NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF PROMETHAZINE HYDROCHLORIDE

(CAS NO. 58-33-3)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

NTP TR 425

NIH Publication No. 94-3156

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

FOREWORD

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

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

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

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

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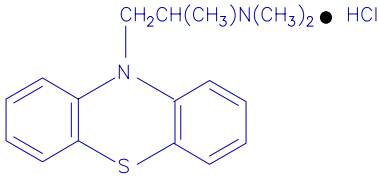
ABSTRACT



PROMETHAZINE HYDROCHLORIDE

CAS No. 58-33-3

Chemical Formula: $C_{17}H_{20}N_2S \bullet HCl$ Molecular Weight: 320.88

Synonyms: Phenothiazine,10-(2-(dimethylamino)propyl)-,monochlorohydrate; 10H-phenothiazine-10-ethanamine; 10-(2-dimethylamino-2-methylethyl)phenothiazine hydrochloride;*N*-(2'-dimethylamino-2'-methyl)ethylphenothiazine hydrochloride **Trade names**: Diprazi; Kinetosin; Phenergan; Phenergan hydrochloride; Promine; Pipolfen; Plletia; Prorex; Promantine; Pyrethia; Romergan hydrochloride

Promethazine hydrochloride is a drug used for the management of allergic conditions, motion sickness and nausea, and as a sedative to treat psychiatric disorders. This drug was nominated for testing by the Food and Drug Administration because of its widespread use in human medicine and because of lack of data on its potential carcinogenicity. Oral administration is the most common route of human exposure. Toxicology and carcinogenicity studies were conducted by administering promethazine hydrochloride (>99% pure) in distilled water by gavage to groups of male and female F344/N rats and B6C3F$_1$ mice for 16 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, in cultured Chinese hamster ovary cells, and in *Drosophila melanogaster*.

16-DAY STUDY IN RATS

Groups of five male and five female rats received 0, 18.5, 55.5, 166.5, 500, or 1,500 mg promethazine hydrochloride/kg body weight once daily, 5 days per week for a total of 12 doses in a 16-day period. All rats receiving 1,500 mg/kg, four males and four females receiving 500 mg/kg, and one male and one female receiving 166.5 mg/kg died during the study. No deaths occurred in the remaining dose groups. Final mean body weights of rats receiving 166.5 mg/kg were significantly lower (12% to 25%) than those of the controls. Clinical findings included decreased activity, ocular discharge, and labored breathing in males and females receiving 166.5, 500, and 1,500 mg/kg as well as tremors in females receiving 166.5 and 500 mg/kg. There were dose-related increases in the absolute and relative liver weights of rats. Focal suppurative inflammation occurred in the nose of some male and female rats receiving 55 or 166.5 mg/kg and in the trachea of some male and female rats receiving 166.5 mg/kg.

16-DAY STUDY IN MICE

Groups of five male and five female mice received 0, 18.8, 37.5, 75, 150, or 300 mg promethazine hydrochloride/kg body weight once daily, 5 days per week for a total of 12 doses in a 16-day period. Two females receiving 75 mg/kg, one male and one female receiving 150 mg/kg, and four females receiving 300 mg/kg died during the study. No deaths occurred in the remaining dose groups. Final mean body weights of mice receiving promethazine hydrochloride were similar to those of the controls. However, in male and female controls, the final mean body weights were 11% to 12% lower than the initial mean body weights. Clinical findings occurred as early as the first day of the study and included decreased activity in male and female mice receiving 150 and 300 mg/kg. Tremors occurred in one male and five females in the 300 mg/kg group on day 1 and in one male in the 150 mg/kg group and five males and one female in the 300 mg/kg group on day 2. Absolute and relative

liver weights of male mice receiving 75, 150, or 300 mg/kg were significantly greater than those of the controls. No chemical-related lesions were present in male or female mice.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female rats received 0, 3.7, 11.1, 33.3, 100, or 300 mg promethazine hydrochloride/kg body weight once daily, 5 days per week for 13 weeks. One female receiving 100 mg/kg and six males and nine females receiving 300 mg/kg died during the study. No deaths occurred in the remaining dose groups. Final mean body weights of male rats receiving 100 or 300 mg/kg were significantly lower (19% to 22%) than those of the controls. Mean body weight gain of females receiving 100 mg/kg was significantly lower (14%) than that of the controls. Clinical findings in rats included hunched posture and labored breathing. Absolute and relative liver weights of males receiving 11.1, 33.3, 100, or 300 mg/kg and females receiving 33.3 or 100 mg/kg were significantly greater than those of the controls. Focal suppurative inflammation of the nose and trachea occurred with an increased incidence in rats receiving 100 and 300 mg/kg. A dose-related increased incidence of vacuolar degeneration of the nasal olfactory epithelium occurred in male and female rats that received 11.1, 33.3, or 100 mg/kg.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female mice received 0, 5, 15, 45, 135, or 405 mg promethazine hydrochloride/kg body weight once daily, 5 days per week for 13 weeks. One control female, one female receiving 5 mg/kg, two females receiving 45 mg/kg, four females receiving 135 mg/kg, and all mice receiving 405 mg/kg died during the study. No deaths occurred in the remaining dose group. Final mean body weights of mice receiving 135 mg/kg were significantly lower (8% to 9%) than those of the controls. Clinical findings of toxicity included labored breathing and decreased activity in one 135 mg/kg female. Absolute and relative liver weights increased in a dose-related trend in both sexes. No chemical-related lesions were observed in mice.

2-YEAR STUDY IN RATS

Based on mortality and body weight differences observed at higher levels, doses of promethazine hydrochloride selected for the 2-year study in rats were 0, 8.3, 16.6, and 33.3 mg/kg. Groups of 60 male or 60 female rats were administered promethazine hydrochloride in deionized water by gavage once daily, 5 days per week for up to 103 weeks. Up to ten male and ten female rats per dose group were evaluated at 15 months.

Survival, Body Weights, and Clinical Findings

There was a significant dose-related decrease in survival of rats. The survival rates in the 16.6 and 33.3 mg/kg male groups and in the 33.3 mg/kg female group were significantly lower than those of the controls. The final mean body weight of male rats receiving 33.3 mg/kg promethazine hydrochloride was 10% lower than that of the controls. Final mean body weights of female rats in the 16.6 and 33.3 mg/kg groups were 9% and 11% lower than that of the controls, respectively.

No chemical-related clinical findings were noted in any dose group. Significant increases in the absolute and relative liver weights of mid- and high-dose female rats and the relative liver weights of mid- and high-dose male rats were observed at the 15-month interim evaluation. There were no biologically significant differences in the hematology or clinical chemistry parameters measured at 15 months.

Pathology Findings

No neoplasms that could be attributed to promethazine hydrochloride administration were found in male or female rats. Several neoplasms occurred with a significantly decreased incidence in rats receiving promethazine hydrochloride. These included adrenal medullary pheochromocytoma (benign or malignant) and pituitary gland adenoma in the 33.3 mg/kg males and uterine stromal polyp in the 33.3 mg/kg females. The decreased incidences of adrenal medullary pheochromocytoma were chemical related. The decreased incidences of pituitary gland adenoma and uterine stromal polyp may have been related to chemical administration. Diffuse fatty change of the liver of male rats increased with dose and was attributed to chemical administration.

2-YEAR STUDY IN MICE

Based on mortality and body weight differences observed at higher levels, the doses of promethazine hydrochloride selected for the 2-year study were 0, 11.25, 22.5, and 45 mg/kg for male mice and 0, 3.75, 7.5, and 15 mg/kg for female mice. Groups of 60 male or 60 female mice were administered promethazine hydrochloride in deionized water by gavage once daily, 5 days per week for up to 103 weeks. Up to 10 male and 10 female mice per dose group were evaluated at 15 months.

Survival, Body Weights, and Clinical Findings

Survival of mice receiving promethazine hydrochloride was similar to that of the controls. Mean body weights of mice were within 7% of those of the controls throughout the study. There were no chemical-related clinical findings in male or female mice. There were no differences in hematology or clinical chemistry parameters measured at 15 months that were attributed to the administration of promethazine hydrochloride.

Pathology Findings

There were no neoplasms or nonneoplastic lesions that were attributed to the administration of promethazine hydrochloride.

GENETIC TOXICOLOGY

Promethazine hydrochloride did not induce gene mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537, or a significant increase in chromosomal aberrations in cultured Chinese hamster ovary cells; both of these tests were conducted with and without exogenous metabolic activation (S9). A small dose-related increase in sister chromatid exchanges was observed in cultured Chinese hamster ovary cells in the presence of S9; this response was considered to be equivocal. No increase in sister chromatid exchanges was observed in the absence of S9. Promethazine hydrochloride did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* administered the chemical by feeding or injection.

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of promethazine hydrochloride in male or female F344/N rats receiving 8.3, 16.6, or 33.3 mg/kg. There was *no evidence of carcinogenic activity* of promethazine hydrochloride in male $B6C3F_1$ mice receiving 11.25, 22.5, or 45 mg/kg. There was *no evidence of carcinogenic activity* of promethazine hydrochloride in female $B6C3F_1$ mice receiving 3.75, 7.5, or 15 mg/kg.

The decrease in the incidences of adrenal medullary pheochromocytoma in male rats was considered to be related to promethazine hydrochloride administration. The decrease in the incidences of pituitary gland adenoma in male rats and uterine stromal polyp in female rats may have been related to promethazine administration.

Promethazine hydrochloride also caused an increased incidence of fatty change in the liver of male rats.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Promethazine Hydrochloride

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 8.3, 16.6 or 33.3 mg/kg in water by gavage	0, 8.3, 16.6 or 33.3 mg/kg in water by gavage	0, 11.25, 22.5 or 45 mg/kg in water by gavage	0, 3.75, 7.5 or 15 mg/kg in water by gavage
Body weights	High-dose group lower than control	Mid- and high-dose groups lower than control	Dosed groups similar to control	Dosed groups similar to control
2-Year survival rates	23/50, 18/50, 9/50, 10/51	32/49, 34/50, 31/50, 24/51	39/50, 44/50, 40/50, 44/50	39/50, 42/50, 39/49, 41/50
Nonneoplastic effects	Liver: diffuse fatty change (4/50, 5/50, 16/50, 28/51)	None	None	None
Neoplastic effects	None	None	None	None
Levels of evidence of carcinogenicity	No evidence	No evidence	No evidence	No evidence
Decreased incidences	Adrenal medulla: benign or malignant pheochromocytoma (16/50, 12/50, 9/49, 4/50) Pituitary gland: adenoma (16/50, 16/50, 16/48, 8/50)	Uterus: stromal polyp (10/50, 6/50, 4/50, 1/53)	None	None

Genetic toxicology

Salmonella typhimurium gene mutation:	Negative with and without S9 in strains TA97, TA98, TA100, TA1535, and TA1537
Sister chromatid exchanges	
Chinese hamster ovary cells *in vitro*:	Equivocal with S9; negative without S9
Chromosomal aberrations	
Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Sex-linked recessive lethal mutation in *Drosophila melanogaster*:	Negative administered in feed or by injection

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 neoplasms 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 neoplasm incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in neoplasm 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 neoplasm increase;
- concurrent control neoplasm 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 promethazine hydrochloride on December 1, 1992, 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 NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On December 1, 1992, the draft Technical Report on the toxicology and carcinogenesis studies of promethazine hydrochloride received public review by the National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. K.M. Abdo, NIEHS, introduced the toxicology and carcinogenesis studies of promethazine hydrochloride by discussing the uses of the chemical and the rationale for the study, describing the experimental design, reporting on survival and body weight effects, and commenting on compound-related nonneoplastic lesions in male rats and decreased incidences of neoplastic lesions in male and female rats and female mice. The proposed conclusions were *no evidence of carcinogenic activity* for male or female F344/N rats and *no evidence of carcinogenic activity* for male or female B6C3F$_1$ mice.

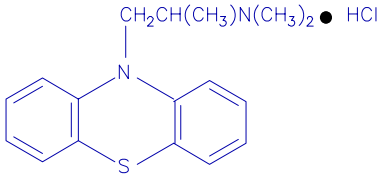
Dr. Bailey, a principal reviewer, agreed with the conclusions. He commented that although mice might have tolerated higher doses, the doses selected were proper based on the results of the 13-week study and were adequate to evaluate carcinogenic potential. He wondered if foreign plant material observed at the sites of nasal inflammatory lesions in the 16-day and 13-week studies might have resulted from a change in animal bedding material. Dr. G.N. Rao, NIEHS, said there was a change in brands, but the hardwood composition of the bedding did not change.

Dr. Ward, the second principal reviewer, agreed in principle with the conclusions. He also thought that mice, especially females, might have tolerated higher doses. He questioned whether reduced incidences of neoplasms were associated with chemical exposure or with the lower survival in the high-dose groups since the reduced incidences were only in high-dose groups and were of marginal statistical significance. Dr. J.K. Haseman, NIEHS, commented that the causes of some of these negative trends were problematic in that they may have been associated with survival and body weight differences. Dr. J.R. Hailey, NIEHS, stated that the known dopaminergic effects of promethazine could be supportive of an association with chemical exposure.

Dr. Davidson, the third principal reviewer, agreed in principle with the conclusions. She said the amount of evidence linking chemical administration with decreased incidence of adrenal neoplasms in male rats was greater than that for pituitary gland neoplasms in male rats and uterine stromal polyps in female rats, and the final conclusions should reflect these differences.

Dr. Bailey moved that the Technical Report on promethazine hydrochloride be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Carlson seconded the motion. Dr. Davidson offered an amendment to revise the second paragraph of the conclusions to reflect her concerns. Mr. Beliczky seconded the amendment, which was approved by seven yes votes to two no votes (Drs. Bailey and Ward) with one abstention (Dr. van Zwieten). Dr. Ward offered an amendment that a sentence be added to the conclusions stating that mice may have tolerated higher doses. The amendment was tabled for lack of a second. The original motion by Dr. Bailey as amended by Dr. Davidson was then accepted by nine yes votes with one abstention (Dr. van Zwieten).

INTRODUCTION



PROMETHAZINE HYDROCHLORIDE

CAS No. 58-33-3

Chemical Formula: $C_{17}H_{20}N_2S \bullet HCl$ Molecular Weight: 320.88

Synonyms: Phenothiazine,10-(2-(dimethylamino)propyl)-,monochlorohydrate; 10H-phenothiazine-10-ethanamine; 10-(2-dimethylamino-2-methylethyl)phenothiazine hydrochloride;*N*-(2'-dimethylamino-2'-methyl)ethylphenothiazine hydrochloride. **Trade names**: Diprazi; Kinetosin; Phenergan; Phenergan hydrochloride; Promine; Pipolfen; Plletia; Prorex; Promantine; Pyrethia; Romergan hydrochloride

CHEMICAL AND PHYSICAL PROPERTIES

Promethazine hydrochloride is a white to faint yellow, virtually odorless, crystalline powder that slowly oxidizes and turns blue with prolonged exposure to air and moisture. It has a melting point range of 230° to 232° C. The compound, prepared from phenothiazinepropyl chloride and dimethylamine in the presence of copper or from Grignard complexes of dimethylaminepropyl halide and phenothiazine, is freely soluble in water, soluble in alcohol and chloroform, and nearly insoluble in acetone, ether, and ethyl acetate (Shearer and Miller, 1976; *Merck Index*, 1983).

USE AND HUMAN EXPOSURE

Promethazine hydrochloride is used as an antihistamine to treat allergies, rhinitis, and mild skin conditions of urticaria and angioedema, and as a cough suppressant. It is also used as a tranquilizer and sedative for the relief of apprehension and for inducement of light sleep. Because of its antiemetic properties, promethazine hydrochloride is used for prevention and control of nausea and vomiting. It is sold as a prescription drug in tablet form (12.5 mg, 25 mg, or 50 mg), as a syrup (6.25 mg or 25 mg promethazine hydrochloride per 5 mL syrup), as a rectal suppository (12.5 mg, 25 mg, or 50 mg), or as an injectable solution (25 mg or 50 mg promethazine hydrochloride per mL) (PDR, 1991). Doses recommended for antiemetic effects are: adults - 25 mg (oral) or 12.5 to 25 mg (intramuscular or intravenous) 4 to 6 times per day; children - 0.25 or 0.5 mg/kg (oral or parenteral) 4 to 6 times per day. Antihistaminic dosage for adults is 12.5 mg given orally 4 times a day or 25 mg given orally at bedtime; intravenous or intramuscular adult dosage is 25 mg repeated in 2 hours, if necessary. Oral or parenteral antihistaminic dose ranges for children are 6.25 to 12.5 mg 3 times per day or 25 mg at bedtime (Osol *et al.*, 1980).

PHYSIOLOGIC EFFECTS

Promethazine hydrochloride is a potent antihistaminic drug. It inhibits the effects of histamine by competitive binding to its H_1-receptors (Garrison, 1990). While complete descriptions of the effects of histamine and promethazine hydrochloride are outside the scope of this report, a brief description is included. The effects of histamine interaction with the H_1-receptors, which are counteracted by promethazine, include smooth muscle stimulation, a drop in blood pressure resulting from a fall in peripheral vessel resistance, gastric acid secretion, and anaphylaxis. Promethazine hydrochloride inhibits the constrictor action of histamine on respiratory smooth muscle in guinea pigs. Guinea pigs challenged with antigens were protected from anaphylactic shock by this drug (Advenier *et al.*, 1979). Promethazine hydrochloride inhibits the chronotropic effect of

histamine. Pretreatment with promethazine hydrochloride (5.4×10^{-3} mmol) decreased by more than 60% the positive chronotropic effect produced by histamine on isolated right atrium of rats (Frkovic *et al.*, 1988). The vasodilator action of histamine in dogs was reduced by an intra-arterial infusion of 10 mg promethazine hydrochloride (Boerth, 1972). Increased vascular permeability induced in rats by mild skin burns, by intrapleural injections of turpentine or rabbit serum, or by intradermal injections of burnt skin extract, was effectively suppressed by pretreatment with intraperitoneal (IP) injections of 25 mg promethazine hydrochloride/kg body weight 30 to 60 minutes before injury (Ryan and Hurley, 1968).

Mice rendered sensitive to the lethal effect of bacterial polysaccharides (LPS) were protected from LPS-induced liver damage and diarrhea accompanying the LPS-induced shock when treated with promethazine (Ferluga *et al.*, 1979). A single intravenous (IV) injection of promethazine hydrochloride (8 mg/kg) inhibited anaphylactic reactions produced by the IP or IV injection of chicken egg white and dextrin (12 mL/kg and 1 mg/kg) or dextran (240 mg/kg) (Ankier and West, 1968).

Histamine stimulation of gastric acid secretion in rats was decreased by an IV injection of 10 mg promethazine hydrochloride/kg, and the rats were protected against gastric ulcers (Farré *et al.*, 1979). However, 50 mg promethazine given intravenously to healthy human subjects did not inhibit stomach gastrin secretion (Kaul *et al.*, 1979).

Promethazine hydrochloride (10 mg, IP injection) potentiated the pressor action of norepinephrine bitartrate (0.001 mg/kg) given by IV injection to rats (Isaac and Goth, 1967). In rats, pulmonary edema induced by an IP injection of adrenaline (12.5 mg/kg) was prevented by pretreatment with promethazine hydrochloride (75 mg/kg) given intramuscularly. The edema was not affected by separate or combined treatment with the alpha adrenergic blocker, tolazoline hydrochloride (9 mg/kg), given intramuscularly. This study suggests that this effect of promethazine involves actions other than alpha-blocking or antihistaminic properties (Achari *et al.*, 1979).

Therapeutic doses of promethazine (25 to 50 mg every 4 to 6 hours) produce central nervous system depression leading to sedation. Promethazine is effective against emesis and motion sickness. The antiemetic effect is due to the dopaminergic antagonistic properties of promethazine (Brunton, 1990). Promethazine may counteract motion sickness by exerting its anticholinergic action on the vestibular apparatus and on the integrative vomiting center and medullary chemoreceptive trigger zone of the midbrain (ANDIS, 1984).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Experimental Animals

Promethazine hydrochloride is readily absorbed from the gastrointestinal tract. In beagles (body weight, 16 to 17 kg), peak plasma concentration was reached 30 minutes after a single intramuscular injection of 50 mg of promethazine hydrochloride and 2 hours after oral administration of a similar dose. The half-life of promethazine hydrochloride in these dogs varied from 8.5 to 27.7 hours. The systemic availability of this drug relative to its availability after intramuscular injection in dogs was estimated to be 55% to 73% and after oral administration was 8.3% to 9.5% (Patel and Welling, 1982). The poor systemic availability of the orally administered promethazine hydrochloride was due to its hepatic metabolism. The contribution of intestinal wall metabolism was minimal (Taylor and Houston, 1983). Rabbits given an intravenous (IV) dose of 5 mg promethazine hydrochloride/kg body weight had a calculated volume of distribution of 17.1 to 33.7 L/kg (Houston and Taylor, 1981). The large volume of distribution is indicative of extensive tissue binding. Whole body autoradiography in squirrel monkeys given an IV infusion of 21.8 mg [^{35}S]-promethazine (specific activity, 6.0 mCi/mg) showed that the drug was distributed solely in lipophilic tissues, including the nervous system, suggesting that this compound is capable of crossing the blood-brain barrier. Wholebody autoradiography in pregnant mice given 0.015 mg/kg (specific activity, 0.3 mCi/g) of [^{35}S]-promethazine showed that this compound can cross the placenta, and distribution in the fetus was not limited to liver and kidneys (Jonkman *et al.*, 1983).

Promethazine hydrochloride was found to be readily metabolized by rats. Maximum excretion occurred in the first 72 hours after administration and lasted no more than 5 days. Six to seven metabolites (identified by their R_f values on thin-layer chromatography) were found in the urine, depending on the dose. Traces of these metabolites were also found in the kidney, spleen, lung,

and stomach (Rusiecki and Wysocka-Pruskazewska, 1969). Hansson and Schimterlöw (1961) found the primary metabolite in the rat to be a sulfoxide. In rat liver homogenates, promethazine hydrochloride has been shown to undergo hydroxylation, dealkylation, and *N*-demethylation (Robinson and Beaven, 1964; Robinson, 1966).

