000 ppm
[b] Results of duplicate analyses
[c] Animal room samples

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	Difference from Target (%)
F344/N Rats				
11 April 1991	12 April 1991	0.1	0.100	0
		0.2	0.196	!2
		0.4	0.396	!1
	2 May 1991[c]	0.1	0.099	!1
		0.2	0.199	0
		0.4	0.398	0
23 May 1991	24 May 1991	0.1	0.099	!1
		0.1	0.099	!1
		0.2	0.198	!1
		0.2	0.198	!1
		0.4	0.394	!1
		0.4	0.399	0
1 July 1991	1-3 July 1991	0.1	0.100	0
		0.1	0.100	0
		0.2	0.202	+1
		0.2	0.201	+1
		0.4	0.388	!3
		0.4	0.211	!47
3 July 1991	3 July 1991	0.4	0.398[d]	0
29 August 1991	30 August 1991	0.1	0.101	+1
		0.1	0.098	!2
		0.2	0.197	!1
		0.2	0.191	!4
		0.4	0.374	!6
		0.4	0.390	!2
	20 September 1991[c]	0.1	0.101	+1
		0.1	0.098	!2
		0.2	0.201	+1
		0.2	0.201	+1
		0.4	0.400	0
		0.4	0.396	!1
24 October 1991	25 October 1991	0.1	0.102	+2
		0.2	0.209	+5
		0.4	0.416	+4
19 December 1991	20 December 1991	0.1	0.099	!1
		0.2	0.197	!1
		0.4	0.398	0

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
F344/N Rats (continued)				
13 February 1992	14 February 1992	0.1	0.100	0
		0.2	0.198	!1
		0.4	0.392	!2
	3 March 1992[c]	0.1	0.098	!2
		0.2	0.195	!2
		0.4	0.397	!1
9 April 1992	10 April 1992	0.1	0.100	0
		0.1	0.098	!2
		0.2	0.197	!1
		0.2	0.199	0
		0.4	0.392	!2
		0.4	0.402	+1
4 June 1992	5 June 1992	0.1	0.097	!3
		0.2	0.198	!1
		0.4	0.396	!1
30 July 1992	31 July 1992	0.1	0.098	!2
		0.2	0.193	!3
		0.4	0.393	!2
	2 September 1992[c]	0.1	0.097	!3
		0.2	0.195	!2
		0.4	0.383	!4
24 September 1992	25 September 1992	0.1	0.102	+2
		0.2	0.201	+1
		0.4	0.399	0
19 November 1992	20-24 November 1992	0.1	0.101	+1
		0.2	0.206	+3
		0.4	0.395	!1
14 January 1993	15 January 1993	0.1	0.098	!2
		0.1	0.099	!1
		0.2	0.193	!3
		0.2	0.198	!1
		0.4	0.395	!1
		0.4	0.392	!2
	8 February 1993[c]	0.1	0.090	!10
		0.1	0.095	!5
		0.2	0.195	!2
		0.2	0.195	!2
		0.4	0.386	!3
		0.4	0.386	!3
11 March 1993	12 March 1993	0.1	0.098	!2
		0.2	0.197	!1
		0.4	0.396	!1

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Wistar Rats				
2 May 1991	2 May 1991	0.1	0.099	!1
		0.2	0.198	!1
		0.4	0.397	!1
	24 May 1991[c]	0.1	0.099	!1
		0.2	0.197	!1
		0.4	0.398	0
1 July 1991	1-2 July 1991	0.1	0.100	0
		0.2	0.190	!5
		0.4	0.396	!1
29 August 1991	30 August 1991	0.1	0.099	!1
		0.2	0.197	!1
		0.4	0.408	+2
24 October 1991	25 October 1991	0.1	0.104	+4
		0.1	0.101	+1
		0.2	0.210	+5
		0.2	0.206	+3
		0.4	0.408	+2
		0.4	0.416	+4
	1 November 1991[c]	0.1	0.095	!5
		0.1	0.098	!2
		0.2	0.197	!1
		0.2	0.197	!1
		0.4	0.403	+1
		0.4	0.403	+1
19 December 1991	20 December 1991	0.1	0.098	!2
		0.2	0.195	!2
		0.4	0.395	!1
13 February 1992	14 February 1992	0.1	0.100	0
		0.2	0.199	0
		0.4	0.398	0
9 April 1992	10 April 1992	0.1	0.100	0
		0.2	0.198	!1
		0.4	0.394	!1
	27 April 1992[c]	0.1	0.099	!1
		0.2	0.198	!1
		0.4	0.421	+5
4 June 1992	5 June 1992	0.1	0.099	!1
		0.2	0.198	!1
		0.4	0.390	!2
30 July 1992	31 July 1992	0.1	0.099	!1
		0.2	0.195	!2
		0.4	0.390	!2

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Wistar Rats (continued)				
24 September 1992	25 September 1992	0.1	0.101	+1
		0.2	0.200	0
		0.4	0.385	!4
	9 October 1992[c]	0.1	0.100	0
		0.2	0.198	!1
		0.4	0.398	0
19 November 1992	20-24 November 1992	0.1	0.101	+1
		0.1	0.099	!1
		0.1	0.099	!1
		0.2	0.202	+1
		0.2	0.198	!1
		0.2	0.199	0
		0.4	0.401	0
		0.4	0.399	0
		0.4	0.394	!1
14 January 1993	15 January 1993	0.1	0.100	0
		0.2	0.193	!3
		0.4	0.389	!3
11 March 1993	12 March 1993	0.1	0.100	0
		0.2	0.197	!1
		0.4	0.394	!1
	1 April 1993[c]	0.1	0.099	!1
		0.2	0.197	!1
		0.4	0.393	!2
22 April 1993	23 April 1993	0.1	0.102	+2
		0.2	0.201	+1
		0.4	0.405	+1
Male Mice				
21 March 1991	22 March 1991	0.25	0.249	0
		0.50	0.498	0
		1.00	0.990	!1
	12 April 1991[c]	0.25	0.246	!2
		0.50	0.492	!2
		1.00	0.979	!2
9 May 1991	10 May 1991	0.25	0.244	!2
		0.50	0.494	!1
		1.00	0.981	!2
1 July 1991	1 July 1991	0.25	0.246	!2
		0.50	0.491	!2
		1.00	0.986	!1

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Male Mice (continued)				
29 August 1991	30 August 1991	0.25	0.236	!6
		0.50	0.479	!4
		1.00	0.944	!6
	20 September 1991[c]	0.25	0.251	0
		0.50	0.513	+3
		1.00	1.000	0
24 October 1991	25 October 1991	0.25	0.258	+3
		0.50	0.520	+4
		1.00	1.025	+3
19 December 1991	20 December 1991	0.25	0.255	+2
		0.50	0.500	0
		1.00	0.991	!1
13 February 1992	14 February 1992	0.25	0.246	!2
		0.50	0.489	!2
		1.00	0.990	!1
	3 March 1992[c]	0.25	0.244	!2
		0.50	0.488	!2
		1.00	0.977	!2
9 April 1992	10 April 1992	0.25	0.245	!2
		0.50	0.484	!3
		1.00	0.981	!2
4 June 1992	5 June 1992	0.25	0.246	!2
		0.50	0.487	!3
		1.00	0.970	!3
30 July 1992	31 July 1992	0.25	0.245	!2
		0.50	0.492	!2
		1.00	0.973	!3
	2 September 1992[c]	0.25	0.244	!2
		0.50	0.501	0
		1.00	0.988	!1
24 September 1992	25 September 1992	0.25	0.253	+1
		0.50	0.495	!1
		1.00	0.999	0
19 November 1992	20-24 November 1992	0.25	0.247	!1
		0.50	0.496	!1
		1.00	0.987	!1

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Male Mice (continued)				
14 January 1993	15 January 1993	0.25	0.250	0
		0.50	0.487	!3
		1.00	0.972	!3
	8 February 1993[c]	0.25	0.245	!2
		0.50	0.476	!5
		1.00	0.961	!4
11 March 1993	12 March 1993	0.25	0.252	+1
		0.50	0.497	!1
		1.00	0.981	!2
Female Mice				
21 March 1991	22 March 1991	0.125	0.124	!1
		0.250	0.248	!1
		0.500	0.504	+1
	12 April 1991[c]	0.125	0.126	+1
		0.250	0.244	!2
		0.500	0.495	!1
9 May 1991	10 May 1991	0.125	0.122	!2
		0.250	0.246	!2
		0.500	0.490	!2
1 July 1991	1 July 1991	0.125	0.124	!1
		0.250	0.251	0
		0.500	0.494	!1
29 August 1991	30 August 1991	0.125	0.118	!6
		0.250	0.234	!6
		0.500	0.473	!5
	20 September 1991[c]	0.125	0.125	0
		0.250	0.245	!2
		0.500	0.499	0
24 October 1991	25 October 1991	0.125	0.126	+1
		0.250	0.260	+4
		0.500	0.517	+3
19 December 1991	20 December 1991	0.125	0.127	+2
		0.250	0.248	!1
		0.500	0.495	!1

TABLE K3
Results of Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 2-Year Drinking Water Studies of Pyridine

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Female Mice (continued)				
13 February 1992	14 February 1992	0.125	0.125	0
		0.250	0.247	!1
		0.500	0.491	!2
	3 March 1992[c]	0.125	0.124	!1
		0.250	0.248	!1
		0.500	0.490	!2
9 April 1992	10 April 1992	0.125	0.123	!2
		0.250	0.245	!2
		0.500	0.491	!2
4 June 1992	5 June 1992	0.125	0.120	!4
		0.250	0.243	!3
		0.500	0.488	!2
30 July 1992	31 July 1992	0.125	0.127	+2
		0.250	0.244	!2
		0.500	0.491	!2
	2 September 1992[c]	0.125	0.126	+1
		0.250	0.249	0
		0.500	0.502	0
24 September 1992	25 September 1992	0.125	0.127	+2
		0.250	0.253	+1
		0.500	0.494	!1
19 November 1992	20-24 November 1992	0.125	0.125	0
		0.250	0.249	0
		0.500	0.482	!4
14 January 1993	15 January 1993	0.125	0.122	!2
		0.250	0.245	!2
		0.500	0.483	!3
	8 February 1993[c]	0.125	0.118	!6
		0.250	0.245	!2
		0.500	0.483	!3
11 March 1993	12 March 1993	0.125	0.127	+2
		0.250	0.247	!1
		0.500	0.498	0