Humans

In volunteers (21 to 27 years old), greater than 80% of a single oral dose (25 mg or 50 mg) of promethazine hydrochloride was absorbed. Peak plasma concentrations were reached within 3 hours, and the mean plasma half-life in volunteers given 25 mg was 12.7 ± 2.4 hours (Moolenaar *et al*., 1981). Volunteers (average age, 25.3 years; average weight, 72.4 kg) given an IV dose of 25 mg had a calculated volume of distribution of 970 ± 262 liters (Taylor *et al*., 1983). In earlier studies with humans, promethazine was highly bound to plasma proteins (93% at 200 ng promethazine/mL plasma and 92.5% at 400 ng promethazine/mL plasma). The elimination half-life measured over a 24-hour period was 4.4 hours after a 12.5 mg IV dose and 7 hours after a 30 mg IV dose (Quinn and Calvert, 1976). Results of a pharmacokinetics study with volunteers receiving a single IV injection (25 mg) or a single oral dose (50 mg) showed that promethazine hydrochloride has a high blood clearance rate (1.14 L/min) and a low renal clearance rate (5.9 mL/min) (Taylor *et al*., 1983). Promethazine (25 to 50 mg) given in a tablet form each day to 147 psychotic patients for periods of one month to several years was excreted mainly as a glucuronide conjugate. The conjugation was not altered by the size of dose or prolonged administration (Nadeau and Sobolewski, 1959).

TOXICITY

Experimental Animals

The reported LD_{50} values for promethazine hydrochloride after various routes of administration were: rats - subcutaneous (400 mg/kg); mice - intravenous (50 mg/kg), subcutaneous (290 mg/kg), and oral (255 mg/kg) (RTECS, 1991). Acute toxicity symptoms included sedation, deterioration of muscle tone followed by tonic-clonic convulsions, and death from respiratory arrest (Leuschner *et al*., 1980).

This drug imitates atropine in reducing the stimulant activity of acetylcholine on the isolated guinea pig ileum (Edge, 1953; Hutcheon, 1953). Perfusion of rat hearts with promethazine hydrochloride (50 to 5,000 ng) caused bradycardia at all doses studied and cardiac arrest at the highest dose (Aronson and Hanno, 1979).

Promethazine hydrochloride, at a dose of 25 mg/kg given by intraperitoneal (IP) injection, protected Sprague-Dawley rats against liver injury caused by carbon tetrachloride. This protective effect may be related to the free radical scavenging property of this drug (Serratoni *et al*., 1969). In *in vitro* studies with rat liver microsome preparations, promethazine hydrochloride was shown to be a potent inhibitor of lipid peroxidation (Malvy *et al*., 1980). The protective effect of promethazine hydrochloride may also be related to its ability to induce liver drug metabolizing enzymes. A 50 mg/kg IP injection given once daily to Sprague-Dawley rats for 2 to 4 days caused an increase (36% to 87%) in cytochrome P_{450} reductase, *N*-demethylase, and P_{450} reductase activities as well as a 10% increase in liver microsomal P_{450} protein (Fernandez and Castro, 1977). Bilirubin metabolism and disposal were enhanced in rats injected subcutaneously with 25 mg promethazine hydrochloride/kg for 21 days (Vaisman *et al*., 1976). This effect was probably due to the induction of enzyme synthesis.

Promethazine hydrochloride blocks luteinizing hormone (LH) stimulation of uterine blood flow (Piacsek and Huth, 1971). It also causes decreased gonadotropin secretion which leads to decreased ovarian weight and prolonged estrous cycle (Koch *et al*., 1971; Simionescu *et al*., 1976). In some studies, promethazine hydrochloride was found to alter prolactin and follicle stimulating hormone secretion (Fuxe *et al*., 1977).

In an immunotoxicity study conducted for NTP, female $B6C3F_1$ mice were given promethazine hydrochloride (0, 20, 40, or 80 mg/kg) in deionized water by gavage once daily for 14 days. Immune tests conducted included delayed cutaneous hypersensitivity reaction (6 animals per dose group), lymphocytic blastogenesis assay (6 animals per dose group), plaque forming assay (6 animals per dose group), and neoplasm susceptibility assay (20 animals per dose group). In addition, hematology, clinical chemistry, body weights, and organ weights were determined. There were no treatment-related effects on hematology or clinical chemistry parameters. Spleen weights were slightly increased in treated animals suggesting that promethazine causes some myelotoxicity. Except for a slight but statistically significant immunosuppression (T cell) in the 80 mg/kg group, there were no other consistent immunotoxic effects

found. The report on the immunology study conducted by Litton Bionetics, Inc., is on file at the National Institute of Environmental Health Sciences. These results are in agreement with the findings of Rubinstein *et al.* (1976), that promethazine decreases neonatal number and function of T cells.

Humans

Adverse reactions to promethazine hydrochloride in clinical trials involved the gastrointestinal tract, the nervous system, the cardiovascular system, and the skin. Gastrointestinal symptoms included dry mouth, epigastric distress, loss of appetite, nausea, vomiting, diarrhea, and constipation (Clarke and Dundee, 1971; Zepp *et al.*, 1975). Symptoms due to nervous system effects included restlessness, dizziness, lassitude, and incoordination (Clarke and Dundee, 1971). Patients with chronic renal failure given promethazine hydrochloride developed extreme restlessness, auditory and visual hallucinations, and episodes of belligerent behavior (McAllister *et al.*, 1978; Shawn and McGuigan, 1984). Tachycardia, bradycardia, fainting, and decrease in blood pressure have been reported after use of promethazine hydrochloride. Venous thrombosis at the injection site has been observed (PDR, 1991). This chemical also produces extrapyramidal effects (diplopia, dyskinesia, and respiratory depression), cholestatic jaundice, leukopenia, agranulocytosis, aplastic anemia, thrombocytopenic purpura, and a disorder of the crystalline lens (*AMA Drug Evaluations*, 1971; PDR, 1991). Photosensitive and contact dermatitis were observed in patients using promethazine ointment (Leong, 1970). An overdose of promethazine hydrochloride may result in deep sleep and coma in adults, and hyperexcitability, abnormal movements, nightmares, and respiratory distress in children (ANDIS, 1984).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Experimental Animals

Promethazine hydrochloride (1 mg/kg per day) given subcutaneously from postcoitum until the fifth day of insemination blocked implantation in mice (El-Din *et al.*, 1988). The authors speculated that this effect may be due to the effect of promethazine on the central nervous system. Complete fetal resorption as well as reduced total uterine-fetal weight and average fetal weights occurred in pregnant rats given this drug at a dose of 20 mg/kg orally on days 5 to 16 of gestation (DiPasquale and Richter, 1974). Female rats, 21 to 41 days of age, given a daily subcutaneous injection of promethazine hydrochloride (10 mg/kg) showed a decrease in ovarian weight, a decrease in the number of follicles and corpora lutea in the ovary, prolongation of the estrous cycle, and a decrease in the amount of gonadotropin-releasing factors in the hypothalamus (Koch *et al.*, 1971). These data suggest that this drug selectively inhibits gonadotropin secretion in the rat.

Humans

Promethazine hydrochloride was found to impair the phagocytic capacity of human fetal macrophages (Gusdon *et al.*, 1974). The ameliorating effect of this drug on erythroblastosis fetalis was attributed to its inhibitory effect of phagocytosis. Maternal promethazine hydrochloride therapy was found to interfere with neonatal immunologic functions (Gusdon, 1981). Infants born to mothers administered 75 to 150 mg promethazine hydrochloride 2 to 24 weeks prior to delivery showed a decrease in the number and function of T cells and B cells in the cord blood (Rubinstein *et al.*, 1976).

CARCINOGENICITY

Experimental Animals

No carcinogenicity studies of promethazine hydrochloride were found in the literature. Chlorpromazine (a structurally related drug) was not carcinogenic to mice given 5 mg/kg per day by gavage for 2 years (Lacassagne *et al.*, 1959; Roe, 1966).

Humans

A human retrospective survey of prescription drug use by cancer patients showed a negative correlation between promethazine hydrochloride use and skin cancer (Freidman and Ury, 1980). A similar negative association was found in a more recent survey of 417 users of this drug (Selby *et al.*, 1989). However, these authors did report a positive association of promethazine with liver cancer in these users.

GENETIC TOXICITY

Promethazine hydrochloride contains no molecular substructures which are alerting for DNA reactivity (Tennant and Ashby, 1991), and the available data indicate that it is not genotoxic. Promethazine hydrochloride did not induce gene mutations in any of several strains of *Salmonella typhimurium* with or without Aroclor-induced S9 activation (Mortelmans

et al., 1986) nor was it mutagenic to germ cells of male *Drosophila melanogaster* treated either by feeding or injection (Yoon *et al.*, 1985). Promethazine hydrochloride did not induce DNA strand breaks (Brambilla *et al.*, 1985) or chromosomal aberrations (Galloway *et al.*, 1987) in cultured Chinese hamster ovary cells; results of a test for induction of sister chromatid exchanges in cultured Chinese hamster ovary cells were considered equivocal (Galloway *et al.*, 1987). Promethazine hydrochloride was reported to be negative for induction of unscheduled DNA synthesis in male F344 rat hepatocytes treated *in vivo* (Mirsalis *et al.*, 1983).

STUDY RATIONALE

Promethazine hydrochloride was nominated by the Food and Drug Administration because of its widespread use in human medicine and because of the lack of data on its carcinogenic potential. Additionally, some structural features and relationship to other drugs made this drug a suspect carcinogen. Phenothiazines, including promethazine hydrochloride, are amines that could be converted to carcinogenic nitroso compounds by reaction with nitrite under acidic conditions. Thus, *N*-nitroso compounds could be formed in the stomach from drugs containing secondary and tertiary amines. Promethazine hydrochloride is a tertiary amine. Furthermore, phenothiazines and other neuroleptic drugs are known to increase prolactin secretion. Increases in prolactin levels were associated with the increase in mammary neoplasms in rats and mice (*AMA Drug Evaluations*, 1971). Oral exposure is the most common route of human exposure; therefore, water gavage administration was chosen for these NTP studies.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PROMETHAZINE HYDROCHLORIDE

Promethazine hydrochloride, United States Pharmacopeia (USP) grade, was obtained in one lot (31321) from Napp Chemicals, Inc. (Lodi, NJ). Certification was received from the supplier that the lot met all USP XX Compendium requirements. 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 promethazine hydrochloride studies are on file at the National Institute of Environmental Health Sciences (NIEHS). The methods and results of these studies are detailed in Appendix H.

The chemical, a white to faint yellow crystalline powder, was identified as promethazine hydrochloride by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopies. The purity was determined by elemental analyses, Karl Fischer water analysis, titration of the amine group, ultraviolet spectroscopy, thin-layer chromatography, and gas chromatography. Elemental analyses for carbon, hydrogen, nitrogen, sulfur, and chlorine were in agreement with the theoretical values for promethazine hydrochloride. Karl Fischer analysis indicated 0.03% ± 0.01% water. Titration of one amine group with perchloric acid indicated a purity of 100.9% ± 0.5%. An ultraviolet spectrophotometric assay versus a USP promethazine hydrochloride reference standard indicated a relative purity of 99.4%. One gas chromatography system resolved a major peak and three impurities with a combined relative area of approximately 1%, while a second gas chromatography system indicated a major peak and a single impurity with an area 0.30% of the major peak area. Gas chromatographic major peak comparison between this lot and a USP standard indicated a relative purity of 99.5% ± 1.2%. The overall purity was determined to be greater than 99%.

Stability studies performed using gas chromatography indicated that promethazine hydrochloride was stable for 2 weeks at temperatures up to 60° C when stored in sealed containers in the dark. Periodic reanalysis of the bulk chemical by the study laboratory using gas chromatography and titration of the amine group indicated no significant deterioration of the bulk chemical during the studies.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by dissolving promethazine hydrochloride in deionized water (Table H1). The mixture was stored in labeled, amber glass dosing bottles for no longer than 3 weeks at 0 ± 5° C.

Dose formulation stability analyses of the 0.5 mg/mL dose formulation were performed by the analytical chemistry laboratory. The stability of the dose formulations was confirmed for at least 3 weeks when stored in the dark at room temperature and for at least 3 hours when stored under simulated dosing room conditions.

Periodic analyses of the dose formulations of promethazine hydrochloride were conducted at the study laboratory using ultraviolet spectrophotometry for the 16-day and 13-week studies and gas chromatography for the 2-year studies. During the 16-day studies, all dose formulations for rats and mice were within 10% of target concentrations (Table H2). During the 13-week studies, 23 of the 28 dose formulations analyzed were within 10% of the target concentrations (Table H3). During the 2-year studies, dose formulations were analyzed approximately every 8 weeks; 122 of the 123 dose formulations analyzed were within 10% of the target concentrations. Results of the dose formulation analyses for the 2-year studies are presented in Table H4. Results of periodic referee analyses performed by the analytical chemistry laboratory using gas chromatography indicated good agreement with the results obtained by the study laboratories (Table H5).

16-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD). At receipt, the rats were an average of 7 weeks old, and the mice were an average of 7 to 8 weeks old. The rats were quarantined for 15 days and the mice for 14 days before dosing began. Before the beginning of the studies, two animals of each species and sex were randomly selected for parasite evaluation and gross observation for evidence of disease.

Groups of five male and five female rats received promethazine hydrochloride in deionized water by gavage at doses of 18.5, 55.5, 166.5, 500, or 1,500 mg/kg body weight, and the control group received deionized water. Groups of five male and five female mice received promethazine hydrochloride by gavage at doses of 18.8, 37.5, 75, 150, or 300 mg/kg body weight, and the control group received deionized water. All doses were given once daily for 5 days per week, with at least two consecutive dosing days at the end of the studies for a total of 12 dosing days. Animals were housed five per cage; water and feed were available *ad libitum*. Clinical findings for rats and mice were recorded once daily. The animals were weighed at study initiation, at day 7, and at the end of the studies. Details of study design and animal maintenance are summarized in Table 1.

At the end of the 16-day studies, blood from the retroorbital sinus of all mice was collected for hematology analyses. The clinical pathology parameters measured are listed in Table 1. A gross necropsy was performed on all rats and mice. The brain, heart, right kidney, liver, lung, right testis, and thymus from all rats and mice were weighed. Histopathologic examinations were conducted on all control animals, all rats receiving 166.5 mg/kg, all male mice receiving 150 mg/kg, and all female mice receiving 75 mg/kg. The tissues routinely examined microscopically are listed in Table 1.

13-WEEK STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD). At receipt, the animals were an average of 7 weeks old. The rats and mice were quarantined for 14 days before dosing began. Before the beginning of the studies, five animals of each species and sex 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 control animals of each species and sex using the protocols of the NTP Sentinel Animal Program (Appendix J).

Groups of 10 male and 10 female rats received promethazine hydrochloride in deionized water by gavage at doses of 3.7, 11.1, 33.3, 100, or 300 mg/kg body weight, and the control group received deionized water alone for 13 weeks. Groups of 10 male and 10 female mice received promethazine hydrochloride by gavage at doses of 5, 15, 45, 135, or 405 mg/kg body weight, and the control group received deionized water for 13 weeks. All doses were given once daily for 5 days per week, with at least two consecutive dosing days at the end of the studies. Animals were housed five per cage; water and feed were available *ad libitum*. Clinical findings were recorded once weekly. The animals were weighed at the beginning of the studies, weekly, and at the end of the studies. Further details of study design and animal maintenance are summarized in Table 1.

At the end of the 13-week study, blood was collected from the retroorbital sinus of mice for hematology and clinical chemistry analyses. The hematology parameters measured are listed in Table 1. A necropsy was performed on all animals. The brain, heart, right kidney, liver, lung, right testis, and thymus of rats and mice 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 6 µm, and stained with hematoxylin and eosin. A complete histopathologic examination was performed on all animals found dead or moribund during the study, all control animals, all 100 mg/kg rats, and all 135 mg/kg mice. Table 1 lists the tissues and organs routinely examined.

2-YEAR STUDIES

Study Design

Groups of 60 male and 60 female rats received promethazine hydrochloride in 5 mL deionized water by gavage at doses of 0, 8.3, 16.6, or 33.3 mg/kg body weight for 103 weeks; groups of 60 male and 60 female mice received promethazine hydrochloride in 10 mL deionized water by gavage at doses of 0, 11.25, 22.5, or 45 mg/kg (male) and 0, 3.75, 7.5, or 15 mg/kg (female) for 103 to 104 weeks. Ten rats and ten mice per dose group were evaluated after 15 months of chemical administration.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility (Frederick, MD) for use in the 2-year studies. Rats were quarantined for 14 to 15 days, and mice were quarantined for 12 to 14 days before the beginning of the studies. Five rats and five mice of each sex were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats and mice were 6 to 7 weeks old at the beginning of the 2-year studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix J).

Animal Maintenance

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

Clinical Examinations and Pathology

All animals were observed twice daily. Animals were weighed and clinical findings were recorded weekly for the first 13 weeks and every 4 weeks thereafter. Up to 10 rats and 10 mice from each group were selected for interim evaluations after 15 months. Blood was collected from the tail of rats and mice to determine hematology parameters and from the external jugular vein for clinical chemistry parameters at the 15-month interim evaluations. The brain, right kidney, and liver were weighed at the 15-month interim evaluations.

A complete necropsy was performed on all animals. At necropsy, all organs and tissues were examined for gross lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. Microscopic examinations were performed on all tissues with grossly visible lesions. A complete histopathologic evaluation was performed on all animals at the 15-month interim evaluation and at the end of the studies; tissues examined 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 microscopic slides, paraffin blocks, and residual wet tissues were sent to the NTP Archive for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated at an independent quality assessment laboratory. A quality assessment pathologist examined the liver, intestine, and ovary in rats and the liver in mice for accuracy and consistency of lesion diagnosis. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated.

The quality assessment report and slides were submitted to the NTP Pathology Working Group (PWG) chair, who reviewed the diagnosis of mononuclear cell leukemia in rats; the liver in rats and mice; the kidney, clitoral gland, and lung in rats; and any tissues for which a disagreement in diagnosis between the laboratory and quality assessment pathologists existed. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chair 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. Thus, the final diagnoses represent a consensus of contractor pathologists 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 diagnosed lesions for each tissue type were evaluated separately or combined according to the guidelines of McConnell *et al.* (1986).

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals found dead of other than natural causes 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 as presented in Tables A1, A5, B1, B5, C1, C4, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the ratio of the number of affected animals to the number of animals with the site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) 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.

Analysis of Neoplasm Incidences

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

In addition to logistic regression, other methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These methods include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal lesions, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart *et al.*, 1979), procedures based on the overall proportion of lesion-bearing animals. Tests of significance included pairwise comparisons of each dosed group with controls, and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of lesion incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, see Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test was used, a procedure based on the overall proportion of affected animals.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between dosed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Clinical chemistry and hematology data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Dunn (1964) and Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of 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). Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

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

Quality Assurance Methods

The 16-day, 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 covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. 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, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of promethazine hydrochloride was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and induction of sex-linked recessive lethal mutations in *Drosophila melanogaster*. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of promethazine hydrochloride 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 structure and responses 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 chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (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 do not correlate 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 currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complimentarity 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 is not yet defined.

TABLE 1
Experimental Design and Materials and Methods in the Carcinogenesis Studies of Promethazine Hydrochloride

16-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
Litton Bionetics, Inc. (Kensington, MD)	Same as 16-day studies	EG&G Mason Research Institute (Worcester, MA)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Same as 16-day studies	Same as 16-day studies
Animal Source		
Frederick Cancer Research Facility (Frederick, MD)	Same as 16-day studies	Same as 16-day studies
Size of Study Groups		
5 males and 5 females	10 males and 10 females	Interim: 10 males and 10 females Terminal: 50 males and 50 females
Doses		
Rats: 18.5, 55.5, 166.5, 500, or 1,500 mg/kg in 5 mL deionized water/kg body weight Mice: 18.8, 37.5, 75, 150, or 300 mg/kg in 10 mL deionized water/kg body weight	Rats: 3.7, 11.1, 33.3, 100, or 300 mg/kg in 5 mL deionized water/kg body weight Mice: 0, 5, 15, 45, 135, or 405 mg/kg in 10 mL deionized water/kg body weight	Rats: 0, 8.3, 16.6, or 33.3 mg/kg in 5 mL deionized water/kg body weight Mice: 0, 11.25, 22.5, or 45 (male) and 0, 3.75, 7.5, or 15 (female) in 10 mL deionized water/kg body weight
Time Held Before Study		
Rats: 15 days Mice: 14 days	Rats: 14 days Mice: 14 days	Rats: 14 days (male) 15 days (female) Mice: 12 days (male) 14 days (female)
Average Age When Placed on Study		
Rats: 9 weeks Mice: 9-10 weeks	Rats: 9 weeks Mice: 9 weeks	Rats: 6-7 weeks Mice: 6-7 weeks
Date of First Dose		
Rats: 24 February 1982 Mice: 23 February 1982	Rats: 15 June 1982 Mice: 8 June 1982	Rats: 6 March 1985 (male) 20 March 1985 (female) Mice: 29 April 1985 (male) 1 May 1985 (female)

TABLE 1
Experimental Design and Materials and Methods in the Carcinogenesis Studies of Promethazine Hydrochloride (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Duration of Dosing		
16 days	13 weeks	Rats: interim - 66 weeks (male), 65 weeks (female); terminal - 103 weeks Mice: interim - 66 weeks; terminal - 103 weeks (male), 104 weeks (female)
Necropsy Dates		
Rats: 12 March 1982 Mice: 11 March 1982	Rats: 16-17 September 1982 Mice: 8-10 September 1982	Rats: interim - 9-10 June 1986 (male) and 12-13 June 1986 (female); terminal - 19 February 1987 (male 33.3 mg/kg group), 27 February-4 March 1987 (all other males), and 18-26 March 1987 (female); Mice: interim - 30 July-1 August 1986 (male); 5-7 August 1986 (female) terminal - 27 April-5 May 1987 (male) and 6-14 May 1987 (female)
Average Age at Necropsy		
11-12 weeks	22-23 weeks	Interim: Rats: 71-73 weeks; Mice: 72-73 weeks Terminal: Rats: 109-112 weeks; Mice: 110-113 weeks
Method of Sacrifice		
CO_2	CO_2	CO_2
Animals per Cage		
5	5	Rats: 5 Mice: 1
Method of Animal Distribution		
Animals were randomized by weight with a computer-generated double randomization program.	Same as 16-day studies	Same as 16-day studies

TABLE 1
Experimental Design and Materials and Methods in the Carcinogenesis Studies of Promethazine Hydrochloride (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Method of Animal Identification Rats: ear tag and cage card Mice: ear punch, toe clip, cage card	Same as 16-day studies	Toe clip
Diet NIH-07 Open Formula Rat and Mouse Ration (Zeigler Brothers, Inc., Gardners, PA); available *ad libitum*	Same as 16-day studies	Same as 16-day studies
Water Tap water from City of Rockville water supply system from Washington Suburban Sanitary Commission acidified with hydrochloric acid to pH of approximately 2.5 and dispensed via 16-oz. (rats) or 8-oz. (mice) glass bottles equipped with stainless steel sipper tubes and hard rubber stoppers (Lab Products, Inc., Garfield, NJ; Ancare Co., Manhasset, NY), replaced twice weekly; available *ad libitum*	Same as 16-days studies	Tap water (City of Worcester) via automatic watering system (Edstrom Industries, Inc., Waterford, WI); available *ad libitum*
Cages Polycarbonate (Lab Products, Inc., Garfield, NJ), changed twice weekly, not rotated	Same as 16-day studies but rotated during course of study	Same as 16-day studies but rotated every 2 weeks
Bedding Sani-chips heat-treated hardwood chips (P.J. Murphy Forest Products, Inc., Rochelle Park, NJ), changed twice weekly	Same as 16-day studies	BetaChips® hardwood chips (Northeastern Products Corporation, Warrensburg, NY), changed twice weekly (rats) and once weekly (mice)
Cage Filters Nonwoven polyester filter material sheets (Snow Filtration Company, Cincinnati, OH), changed once every 2 weeks	Same as 16-day studies	Same as 16-day studies

TABLE 1
Experimental Design and Materials and Methods in the Carcinogenesis Studies of Promethazine Hydrochloride (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Racks		
Aluminum (Lab Products, Inc., Garfield, NY), changed once every 2 weeks, not rotated	Same as 16-day studies	Stainless steel (Lab Products, Inc., Garfield, NY), changed once every 2 weeks, rotated clockwise within study room every 2 weeks.
Animal Room Environment		
Average temperature: 22°-24° C Relative humidity: 30%-70% Fluorescent light: 12 hours/day Room air changes: 12-15 changes/hour	Same as 16-day studies	Average temperature: 21°-23° C Relative humidity: 39%-53% Fluorescent light: 12 hours/day
Type and Frequency of Observation		
Observed and clinical observations recorded once daily; weighed initially, after first week, and at end of the studies	Observed and clinical observations recorded once weekly; weighed initially, weekly, and at the end of the studies	Observed and clinical observations recorded once/week for 13 weeks and every 4 weeks thereafter; weighed initially, once/week for 13 weeks and every 4 weeks thereafter; feed consumption measured every 4 weeks
Clinical Pathology		
Hematology (mice only): hematocrit, hemoglobin, erythrocyte count, reticulocytes, and leukocyte count and differential	***Hematology (mice only):*** hematocrit, hemoglobin, erythrocyte count, reticulocytes, and leukocyte count and differential	Clinical pathology studies on 10 rats and 10 mice from each dose group at 15 months. ***Hematology:*** hematocrit, hemoglobin, erythrocyte count, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, leukocyte count and differential, and nucleated erythrocytes ***Clinical Chemistry:*** alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, sorbitol dehydrogenase, 5'-nucleotidase
Necropsy		
Necropsy was performed on all animals. The following organs were weighed: brain, heart, right kidney, liver, lung, right testis, and thymus.	Same as 16-day studies	Necropsy was performed on all animals. The following organs were weighed at 15 months: brain, right kidney, and liver.