[a] 0.1 mg/mL=100 ppm; 0.125 mg/mL=125 ppm; 0.2 mg/mL=200 ppm; 0.25 mg/mL=250 ppm; 0.4 mg/mL=400 ppm; 0.50 mg/mL=500 ppm; 1.00 mg/mL=1,000 ppm
[b] Results of duplicate analyses
[c] Animal room samples
[d] Results of remix

TABLE K4
Results of Referee Analyses of Dose Formulations Administered to F344/N Rats, Wistar Rats, and Mice in the 13-Week Drinking Water Studies of Pyridine

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
F344/N Rats			
11 January 1990	0.50	0.492	0.512 ± 0.005
Wistar Rats			
15 February 1990	1.00	1.005	0.994 ± 0.002
Mice			
7 December 1989	0.10	0.097	0.106 ± 0.000

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

APPENDIX L
WATER AND COMPOUND CONSUMPTION IN THE 2-YEAR DRINKING WATER STUDIES OF PYRIDINE

TABLE L1
Water and Compound Consumption by Male F344/N Rats in the 2-Year Drinking Water Study of Pyridine

Week	0 ppm		100 ppm			200 ppm			400 ppm		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	20.4	136	19.5	135	14	18.6	135	28	18.5	136	55
2	21.4	173	20.7	172	12	20.9	169	25	21.5	167	51
3	22.6	207	22.1	208	11	21.8	206	21	24.3	201	48
4	20.5	236	21.2	234	9	19.9	232	17	24.1	227	43
5	22.1	255	21.6	253	9	23.0	250	18	23.4	245	38
6	20.6	275	21.1	267	8	21.7	272	16	22.6	258	35
7	20.4	293	20.7	286	7	21.5	289	15	22.8	272	34
8	22.4	302	22.8	295	8	22.6	295	15	24.9	282	35
9	22.4	314	22.4	309	7	22.5	306	15	24.7	291	34
10	23.3	331	22.9	326	7	21.8	323	14	25.8	309	33
11	22.3	333	21.4	329	7	22.0	328	13	26.9	311	35
12	24.9	342	23.6	339	7	22.7	340	13	26.9	323	33
13	21.5	351	20.6	349	6	21.6	348	12	24.6	328	30
17	21.8	384	21.4	382	6	20.3	378	11	23.8	355	27
21	22.5	409	21.3	405	5	22.1	404	11	23.6	376	25
25	22.4	426	22.2	420	5	22.7	420	11	25.7	392	26
29	22.7	437	23.0	431	5	22.7	433	11	25.7	403	26
33	22.9	453	23.3	448	5	23.5	448	11	24.8	421	24
37	24.5	465	21.8	461	5	22.3	460	10	25.0	434	23
41	25.3	478	22.8	468	5	25.0	469	11	25.7	443	23
45	21.6	483	20.8	480	4	20.8	480	9	23.1	452	20
49	22.4	489	20.9	479	4	22.3	480	9	24.1	453	21
53	21.7	487	21.6	482	5	22.3	482	9	25.8	453	23
57	23.8	502	23.0	489	5	26.1	484	11	29.3	462	25
61	24.1	503	22.7	491	5	25.4	487	10	28.7	459	25
65	26.0	508	25.4	492	5	28.8	484	12	32.3	455	28
69	25.0	511	24.3	500	5	29.0	485	12	35.2	457	31
73	25.6	511	25.7	500	5	30.0	480	13	37.4	446	34
77	24.5	510	24.1	497	5	27.9	475	12	35.8	446	32
81	26.1	494	26.5	497	5	30.1	467	13	40.3	441	37
85	27.7	501	28.3	486	6	35.5	462	15	45.1	428	42
89	29.3	499	29.8	484	6	34.7	440	16	43.7	414	42
93	32.5	501	31.7	478	7	38.0	428	18	46.7	406	46
97	30.6	491	29.2	464	6	35.0	414	17	40.3	391	41
101	36.3	468	36.6	458	8	37.0	397	19	49.0	388	51
Mean for weeks											
1-13	21.9	273	21.6	270	9	21.6	269	17	23.9	258	39
14-52	22.9	447	21.9	441	5	22.4	441	10	24.6	414	24
53-101	27.2	499	26.8	486	6	30.8	460	14	37.6	434	35

[a] Grams of water consumed per animal per day
[b] Milligrams of pyridine consumed per kilogram body weight per day

TABLE L2
Water and Compound Consumption by Female F344/N Rats in the 2-Year Drinking Water Study of Pyridine