TABLE 1
Experimental Design and Materials and Methods in the Carcinogenesis Studies of Promethazine Hydrochloride (continued)

16-Day Studies	13-Week Studies	2-Year Studies
Histopathology		
Complete histopathology was performed on all control animals, all rats that received 166.5 mg/kg, all male mice that received 150 mg/kg, and all female mice that received 75 mg/kg. Tissues examined included: adrenal gland, brain, clitoral gland, epididymis, esophagus, gallbladder (mice), gross lesions, heart, large intestine (cecum, colon, rectum), kidney, liver, lung, lymph node (mandibular), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland (mice), skin, small intestine, spleen, sternum (with marrow), stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. The nose, trachea, and lung from all 0, 18.5, 55.5, and 166.5 mg/kg rats and from all mice except the 300 mg/kg dose group and 150 mg/kg females were also examined microscopically.	Complete histopathology was performed on all animals found dead or moribund during the studies, on 0 and 100 mg/kg rats, and on 0 and 135 mg/kg mice. Tissues examined included: adrenal gland, brain, clitoral gland, epididymis, esophagus, gallbladder (mice), gross lesions, heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph node (mandibular), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, small intestine (duodenum, jejunum, ileum), spleen, sternum (with marrow), stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus. The nose, trachea, and lung of 3.7, 11.1, 33.3, and 300 mg/kg rats and 5, 15, 45, and 405 mg/kg mice were also examined microscopically.	Complete histopathology was performed on all animals. Tissues examined included: adrenal gland, brain, clitoral gland, epididymis, esophagus, gallbladder (mice), gross lesions, heart, kidney, large intestine (cecum, colon, rectum), liver, lung, lymph node (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, small intestine (duodenum, jejunum, ileum), spleen, sternum (with marrow), stomach, testis, thymus, thyroid gland, trachea, urinary bladder, and uterus.

RESULTS

RATS

16-DAY STUDY

One male and one female rat receiving 166.5 mg/kg, four males and four females receiving 500 mg/kg, and all male and female rats receiving 1,500 mg/kg promethazine hydrochloride died before the end of the study (Table 2). Most deaths occurred within the first four days of dosing. Final mean body weights and body weight gains in rats that received 166.5 mg/kg were significantly lower than those of the controls. The mean body weight gains in the 55.5 mg/kg groups were also

TABLE 2
Survival and Mean Body Weights of Rats in the 16-Day Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	150 ± 5	203 ± 5	54 ± 1	
18.5	5/5	151 ± 2	202 ± 3	50 ± 2	99
55.5	5/5	145 ± 3	182 ± 5	37 ± 4*	89
166.5	4/5[c]	146 ± 4	154 ± 16**	8 ± 12**	75
500	1/5[d]	143 ± 4	136	–14	67
1,500	0/5[e]	147 ± 1	)	)	)
Female					
0	5/5	127 ± 3	142 ± 3	15 ± 1	
18.5	5/5	126 ± 3	141 ± 3	14 ± 2	99
55.5	5/5	127 ± 2	132 ± 3	5 ± 1**	93
166.5	4/5[c]	124 ± 5	125 ± 6**	1 ± 1**	88
500	1/5[f]	127 ± 1	107	–20	75
1,500	0/5[g]	126 ± 1	)	)	)

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Number of animals surviving/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. No data were calculated for groups with 100% mortality. No standard errors were calculated for groups with high mortality.
[c] Day of death: 4
[d] Day of death: 2, 3, 4, 6
[e] Day of death: 1, 2, 2, 3, 3
[f] Day of death: 2, 3, 4, 11
[g] Day of death: 1 (accidental death), 2, 2, 2, 2

significantly lower than those of the controls.

Clinical findings included decreased activity and ocular discharge throughout the study in most males and females receiving 166.5, 500, or 1,500 mg/kg promethazine hydrochloride. Abnormal respiratory sounds also occurred in these dose groups and peaked on day 3. Rats receiving 166.5 or 500 mg/kg also had crusts around the nose. Additionally, females receiving 166.5 or 500 mg/kg experienced tremors during the first 3 days of dosing. Absolute and relative thymus weights of rats receiving 166.5 mg/kg were significantly lower than those of controls (Table F1). There were dose-related increases in absolute liver weights and statistically significant increases in relative liver weights of rats receiving 18.5, 55.5, and 166.5 mg/kg. This effect was probably related to debilitation as evidenced by the very low mean body weight gain. Other relative organ weight increases were attributed to disproportional differences in overall body weight (Table F1). No dose-related gross lesions were observed at necropsy, and the only microscopic changes observed included a dose-related increase in the incidence of suppurative inflammation in the respiratory tract mucosa in rats receiving 55.5 (nose) or 166.5 mg/kg (nose and trachea) (Table 3). Foreign plant material was occasionally observed at the sites of these inflammatory lesions.

TABLE 3
Incidences of Selected Lesions in Rats in the 16-Day Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	0	18.5	55.5	166.5
Male				
Nose[a]	5	5	5	5
Inflammation[b]	0	0	1 (2.0)[c]	2 (3.0)
Trachea	5	5	5	5
Inflammation	0	0	0	2 (3.5)
Female				
Nose	5	5	5	5
Inflammation	0	0	3 (2.3)	3 (2.7)
Trachea	5	5	5	5
Inflammation	0	0	0	1 (5.0)

[a] Number of animals with organ examined microscopically. Animals in the 500 and 1,500 mg/kg groups died within the first 4 days of the study, and tissues were not 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; 5 = severe

13-WEEK STUDY

Six males and nine females receiving 300 mg/kg and one female receiving 100 mg/kg died at random intervals throughout the study (Table 4). One additional male receiving 300 mg/kg died after dosing was completed. Final mean body weights and mean body weight gains (body weights, 19 to 22%; weight gain, 29% to 36%) in male rats receiving 100 and 300 mg/kg were significantly lower than those of the controls. The mean body weight gain of 100 mg/kg females was significantly (14%) lower than that of the controls.

Clinical findings were noted throughout the study, especially in animals receiving 100 or 300 mg/kg. Clinical findings of hunched posture, labored respiration, and abnormal respiratory sounds were more evident in these two dose groups beginning week 9. The relative brain, kidney, heart, and testis weights of 100 mg/kg males were significantly greater than those of the controls and were attributed to disproportional whole body weight decreases relative to the decreases in these organ weights (Table F2). The absolute and relative thymus weights of male rats receiving 300 mg/kg were significantly lower than those of the controls and are likely related to debilitation and stress. The absolute and relative liver weights of all male and female rats receiving promethazine hydrochloride were greater than those of the controls. The absolute and relative liver weights of males in the 11.1 mg/kg group and males and females in the 33.3 and 100 mg/kg groups were significantly greater than those of the controls.

TABLE 4
Survival and Mean Body Weights of Rats in the 13-Week Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	119 ± 4	337 ± 7	218 ± 5	
3.7	10/10	120 ± 4	330 ± 8	211 ± 5	98
11.1	10/10	119 ± 4	334 ± 8	215 ± 5	99
33.3	10/10	120 ± 3	321 ± 7	202 ± 5	95
100	10/10	118 ± 4	272 ± 9**	154 ± 7**	81
300	4/10[c]	119 ± 5	262 ± 22**	140 ± 16**	78
Female					
0	10/10	102 ± 2	187 ± 4	85 ± 3	
3.7	10/10	104 ± 2	197 ± 3	93 ± 3	105
11.1	10/10	104 ± 2	194 ± 3	90 ± 2	104
33.3	10/10	104 ± 1	185 ± 4	81 ± 3	99
100	9/10[d]	104 ± 2	177 ± 4	73 ± 4*	95
300	1/10[e]	105 ± 2	129	25	69

* Significantly different ($P \le 0.05$) from the control group by Williams' or Dunnett's test
** $P \le 0.01$
[a] Number of animals surviving/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. No standard errors were calculated for groups with high mortality.
[c] Week of death: 3, 6, 6, 8, 11, 13
[d] Week of death: 4
[e] Week of death: 1, 1, 2, 3, 4, 7, 10, 12, 13

No chemical-related gross lesions were observed at necropsy, and the only significant microscopic changes included a marginal increase in the incidence of inflammation in the respiratory tract (nose, trachea, lung) in all rats receiving 100 or 300 mg/kg (Table 5). Generally, nasal inflammation (acute rhinitis) consisted of serous exudate, low numbers of neutrophils, and a minimal amount of fibrin. In the more severe inflammatory lesions, neutrophils were the most prominent component. Necrosis and desquamation of epithelial cells were occasionally observed and, at some sites, basement membranes were covered by attenuated cells (regeneration). Foreign plant material was occasionally present within the respiratory tract and was generally associated with substantial neutrophilic exudation. Lesions in the trachea and bronchiolar airways were similar to those described in the nose. Fibrinopurulent tracheitis and bronchopneumonia were seen only in rats with moderate to severe suppurative rhinitis. Severe tracheitis and bronchopneumonia occurred only in animals that died early in the study; bronchopneumonia usually involved only a portion of a lung lobe and was characterized by an exudate of neutrophils and fibrin (fibrinopurulent) within terminal airways and the surrounding alveoli. In some animals, the respiratory tract lesions were considered severe enough to have caused debilitation or death. These clinical signs and respiratory tract lesions were similar to those observed in the 16-day studies, and it was not determined whether promethazine hydrochloride was introduced into the respiratory tract systemically or as refluxed material subsequent to the gavage procedure. Gavage errors may have exacerbated the bronchopneumonia in some of these animals. The plant material observed in some nasal lesions was attributed to inhalation of feed or bedding material by animals, probably during times of respiratory distress. Alternatively, if there indeed was gastric reflux, plant material (from feed) could have been included.

There was a dose-related increase in the incidence and severity of olfactory epithelium degeneration, a minimal to mild change affecting scattered olfactory epithelial cells in the posteriodorsal region of the nasal cavity. Affected cells contained variably sized single or, less frequently, multiple clear vacuoles, which occasionally contained eosinophilic fibrillar strands. The change has not been observed in previous studies, and its significance was undetermined. The low incidences in the 300 mg/kg groups were attributed to insufficient time for development, because most animals in these groups died very early in the study (Table 5).

Dose Selection Rationale

Based on mortality and body weight changes observed at higher levels, gavage doses of promethazine hydrochloride selected for the 2-year study in rats were 0, 8.3, 16.6, and 33.3 mg/kg.

TABLE 5
Incidences of Selected Lesions in Rats in the 13-Week Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	0	3.7	11.1	33.3	100	300
Male						
Nose[a]	10	10	10	10	10	6
Inflammation[b]	0	0	0	0	1 (3.0)[c]	5** (2.0)
Trachea	10	10	10	10	10	6
Inflammation	0	0	0	0	1 (1.0)	4** (2.8)
Lung	10	10	10	10	10	7
Hemorrhage	1 (1.0)	0	0	0	0	4 (2.3)
Edema	0	0	0	0	0	2 (2.5)
Bronchopneumonia	0	0	0	0	0	3 (2.7)
Olfactory Epithelium	10	10	10	10	10	6
Vacuolar Degeneration	0	0	3 (1.0)	10** (1.8)	10** (2.1)	2 (1.0)
Female						
Nose	10	10	10	10	10	9
Inflammation	0	0	0	0	1 (2.0)	8** (3.3)
Trachea	10	10	10	10	10	8
Inflammation	0	0	0	0	0	6** (3.5)
Lung	10	10	10	10	10	9
Hemorrhage	0	0	0	0	1 (3.0)	2 (2.0)
Edema	0	0	0	0	0	2 (2.5)
Bronchopneumonia	0	0	0	0	0	1 (5.0)
Olfactory Epithelium	10	10	10	10	10	8
Vacuolar Degeneration	0	0	7** (1.1)	9** (2.7)	8** (1.4)	0

** Significantly different ($P \leq 0.01$) from the control group by Fisher's exact test
[a] Number of animals with organ 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; 5 = severe

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female rats are shown in Table 6 and in the Kaplan-Meier curves in Figure 1. Survival was significantly lower in male rats receiving 16.6 mg/kg and in males and females receiving 33.3 mg/kg.

Body Weights and Clinical Findings

The mean body weight of male rats receiving 33.3 mg/kg was lower than that of the controls throughout the study and was 10% lower than that of the controls at the end of the study (Figure 2 and Table 7). Final mean body weights of females receiving 16.6 and 33.3 mg/kg were 9% and 11% lower than those of the controls (Figure 2 and Table 8); in the 10 females evaluated at 15 months from these two dose groups, the final mean body weights were 10% and 11% lower, respectively (Table F3).

Abnormal posture was observed primarily in the 33.3 mg/kg females (vehicle control, 0/60; 8.3 mg/kg, 2/60; 16.6 mg/kg, 3/60; 33.3 mg/kg, 39/60). This behavior was first noticed in 39 of 60 females in the 33.3 mg/kg group on study day 37 and with much less frequency at subsequent time points, but was noted as late as day 616. Abnormal posture was observed immediately after oral gavage dosing when the 33.3 mg/kg females moved to the rear of the cage and assumed a hunched posture; therefore, this was not considered a chemical-related effect, but was likely related to discomfort associated with the gavage administration.

Hematology and Clinical Chemistry

There were no biologically significant differences in the hematology or clinical chemistry parameters measured in males and females at the 15-month interim evaluation (Table G1).

TABLE 6
Survival of Rats in the 2-Year Gavage Study of Promethazine Hydrochloride

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	9
Moribund	24	27	27	21
Natural deaths	3	5	12	20
Animals surviving to study termination[b]	23	18	11	10
Percent probability of survival at end of study[c]	46	36	22	20
Mean survival (days)[d]	635	597	604	570
Survival analyses[e]	P<0.001	P=0.153	P=0.009	P<0.001
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	7
Accidental deaths[a]	1	0	0	2
Moribund	12	12	10	11
Natural deaths	5	4	9	16
Animals surviving to study termination[f]	32	34	31	24
Percent probability of survival at end of study	66	68	62	49
Mean survival (days)	628	655	633	565
Survival analyses	P=0.009	P=0.808N	P=0.880	P=0.047

[a] Censored from survival analyses
[b] Includes four males receiving 8.3 mg/kg and two males receiving 16.6 mg/kg that died during the last week of the study.
[c] Kaplan-Meier determinations
[d] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[e] The result of the life table trend test (Tarone, 1975) is in the control column, and the results of the life table pairwise comparisons (Cox, 1972) with the controls are in the dosed columns. A lower mortality in a dose group is indicated by N.
[f] Includes three control females and one female receiving 8.3 mg/kg that died during the last week of the study.

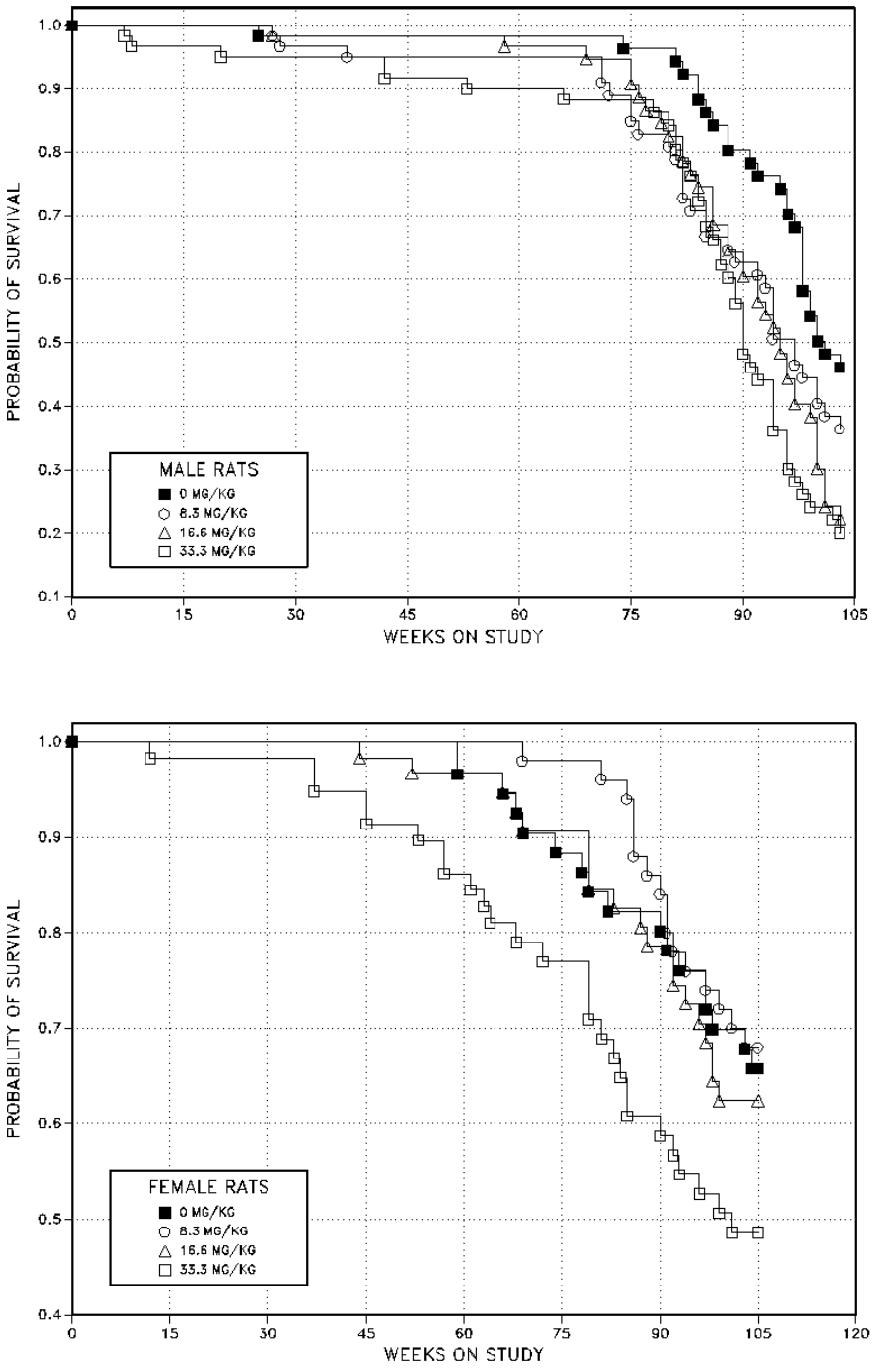


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Promethazine Hydrochloride by Gavage for 2 Years