Week	0 ppm		100 ppm			200 ppm			400 ppm		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	16.2	110	16.9	110	15	16.7	110	30	17.4	111	63
2	16.4	129	16.7	128	13	17.1	127	27	18.7	124	60
3	16.4	144	16.9	145	12	18.0	143	25	17.7	139	51
4	15.2	152	16.1	152	11	16.8	151	22	16.9	148	46
5	17.2	160	15.2	160	10	15.1	159	19	17.1	155	44
6	16.7	167	14.5	167	9	14.5	164	18	16.5	160	41
7	15.3	173	15.5	173	9	15.3	171	18	16.6	167	40
8	16.2	180	16.7	179	9	16.0	176	18	17.2	170	41
9	16.3	183	17.5	183	10	17.0	178	19	18.8	173	43
10	16.2	186	16.9	185	9	17.0	181	19	18.5	175	42
11	16.0	192	16.5	190	9	17.6	185	19	17.1	178	38
12	15.3	196	15.9	194	8	16.1	187	17	16.2	182	36
13	14.3	198	14.7	197	8	15.0	191	16	15.7	185	34
17	14.3	213	16.1	210	8	17.0	204	17	17.3	196	35
21	14.8	223	15.4	220	7	16.6	212	16	17.4	205	34
25	15.9	228	16.1	225	7	16.3	218	15	18.2	208	35
29	15.1	234	16.3	233	7	17.3	224	15	18.7	214	35
33	17.0	242	17.2	238	7	17.7	228	16	19.3	220	35
37	14.9	251	15.6	247	6	16.4	239	14	16.8	225	30
41	16.9	261	17.2	257	7	17.7	247	14	20.0	234	34
45	14.6	270	15.6	269	6	16.7	257	13	17.6	240	29
49	15.5	279	16.2	280	6	15.3	266	12	17.9	247	29
53	15.8	285	16.4	287	6	17.3	273	13	18.6	252	30
57	17.2	288	18.1	290	6	17.7	273	13	21.0	255	33
61	16.5	299	17.1	297	6	18.7	280	13	20.7	258	32
65	18.7	301	19.1	302	6	18.8	284	13	22.6	259	35
69	18.7	310	18.7	308	6	20.4	289	14	23.1	269	34
73	19.0	314	18.8	313	6	20.9	292	14	24.2	275	35
77	19.3	322	19.7	313	6	19.6	299	13	23.3	282	33
81	19.5	326	21.3	323	7	21.6	299	15	23.6	283	33
85	21.0	330	23.0	327	7	24.0	306	16	26.5	281	38
89	18.0	331	20.0	328	6	19.9	306	13	22.5	286	32
93	21.2	338	24.6	332	7	24.3	307	16	27.7	286	39
95	19.5	334	20.8	335	6	21.4	305	14	23.9	281	34
97	20.3	344	21.9	332	7	24.0	306	16	23.9	286	34
99	19.6	340	20.7	333	6	21.5	301	14	21.2	286	30
101	18.9	337	21.6	333	7	24.0	298	16	23.3	284	33
104	20.6	342	21.2	327	7	24.4	303	16	26.2	289	36
Mean for weeks											
1-13	16.0	167	16.2	166	10	16.3	163	21	17.3	159	45
14-52	15.4	245	16.2	242	7	16.8	233	15	18.1	221	33
53-104	19.0	321	20.2	318	6	21.2	295	14	23.3	276	34

[a] Grams of water consumed per animal per day
[b] Milligrams of pyridine consumed per kilogram body weight per day

TABLE L3
Water and Compound Consumption by Male Wistar Rats in the 2-Year Drinking Water Study of Pyridine

Week	0 ppm		100 ppm			200 ppm			400 ppm		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	37.6	201	37.5	198	19	39.3	199	40	35.9	198	72
2	40.9	255	38.9	250	16	39.8	246	32	37.9	240	63
3	38.9	294	40.2	289	14	41.3	285	29	41.9	280	60
4	42.1	327	42.1	326	13	43.9	321	27	42.7	312	55
5	46.3	357	48.6	359	14	48.5	347	28	45.7	345	53
6	39.4	382	39.3	380	10	39.9	372	21	38.9	358	43
7	40.8	413	44.3	411	11	44.4	402	22	46.0	388	47
8	47.4	426	43.5	428	10	47.1	412	23	45.6	400	46
9	53.3	448	49.2	446	11	49.5	435	23	48.7	419	47
10	42.7	464	41.4	463	9	43.3	452	19	43.2	431	40
11	50.3	479	46.3	478	10	47.0	463	20	47.0	443	42
12	48.2	494	47.3	492	10	47.3	479	20	43.9	457	38
13	46.8	506	46.7	503	9	46.6	490	19	46.3	466	40
17	44.0	546	42.3	542	8	41.9	527	16	41.0	502	33
21	46.5	569	42.8	575	7	41.5	562	15	44.8	528	34
25	41.9	599	39.4	602	7	41.0	583	14	42.9	552	31
29	40.4	627	36.7	630	6	40.0	612	13	41.6	576	29
33	43.6	658	42.8	657	7	39.9	638	13	44.2	599	30
37	46.8	672	46.6	673	7	48.1	651	15	48.6	610	32
41	38.4	691	38.8	686	6	39.2	664	12	40.3	627	26
45	43.5	715	42.9	711	6	43.0	684	13	44.0	642	27
49	40.5	736	40.5	719	6	41.9	695	12	44.5	654	27
53	50.9	755	48.3	735	7	52.6	705	15	53.5	662	32
57	45.4	774	47.3	748	6	48.8	714	14	50.7	668	30
61	54.7	789	53.9	753	7	59.4	718	17	57.4	669	34
65	49.8	795	52.5	757	7	55.6	720	15	55.7	661	34
69	54.3	800	55.5	739	8	56.7	699	16	58.2	658	35
73	54.6	803	60.1	736	8	59.8	706	17	62.6	657	38
77	56.3	797	60.5	725	8	63.2	717	18	63.7	644	40
81	58.1	799	66.8	698	10	64.3	698	18	62.2	624	40
85	60.1	782	65.1	707	9	64.4	699	18	57.4	630	36
89	60.5	775	68.4	692	10	67.0	676	20	64.6	614	42
93	69.3	779	69.2	678	10	67.7	657	21	57.7	612	38
97	66.1	757	71.2	675	11	61.2	618	20	55.7	590	38
101	59.6	725	59.0	675	9	54.5	578	19	57.5	604	38
Mean for weeks											
1-13	44.2	388	43.5	386	12	44.5	377	25	43.4	364	50
14-52	42.8	646	41.4	644	6	41.8	624	14	43.5	588	30
53-101	56.9	779	59.8	717	8	59.6	685	17	58.2	638	37