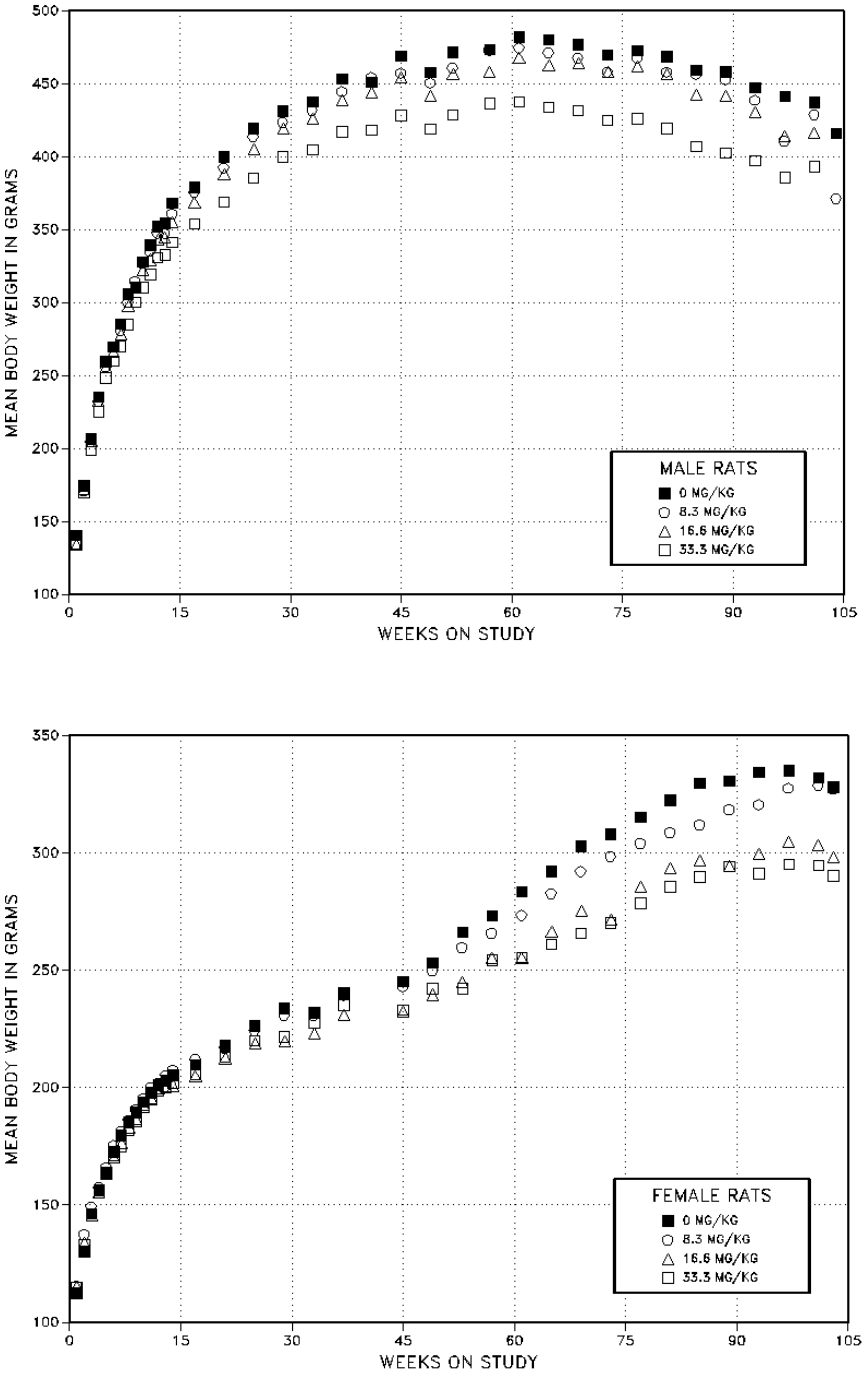


FIGURE 2
Growth Curves for Male and Female Rats Administered Promethazine Hydrochloride by Gavage for 2 Years

TABLE 7
Mean Body Weights and Survival of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride

Weeks on Study	Vehicle Control		8.3 mg/kg			16.6 mg/kg			33.3 mg/kg		
	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	140	60	135	96	60	134	96	60	134	96	60
2	174	60	171	98	60	172	99	60	170	97	60
3	207	60	205	99	60	205	99	60	199	96	60
4	235	60	232	99	60	233	99	60	225	96	60
5	260	60	256	99	60	256	99	60	248	96	60
6	270	60	270	100	60	266	99	60	260	97	60
7	285	60	281	99	60	278	98	60	270	95	60
8	306	60	300	98	60	298	97	60	285	93	59
9	311	60	314	101	60	311	100	60	300	97	58
10	328	60	327	100	60	322	98	60	310	95	58
11	340	60	335	99	60	329	97	60	319	94	58
12	352	60	348	99	60	343	97	60	331	94	58
13	354	60	348	98	60	345	97	60	333	94	58
14	368	60	361	98	60	355	96	60	341	93	58
17	379	60	376	99	60	369	97	60	354	93	58
21	400	60	392	98	60	388	97	60	369	92	57
25	419	60	414	99	60	405	97	60	386	92	57
29	431	59	424	98	58	419	97	59	400	93	57
33	438	59	432	99	58	426	97	59	405	93	57
37	453	59	445	98	58	439	97	59	417	92	57
41	451	59	455	101	57	444	99	59	419	93	57
45	469	59	458	98	57	454	97	59	428	91	55
49	458	59	451	98	57	442	97	59	419	92	55
52	472	59	461	98	57	456	97	59	429	91	55
57	474	59	473	100	57	458	97	59	437	92	54
61	482	59	475	98	57	468	97	58	438	91	54
65	480	59	471	98	57	462	96	58	434	90	54
69 [a]	477	49	468	98	47	464	97	48	432	91	44
73	470	49	458	98	44	458	98	47	425	91	44
77	473	48	468	99	41	462	98	44	426	90	44
81	469	47	458	98	40	457	98	41	420	90	41
85	459	44	457	99	33	443	96	37	407	89	36
89	458	40	453	99	32	442	96	32	403	88	29
93	447	38	439	98	29	431	96	27	397	89	22
97	442	34	411	93	25	414	94	20	386	87	15
101	437	25	429	98	20	417	95	13	393	90	12
Mean for weeks											
1-13	274		271	99		269	98		260	95	
14-52	431		424	98		418	97		397	92	
53-101	464		455	98		448	97		417	90	

[a] Interim evaluation occurred during week 66.

TABLE 8
Mean Body Weights and Survival of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	8.3 mg/kg Av. Wt. (g)	8.3 mg/kg Wt. (% of controls)	8.3 mg/kg No. of Survivors	16.6 mg/kg Av. Wt. (g)	16.6 mg/kg Wt. (% of controls)	16.6 mg/kg No. of Survivors	33.3 mg/kg Av. Wt. (g)	33.3 mg/kg Wt. (% of controls)	33.3 mg/kg No. of Survivors
1	112	60	115	103	60	115	103	60	115	102	60
2	130	60	137	106	60	134	103	60	133	102	60
3	146	60	149	102	60	145	99	60	146	100	60
4	156	60	157	101	60	155	99	60	155	99	60
5	164	59	166	101	60	164	100	60	163	100	58
6	173	59	175	102	60	171	99	60	171	99	58
7	180	59	181	101	60	176	98	60	175	97	58
8	185	59	186	101	60	183	99	60	182	98	58
9	190	59	191	101	60	187	98	60	185	98	58
10	194	59	195	101	60	193	99	60	192	99	58
11	198	59	200	101	60	195	99	60	195	99	58
12	201	59	202	100	60	200	99	60	199	99	58
13	203	59	205	101	60	201	99	60	200	99	57
14	205	59	208	101	60	201	98	60	202	98	57
17	210	59	212	101	60	205	98	60	206	98	57
21	218	59	217	100	60	213	98	60	213	98	57
25	226	59	224	99	60	219	97	60	220	97	57
29	234	59	231	99	60	220	94	60	222	95	57
33	232	59	231	100	60	223	96	60	228	98	57
37	240	59	239	100	60	231	96	60	235	98	57
45	245	59	243	99	60	232	95	59	233	95	55
49	253	59	250	99	60	240	95	59	242	96	53
53	266	59	260	98	60	245	92	58	242	91	53
57	273	59	266	97	60	255	93	58	254	93	50
61	283	57	273	97	60	255	90	58	255	90	49
65 [a]	292	50	283	97	55	266	91	54	261	89	43
69	303	44	292	97	50	275	91	46	266	88	39
73	308	44	298	97	49	272	88	45	270	88	38
77	315	43	304	96	49	286	91	45	279	88	38
81	322	41	309	96	49	293	91	42	286	89	34
85	330	40	312	95	48	297	90	41	290	88	31
89	331	40	318	96	43	294	89	39	294	89	30
93	334	37	321	96	39	300	90	37	291	87	28
97	335	37	328	98	38	305	91	35	295	88	26
101	332	34	329	99	36	303	91	31	295	89	24
Mean for weeks											
1-13	171		174	102		171	100		170	99	
14-52	229		228	100		220	96		222	97	
53-101	310		299	96		280	90		275	89	

[a] Interim evaluation occurred during week 65.

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with nonneoplastic lesions of the liver and neoplasms of the adrenal gland, pituitary gland, uterus, and mammary gland. 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 rats and Appendix B for female rats.

Liver: At the 15-month interim evaluation, absolute liver weights of females in the 16.6 and 33.3 mg/kg groups as well as the relative liver weights of all female groups receiving promethazine hydrochloride were significantly greater than those of the controls (Table F3). In males, however, there were no statistically significant increases in absolute liver weights, and the only significant increases observed were in the relative liver weights of males in the 16.6 and 33.3 mg/kg groups. Microscopic examination of the liver revealed a hepatocellular vacuolation that occurred in all groups of male rats evaluated at 15 months but was increased in severity in the 16.6 and 33.3 mg/kg groups (Table 9). No chemical-related lesions were present in females. Clusters of affected hepatocytes occurred throughout the hepatic parenchyma and were located predominantly in the centrilobular and midzonal regions. Most affected hepatocytes contained a well-defined, single, large cytoplasmic vacuole, but some other hepatocytes contained multiple, smaller vacuoles within the cytoplasm. The morphology of the vacuoles was consistent with that generally observed with fat accumulation rather than glycogen accumulation or hydropic change and was diagnosed as fatty change. Additionally, at 15 months, an increased incidence of centrilobular hypertrophy occurred in males receiving 33.3 mg/kg (Table 9). Hepatocytes within the centrilobular region of the hepatic lobule were variably increased in size (hepatocytomegaly) with abundant pale eosinophilic cytoplasm. At the end of the 2-year study, the incidence of vacuolation (fatty change) in males increased with dose; however, severity was similar among groups, and centrilobular hypertrophy was not recognized in any group. With advancing age, rats develop a number of primary and secondary lesions in the liver.

TABLE 9
Incidences of Nonneoplastic Lesions of the Liver in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	0	8.3	16.6	33.3
15-Month Interim Evaluation				
Liver[a]	10	10	10	9
Centrilobular Hypertrophy[b]	0	0	1 (1.0)[c]	8** (1.0)
Fatty Change	9 (1.0)	10 (1.1)	9 (1.9)	9 (2.2)
2-Year Study				
Liver	50	50	50	51
Fatty Change	4 (1.0)	5 (1.2)	16** (1.1)	28** (1.6)

** Significantly different ($P \leq 0.01$) from the control group by Fisher's exact test (15-month interim evaluation) or logistic regression (2-year study)
[a] Number of animals with liver 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

Adrenal gland: In male rats, the incidence of pheochromocytomas (benign or malignant) of the adrenal medulla occurred with a statistically significant negative trend, and the incidence in the high-dose group was significantly lower than that of the controls (Table 10). The overall historical control incidence for benign or malignant pheochromo-cytomas in water gavage studies in male rats is 129/356 (36%) with a range of 25% to 50% (Table A4a). The historical control incidence of benign or malignant pheochromocytomas in male rats in feed studies is 445/1,234 (36%) with a range of 14% to 63% (Table A4a). Proliferative lesions of the adrenal medulla are very common in male F344/N rats, and hyperplasia, benign pheochromocytoma, and malignant pheochromocytoma constitute a morphologic and biological continuum in the progression of these lesions. While not necessarily supportive of a treatment-related effect, the incidence of hyperplasia in the medulla of the adrenal gland was marginally decreased in the 33.3 mg/kg males (15/60, 15/60, 14/59, 9/59; Table A5). The decreased incidence of pheochromocytomas was considered to be chemical related because of the strong negative trend coupled with the low incidence of pheochromocytomas in the 16.6 and 33.3 mg/kg groups; the incidences were outside historical control ranges in water gavage studies.

Pituitary gland: The incidence of adenomas of the pars distalis of the pituitary gland in male rats (inclusive of animals evaluated at 15 months) occurred with a statistically significant negative trend, and the incidence in the high-dose group was significantly lower than that of the controls (Table 11). The overall historical control incidence for pars distalis adenoma in water gavage studies in male rats is 116/363 (32%) with a range of 24% to 43% (Table A4b). In the larger feed study database, the historical control incidence for male rats is 352/1,235 (28%) with a range of 12% to 60% (Table A4b). Proliferative lesions of the pars distalis of the pituitary gland are very common in F344/N rats, particularly in females, and, as with most endocrine organs, hyperplasia, adenoma, and carcinoma are considered to constitute a morphologic and biological continuum in the progression of these lesions. Supportive of a chemical-related response, the incidence of hyperplasia of the pars distalis was also lower in the male dose groups (22/60, 14/60, 16/58, 9/59; Table A5), and the incidence of pituitary gland adenomas occurred with a slight negative trend in females (28/59, 26/58, 23/58, 18/58; Table B1) as well. However, evidence that this response is related to promethazine hydrochloride administration is weakened by several factors: a) the incidence in the control group is greater than the average historical rate, thus potentially exaggerating the difference between the incidences in control and dosed animals; b) the incidence in the 33.3 mg/kg group is within the historical control range; and c) decreased survival and longevity of males receiving 16.6 and 33.3 mg/kg reduce the potential for development and recognition of these age-related neoplasms. Nevertheless, the decreased incidence of adenomas of the pars distalis of the pituitary gland in all rats may have been chemical related. There was also a slight decrease in the incidence of angiectasis of the pars distalis of the pituitary gland in males (a common finding in older rats) (12/60, 7/60, 6/58, 3/59; Table A5).

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Gland Medulla in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	0	8.3	16.6	33.3
15-Month Interim Evaluation				
Adrenal Medulla[a]	10	10	10	10
Hyperplasia[b]	2	0	0	0
Adrenal Medulla	10	10	10	9
Benign Pheochromocytoma	0	0	1	0
2-Year Study				
Adrenal Medulla	50	50	49	50
Hyperplasia	13	15	14	9
Adrenal Medulla				
Benign Pheochromocytoma				
Overall rate[c]	14/50 (28%)	11/50 (22%)	8/50 (16%)	2/51 (4%)
Adjusted rate[d]	42.3%	43.5%	32.0%	7.9%
Terminal rate[e]	6/23 (26%)	5/18 (28%)	0/11 (0%)	0/10 (0%)
First incidence (days)	570	568	625	565
Logistic regression test[f]	P=0.004N	P=0.506N	P=0.194N	P = 0 . 0 0 4 N
Malignant Pheochromocytoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	1/51 (2%)
Adjusted rate	8.4%	5.6%	5.0%	4.8%
Terminal rate	0/23 (0%)	1/18 (6%)	0/11 (0%)	0/10 (0%)
First incidence (days)	570	717 (T)	691	657
Logistic regression test	P=0.298N	P=0.329N	P=0.313N	P = 0 . 3 2 8 N
Benign or Malignant Pheochromocytoma[g]				
Overall rate	16/50 (32%)	12/50 (24%)	9/49 (18%)	4/50 (8%)
Adjusted rate	46.0%	47.9%	35.4%	15.2%
Terminal rate	6/23 (26%)	6/18 (33%)	0/11 (0%)	0/10 (0%)
First incidence (days)	570	568	625	565
Logistic regression test	P=0.003N	P=0.446N	P=0.114N	P=0.009N

(T)Terminal sacrifice
[a] Number of animals with adrenal gland examined microscopically
[b] Number of animals with lesion
[c] Number of animals with neoplasm per number of animals with adrenal gland examined microscopically
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals surviving until the end of the study
[f] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards these lesions as nonfatal. A negative trend or a lower incidence in a dose group is indicated by N.
[g] Historical incidence for 2-year NTP water gavage studies with vehicle control groups (mean ± standard deviation): 129/356 (36.2% ± 10.0%), range 25%-50%; historical incidence for 2-year NTP feed studies with untreated control groups: 445/1,234 (36.1% ± 11.0%), range 14%-63%

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Pituitary Gland in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	0	8.3	16.6	33.3
15-Month Interim Evaluation				
Pituitary Gland[a]	10	10	10	9
Pars Distalis, Hyperplasia[b]	3	2	2	1
Pituitary Gland	10	10	10	9
Pars Distalis Adenoma	5	2	1	0
2-Year Study				
Pituitary Gland	50	50	48	50
Pars Distalis, Hyperplasia	19	12	14	8
Pituitary Gland				
Pars Distalis Adenoma[c]				
Overall rate[d]	16/50 (32%)	16/50 (32%)	16/48 (33%)	8/50 (16%)
Adjusted rate[e]	44.8%	55.7%	56.2%	48.6%
Terminal rate[f]	5/23 (22%)	7/18 (39%)	2/11 (18%)	4/10 (40%)
First incidence (days)	561	497	401	565
Logistic regression test[g]	P=0.097N	P=0.425	P=0.462	P=0.178N
15-Month Interim Evaluation and 2-Year Study				
Pituitary Gland	60	60	58	59
Pars Distalis, Hyperplasia	22	14	16	9
Pituitary Gland				
Pars Distalis Adenoma				
Overall rate	21/60 (35%)	18/60 (30%)	17/58 (29%)	8/59 (14%)
Adjusted rate	49.7%	57.3%	56.8%	48.6%
Terminal rate	5/23 (22%)	7/18 (39%)	2/11 (18%)	4/10 (40%)
First incidence (days)	462 (I)	462 (I)	401	565
Logistic regression test	P=0.012N	P=0.424N	P=0.360N	P=0.014N

(I) Interim evaluation

[a] Number of animals with pituitary gland examined microscopically

[b] Number of animals with lesion

[c] Historical incidence for 2-year NTP water gavage studies with vehicle control groups (mean ± standard deviation): 116/363 (32.0% ± 7.7%), range 24%-43%; historical incidence for 2-year NTP feed studies with untreated control groups: 352/1,235 (28.5% ± 11.3), range 12%-60%

[d] Number of animals with neoplasm per number of animals with pituitary gland examined microscopically

[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality

[f] Observed incidence in animals surviving until the end of the study

[g] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards these lesions as nonfatal. A negative trend or a lower incidence in a dose group is indicated by N.

Uterus: In female rats, the incidence of stromal polyps of the uterus occurred with a statistically significant negative trend, and the incidence in the high-dose group was significantly lower than that of the controls (Table 12). The overall historical control incidence for stromal polyps of the uterus in water gavage studies in female rats is 54/368 (15%) with a range of 2% to 22% (Table B4a). In feed studies, the historical control incidence in female rats is 205/1,251 (16%) with a range of 2% to 30% (Table B4a). The decreased incidence of uterine stromal polyps may have been related to promethazine hydrochloride administration.

Mammary gland: The incidence of fibroadenoma of the mammary gland, though not statistically significant, occurred with a negative trend in females (Table 12). The overall historical control incidence for fibroadenomas of the mammary gland in water gavage studies in female rats is 143/368 (39%) with a range of 16% to 53% (Table B4b). In feed studies, the historical control incidence in female rats is 484/1,251 (39%) with a range of 8% to 58% (Table B4b). A marginal decreased incidence was also observed in the males (4/50, 2/50, 0/50, 0/51; Table A3). The average rate of fibroadenoma for male rats in the NTP feed study historical control database is 5%, and of the 20 control groups, only two showed no diagnosed fibroadenomas. In water gavage studies the average rate of fibroadenoma for males in control groups is 4%, and of the 7 control groups studied, at least one fibroadenoma was diagnosed in each. Additionally, the incidence of galactoceles in mammary glands of females (inclusive of animals evaluated at 15 months) was lower in dosed than in control females (14/60, 5/56, 5/60, 5/53; Table B5). Due to the slight negative trend in the incidences of fibroadenoma and because the incidence in the 33.3 mg/kg group fell outside the historical range for water gavage controls, these responses appear to be chemical related. However, the evidence that these responses are related to promethazine hydrochloride administration is weakened by several factors: a) the incidence in the 33.3 mg/kg group is within the range observed in historical untreated control groups, and b) decreased survival and longevity of females receiving 33.3 mg/kg and of males receiving 16.6 and 33.3 mg/kg reduce the potential for development of these age-related neoplasms.

TABLE 12
Incidences of Selected Neoplasms in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	0	8.3	16.6	33.3
15-Month Interim Evaluation				
Uterus[a]	10	10	10	7
Stromal Polyp[b]	2	1	1	0
Mammary Gland	10	10	10	7
Fibroadenoma	0	0	0	0
2-Year Study				
Uterus				
Stromal Polyp[c]				
Overall rate[d]	10/50 (20%)	6/50 (12%)	4/50 (8%)	1/53 (2%)
Adjusted rate[e]	25.9%	16.0%	12.9%	4.2%
Terminal rate[f]	5/32 (16%)	4/34 (12%)	4/31 (13%)	1/24 (4%)
First incidence (days)	473	566	729 (T)	729 (T)
Logistic regression test[g]	P=0.004N	P=0.207N	P=0.073N	P = 0 . 0 0 7 N
Mammary Gland				
Fibroadenoma[h]				
Overall rate	14/50 (28%)	13/50 (26%)	10/50 (20%)	6/53 (11%)
Adjusted rate	42.0%	36.1%	29.0%	20.1%
Terminal rate	13/32 (41%)	11/34 (32%)	7/31 (23%)	3/24 (13%)
First incidence (days)	547	692	652	421
Logistic regression test	P=0.070N	P=0.412N	P=0.247N	P = 0 . 0 8 5 N

(T)Terminal sacrifice
[a] Number of animals necropsied
[b] Number of animals with neoplasm
[c] Historical incidence for 2-year NTP water gavage studies with vehicle control groups (mean ± standard deviation): 54/368 (14.7% ± 6.7%), range 2%-22%; historical incidence for 2-year NTP feed studies with untreated control groups: 205/1,251 (16.4% ± 6.6%), range 2%-30%
[d] Number of animals with neoplasm per number of animals necropsied
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards these lesions as nonfatal. A negative trend or a lower incidence in a dose group is indicated by N.
[h] Historical incidence for 2-year NTP water gavage studies with vehicle control groups (mean ± standard deviation): 143/368 (38.9% ± 13.6%), range 16%-53%; historical incidence for 2-year NTP feed studies with untreated control groups: 484/1,251 (38.7% ± 13.5), range 8%-58%

MICE

16-DAY STUDY

One male and one female receiving 150 mg/kg promethazine hydrochloride died on day 8; four females in the 300 mg/kg group died within the first two days of dosing while two females in the 75 mg/kg group died on day 8 (Table 13). Final mean body weights and mean body weight gains of dosed mice were similar to those of the controls. However, the final mean body weights were lower than the initial mean body weights in all dosed and control males and females.

Clinical findings in males and females included decreased activity of nearly all animals in the 150 and 300 mg/kg groups on days 1 and 2. Tremors were observed in one male and five females in the 300 mg/kg group on day 1 and in one male in the 150 mg/kg group and in five males and one female in the 300 mg/kg group on day 2. Clinical findings decreased during the remainder of the study. Absolute and relative liver weights of males and females that received 75, 150, or 300 mg/kg were significantly greater than those of the controls (Table F4). There were no biologically significant differences in the hematology parameters measured (Table G2). No chemical-related gross lesions were observed, and the only microscopic change observed was moderate suppurative inflammation of the nasal mucosa in two of five males receiving 150 mg/kg.

TABLE 13
Survival and Mean Body Weights of Mice in the 16-Day Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	20.4 ± 0.4	18.0 ± 0.3	–2.4 ± 0.1	
18.8	5/5	21.4 ± 0.3	20.2 ± 0.4	–1.2 ± 0.2	112
37.5	5/5	21.4 ± 0.4	19.8 ± 0.6	–1.6 ± 0.2	110
75	5/5	21.8 ± 0.5	19.6 ± 0.8	–2.2 ± 0.7	109
150	4/5[c]	20.7 ± 0.2	19.0 ± 0.4	–1.7 ± 0.4	106
300	5/5	20.6 ± 0.6	18.8 ± 0.8	–1.8 ± 0.3	104
Female					
0	5/5	16.2 ± 0.6	14.4 ± 0.2	–1.8 ± 0.5	
18.8	5/5	15.7 ± 0.6	14.0 ± 0.6	–1.7 ± 0.1	97
37.5	5/5	15.7 ± 0.2	14.4 ± 0.2	–1.3 ± 0.2	100
75	3/5[c]	16.2 ± 0.5	15.0 ± 0.0	–2.0 ± 0.4	104
150	4/5[c]	16.1 ± 0.5	15.3 ± 0.3	–1.1 ± 0.4	106
300	1/5[d]	15.9 ± 0.3	13.0	–2.4	90

[a] Number of animals surviving/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. No standard errors were calculated for groups with high mortality. Differences from the control group are not significant by Williams' or Dunnett's test.
[c] Day of death: 8
[d] Day of death: 1, 2, 2, 2

13-WEEK STUDY

All mice receiving 405 mg/kg promethazine hydrochloride died during the first week of the study. Two females receiving 45 mg/kg and four receiving 135 mg/kg died between weeks 1 and 12. One control female and one female that received 5 mg/kg died due to the gavage procedure (Table 14). Final mean body weights of mice receiving 135 mg/kg were significantly lower than those of the controls. Mean body weight gains of females in the 135 mg/kg group were significantly lower (28%) than those of the controls and were marginally decreased in males receiving 135 mg/kg and females receiving 45 mg/kg. Labored breathing and decreased activity were noted in one female receiving 135 mg/kg at week 11 of

TABLE 14
Survival and Mean Body Weights of Mice in the 13-Week Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	20.2 ± 0.5	30.1 ± 0.7	9.8 ± 0.6	
5	10/10	19.7 ± 0.5	29.6 ± 1.0	9.9 ± 1.0	98
15	10/10	19.6 ± 0.4	29.7 ± 0.3	10.1± 0.6	99
45	10/10	20.1 ± 0.5	30.5 ± 0.8	10.4± 0.8	101
135	10/10	19.8 ± 0.3	27.7 ± 0.4*	7.9 ± 0.4	92
405	0/10[c]	20.3 ± 0.5	)	)	)
Female					
0	9/10[d]	16.8 ± 0.3	23.5 ± 0.4	6.5 ± 0.3	
5	9/10[e]	16.6 ± 0.2	23.1 ± 0.4	6.5 ± 0.5	98
15	10/10	16.7 ± 0.3	23.2 ± 0.5	6.5 ± 0.5	99
45	8/10[f]	16.6 ± 0.3	22.4 ± 0.6	5.8 ± 0.5	95
135	6/10[g]	16.8 ± 0.3	21.5 ± 0.6**	4.7 ± 0.6*	91
405	0/10[c]	17.0 ± 0.4	)	)	)

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
a Number of animals surviving/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. No data were calculated for groups with 100% mortality.
c Week of death: all deaths during week 1
d Week of death: 1 (accidental)
e Week of death: 2 (accidental)
f Week of death: 1, 10
g Week of death: 1, 8, 8, 12

the study. No other significant clinical findings were noted in males or females. There were no bio-logically significant chemical-related differences in any of the hematological parameters measured in any dose group (Table G3). Relative liver weights of males receiving 15 mg/kg, and absolute and relative liver weights of males receiving 45 or 135 mg/kg and females receiving 15, 45, or 135 mg/kg were significantly greater than those of the controls (Table F5). Liver weight increases may have been associated with chemical metabolism and enzyme induction. No chemical-related gross lesions were observed at necropsy, and the predominant microscopic changes included an increase in the incidence and severity of inflammation in the respiratory tract (nose and trachea) in mice (Table 15). The components of the inflammatory process were as described for the rats in the 13-week study; however, in the mice, the lesions occurred less frequently and were less severe than those observed in the rats. Also, bronchopneumonia was not present in mice. The probable cause(s) of these respiratory tract lesions are as discussed for the rats. Six of ten male mice that were found dead had a minimal to mild hepatocellular cytoplasmic vacuolation.

Dose Selection Rationale

Based on mortality and body weight changes at higher levels, the doses of promethazine hydrochloride selected for the 2-year study were 0, 11.25, 22.5, and 45 mg/kg for male mice and 0, 3.75, 7.5, and 15 mg/kg for female mice.

TABLE 15
Incidences of Selected Lesions in Mice in the 13-Week Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	0	5	15	45	135	405
Male						
Nose[a]	10	10	10	10	10	10
Inflammation[b]	0	0	1 (3.0)[c]	3 (2.3)	4* (2.0)	2 (1.5)
Trachea	10	10	10	10	10	10
Inflammation	0	0	0	0	0	3 (2.3)
Female						
Nose	10	10	10	10	10	10
Inflammation	0	1 (1.0)	2 (1.0)	3 (2.7)	2 (1.5)	0
Trachea	10	10	10	10	10	10
Inflammation	0	0	0	0	0	1 (3.0)

* Significantly different ($P \leq 0.05$) from the control group by Fisher's exact test
[a] Number of animals with organ 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; 5 = severe

2-YEAR STUDY

Survival

Estimates of survival probabilities for male and female mice are shown in Table 16 and in the Kaplan-Meier curves in Figure 3. Survival of dosed male and female mice was similar to that of the controls.

Body Weights and Clinical Findings

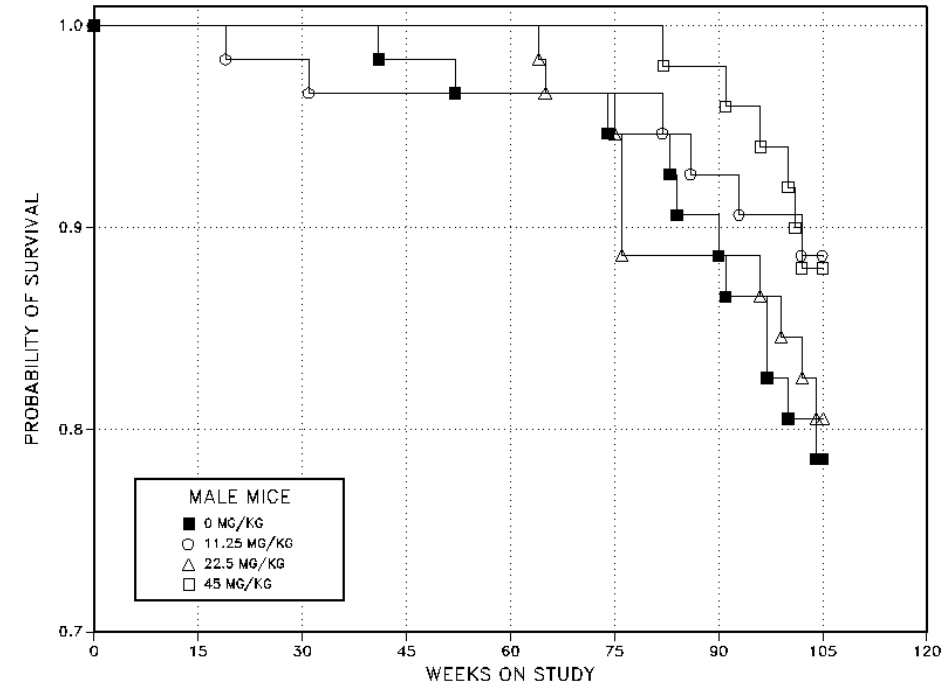
Final mean body weights of dosed males and females were similar to those of the controls (Figure 4 and Tables 17 and 18). There were no clinical findings attributed to promethazine hydrochloride administration.

TABLE 16
Survival of Mice in the 2-Year Gavage Study of Promethazine Hydrochloride

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
Male				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	10	10
Moribund	8	4	6	6
Natural deaths	3	2	4	0
Animals surviving to study termination	39	44	40	44
Percent probability of survival at end of study[b]	79	89	81	88
Mean survival (days)[c]	656	659	659	678
Survival analyses[d]	P=0.353N	P=0.298N	P=0.988N	P=0.253N

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
Female				
Animals initially in study	60	60	60	60
15-Month interim evaluation[a]	10	10	9	9
Accidental deaths[a]	0	0	2	1
Moribund	10	7	9	6
Natural deaths	1	1	1	3
Animals surviving to study termination	39[e]	42	39	41
Percent probability of survival at end of study	78	84	80	82
Mean survival (days)	673	684	672	658
Survival analyses	P=0.893N	P=0.553N	P=0.983N	P=0.819N

[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 dosed columns. A negative trend or lower mortality in a dose group is indicated by N.
[e] Includes two animals that died during the last week of the study.



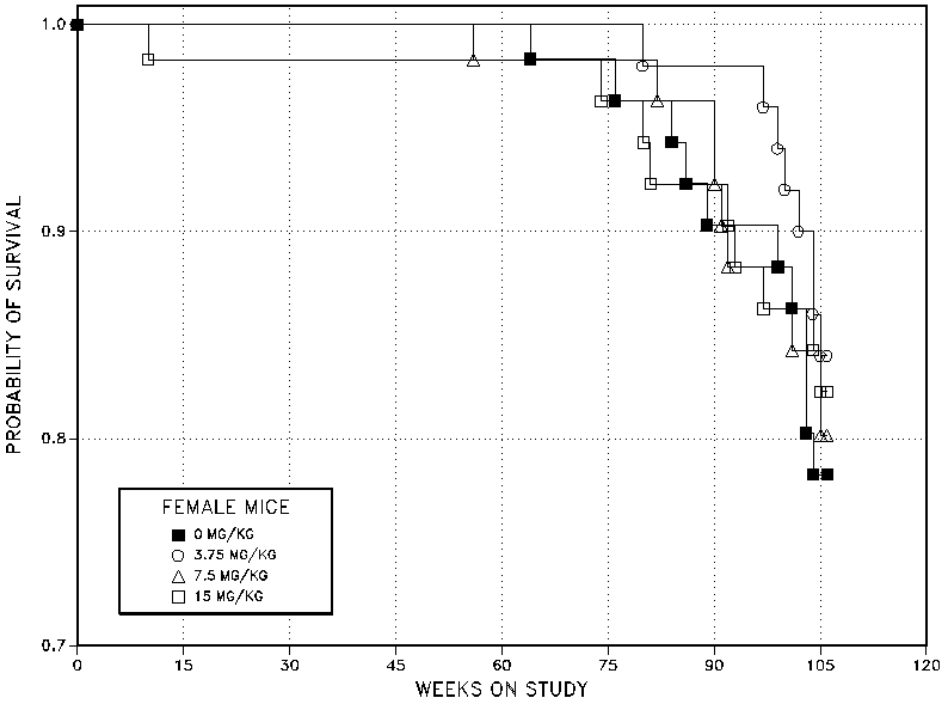
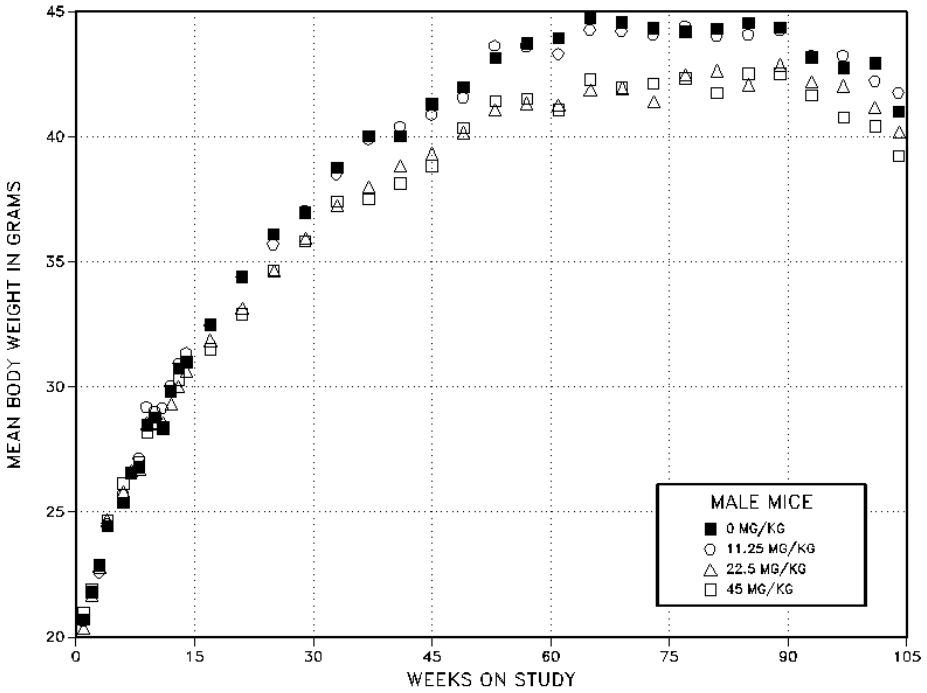


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Promethazine Hydrochloride by Gavage for 2 Years



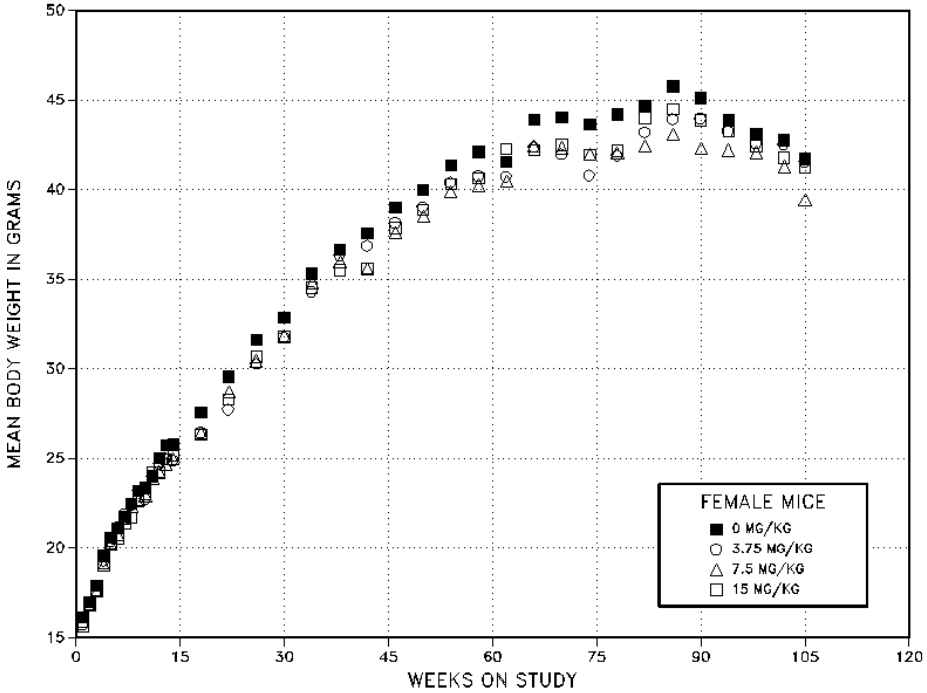


FIGURE 4
Growth Curves for Male and Female Mice Administered Promethazine Hydrochloride by Gavage for 2 Years

TABLE 17
Mean Body Weights and Survival of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride

Weeks on Study	Vehicle Control		11.25 mg/kg			22.5 mg/kg			45 mg/kg		
	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	20.7	60	20.7	100	60	20.3	98	60	21.0	101	60
2	21.8	60	21.8	100	60	21.7	100	60	21.9	101	60
3	22.9	60	22.6	99	60	22.8	100	60	22.8	100	60
4	24.5	60	24.5	100	60	24.7	101	60	24.7	101	60
6	25.4	60	25.7	101	60	25.8	102	60	26.1	103	60
7	26.5	60	26.5	100	60	26.6	100	60	26.6	100	60
8	26.8	60	27.1	101	60	26.7	100	60	27.0	101	60
9	28.5	60	29.2	103	60	28.5	100	60	28.2	99	60
10	28.8	60	29.0	101	60	28.6	99	60	28.6	99	60
11	28.4	60	29.2	103	60	28.6	101	60	28.3	100	60
12	29.8	60	30.0	101	60	29.3	98	60	29.9	100	60
13	30.8	60	30.9	100	60	30.0	97	60	30.3	98	60
14	31.0	60	31.4	101	60	30.6	99	60	31.0	100	60
17	32.5	60	32.5	100	60	31.9	98	60	31.5	97	60
21	34.4	60	34.4	100	59	33.2	97	60	32.9	96	60
25	36.1	60	35.7	99	59	34.7	96	60	34.7	96	60
29	37.0	60	37.0	100	59	36.0	97	60	35.8	97	60
33	38.8	60	38.5	99	58	37.3	96	60	37.4	96	60
37	40.0	60	39.9	100	58	38.0	95	60	37.5	94	60
41	40.0	60	40.4	101	58	38.8	97	60	38.1	95	60
45	41.3	59	40.9	99	58	39.3	95	60	38.8	94	60
49	42.0	59	41.6	99	58	40.2	96	60	40.4	96	60
53	43.2	58	43.7	101	58	41.1	95	60	41.4	96	60
57	43.7	58	43.6	100	58	41.3	95	60	41.5	95	60
61	44.0	58	43.3	98	58	41.3	94	60	41.1	93	60
65 [a]	44.7	58	44.3	99	58	41.9	94	59	42.3	95	60
69	44.6	48	44.2	99	48	41.9	94	48	42.0	94	50
73	44.3	48	44.1	100	48	41.4	94	48	42.1	95	50
77	44.2	47	44.4	101	48	42.5	96	44	42.3	96	50
81	44.3	47	44.1	100	48	42.6	96	44	41.8	94	50
85	44.6	45	44.1	99	47	42.1	94	44	42.5	95	49
89	44.4	45	44.3	100	46	42.9	97	44	42.5	96	49
93	43.2	43	43.3	100	46	42.2	98	44	41.7	97	48
97	42.8	43	43.3	101	45	42.0	98	43	40.8	95	47
101	42.9	40	42.2	98	45	41.2	96	42	40.4	94	46
104	41.0	40	41.8	102	44	40.2	98	41	39.3	96	44
Mean for weeks											
1-13	24.2		24.4	101		24.1	100		24.3	100	
14-52	37.3		37.2	100		36.0	97		35.8	96	
53-104	43.7		43.6	100		41.8	96		41.6	95	

[a] Interim evaluation occurred during week 66.

TABLE 18
Mean Body Weights and Survival of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride

Weeks on Study	Vehicle Control Av. Wt. (g)	Vehicle Control No. of Survivors	3.75 mg/kg Av. Wt. (g)	3.75 mg/kg Wt. (% of controls)	3.75 mg/kg No. of Survivors	7.5 mg/kg Av. Wt. (g)	7.5 mg/kg Wt. (% of controls)	7.5 mg/kg No. of Survivors	15 mg/kg Av. Wt. (g)	15 mg/kg Wt. (% of controls)	15 mg/kg No. of Survivors
1	16.1	60	15.7	98	60	15.9	99	60	15.6	97	60
2	17.0	60	16.8	99	60	16.8	99	60	16.9	99	59
3	17.9	60	17.6	98	60	17.6	98	60	17.7	99	59
4	19.6	60	19.3	99	60	19.1	97	60	19.1	97	59
5	20.6	60	20.4	99	60	20.2	98	60	20.3	99	59
6	21.1	60	21.2	101	60	20.8	99	60	20.5	97	59
7	21.7	60	21.9	101	60	21.7	100	60	21.4	99	59
8	22.5	60	22.4	100	60	22.3	99	60	21.7	96	59
9	23.2	60	23.2	100	60	22.7	98	60	22.6	97	59
10	23.3	60	22.7	97	60	22.9	98	60	23.0	99	59
11	24.0	60	24.0	100	60	23.9	100	60	24.2	101	58
12	25.0	60	24.7	99	60	24.3	97	60	24.2	97	58
13	25.7	60	25.0	97	60	24.6	96	60	24.9	97	58
14	25.8	60	24.9	97	60	25.0	97	60	25.2	98	58
18	27.6	60	26.5	96	60	26.4	96	60	26.3	95	58
22	29.5	60	27.7	94	60	28.7	97	60	28.3	96	58
26	31.6	60	30.3	96	60	30.4	96	60	30.7	97	58
30	32.8	60	31.7	97	60	31.9	97	60	31.8	97	58
34	35.3	60	34.3	97	60	34.8	99	60	34.5	98	58
38	36.7	60	36.3	99	60	35.9	98	60	35.5	97	58
42	37.5	60	36.9	98	60	35.6	95	60	35.6	95	58
46	39.0	60	38.2	98	60	37.6	96	60	37.9	97	58
50	40.0	60	39.0	98	60	38.5	96	60	38.9	97	58
54	41.4	60	40.4	98	60	39.9	96	59	40.3	97	58
58	42.1	60	40.8	97	60	40.2	96	58	40.6	96	58
62	41.6	60	40.7	98	60	40.4	97	58	42.3	102	58
66 [a]	43.9	59	42.4	97	60	42.4	97	58	42.2	96	58
70	44.0	49	42.0	96	50	42.3	96	49	42.5	97	49
74	43.7	49	40.8	93	50	42.0	96	49	41.9	96	49
78	44.2	48	41.9	95	50	42.0	95	49	42.2	96	48
82	44.7	48	43.2	97	49	42.4	95	49	44.0	98	46
86	45.8	47	43.9	96	49	43.1	94	48	44.5	97	46
90	45.1	45	43.9	97	49	42.3	94	48	43.9	97	46
94	43.9	45	43.2	98	49	42.2	96	44	43.2	98	44
98	43.1	45	42.6	99	48	42.1	98	44	42.4	98	43
102	42.8	43	42.5	99	46	41.3	97	42	41.8	98	43
Mean for weeks											
1-13	21.4		21.1	99		21.0	98		20.9	98	
14-52	33.6		32.6	97		32.5	97		32.5	97	
53-102	43.6		42.2	97		41.7	96		42.4	97	

[a] Interim evaluation occurred during week 66.