[a] Grams of water consumed per animal per day
[b] Milligrams of pyridine consumed per kilogram body weight per day

TABLE L4
Water and Compound Consumption by Male Mice in the 2-Year Drinking Water Study of Pyridine

Week	0 ppm		250 ppm			500 ppm			1,000 ppm		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	6.5	26.1	6.8	25.9	66	5.7	25.8	109	5.6	25.8	218
2	5.7	27.6	5.6	27.4	51	5.2	27.3	95	4.5	26.6	171
3	5.6	29.2	5.3	28.7	46	5.2	29.0	90	4.3	28.4	150
4	5.7	30.9	5.3	30.5	44	5.0	30.7	82	4.3	30.1	142
5	5.6	32.8	5.3	32.3	41	5.5	32.2	85	4.9	30.6	160
6	5.3	33.9	5.0	34.2	36	4.6	33.5	69	3.9	32.0	123
7	5.5	35.4	5.0	35.4	35	4.9	35.3	69	3.8	33.9	112
8	5.0	37.6	4.9	37.1	33	4.6	36.7	63	3.9	35.6	110
9	5.4	38.7	5.2	37.9	34	5.0	37.7	66	4.3	36.5	119
10	5.4	39.6	5.7	40.1	36	5.2	39.8	65	4.4	37.7	117
11	5.7	40.6	6.4	41.0	39	5.3	41.0	64	4.5	38.8	117
12	5.5	41.8	5.8	42.3	34	5.0	41.7	60	5.0	39.8	126
13	5.5	42.4	5.9	42.9	34	5.6	42.7	66	5.2	40.6	129
17	5.2	47.0	5.3	46.2	28	5.2	45.9	57	4.3	43.5	99
21	6.9	48.1	6.5	48.3	34	5.8	47.4	61	4.1	45.2	90
25	5.3	50.0	5.4	49.6	27	5.1	49.9	51	4.7	47.5	98
29	7.0	49.6	6.6	50.8	32	7.1	51.3	69	5.6	48.5	116
33	5.2	51.6	5.1	51.7	25	4.9	51.1	48	4.5	50.0	91
37	5.4	53.2	5.2	52.9	24	4.7	53.0	45	4.3	51.8	84
41	6.8	54.5	6.9	53.8	32	6.4	53.7	60	6.6	52.5	126
45	5.8	54.1	6.4	53.9	30	6.0	54.4	55	5.0	52.7	95
49	6.6	55.3	6.0	54.6	28	7.2	55.4	65	4.9	53.4	92
53	6.1	55.4	5.8	55.6	26	5.7	56.2	51			
57	6.5	55.2	6.6	55.4	30	6.3	56.0	56	5.7	54.0	106
61	5.9	55.2	6.0	56.1	27	5.7	56.4	51	4.7	54.2	88
65	5.6	54.4	6.0	56.3	27	5.6	56.1	50	4.3	54.1	80
69	5.8	55.1	6.8	56.5	30	6.7	55.5	61	5.2	54.4	96
73	5.8	54.4	6.5	56.6	29	6.6	53.9	61	4.7	54.1	87
77	5.8	52.8	7.2	55.1	32	7.0	52.2	67	5.2	52.4	99
81	5.8	51.4	7.7	53.7	36	7.4	50.2	74	5.1	49.2	105
85	6.0	49.2	7.4	51.5	36	7.2	47.8	75	5.2	47.3	109
89	5.5	46.6	8.4	49.7	42	7.0	45.8	76	5.4	45.6	119
93	5.4	45.5	8.2	46.4	44	7.3	44.7	81	5.4	43.7	122
97	6.6	43.8	8.0	43.6	46	7.7	42.9	89	6.0	41.8	144
99	6.2	44.5	8.4	43.5	48	7.7	42.7	91	6.0	41.2	146
101	6.3	44.2	7.7	41.9	46	8.0	41.6	96	6.1	40.6	150
Mean for weeks											
1-13	5.6	35.1	5.6	35.1	41	5.1	34.9	75	4.5	33.6	138
14-52	6.0	51.5	5.9	51.3	29	5.8	51.3	57	4.9	49.5	99
53-101	6.0	50.6	7.2	51.6	36	6.9	50.1	70	5.3	48.7	112

[a] Grams of water consumed per animal per day
[b] Milligrams of pyridine consumed per kilogram body weight per day

TABLE L5
Water and Compound Consumption by Female Mice in the 2-Year Drinking Water Study of Pyridine

Week	0 ppm		125 ppm			250 ppm			500 ppm		
	Water (g/day)[a]	Body Weight (g)	Water (g/day)	Body Weight (g)	Dose/ Day[b] (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)	Water (g/day)	Body Weight (g)	Dose/ Day (mg/kg)
1	7.3	20.8	7.5	20.7	45	6.8	20.6	82	6.3	20.5	154
2	6.9	21.8	6.6	21.4	39	6.6	21.6	76	5.7	21.5	132
3	7.5	23.2	7.1	22.8	39	7.4	22.8	81	6.5	22.6	144
4	6.5	24.1	6.8	24.0	35	6.4	23.9	67	5.6	23.7	118
5	7.7	25.5	7.0	25.3	34	6.9	25.5	68	5.4	25.6	106
6	6.1	26.7	5.8	26.5	28	6.3	26.3	59	4.9	26.9	90
7	5.8	28.2	5.8	28.4	25	6.1	28.8	53	5.1	28.5	89
8	6.0	29.6	5.4	29.9	23	5.6	29.8	47	5.0	30.0	84
9	5.9	31.1	5.7	30.1	24	5.7	30.8	46	5.2	30.4	85
10	5.5	31.7	6.3	32.0	24	6.4	32.7	49	5.7	32.9	86
11	6.7	33.3	6.3	33.2	24	6.2	33.7	46	5.7	33.7	85
12	7.1	34.1	6.4	34.2	23	6.0	35.2	43	5.4	35.1	76
13	6.1	35.8	5.7	35.5	20	5.4	36.5	37	5.4	36.3	74
17	5.0	40.2	4.8	39.4	15	5.1	40.5	31	5.1	40.4	64
21	11.5	41.1	6.8	40.0	21	6.9	41.6	41	8.6	41.4	104
25	4.5	45.9	4.6	44.2	13	4.4	45.8	24	4.3	45.1	48
29	5.3	45.7	5.0	44.9	14	4.4	47.2	23	5.5	46.5	60
33	4.9	49.1	4.6	47.7	12	4.4	49.5	22	4.3	48.7	44
37	4.4	51.0	4.4	49.4	11	4.4	51.0	22	4.2	50.1	42
41	5.9	53.1	6.3	51.1	15	5.8	53.2	27	6.2	52.0	60
45	5.8	54.0	5.7	52.5	14	5.6	54.1	26	6.1	52.2	58
49	5.5	56.2	5.4	54.5	12	6.3	55.6	28	6.3	54.4	58
53	5.2	56.9	5.0	55.6	11	5.2	57.1	23	5.8	55.5	52
57	5.4	58.2	5.1	56.4	11	5.6	58.0	24	5.2	56.8	46
61	4.8	59.5	4.8	57.9	10	4.8	59.3	20	4.9	58.1	42
65	4.6	59.9	5.0	58.5	11	4.6	61.0	19	5.0	58.6	42
69	5.1	61.6	6.0	59.3	13	5.7	62.1	23	6.1	58.2	53
73	4.9	62.8	5.4	60.2	11	5.1	62.2	20	6.4	58.0	55
77	5.0	63.3	5.4	61.0	11	6.2	61.9	25	7.8	55.4	71
81	4.6	62.2	4.9	60.3	10	5.8	60.4	24	7.3	51.6	70
85	4.9	61.1	5.4	58.6	11	7.7	58.8	33	8.6	48.7	89
89	2.6	60.0	2.7	58.0	6	3.4	54.4	16	3.2	45.8	35
93	5.8	57.4	7.1	56.3	16	9.7	50.9	47	8.5	43.7	97
97	6.0	55.7	7.8	52.7	18	10.4	47.1	55	8.6	40.2	106
99	6.0	56.1	8.4	53.3	20	10.1	46.1	55	8.0	40.1	100
101	5.4	55.5	9.2	52.5	22	10.7	42.8	62	8.0	39.9	100
104	5.9	55.3	8.7	49.0	22	10.7	41.5	64	8.0	38.0	106
Mean for weeks											
1-13	6.5	28.1	6.3	28.0	30	6.3	28.3	58	5.5	28.3	102
14-52	5.8	48.5	5.3	47.1	14	5.3	48.7	27	5.6	47.9	60
53-104	5.1	59.0	6.1	56.6	14	7.0	54.9	34	6.8	49.9	71