Hematology and Clinical Chemistry

No biologically significant differences in hematology or clinical pathology parameters measured at the 15-month interim evaluation were observed (Table G4). There was a statistically significant increase in 5'-nucleotidase activity in all groups of females receiving promethazine hydrochloride. However, this increase was not considered to be chemical related, because it was not dose related, and it was not observed in males.

Pathology and Statistical Evaluation

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms of the liver and lung. 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 dose group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Liver: In female mice, the incidence of hepato-cellular adenoma or carcinoma (combined) occurred with a statistically significant positive trend, but the incidences in the dosed groups were not significantly greater than those of the controls by pairwise comparison (Table 19). The overall historical control incidence for hepatocellular adenoma or carcinoma (combined) in female mice in water gavage studies is 21/315 (7%) with a range of 2% to 12% (Table D4a). However, in feed studies in which the database is larger, the historical control incidence is 223/1,363 (16%) with a range of 3% to 42% (Table D4a). Foci of hepatocellular alteration, hepatocellular adenoma, and hepatocellular carcinoma are thought to constitute a spectrum that represents the progression of proliferative liver lesions. There was no increased incidence of hepatocellular foci in female mice. Because the trend was marginal and the incidences in the dosed groups were within the range of historical controls, the slight increase was not considered chemical related.

Lung: In female mice, the combined incidences of alveolar/bronchiolar adenomas or carcinomas (inclusive of animals evaluated at 15 months) occurred with a statistically significant negative trend and were significantly decreased in all dosed groups (Table 20). The overall historical control incidence for alveolar/bronchiolar adenoma or carcinoma (combined) in female mice in water gavage studies is 19/315 (6%) with a range of 0% to 12% (Table D4b). However, in feed studies the historical control incidence is 106/1,371 (8%) with a range of 2% to 26% (Table D4b). As noted in discussions of other neoplasms in this report, hyperplasia, adenoma, and carcinoma are thought to constitute a morphologic and biological continuum in the development of alveolar/bronchiolar neoplasia, and the incidence of hyperplasia was similar among groups in this study. It is uncertain if the decreased incidence of alveolar/bronchiolar adenoma or carcinoma (combined) in female mice is chemical related because the incidence in the control group was slightly high, the decreased incidence was not dose related, and there was no chemical-related decreased incidence of hyperplasia.

TABLE 19
Incidences of Neoplasms of the Liver in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	0	3.75	7.5	15
15-Month Interim Evaluation				
Liver[a] 10	10	9	9	
Hepatocellular Adenoma[b]	0	0	0	1
2-Year Study				
Liver				
Hepatocellular Adenoma				
Overall rate[c]	3/50 (6%)	4/50 (8%)	6/51 (12%)	8/51 (16%)
Adjusted rate[d]	7.7%	9.3%	14.7%	19.5%
Terminal rate[e]	3/39 (8%)	3/42 (7%)	5/39 (13%)	8/41 (20%)
First incidence (days)	736 (T)	725	629	736 (T)
Logistic regression test[f]	P=0.049	P=0.540	P=0.245	P=0.115
Hepatocellular Carcinoma				
Overall rate	1/50 (2%)	1/50 (2%)	1/51 (2%)	2/51 (4%)
Adjusted rate	2.6%	2.4%	2.0%	4.8%
Terminal rate	1/39 (3%)	1/42 (2%)	0/39 (0%)	1/41 (2%)
First incidence (days)	736 (T)	736 (T)	569	734
Logistic regression test	P=0.368	P=0.745N	P=0.734N	P=0.510
Hepatocellular Adenoma or Carcinoma[g]				
Overall rate	4/50 (8%)	4/50 (8%)	7/51 (14%)	10/51 (20%)
Adjusted rate	10.3%	9.3%	16.4%	23.8%
Terminal rate	4/39 (10%)	3/42 (7%)	5/39 (13%)	9/41 (22%)
First incidence (days)	736 (T)	725	569	734
Logistic regression test	P=0.025	P=0.604N	P=0.273	P=0.079

(T)Terminal sacrifice
[a] Number of animals with liver examined microscopically
[b] Number of animals with neoplasm
[c] Number of animals with neoplasm per number of animals with liver examined microscopically
[d] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[e] Observed incidence in animals surviving until the end of the study
[f] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards these lesions as nonfatal. A lower incidence in a dose group is indicated by N.
[g] Historical incidence for 2-year NTP water gavage studies with vehicle control groups (mean ± standard deviation): 21/315 (6.7% ±4.2%), range 2%-12%; historical incidence for 2-year NTP feed studies with untreated control groups: 223/1,363 (16.4% ± 10.7%), range 3%-42%

TABLE 20
Incidences of Alveolar/bronchiolar Neoplasms in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride

Dose (mg/kg)	0	3.75	7.5	15
15-Month Interim Evaluation				
Lung[a]	10	10	9	9
Alveolar/bronchiolar Adenoma[b]	2	0	0	0
2-Year Study				
Lung				
Alveolar/bronchiolar Adenoma or Carcinoma[c]				
Overall rate[d]	8/50 (16%)	2/50 (4%)	0/50 (0%)	2/51 (4%)
Adjusted rate[e]	18.4%	4.8%	0.0%	4.9%
Terminal rate[f]	4/39 (10%)	2/42 (5%)	0/38 (0%)	2/41 (5%)
First incidence (days)	693	736 (T)	)[h]	736 (T)
Logistic regression test[g]	P=0.023N	P=0.042N	P=0.005N	P=0.049N
15-Month Interim Evaluation and 2-Year Study				
Lung				
Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	10/60 (17%)	2/60 (3%)	0/59 (0%)	2/60 (3%)
Adjusted rate	21.5%	4.8%	0.0%	4.9%
Terminal rate	4/39 (10%)	2/42 (5%)	0/38 (0%)	2/41 (5%)
First incidence (days)	464 (I)	736 (T)	)	736 (T)
Logistic regression test	P=0.006N	P=0.016N	P=0.002N	P=0.017N

(I)Interim evaluation
(T)Terminal sacrifice
[a] Number of animals with lung examined microscopically
[b] Number of animals with neoplasm
[c] Historical incidence for 2-year NTP water gavage studies with vehicle control groups (mean ± standard deviation): 19/315 (6.0% ± 5.4%), range 0%-12%; historical incidence for 2-year NTP feed studies with untreated control groups: 106/1,371 (7.7% ± 5.0%), range 2%-26%
[d] Number of animals with neoplasm per number animals with lung examined microscopically
[e] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[f] Observed incidence in animals surviving until the end of the study
[g] In the control column are the P values associated with the trend test. In the dosed group columns are the P values corresponding to pairwise comparisons between the controls and that dosed group. The logistic regression test regards these lesions as nonfatal. A negative trend or a lower incidence in a dose group is indicated by **N**.
[h] Not applicable; no neoplasms in animal group

GENETIC TOXICOLOGY

Promethazine hydrochloride (1 to 666 µg/plate), tested at two laboratories with a preincubation protocol in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9, was negative for the induction of gene mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 (Table E1; Mortelmans *et al.*, 1986). In cytogenetic tests with cultured Chinese hamster ovary cells, promethazine hydrochloride did not induce sister chromatid exchanges or chromosomal aberrations in the absence of S9 activation (Tables E2 and E3; Galloway *et al.*, 1987). When tested in the presence of Aroclor 1254-induced male Sprague-Dawley rat liver S9, promethazine hydrochloride did not induce a significant increase in the percent cells with chromosomal aberrations, but a small dose-related increase in sister chromatid exchanges occurred. This increase was of insufficient magnitude to be considered positive, and the sister chromatid exchange test with promethazine hydrochloride was concluded to be equivocal. Promethazine hydrochloride did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* administered the chemical by feeding (1,000 ppm) or by injection (2,500 ppm) (Table E4; Yoon *et al.*, 1985).

DISCUSSION AND CONCLUSIONS

Promethazine hydrochloride, a white to faint yellow crystalline powder, is used as a drug for the management of allergic conditions, motion sickness, and nausea, and as a sedative for psychotic disorders. The Food and Drug Administration recommended the testing of this drug because of its widespread use in human medicine and because of the lack of data on its carcinogenic potential. Because promethazine hydrochloride is an amine compound it could potentially be converted to a carcinogenic *N*-nitroso compound by reaction with nitrite under the acidic conditions in the stomach. The potential toxicity and carcinogenicity of promethazine hydrochloride was evaluated by administering the chemical in water by gavage to groups of male and female F344/N rats and B6C3F$_1$ mice once daily, 5 days per week for up to 16 days, 13 weeks, or 2 years.

The lowest doses of promethazine hydrochloride that caused deaths in the 13-week studies were 300 mg/kg for male rats, 100 mg/kg for female rats, 405 mg/kg for male mice, and 45 mg/kg for female mice. This suggests that males are less sensitive than females to the lethal effects of promethazine hydrochloride.

Chemical-related clinical findings in the 13-week studies in male and female rats and mice were decreased activity, labored breathing, and tremors. The decreased activity could be due to weight loss and debilitation. The labored breathing could be due to the pulmonary lesions observed in these animals. Additionally, the clinical findings in this study could be related to the sedative action of this drug and its ability to reduce the stimulatory effect of acetylcholine (Edge, 1953; Hutcheon, 1953; Leuschner *et al.*, 1980). These effects led to a decrease in smooth muscle tone, including those of the bronchi and bronchioles. The increase in relative liver weights was probably due to hepatic microsomal drug-metabolizing enzyme induction and the increase in the number of free ribosomes in liver cells by promethazine hydrochloride. This induction was previously observed in Sprague-Dawley rats given intraperitoneal (IP) injections of 50 mg/kg per day for 2 to 4 days (Fernández and Castro, 1977). Promethazine hydrochloride, administered at 25 mg/kg by IP injection to male Sprague-Dawley rats, caused an increase in the number of free ribosomes in liver cells (Serratoni *et al.*, 1969).

Suppurative inflammation of the respiratory tract (nasal and tracheal mucosa) observed in the dosed rats and mice during the 13-week studies was considered to be directly related to inhalation of feed and bedding material and indirectly to promethazine hydrochloride administration. Because of the known sedative effect of this drug and its ability to decrease smooth muscle tone, animals receiving promethazine hydrochloride were probably unable to eliminate inhaled plant particles from the respiratory tract.

No differences in hematology parameters measured in mice in the 13-week study were found that could be attributed to promethazine hydrochloride administration. However, promethazine and chlorpromazine (a structurally related drug) were reported to produce neutropenia and aplastic anemia in humans (Bowman and Rand, 1980).

Doses selected for rats in the 2-year study were considered adequate for the evaluation of the potential carcinogenic activity of promethazine hydrochloride. This conclusion was based on the occurrence of chemical-related effects including fatty change in the liver (males only), decreased body weights (high-dose males and mid- and high-dose females) and increased relative liver weights in the 2-year study. The reduced survival of males receiving 16.6 or 33.6 mg/kg and of females receiving 33.3 mg/kg was not considered to have any influence on study adequacy because a sufficient number (over 50%) of rats in these groups lived long enough (85 weeks) to develop neoplasms and because the survival of rats receiving lower doses of the drug (8.3 mg/kg for males and 8.3 or 16.6 mg/kg for females) was similar to that of the controls. Lack of a response in the body weight or survival of mice in the 2-year study indicates that higher doses could have been tolerated. Based on the results of the 13-week study, however, doses higher than 45 mg/kg for males and 15 mg/kg for females would not have been selected for the 2-year studies. At the higher doses, males had statistically significant lower body weights and females experienced mortality or had statistically significant lower body weights. Dose levels that caused significantly lower body weights and mortality in the short-term studies were

considered too high for 2-year studies because of a possible negative effect on survival.

The 15-month interim evaluation results were similar to those observed in the short-term studies of promethazine hydrochloride. Decreased final mean body weights and increased relative liver and kidney weights were observed in dosed rats. The increase in the severity of hepatocellular vacuolation (fatty change) could be attributed to promethazine hydrochloride administration. The fatty change was also observed in the liver of male rats receiving promethazine hydrochloride at the end of the 2-year study, and it may be similar to changes produced by similar drugs. Administration of various cationic amphophilic drugs such as chlorpromazine has been known to induce phospholipid storage disease (phospholipidosis) in humans and other animals (Lüllman-Rauch, 1979). Phospholipids accumulate in the lysosomes of animals receiving such drugs. Results from *in vitro* studies suggested that lipidosis may have been caused by the inhibitory effect of the drugs on lysosomal phospholipases (Hostetler and Matsuzawa, 1981). No chemical-related nonneoplastic lesions were observed in female rats.

In the 2-year rat study, there were no increased incidences of neoplasms that could be attributed to promethazine hydrochloride administration. However, several neoplasms occurred with a negative trend. Negative trends were observed in the incidences of adrenal medulla pheochromocytoma, mammary gland fibroadenoma, and pituitary gland adenoma in males and mammary gland fibroadenoma and uterine stromal polyp in females. These negative trends might have been related to promethazine hydrochloride administration.

The pituitary gland has a central role in the interaction between the nervous and endocrine systems. The neural and vascular connections between the pituitary gland and the brain provide a sensitive and precise mechanism for the release of hormones from the pituitary gland. The pituitary gland has recipro cal interactions with other endocrine glands that, when disturbed, result in functional and morphologic changes. Adrenal medullary and mammary gland proliferative lesions are sometimes observed in conjunction with proliferative lesions of the pituitary (pars distalis) gland and with the administration of growth hormones and estrogens (MacKenzie and Boorman, 1990). Hypophysectomy was reported to eliminate proliferative adrenal medullary and mammary gland lesions in rats (Boorman *et al*. 1990; Hamlin and Banas, 1990). Additionally, it is known that dietary or age-related decreases in body weight are associated with decreased incidences of proliferative lesions and tumors at these sites. Thus, the dopaminergic actions and/or body weight decreases associated with the administration of promethazine hydrochloride resulted in the observed decrease in the incidence of pituitary (pars distalis) gland adenomas, adrenal medullary pheochromocytomas, and mammary gland tumors.

Hepatocellular adenoma or carcinoma (combined) occurred with a statistically significant positive trend in female mice, and the incidence in the high-dose group was marginally, but not significantly, increased. The marginal increase in hepatocellular neoplasms was not considered related to the administration of promethazine hydrochloride because: a) the marginal increase is not significant, b) the incidences of potentially "preneoplastic" foci were not increased, and c) although the incidence (20%) in the 15 mg/kg group is outside the historical control range from water gavage studies, it is similar to the mean and is well within the range from the larger historical control database for feed studies (mean, 16%; range, 3%-42%).

Alveolar/bronchiolar adenoma or carcinoma (combined) occurred with a statistically significant negative trend in female mice, and the incidence in all dosed groups was significantly decreased. Whether the decreased incidence of alveolar/bronchiolar neoplasms was due to chemical administration is yet to be determined. However, previous studies showed a negative association between orally administered promethazine and skin cancers (Freidman and Ury, 1980; Selby *et al*., 1989). In addition, promethazine was found to suppress the transmitability of Ehrlich carcinomas in rodents (Motohashi, 1983).

No increased incidences of nonneoplastic lesions that could be attributed to promethazine hydrochloride administration occurred in male or female mice.

The lack of carcinogenic activity for promethazine hydrochloride in rats and mice is in agreement with its lack of genotoxic activity. Promethazine hydrochloride was negative for induction of gene mutations in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 (Mortelmans *et al.*, 1986). It did not induce a significant increase in chromosomal aberrations or sister chromatid exchanges in cultured Chinese hamster ovary cells (Galloway *et al.*, 1987). These *in vitro* tests were conducted with and without exogenous metabolic activation (S9). Promethazine hydrochloride did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* (Yoon *et al.*, 1985) and no induction of unscheduled DNA synthesis was observed in male F344/N rat hepatocytes treated with promethazine hydrochloride *in vivo* (Mirsalis *et al.*, 1983).

CONCLUSIONS

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of promethazine hydrochloride in male or female F344/N rats receiving 8.3, 16.6, or 33.3 mg/kg. There was *no evidence of carcinogenic activity* of promethazine hydrochloride in male $B6C3F_1$ mice receiving 11.25, 22.5, or 45 mg/kg. There was *no evidence of carcinogenic activity* of promethazine hydrochloride in female $B6C3F_1$ mice receiving 3.75, 7.5, or 15 mg/kg.

The decrease in the incidences of adrenal medullary pheochromocytoma in male rats was considered to be related to promethazine hydrochloride administration. The decrease in the incidences of pituitary gland adenoma in male rats and uterine stromal polyp in female rats may have been related to promethazine hydrochloride administration.

Promethazine hydrochloride also caused an increased incidence of fatty change in the liver of male rats.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR GAVAGE STUDY OF PROMETHAZINE HYDROCHLORIDE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride [a]

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	9
Early deaths				
Moribund	24	27	27	21
Natural deaths	3	5	12	20
Survivors				
Died last week of study		4	2	
Terminal sacrifice	23	14	9	10
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, cecum	(10)	(10)	(10)	(9)
Polyp adenomatous				1 (11%)
Tongue	(1)			(1)
Squamous cell papilloma	1 (100%)			
Cardiovascular System				
None				
Endocrine System				
Adrenal medulla	(10)	(10)	(10)	(9)
Pheochromocytoma benign			1 (10%)	
Islets, pancreatic	(10)	(10)	(10)	(9)
Adenoma	1 (10%)			
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, adenoma	5 (50%)	2 (20%)	1 (10%)	
Thyroid gland	(10)	(10)	(10)	(9)
C-cell, adenoma				1 (11%)
General Body System				
None				
Genital System				
Testes	(10)	(10)	(10)	(9)
Bilateral, interstitial cell, adenoma	1 (10%)	2 (20%)	2 (20%)	1 (11%)
Interstitial cell, adenoma	4 (40%)	2 (20%)	4 (40%)	6 (67%)
Hematopoietic System				
None				

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
15-Month Interim Evaluation (continued)				
Integumentary System				
Skin	(10)	(10)	(10)	(9)
Trichoepithelioma	1 (10%)			
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(9)
Alveolar/bronchiolar adenoma				1 (11%)
Special Senses System				
None				
Urinary System				
Urinary bladder	(10)	(10)	(10)	(9)
Transitional epithelium, papilloma		1 (10%)		
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(49)	(50)
Squamous cell carcinoma, metastatic, uncertain primary site			1 (2%)	
Intestine large, cecum	(47)	(46)	(42)	(36)
Adenocarcinoma				1 (3%)
Intestine small, duodenum	(49)	(48)	(46)	(44)
Intestine small, ileum	(46)	(47)	(43)	(36)
Liver	(50)	(50)	(50)	(51)
Hepatocellular carcinoma			1 (2%)	
Hepatocellular adenoma	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Histiocytic sarcoma			2 (4%)	
Mesentery	(2)	(6)	(3)	(3)
Hemangiosarcoma			1 (33%)	
Pancreas	(50)	(50)	(49)	(51)
Acinus, adenoma	2 (4%)	2 (4%)	1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Stomach, forestomach	(49)	(50)	(50)	(51)
Squamous cell papilloma				1 (2%)
Stomach, glandular	(49)	(50)	(47)	(45)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(51)
Adrenal medulla	(50)	(50)	(49)	(50)
Pheochromocytoma malignant	3 (6%)	1 (2%)	1 (2%)	1 (2%)
Pheochromocytoma complex				1 (2%)
Pheochromocytoma benign	10 (20%)	6 (12%)	7 (14%)	1 (2%)
Bilateral, pheochromocytoma benign	4 (8%)	5 (10%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(49)	(49)
Adenoma	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Parathyroid gland	(48)	(48)	(48)	(47)
Pituitary gland	(50)	(50)	(48)	(50)
Pars distalis, adenoma	15 (30%)	15 (30%)	15 (31%)	8 (16%)
Pars distalis, adenoma, multiple	1 (2%)	1 (2%)	1 (2%)	
Thyroid gland	(49)	(49)	(44)	(41)
Bilateral, C-cell, adenoma		1 (2%)		
C-cell, adenoma	4 (8%)	4 (8%)	3 (7%)	1 (2%)
Follicular cell, adenoma	1 (2%)	1 (2%)	1 (2%)	
General Body System				
Tissue NOS			(1)	
Squamous cell carcinoma, metastatic, uncertain primary site			1 (100%)	
Genital System				
Epididymis	(50)	(50)	(50)	(51)
Preputial gland	(48)	(50)	(48)	(50)
Adenoma	2 (4%)	5 (10%)	2 (4%)	2 (4%)
Bilateral, adenoma				1 (2%)
Prostate	(48)	(50)	(50)	(48)
Seminal vesicle	(49)	(50)	(49)	(51)
Testes	(50)	(50)	(50)	(51)
Bilateral, interstitial cell, adenoma	33 (66%)	28 (56%)	31 (62%)	36 (71%)
Interstitial cell, adenoma	14 (28%)	16 (32%)	13 (26%)	7 (14%)
Hematopoietic System				
Blood	(11)	(11)	(13)	(7)
Bone marrow	(50)	(50)	(48)	(50)
Histiocytic sarcoma			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node	(15)	(16)	(15)	(5)
Lymph node, mandibular	(50)	(50)	(50)	(50)
Lymph node, mesenteric	(49)	(50)	(50)	(50)
Spleen	(50)	(50)	(49)	(51)
Fibroma			1 (2%)	
Thymus	(42)	(45)	(46)	(46)
Histiocytic sarcoma				1 (2%)
Integumentary System				
Mammary gland	(49)	(45)	(38)	(42)
Adenoma		1 (2%)		1 (2%)
Adenoma, multiple	1 (2%)			
Fibroadenoma	4 (8%)	2 (4%)		
Skin	(50)	(50)	(50)	(51)
Basosquamous tumor benign			1 (2%)	
Keratoacanthoma			2 (4%)	
Squamous cell carcinoma	1 (2%)			
Squamous cell papilloma	2 (4%)	1 (2%)		
Subcutaneous tissue, fibroma	3 (6%)	3 (6%)	3 (6%)	2 (4%)
Subcutaneous tissue, fibroma, multiple			1 (2%)	
Subcutaneous tissue, osteosarcoma	1 (2%)			
Subcutaneous tissue, sarcoma			1 (2%)	
Subcutaneous tissue, schwannoma malignant	1 (2%)			
Musculoskeletal System				
Skeletal muscle	(1)	(6)		(1)
Nervous System				
Brain	(50)	(50)	(50)	(51)
Astrocytoma malignant	1 (2%)	1 (2%)		
Glioma malignant			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(49)	(51)
Alveolar/bronchiolar adenoma	1 (2%)			
Alveolar/bronchiolar carcinoma			1 (2%)	
Osteosarcoma, metastatic, skin	1 (2%)			
Squamous cell carcinoma, multiple			1 (2%)	
Nose	(50)	(50)	(50)	(51)
Fibroma	1 (2%)			
Squamous cell papilloma	1 (2%)			
Special Senses System				
Zymbal's gland				(1)
Carcinoma				1 (100%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(51)
Histiocytic sarcoma				1 (2%)
Lipoma				1 (2%)
Liposarcoma			1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site			1 (2%)	
Renal tubule, adenoma		1 (2%)	1 (2%)	
Renal tubule, carcinoma	2 (4%)			
Urinary bladder	(49)	(48)	(49)	(48)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(51)
Histiocytic sarcoma			2 (4%)	1 (2%)
Leukemia mononuclear	22 (44%)	31 (62%)	24 (48%)	19 (37%)
Mesothelioma malignant			1 (2%)	1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	9	5	7	8
2-Year study	48	47	50	46
Total primary neoplasms				
15-Month interim evaluation	13	7	8	10
2-Year study	138	129	123	89
Total animals with benign neoplasms				
15-Month interim evaluation	9	5	7	8
2-Year study	48	47	47	44
Total benign neoplasms				
15-Month interim evaluation	13	7	8	10
2-Year study	107	96	88	64
Total animals with malignant neoplasms				
2-Year study	28	32	29	23
Total malignant neoplasms				
2-Year study	31	33	35	25
Total animals with metastatic neoplasms				
2-Year study	1		1	
Total metastatic neoplasms				
2-Year study	1		3	
Total animals with malignant neoplasms of uncertain primary site				
2-Year study			1	

[a] Number of animals examined microscopically at site and number of animals with lesion
[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 Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control

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

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	7 0 3	7 1 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 0 5 2	0 0 6 2	0 0 1 1	0 0 2 1	0 0 3 1	0 0 3 2	0 0 3 3	0 0 4 1	0 0 4 2	0 0 4 3	0 0 5 1	0 0 6 1	0 0 7 1	0 0 7 2	0 0 8 1	0 0 8 2	0 0 8 3	0 0 8 4	0 0 8 5	0 0 9 1	0 0 9 2	0 0 9 3	0 1 0 1	0 1 2 1	0 1 2 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma										X											X				X	4
Mesentery																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma														X												2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										3
Pheochromocytoma benign		X							X				X	X							X					10
Bilateral, pheochromocytoma benign	X									X														X		4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X		X												X	4
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X						X				X						X				X				15
Pars distalis, adenoma, multiple			X																							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma																		X								4
Follicular cell, adenoma																					X					1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X			X																					2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X	X	X		X	X	X	X	X	X		X		X	X	X	X	X	X	X		X	X	X	33
Interstitial cell, adenoma	X				X							X		X								X				14

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	1 7 0	5 1 2	5 6 1	5 7 0	5 8 2	5 8 4	5 9 5	6 0 2	6 1 0	6 1 2	6 3 2	6 4 1	6 6 0	6 7 1	6 7 1	6 7 3	6 8 4	6 8 6	6 8 6	6 8 6	6 8 6	6 8 7	6 9 1	6 9 7	6 9 7
Carcass ID Number	0 0 4 5	0 0 4 9	0 1 1 5	0 0 5 4	0 1 1 4	0 0 3 5	0 0 6 5	0 1 1 3	1 2 2 5	1 1 1 3	0 0 7 3	0 2 2 3	0 2 2 4	1 0 1 2	0 1 0 3	1 0 6 4	0 0 3 4	0 0 4 4	0 1 6 3	1 0 0 2	1 1 1 2	0 2 2 2	1 1 1 1	0 1 5 3	1 2 2 3
Hematopoietic System																									
Blood					+			+	+	+	+					+			+			+			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+			+	+	+	+		+			+			+	+			+		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	M	+	+	M	+	+	M	+
Leukemia mononuclear, multifocal																									
Integumentary System																									
Mammary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, multiple																									
Fibroadenoma																						X			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma							X														X	X			
Subcutaneous tissue, osteosarcoma						X																			
Subcutaneous tissue, schwannoma malignant																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																+									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																		X							
Peripheral nerve																	+								
Spinal cord																	+								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Osteosarcoma, metastatic, skin						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Squamous cell papilloma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye								+																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X			X	X	X	X					X			X	X		X	X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	7 0 3	7 1 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 0 5 2	0 0 6 2	0 0 1 1	0 0 2 1	0 0 3 1	0 0 3 2	0 0 3 3	0 0 4 1	0 0 4 2	0 0 4 3	0 0 5 1	0 0 6 1	0 0 7 1	0 0 7 2	0 0 8 1	0 0 8 2	0 0 8 3	0 0 8 4	0 0 8 5	0 0 9 1	0 0 9 2	0 0 9 3	0 1 0 1	0 1 2 1	0 1 2 2	Total Tissues/ Tumors
Hematopoietic System																										
Blood		+				+				+																11
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+								+					+											15
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	42
Leukemia mononuclear, multifocal		X																								1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, multiple												X														1
Fibroadenoma					X	X			X																	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma													X													1
Squamous cell papilloma										X												X				2
Subcutaneous tissue, fibroma																										3
Subcutaneous tissue, osteosarcoma																										1
Subcutaneous tissue, schwannoma malignant														X												1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																							1
Osteosarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma														X												1
Squamous cell papilloma			X																							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye												+														2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma				X			X																			2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X			X		X		X		X		X		X	X						X			22

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 8.3 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 8.3 mg/kg (continued)

Number of Days on Study	6 7 5	6 7 5	6 8 1	6 9 6	7 0 0	7 0 4	7 1 6	7 2 4	7 2 5	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 2 3 4	0 2 3 5	0 1 5 2	0 1 9 2	0 2 0 1	0 1 8 3	0 1 6 3	0 1 9 1	0 2 3 3	0 2 1 1	0 1 3 1	0 1 3 2	0 1 4 1	0 1 4 2	0 1 4 4	0 1 5 1	0 1 6 1	0 1 6 2	0 1 7 1	0 1 8 1	0 1 8 2	0 1 8 5	0 2 2 1	0 2 3 1	0 2 3 2	0 2 4 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X													X									2
Mesentery			+		+			+						+							+					6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinus, adenoma							X				X															2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																							+			1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant													X													1
Pheochromocytoma benign	X				X									X						X						6
Bilateral, pheochromocytoma benign		X					X	X	X	X																5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																	X			X						2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X		X												X	X		X		X	X		X	X	15
Pars distalis, adenoma, multiple							X																			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, C-cell, adenoma																										1
C-cell, adenoma			X		X							X								X						4
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X					X																		5
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X			X			X		X	28
Interstitial cell, adenoma												X							X	X		X	X		X		16

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 8.3 mg/kg (continued)

Number of Days on Study	1 8 4	1 9 2	2 5 9	4 9 1	4 9 7	5 0 1	5 2 5	5 2 5	5 2 9	5 5 5	5 6 3	5 6 8	5 6 8	5 7 0	5 7 8	5 8 9	5 8 9	6 1 2	6 2 3	6 4 1	6 4 7	6 5 4	6 5 5	6 5 6	6 5 8
Carcass ID Number	0 2 4 5	0 1 7 5	0 2 1 5	0 1 8 4	0 2 0 3	0 1 9 4	0 1 5 4	0 2 2 5	0 1 7 3	0 1 5 3	0 2 2 4	0 1 6 5	0 2 1 4	0 1 4 2	0 1 6 4	0 1 1 4	0 1 4 3	0 1 9 3	0 2 2 3	0 2 1 3	0 2 0 2	0 1 3 4	0 1 1 2	0 2 1 3	0 1 2 2	0 1 7 2
Hematopoietic System																									
Blood										+		+		+		+				+			+	+	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+		+		+		+				+	+	+		+	+		+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+
Adenoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, fibroma									X		X							X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+						+		+							+					+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																						X			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Urinary bladder	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X	X		X		X	X	X		X	X	X		X	X	X	X	X	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 8.3 mg/kg (continued)

Number of Days on Study	6 7 5	6 7 5	6 8 1	6 9 6	7 0 0	7 0 4	7 1 6	7 2 4	7 2 5	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 2 3 4	0 2 3 5	0 1 5 2	0 1 9 2	0 2 0 1	0 1 8 3	0 1 6 3	0 1 9 1	0 2 3 3	0 2 1 1	0 1 3 1	0 1 3 2	0 1 4 1	0 1 4 2	0 1 5 1	0 1 6 1	0 1 6 2	0 1 7 1	0 1 8 1	0 1 8 2	0 1 8 5	0 2 2 1	0 2 3 1	0 2 3 2	0 2 3 4 1	Total Tissues/ Tumors
Hematopoietic System																										
Blood			+									+							+		+					11
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node										+		+								+	+					16
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	M	M	45
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Adenoma													X													1
Fibroadenoma										X								X								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma															X											1
Subcutaneous tissue, fibroma																										3
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										6
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear		+																								1
Eye					+															+						2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma				X																						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X	X		X			X	X	X	X		X			X		X	X	X	X	X		X	31

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 16.6 mg/kg

Number of Days on Study	1 8 4	4 0 1	4 7 9	5 2 0	5 2 2	5 3 2	5 3 6	5 5 0	5 5 5	5 7 0	5 7 1	5 7 5	5 8 2	5 9 7	5 9 8	5 9 9	6 1 6	6 1 6	6 2 5	6 2 6	6 3 9	6 4 2	6 4 7	6 5 6	6 6 5	6 6 5
Carcass ID Number	0 3 1 5	0 2 8 5	0 2 7 5	0 2 6 4	0 3 6 3	0 3 4 4	0 3 4 4	0 2 9 5	0 3 5 3	0 3 6 2	0 3 5 2	0 2 6 3	0 2 5 4	0 2 5 3	0 2 7 4	0 3 2 5	0 2 5 2	0 3 0 5	0 2 9 4	0 3 0 4	0 3 6 1	0 3 0 3	0 3 4 3	0 3 2 4	0 2 6 2	0 3 3 3
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Squamous cell carcinoma, metastatic, uncertain primary site																										
Intestine large, colon	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	A
Intestine large, rectum	+	+	+	A	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	A	A
Intestine large, cecum	+	+	+	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	+	+	M	+	+	+	+	+	+	A	A
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma			X																							
Hepatocellular adenoma															X											
Histiocytic sarcoma	X																									
Mesentery																										
Hemangiosarcoma																										
Pancreas	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, adenoma																										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																										
Pheochromocytoma benign																			X		X	X			X	
Bilateral, pheochromocytoma benign																										
Islets, pancreatic	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pars distalis, adenoma		X							X				X			X		X			X		X			
Pars distalis, adenoma, multiple																										
Thyroid gland	+	+	+	A	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	A
C-cell, adenoma																			X							
Follicular cell, adenoma																										
General Body System																										
Tissue NOS																										
Squamous cell carcinoma, metastatic, uncertain primary site																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 16.6 mg/kg (continued)

Number of Days on Study	6 6 6	6 6 6	6 7 3	6 7 3	6 9 1	6 9 4	6 9 7	7 0 0	7 0 0	7 0 1	7 0 2	7 0 4	7 1 5	7 1 8	7 2 2	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	
Carcass ID Number	0 2 7 3	0 2 8 3	0 2 9 3	0 3 1 3	0 3 2 3	0 3 2 2	0 3 1 2	0 2 8 2	0 3 4 2	0 2 7 2	0 3 4 1	0 3 1 1	0 3 3 2	0 3 5 1	0 2 6 1	0 2 5 1	0 2 7 1	0 2 8 1	0 2 9 1	0 2 9 2	0 3 0 1	0 3 0 2	0 3 2 1	0 3 3 1	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic, uncertain primary site					X																				1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	41
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	A	A	A	+	+	+	+	+	+	+	+	+	40
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																									1
Hepatocellular adenoma																			X						2
Histiocytic sarcoma	X																								2
Mesentery				+			+							+											3
Hemangiosarcoma														X											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, adenoma												X													1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant					X																				1
Pheochromocytoma benign						X			X		X														7
Bilateral, pheochromocytoma benign							X																		1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X			X																					2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X		X		X		X	X	X			X					X							15
Pars distalis, adenoma, multiple																				X					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	44
C-cell, adenoma		X													X										3
Follicular cell, adenoma					X																				1
General Body System																									
Tissue NOS					+																				1
Squamous cell carcinoma, metastatic, uncertain primary site					X																				1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 16.6 mg/kg (continued)

Number of Days on Study	1 8 4	4 0 1	4 7 9	5 2 0	5 2 2	5 3 2	5 3 6	5 5 0	5 5 5	5 7 0	5 7 1	5 7 5	5 8 2	5 9 7	5 9 8	5 9 9	6 1 6	6 1 6	6 2 5	6 2 6	6 3 9	6 4 2	6 4 7	6 5 6	6 6 5	6 6 5
Carcass ID Number	0 3 1 5	0 2 8 5	0 2 7 5	0 2 6 4	0 3 6 3	0 3 4 4	0 3 3 4	0 2 9 5	0 3 5 3	0 3 6 2	0 3 5 2	0 2 6 3	0 2 5 4	0 2 5 3	0 2 7 4	0 3 2 5	0 2 5 2	0 3 0 5	0 2 9 4	0 3 0 4	0 3 6 1	0 3 0 3	0 3 4 3	0 3 2 4	0 2 6 2	0 3 3 3
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X						X		X	X		X		X			X	X	X	X	X
Interstitial cell, adenoma				X	X			X	X	X	X		X							X	X					
Hematopoietic System																										
Blood					+	+	+			+	+	+					+						+			
Bone marrow	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Lymph node			+	+	+	+	+			+	+	+					+						+			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																										
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	M	M	M	M	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign																										
Keratoacanthoma																										
Subcutaneous tissue, fibroma				X									X													
Subcutaneous tissue, fibroma, multiple																								X		
Subcutaneous tissue, sarcoma								X																		
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant																										
Peripheral nerve																										
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																										
Squamous cell carcinoma, multiple																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 16.6 mg/kg (continued)

Number of Days on Study	6 6 6	6 6 6	6 7 3	6 7 3	6 9 1	6 9 4	6 9 7	7 0 0	7 0 0	7 0 1	7 0 2	7 0 4	7 1 5	7 1 8	7 2 2	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	
Carcass ID Number	0 2 7 3	0 2 8 3	0 2 9 3	0 3 1 3	0 3 2 3	0 3 2 2	0 3 1 2	0 2 8 2	0 3 4 2	0 2 7 2	0 3 4 1	0 3 1 1	0 3 3 2	0 3 5 1	0 2 6 1	0 2 5 1	0 2 7 1	0 2 8 1	0 2 9 1	0 2 9 2	0 3 0 1	0 3 0 2	0 3 2 1	0 3 3 1	Total Tissues/ Tumors
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																					X				2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma			X	X	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	31
Interstitial cell, adenoma	X	X							X				X												13
Hematopoietic System																									
Blood		+	+				+			+													+		13
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma	X																								1
Lymph node		+	+	+						+				+											15
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibroma				X																					1
Thymus	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	46
Integumentary System																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	38
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor benign							X																		1
Keratoacanthoma												X				X									2
Subcutaneous tissue, fibroma				X																					3
Subcutaneous tissue, fibroma, multiple																									1
Subcutaneous tissue, sarcoma																									1
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant								X																	1
Peripheral nerve										+									+						2
Respiratory System																									
Lung	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma																					X				1
Squamous cell carcinoma, multiple						X																			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 16.6 mg/kg (continued)

Number of Days on Study	1 8 4	4 0 1	4 7 9	5 2 0	5 2 2	5 3 2	5 3 6	5 5 0	5 5 5	5 7 0	5 7 1	5 7 5	5 8 2	5 9 7	5 9 8	5 9 9	6 1 6	6 1 6	6 2 5	6 2 6	6 3 9	6 4 2	6 4 7	6 5 6	6 6 5	6 6 5
Carcass ID Number	0 3 1 5	0 2 8 5	0 2 7 5	0 2 6 4	0 3 6 3	0 3 4 4	0 3 3 4	0 2 9 5	0 3 5 3	0 3 6 2	0 3 5 2	0 2 6 3	0 2 5 4	0 2 5 3	0 2 7 4	0 3 2 5	0 2 5 2	0 3 0 5	0 2 9 4	0 3 0 4	0 3 6 1	0 3 0 3	0 4 4 3	0 3 2 4	0 2 6 2	0 3 3 3
Special Senses System																										
Eye																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma																										
Squamous cell carcinoma, metastatic, uncertain primary site																										
Renal tubule, adenoma																										
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																									
Leukemia mononuclear			X	X	X	X	X			X	X	X				X	X			X			X			
Mesothelioma malignant																										

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 16.6 mg/kg (continued)

Number of Days on Study	6 6 6	6 6 6	6 7 3	6 7 3	6 9 1	6 9 4	6 9 7	7 0 0	7 0 0	7 0 1	7 0 2	7 0 4	7 1 5	7 1 8	7 2 2	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	7 2 5	
Carcass ID Number	0 2 7 3	0 2 8 3	0 2 9 3	0 3 1 3	0 3 2 3	0 3 2 2	0 3 1 2	0 2 8 2	0 3 4 2	0 2 7 2	0 3 4 1	0 3 1 1	0 3 3 2	0 3 5 1	0 2 6 1	0 2 5 1	0 2 7 1	0 2 8 1	0 2 9 1	0 3 9 2	0 3 0 1	0 3 0 2	0 3 2 1	0 3 3 1	Total Tissues/ Tumors
Special Senses System																									
Eye		+									+														2
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma														X											1
Squamous cell carcinoma, metastatic, uncertain primary site					X																				1
Renal tubule, adenoma														X											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma	X																								2
Leukemia mononuclear	X	X	X	X		X	X			X							X	X			X		X	X	24
Mesothelioma malignant	X																								1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 33.3 mg/kg

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 33.3 mg/kg (continued)

Number of Days on Study	6 2 4	6 2 5	6 3 2	6 3 9	6 5 6	6 5 7	6 5 8	6 5 8	6 6 6	6 6 7	6 6 7	6 7 5	6 8 0	6 9 3	7 0 8	7 1 5	7 1 7	7 1 7	7 1 7	7 1 7	7 1 7	7 1 7	7 1 7	7 1 7	7 1 7	
Carcass ID Number	0 4 8 3	0 3 8 1	0 4 4 4	0 4 7 3	0 3 7 3	0 4 5 3	0 3 7 2	0 4 3 1	0 4 4 3	0 4 0 1	0 4 6 3	0 3 9 1	0 4 4 2	0 4 5 2	0 4 7 2	0 4 2 2	0 3 7 1	0 4 1 2	0 4 1 3	0 4 2 1	0 4 4 1	0 4 5 1	0 4 6 1	0 4 6 2	0 4 7 1	0 4 8 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Adenocarcinoma											X															1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	36
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular adenoma											X															1
Mesentery							+											+								3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pharynx													+				+									2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma																					X					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant						X																				1
Pheochromocytoma complex																										1
Pheochromocytoma benign																										1
Bilateral, pheochromocytoma benign									X																	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma					X																					1
Parathyroid gland	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X		X														X			X	X	X		8
Thyroid gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
C-cell, adenoma																				X						1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		2
Bilateral, adenoma																						X				1
Prostate	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Bilateral, interstitial cell, adenoma	X	X		X		X		X	X	X	X	X	X		X	X	X	X	X	X	X	X		X	X	36
Interstitial cell, adenoma			X		X		X							X									X			7

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 33.3 mg/kg (continued)

Number of Days on Study	0 4 9	0 5 3	1 3 8	2 8 8	2 8 9	3 6 5	4 5 8	5 4 1	5 5 5	5 6 2	5 6 5	5 6 8	5 7 6	5 8 3	5 8 4	5 9 2	5 9 2	6 0 2	6 0 4	6 0 8	6 1 2	6 1 7	6 2 0	6 2 4	6 2 4
Carcass ID Number	0 3 9 5	0 4 8 5	0 3 8 5	0 4 1 1	0 4 7 5	0 4 0 5	0 4 5 5	0 4 5 4	0 4 4 5	0 3 8 3	0 4 0 3	0 3 7 5	0 4 2 4	0 4 8 4	0 4 0 2	0 3 8 2	0 3 3 4	0 4 3 3	0 3 7 4	0 4 6 4	0 4 2 3	0 4 1 4	0 4 8 1	0 3 9 2	0 4 3 2
Hematopoietic System																									
Blood																		+			+				+
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node						+																			+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+
Histiocytic sarcoma																									
Integumentary System																									
Mammary gland	M	M	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																						X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye		+	+																						
Zymbal's gland																									
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lipoma																									X
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear						X			X				X				X	X		X	X		X	X	X
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 33.3 mg/kg (continued)