[a] Grams of water consumed per animal per day
[b] Milligrams of pyridine consumed per kilogram body weight per day

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

TABLE M1
Ingredients of NIH-07 Rat and Mouse Ration[a]

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

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

TABLE M2
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 M3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.45 ± 0.49	22.3) 24.3	26
Crude fat (% by weight)	5.34 ± 0.18	5.00) 5.90	26
Crude fiber (% by weight)	3.32 ± 0.32	2.60) 4.30	26
Ash (% by weight)	6.42 ± 0.21	5.94) 6.81	26
Amino Acids (% of total diet)			
Arginine	1.273 ± 0.083	1.100) 1.390	12
Cystine	0.307 ± 0.068	0.181) 0.400	12
Glycine	1.152 ± 0.051	1.060) 1.220	12
Histidine	0.581 ± 0.029	0.531) 0.630	12
Isoleucine	0.913 ± 0.034	0.867) 0.965	12
Leucine	1.969 ± 0.053	1.850) 2.040	12
Lysine	1.269 ± 0.050	1.200) 1.370	12
Methionine	0.436 ± 0.104	0.306) 0.699	12
Phenylalanine	0.999 ± 0.114	0.665) 1.110	12
Threonine	0.899 ± 0.059	0.824) 0.985	12
Tryptophan	0.216 ± 0.146	0.107) 0.671	12
Tyrosine	0.690 ± 0.091	0.564) 0.794	12
Valine	1.079 ± 0.057	0.962) 1.170	12
Essential Fatty Acids (% of total diet)			
Linoleic	2.389 ± 0.223	1.830) 2.570	11
Linolenic	0.273 ± 0.034	0.210) 0.320	11
Vitamins			
Vitamin A (IU/kg)	6,681 ± 1,265	5,280) 11,450	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000) 6,300	4
α-Tocopherol (ppm)	35.24 ± 8.58	22.5) 48.9	12
Thiamine (ppm)	17.27 ± 2.14	13.0) 22.0	26
Riboflavin (ppm)	7.78 ± 0.899	6.10) 9.00	12
Niacin (ppm)	98.73 ± 23.21	65.0) 150.0	12
Pantothenic acid (ppm)	32.94 ± 8.92	23.0) 59.2	12
Pyridoxine (ppm)	9.28 ± 2.49	5.60) 14.0	12
Folic acid (ppm)	2.56 ± 0.70	1.80) 3.70	12
Biotin (ppm)	0.265 ± 0.046	0.190) 0.354	12
Vitamin B_{12} (ppb)	41.6 ± 18.6	10.6) 65.0	12
Choline (ppm)	2,955 ± 382	2,300) 3,430	11
Minerals			
Calcium (%)	1.16 ± 0.05	1.09) 1.28	26
Phosphorus (%)	0.92 ± 0.05	0.760) 1.00	26
Potassium (%)	0.886 ± 0.059	0.772) 0.971	10
Chloride (%)	0.531 ± 0.082	0.380) 0.635	10
Sodium (%)	0.316 ± 0.031	0.258) 0.370	12
Magnesium (%)	0.165 ± 0.010	0.148) 0.180	12
Sulfur (%)	0.266 ± 0.060	0.208) 0.420	11
Iron (ppm)	348.0 ± 83.7	255.0) 523.0	12
Manganese (ppm)	93.27 ± 5.62	81.7) 102.0	12
Zinc (ppm)	59.42 ± 9.73	46.1) 81.6	12
Copper (ppm)	11.63 ± 2.46	8.09) 15.4	12
Iodine (ppm)	3.49 ± 1.14	1.52) 5.83	11
Chromium (ppm)	1.57 ± 0.53	0.60) 2.09	12
Cobalt (ppm)	0.81 ± 0.27	0.49) 1.23	8

TABLE M4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.49 ± 0.16	0.10) 0.70	26
Cadmium (ppm)	0.13 ± 0.07	0.04) 0.20	26
Lead (ppm)	0.36 ± 0.24	0.10) 1.00	26
Mercury (ppm)[c]	<0.02	0.02) 0.03	26
Selenium (ppm)	0.32 ± 0.10	0.05) 0.40	26
Aflatoxins (ppb)	<5.0		26
Nitrate nitrogen (ppm)[d]	7.78 ± 3.83	2.90) 17.0	26
Nitrite nitrogen (ppm)[d]	0.18 ± 0.12	0.10) 0.50	26
BHA (ppm)[e]	2.46 ± 4.04	1.0) 20.0	26
BHT (ppm)[e]	1.35 ± 0.84	1.0) 5.0	26
Aerobic plate count (CFU/g)	95,542 ± 158,814	6,500) 710,000	26
Coliform (MPN/g)	3.1 ± 0.3	3) 4	26
Escherichia coli (MPN/g)	<3		26
Salmonella (MPN/g)	Negative		26
Total nitrosoamines (ppb)[f]	7.87 ± 1.92	4.7) 11.4	26
N-Nitrosodimethylamine (ppb)[f]	5.73 ± 1.31	2.9) 8.2	26
N-Nitrosopyrrolidine (ppb)[f]	2.14 ± 1.26	1.0) 6.0	26
Pesticides (ppm)			
α-BHC	<0.01		26
β-BHC	<0.02		26
γ-BHC	<0.01		26
δ-BHC	<0.01		26
Heptachlor	<0.01		26
Aldrin	<0.01		26
Heptachlor epoxide	<0.01		26
DDE	<0.01		26
DDD	<0.01		26
DDT	<0.01		26
HCB	<0.01		26
Mirex	<0.01		26
Methoxychlor	<0.05		26
Dieldrin	<0.01		26
Endrin	<0.01		26
Telodrin	<0.01		26
Chlordane	<0.05		26
Toxaphene	<0.10		26
Estimated PCBs	<0.20		26
Ronnel	<0.01		26
Ethion	<0.02		26
Trithion	<0.05		26
Diazinon	<0.10		26
Methyl parathion	<0.02		26
Ethyl parathion	<0.02		26
Malathion	0.24 ± 0.23	0.05) 0.97	26
Endosulfan I	<0.01		26
Endosulfan II	<0.01		26
Endosulfan sulfate	<0.03		26

[a] CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] All values except for the lots milled November and December 1991 were less than the detection limit. The detection limit is given as the mean.
[d] Sources of contamination: alfalfa, grains, and fish meal
[e] Sources of contamination: soy oil and fish meal
[f] All values were corrected for percent recovery.

APPENDIX N
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Serum samples were collected from randomly selected rats and mice during the 13-week and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates, Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which blood was collected during the studies are also listed.

Method and Test	Time of Analysis
F344/N RATS	
13-Week Study	
ELISA	
PVM (pneumonia virus of mice)	Study termination
RCV/SDA (rat coronavirus/ sialodacryoadenitis)	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
2-Year Study	
ELISA	
Mycoplasma arthritidis	Study termination
Mycoplasma pulmonis	Study termination
PVM	6, 12, 16, 18, and 19 months, study termination
RCV/SDA	6, 12, 16, 18, and 19 months, study termination
Sendai	6, 12, 16, 18, and 19 months, study termination
Immunofluorescence Assay	
Parvovirus	6 months
RCV/SDA	Study termination
Sendai	12 months
Hemagglutination Inhibition	
H-1	6, 12, 16, 18, and 19 months, study termination
KRV	6, 12, 16, 18, and 19 months, study termination

WISTAR RATS

13-Week Study

ELISA	
PVM	Study termination
RCV/SDA	Study termination
Sendai	Study termination
Hemagglutination Inhibition	
H-1	Study termination
KRV	Study termination

2-Year Study

ELISA	
M. arthritidis	6 months, study termination
M. pulmonis	6 months, study termination
PVM	1 week, 3, 5, 6, 12, 14, and 18 months, study termination
RCV/SDA	1 week, 3, 5, 6, 12, 14, and 18 months, study termination
Sendai	1 week, 3, 5, 6, 12, 14, and 18 months, study termination
Immunofluorescence Assay	
Parvovirus	3 months, study termination
RCV/SDA	Study termination
Hemagglutination Inhibition	
H-1	1 week, 3, 5, 6, 12, 14, and 18 months, study termination
KRV	1 week, 3, 5, 6, 12, 14, and 18 months, study termination

MICE

13-Week Study

ELISA	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
MHV (mouse hepatitis virus)	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	Study termination
Mouse adenoma virus	Study termination
MVM (minute virus of mice)	Study termination
Hemagglutination Inhibition	
K (papovavirus)	Study termination
Polyoma virus	Study termination

MICE (continued)

2-Year Study

ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM	6, 12, and 18 months, study termination
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
Mouse adenoma virus-FL	6, 12, and 18 months, study termination
MHV	6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
GDVII	12 months
MHV	12 months, study termination
Hemagglutination Inhibition	
K	6, 12, and 18 months, study termination
MVM	6, 12, and 18 months, study termination
Polyoma virus	6, 12, and 18 months, study termination

Results of serology tests are presented in Table N1.

TABLE N1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Studies of Pyridine

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies		
F344/N Rats		
Study termination	0/10	None positive
Wistar Rats		
Study termination	0/5	None positive
Mice		
Study termination	0/10	None positive
2-Year Studies		
F344/N Rats		
6 Months	1/10	Parvovirus
	1/10	H-1
12 Months	0/10	None positive
16 Months	0/1	None positive
18 Months	0/8	None positive
19 Months	0/1	None positive
Study termination	6/16[a]	*M. arthritidis*
Wistar Rats		
1 Week	0/8	None positive
3 Months	1/2	Parvovirus
	1/2	H-1
5 Months	0/1	None positive
6 Months	0/6	None positive
12 Months	0/5	None positive
14 Months	0/1	None positive
18 Months	0/5	None positive
Study termination	0/10	None positive
Mice		
6 Months	0/10	None positive
12 Months	0/8	None positive
18 Months	0/8	None positive
Study termination	0/10	None positive

[a] Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibodies of nonpathogenic *Mycoplasma* or other agents. There were no clinical findings or histopathologic changes of *M. arthritidis* infection in animals with positive titers. Accordingly, *M. arthritidis*-positive titers were considered false positives.

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