Number of Days on Study	6 2 4	6 2 5	6 3 2	6 3 9	6 5 6	6 5 7	6 5 8	6 5 8	6 6 6	6 6 7	6 6 7	6 7 5	6 8 0	6 9 3	7 0 8	7 1 5	7 1 7	7 1 7	7 1 7	7 1 7	7 1 7	7 1 7	7 1 7	7 1 7	7 1 7	
Carcass ID Number	0 4 8 3	0 3 8 1	0 4 4 4	0 4 7 3	0 3 7 3	0 4 5 3	0 3 7 2	0 4 3 1	0 4 4 3	0 4 0 1	0 4 6 3	0 3 9 1	0 4 4 2	0 4 5 2	0 4 7 2	0 4 2 2	0 3 7 1	0 4 1 2	0 4 1 3	0 4 2 1	0 4 4 1	0 4 5 1	0 4 6 1	0 4 6 2	0 4 7 1	0 4 8 2	Total Tissues/ Tumors
Hematopoietic System																										
Blood							+	+					+	+												7
Bone marrow	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+	+							+											5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	46
Histiocytic sarcoma		X																								1
Integumentary System																										
Mammary gland	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	42
Adenoma																							X			1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, fibroma										X																2
Musculoskeletal System																										
Bone	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle											+															1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																										
Eye																										2
Zymbal's gland														+												1
Carcinoma														X												1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma		X																								1
Lipoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma		X																								1
Leukemia mononuclear							X	X	X	X				X	X				X				X		X	19
Mesothelioma malignant											X															1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	14/50 (28%)	11/50 (22%)	8/50 (16%)	2/51 (4%)
Adjusted rate[b]	42.3%	43.5%	32.0%	7.9%
Terminal rate[c]	6/23 (26%)	5/18 (28%)	0/11 (0%)	0/10 (0%)
First incidence (days)	570	568	625	565
Life table test[d]	P=0.057N	P=0.578	P=0.505N	P=0.050N
Logistic regression test[d]	P=0.004N	P=0.506N	P=0.194N	P=0.004N
Cochran-Armitage test[d]	P<0.001N			
Fisher exact test[d]		P=0.322N	P=0.114N	P<0.001N
Adrenal Medulla: Malignant Pheochromocytoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	1/51 (2%)
Adjusted rate	8.4%	5.6%	5.0%	4.8%
Terminal rate	0/23 (0%)	1/18 (6%)	0/11 (0%)	0/10 (0%)
First incidence (days)	570	717 (T)	691	657
Life table test	P=0.448N	P=0.416N	P=0.432N	P=0.541N
Logistic regression test	P=0.298N	P=0.329N	P=0.313N	P=0.328N
Cochran-Armitage test	P=0.237N			
Fisher exact test		P=0.309N	P=0.309N	P=0.301N
Adrenal Medulla: Benign, Malignant, or Complex Pheochromocytoma				
Overall rate	16/50 (32%)	12/50 (24%)	9/49 (18%)	4/50 (8%)
Adjusted rate	46.0%	47.9%	35.4%	15.2%
Terminal rate	6/23 (26%)	6/18 (33%)	0/11 (0%)	0/10 (0%)
First incidence (days)	570	568	625	565
Life table test	P=0.123N	P=0.544N	P=0.471N	P=0.124N
Logistic regression test	P=0.003N	P=0.446N	P=0.114N	P=0.009N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.252N	P=0.091N	P=0.003N
Liver: Hepatocellular Adenoma				
Overall rate	4/50 (8%)	2/50 (4%)	2/50 (4%)	1/51 (2%)
Adjusted rate	16.0%	9.8%	11.6%	5.9%
Terminal rate	3/23 (13%)	1/18 (6%)	1/11 (9%)	0/10 (0%)
First incidence (days)	687	696	598	667
Life table test	P=0.389N	P=0.454N	P=0.619N	P=0.487N
Logistic regression test	P=0.264N	P=0.467N	P=0.469N	P=0.387N
Cochran-Armitage test	P=0.133N			
Fisher exact test		P=0.339N	P=0.339N	P=0.175N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	4/50 (8%)	2/50 (4%)	3/50 (6%)	1/51 (2%)
Adjusted rate	16.0%	9.8%	13.5%	5.9%
Terminal rate	3/23 (13%)	1/18 (6%)	1/11 (9%)	0/10 (0%)
First incidence (days)	687	696	479	667
Life table test	P=0.422N	P=0.454N	P=0.549	P=0.487N
Logistic regression test	P=0.229N	P=0.467N	P=0.528N	P=0.387N
Cochran-Armitage test	P=0.157N			
Fisher exact test		P=0.339N	P=0.500N	P=0.175N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Mammary Gland: Fibroadenoma				
Overall rate	4/50 (8%)	2/50 (4%)	0/50 (0%)	0/51 (0%)
Adjusted rate	16.0%	11.1%	0.0%	0.0%
Terminal rate	3/23 (13%)	2/18 (11%)	0/11 (0%)	0/10 (0%)
First incidence (days)	687	717 (T)	)[e]	)
Life table test	P=0.072N	P=0.457N	P=0.171N	P=0.212N
Logistic regression test	P=0.059N	P=0.466N	P=0.134N	P=0.181N
Cochran-Armitage test	P=0.017N			
Fisher exact test		P=0.339N	P=0.059N	P=0.056N
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	5/50 (10%)	3/50 (6%)	0/50 (0%)	1/51 (2%)
Adjusted rate	20.2%	16.7%	0.0%	10.0%
Terminal rate	4/23 (17%)	3/18 (17%)	0/11 (0%)	1/10 (10%)
First incidence (days)	687	717 (T)	)	717 (T)
Life table test	P=0.175N	P=0.499N	P=0.119N	P=0.380N
Logistic regression test	P=0.149N	P=0.509N	P=0.088N	P=0.345N
Cochran-Armitage test	P=0.036N			
Fisher exact test		P=0.357N	P=0.028N	P=0.098N
Pancreatic Islets: Adenoma				
Overall rate	4/50 (8%)	2/50 (4%)	2/49 (4%)	1/49 (2%)
Adjusted rate	15.6%	11.1%	8.5%	4.5%
Terminal rate	3/23 (13%)	2/18 (11%)	0/11 (0%)	0/10 (0%)
First incidence (days)	684	717 (T)	666	656
Life table test	P=0.409N	P=0.470N	P=0.629N	P=0.479N
Logistic regression test	P=0.283N	P=0.467N	P=0.487N	P=0.371N
Cochran-Armitage test	P=0.142N			
Fisher exact test		P=0.339N	P=0.349N	P=0.187N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	16/50 (32%)	16/50 (32%)	16/48 (33%)	8/50 (16%)
Adjusted rate	44.8%	55.7%	56.2%	48.6%
Terminal rate	5/23 (22%)	7/18 (39%)	2/11 (18%)	4/10 (40%)
First incidence (days)	561	497	401	565
Life table test	P=0.504	P=0.272	P=0.127	P=0.577
Logistic regression test	P=0.097N	P=0.425	P=0.462	P=0.178N
Cochran-Armitage test	P=0.037N			
Fisher exact test		P=0.585N	P=0.530	P=0.050N
Preputial Gland: Adenoma				
Overall rate	2/48 (4%)	5/50 (10%)	2/48 (4%)	3/50 (6%)
Adjusted rate	8.3%	16.6%	11.8%	22.1%
Terminal rate	1/23 (4%)	1/18 (6%)	1/11 (9%)	2/10 (20%)
First incidence (days)	716	491	616	583
Life table test	P=0.280	P=0.146	P=0.467	P=0.206
Logistic regression test	P=0.537	P=0.239	P=0.607	P=0.312
Cochran-Armitage test	P=0.565N			
Fisher exact test		P=0.235	P=0.692N	P=0.520

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Skin: Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	0/51 (0%)
Adjusted rate	13.0%	5.6%	0.0%	0.0%
Terminal rate	3/23 (13%)	1/18 (6%)	0/11 (0%)	0/10 (0%)
First incidence (days)	717 (T)	717 (T)	)	)
Life table test	P=0.121N	P=0.394N	P=0.275N	P=0.298N
Logistic regression test	P=0.121N	P=0.394N	P=0.275N	P=0.298N
Cochran-Armitage test	P=0.043N			
Fisher exact test		P=0.309N	P=0.121N	P=0.118N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Squamous Cell Carcinoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	0/51 (0%)
Adjusted rate	13.0%	5.6%	16.1%	0.0%
Terminal rate	3/23 (13%)	1/18 (6%)	1/11 (9%)	0/10 (0%)
First incidence (days)	717 (T)	717 (T)	704	)
Life table test	P=0.291N	P=0.394N	P=0.557	P=0.298N
Logistic regression test	P=0.268N	P=0.394N	P=0.616	P=0.298N
Cochran-Armitage test	P=0.101N			
Fisher exact test		P=0.309N	P=0.500N	P=0.118N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	3/50 (6%)	3/50 (6%)	4/50 (8%)	2/51 (4%)
Adjusted rate	8.5%	7.7%	12.4%	9.0%
Terminal rate	0/23 (0%)	0/18 (0%)	0/11 (0%)	0/10 (0%)
First incidence (days)	595	529	520	617
Life table test	P=0.540	P=0.543	P=0.348	P=0.601
Logistic regression test	P=0.378N	P=0.613N	P=0.541	P=0.540N
Cochran-Armitage test	P=0.410N			
Fisher exact test		P=0.661N	P=0.500	P=0.491N
Skin (Subcutaneous Tissue): Fibroma or Sarcoma				
Overall rate	3/50 (6%)	3/50 (6%)	5/50 (10%)	2/51 (4%)
Adjusted rate	8.5%	7.7%	14.4%	9.0%
Terminal rate	0/23 (0%)	0/18 (0%)	0/11 (0%)	0/10 (0%)
First incidence (days)	595	529	520	617
Life table test	P=0.517	P=0.543	P=0.229	P=0.601
Logistic regression test	P=0.386N	P=0.613N	P=0.410	P=0.540N
Cochran-Armitage test	P=0.431N			
Fisher exact test		P=0.661N	P=0.357	P=0.491N
Testes: Adenoma				
Overall rate	47/50 (94%)	44/50 (88%)	44/50 (88%)	43/51 (84%)
Adjusted rate	100.0%	97.8%	100.0%	97.7%
Terminal rate	23/23 (100%)	17/18 (94%)	11/11 (100%)	9/10 (90%)
First incidence (days)	512	491	520	458
Life table test	P=0.001	P=0.153	P=0.010	P=0.002
Logistic regression test	P=0.478	P=0.645	P=0.689	P=0.600
Cochran-Armitage test	P=0.103N			
Fisher exact test		P=0.243N	P=0.243N	P=0.106N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/49 (8%)	5/49 (10%)	3/44 (7%)	1/41 (2%)
Adjusted rate	11.6%	21.0%	15.6%	10.0%
Terminal rate	1/23 (4%)	2/18 (11%)	1/11 (9%)	1/10 (10%)
First incidence (days)	602	563	625	717 (T)
Life table test	P=0.325N	P=0.346	P=0.580	P=0.402N
Logistic regression test	P=0.195N	P=0.462	P=0.571N	P=0.271N
Cochran-Armitage test	P=0.143N			
Fisher exact test		P=0.500	P=0.561N	P=0.241N
All Organs: Mononuclear Cell Leukemia				
Overall rate	22/50 (44%)	31/50 (62%)	24/50 (48%)	19/51 (37%)
Adjusted rate	58.6%	82.1%	72.3%	65.0%
Terminal rate	9/23 (39%)	12/18 (67%)	5/11 (45%)	3/10 (30%)
First incidence (days)	512	501	479	365
Life table test	P=0.145	P=0.013	P=0.044	P=0.097
Logistic regression test	P=0.203N	P=0.025	P=0.411	P=0.502N
Cochran-Armitage test	P=0.106N			
Fisher exact test		P=0.054	P=0.421	P=0.313N
All Organs: Benign Neoplasms				
Overall rate	48/50 (96%)	48/50 (96%)	48/50 (96%)	48/51 (94%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	23/23 (100%)	18/18 (100%)	11/11 (100%)	10/10 (100%)
First incidence (days)	512	184	184	49
Life table test	P<0.001	P=0.073	P=0.004	P<0.001
Logistic regression test	P=0.334	P=0.348	P=0.599	P=0.462
Cochran-Armitage test	P=0.396N			
Fisher exact test		P=0.691N	P=0.691N	P=0.509N
All Organs: Malignant Neoplasms				
Overall rate	28/50 (56%)	32/50 (64%)	29/50 (58%)	23/51 (45%)
Adjusted rate	69.9%	85.1%	80.2%	71.0%
Terminal rate	12/23 (52%)	13/18 (72%)	6/11 (55%)	3/10 (30%)
First incidence (days)	512	501	184	365
Life table test	P=0.102	P=0.060	P=0.040	P=0.094
Logistic regression test	P=0.172N	P=0.155	P=0.547	P=0.374N
Cochran-Armitage test	P=0.086N			
Fisher exact test		P=0.270	P=0.500	P=0.185N
All Organs: Benign or Malignant Neoplasms				
Overall rate	48/50 (96%)	48/50 (96%)	50/50 (100%)	49/51 (96%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	23/23 (100%)	18/18 (100%)	11/11 (100%)	10/10 (100%)
First incidence (days)	512	184	184	49
Life table test	P<0.001	P=0.073	P=0.002	P<0.001
Logistic regression test	P=0.098	P=0.348	P=0.163	P=0.233
Cochran-Armitage test	P=0.549			
Fisher exact test		P=0.691N	P=0.247	P=0.684

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

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

TABLE A4a
Historical Incidence of Adrenal Medulla Neoplasms in Untreated Male F344/N Rats [a]

Study	Incidence in Controls		
	Benign Pheochromocytoma	Malignant Pheochromocytoma	Benign or Malignant Pheochromocytoma
Overall Historical Incidence: Water Gavage			
Total	116/356 (32.6%)	14/356 (3.9%)	129/356 (36.2%)
Standard deviation	10.2%	3.1%	10.0%
Range	18%-45%	2%-10%	25%-50%
Overall Historical Incidence: Feed			
Total	414/1,234 (33.5%)	48/1,234 (3.9%)	445/1,234 (36.1%)[b]
Standard deviation	11.6%	4.8%	11.0%
Range	10%-63%	0%-20%	14%-63%

[a] Data as of 20 August 1992
[b] Includes three complex pheochromocytomas

TABLE A4b
Historical Incidence of Pituitary Gland Neoplasms in Untreated Male F344/N Rats [a]

Study	Incidence in Controls		
	Pars Distalis Adenoma	Pars Distalis Carcinoma	Pars Distalis Adenoma or Carcinoma
Overall Historical Incidence: Water Gavage			
Total	116/363 (32.0%)	1/363 (0.3%)	117/363 (32.2%)
Standard deviation	7.7%	0.8%	7.5%
Range	24%-43%	0%-2%	24%-43%
Overall Historical Incidence: Feed			
Total	352/1,235 (28.5%)	5/1,235 (0.4%)	357/1,235 (28.9%)
Standard deviation	11.3%	1.0%	11.3%
Range	12%-60%	0%-4%	12%-60%

[a] Data as of 20 August 1992

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride[a]

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	9
Early deaths				
Moribund	24	27	27	21
Natural deaths	3	5	12	20
Survivors				
Died last week of study		4	2	
Terminal sacrifice	23	14	9	10
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(9)
Basophilic focus	2 (20%)	3 (30%)	2 (20%)	2 (22%)
Clear cell focus	3 (30%)	1 (10%)	2 (20%)	2 (22%)
Fatty change, diffuse	9 (90%)	10 (100%)	9 (90%)	9 (100%)
Hepatodiaphragmatic nodule	4 (40%)			
Necrosis, focal	1 (10%)	1 (10%)		1 (11%)
Bile duct, hyperplasia	7 (70%)	9 (90%)	4 (40%)	1 (11%)
Centrilobular, hypertrophy			1 (10%)	8 (89%)
Salivary glands	(10)	(10)	(10)	(9)
Duct, metaplasia, squamous		1 (10%)	1 (10%)	2 (22%)
Stomach, forestomach	(10)	(10)	(10)	(9)
Hyperkeratosis	1 (10%)			
Hyperplasia, basal cell	1 (10%)			1 (11%)
Stomach, glandular	(10)	(10)	(10)	(9)
Hyperplasia	1 (10%)			
Tongue	(1)			(1)
Hyperkeratosis				1 (100%)
Inflammation, acute	1 (100%)			
Cardiovascular System				
Heart	(10)	(10)	(10)	(9)
Cardiomyopathy	7 (70%)	7 (70%)	6 (60%)	7 (78%)
Endocrine System				
Islets, pancreatic	(10)	(10)	(10)	(9)
Hyperplasia				1 (11%)
Pituitary gland	(10)	(10)	(10)	(9)
Pars distalis, angiectasis	1 (10%)		1 (10%)	
Pars distalis, hyperplasia	3 (30%)	2 (20%)	2 (20%)	1 (11%)
Thyroid gland	(10)	(10)	(10)	(9)
Follicular cell, hyperplasia			1 (10%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
15-Month Interim Evaluation (continued)				
General Body System				
None				
Genital System				
Testes	(10)	(10)	(10)	(9)
Atrophy	1 (10%)			
Interstitial cell, hyperplasia	10 (100%)	10 (100%)	10 (100%)	9 (100%)
Hematopoietic System				
Spleen	(10)	(10)	(10)	(9)
Fibrosis	1 (10%)			
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(9)
Alveolar epithelium, hyperplasia	1 (10%)	1 (10%)		
Nose	(10)	(10)	(10)	(9)
Fungus		1 (10%)	1 (10%)	1 (11%)
Inflammation, acute	1 (10%)	2 (20%)	1 (10%)	1 (11%)
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(10)	(9)
Nephropathy	10 (100%)	10 (100%)	10 (100%)	9 (100%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(49)	(50)
Hemorrhage		1 (2%)	1 (2%)	
Hyperkeratosis			1 (2%)	3 (6%)
Inflammation, acute	1 (2%)	1 (2%)		1 (2%)
Necrosis				1 (2%)
Intestine large, colon	(49)	(47)	(44)	(40)
Artery, inflammation, chronic active		2 (4%)		
Intestine large, cecum	(47)	(46)	(42)	(36)
Hyperplasia			1 (2%)	
Intestine small, ileum	(46)	(47)	(43)	(36)
Necrosis		1 (2%)		
Liver	(50)	(50)	(50)	(51)
Angiectasis	2 (4%)	7 (14%)	2 (4%)	
Basophilic focus	18 (36%)	29 (58%)	23 (46%)	21 (41%)
Clear cell focus	5 (10%)	6 (12%)	6 (12%)	11 (22%)
Degeneration, cystic	5 (10%)	4 (8%)	7 (14%)	4 (8%)
Eosinophilic focus	2 (4%)	5 (10%)	5 (10%)	4 (8%)
Fatty change, diffuse	4 (8%)	5 (10%)	16 (32%)	28 (55%)
Fatty change, focal				1 (2%)
Fibrosis		1 (2%)		
Hematopoietic cell proliferation			1 (2%)	
Hepatodiaphragmatic nodule	7 (14%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia	1 (2%)			1 (2%)
Infarct		2 (4%)		
Leukocytosis	1 (2%)			
Mixed cell focus	4 (8%)	3 (6%)	8 (16%)	11 (22%)
Necrosis			5 (10%)	1 (2%)
Thrombosis		2 (4%)		1 (2%)
Artery, necrosis		1 (2%)		
Bile duct, cyst			1 (2%)	
Bile duct, hyperplasia	39 (78%)	30 (60%)	18 (36%)	11 (22%)
Mesentery	(2)	(6)	(3)	(3)
Artery, inflammation, chronic active		1 (17%)		
Fat, fibrosis				1 (33%)
Fat, hemorrhage		3 (50%)	1 (33%)	
Fat, inflammation, chronic active				1 (33%)
Fat, mineralization	1 (50%)		1 (33%)	
Fat, necrosis		2 (33%)	2 (67%)	1 (33%)
Fat, pigmentation		1 (17%)		
Pancreas	(50)	(50)	(49)	(51)
Acinus, hyperplasia	2 (4%)	1 (2%)		
Artery, fibrosis		1 (2%)		
Artery, inflammation, chronic active	1 (2%)	3 (6%)		
Pharynx				(2)
Inflammation, acute				1 (50%)
Palate, inflammation, acute				1 (50%)
Salivary glands	(50)	(50)	(50)	(50)
Duct, metaplasia, squamous		1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Stomach, forestomach	(49)	(50)	(50)	(51)
Cyst epithelial inclusion				1 (2%)
Hyperkeratosis	1 (2%)	5 (10%)	1 (2%)	4 (8%)
Hyperplasia, basal cell	4 (8%)	7 (14%)	2 (4%)	5 (10%)
Hyperplasia, squamous		1 (2%)		1 (2%)
Inflammation, acute			1 (2%)	
Mineralization		1 (2%)		
Necrosis	3 (6%)	6 (12%)	2 (4%)	1 (2%)
Ulcer	4 (8%)		1 (2%)	4 (8%)
Stomach, glandular	(49)	(50)	(47)	(45)
Erosion		1 (2%)		
Inflammation, chronic active	1 (2%)			
Mineralization	1 (2%)	10 (20%)	8 (17%)	
Necrosis				2 (4%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Cardiomyopathy	46 (92%)	32 (64%)	40 (80%)	45 (88%)
Congestion				1 (2%)
Inflammation, acute		1 (2%)	1 (2%)	
Mineralization		6 (12%)	5 (10%)	2 (4%)
Thrombosis		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(51)
Accessory adrenal cortical nodule			1 (2%)	
Hyperplasia		2 (4%)		
Hypertrophy	2 (4%)			
Adrenal medulla	(50)	(50)	(49)	(50)
Hyperplasia	13 (26%)	15 (30%)	14 (29%)	9 (18%)
Bilateral, hyperplasia	2 (4%)			
Islets, pancreatic	(50)	(50)	(49)	(49)
Hyperplasia	1 (2%)		2 (4%)	2 (4%)
Parathyroid gland	(48)	(48)	(48)	(47)
Hyperplasia	1 (2%)	8 (17%)	8 (17%)	3 (6%)
Bilateral, hyperplasia	1 (2%)			
Pituitary gland	(50)	(50)	(48)	(50)
Pars distalis, angiectasis	11 (22%)	7 (14%)	5 (10%)	3 (6%)
Pars distalis, cyst	4 (8%)	3 (6%)	4 (8%)	
Pars distalis, fibrosis			1 (2%)	
Pars distalis, hyperplasia	19 (38%)	12 (24%)	14 (29%)	8 (16%)
Pars distalis, infarct				1 (2%)
Pars nervosa, cyst			1 (2%)	
Thyroid gland	(49)	(49)	(44)	(41)
C-cell, hyperplasia	9 (18%)	2 (4%)	1 (2%)	1 (2%)
Follicle, cyst		1 (2%)	1 (2%)	1 (2%)
Follicular cell, hyperplasia	3 (6%)			1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
General Body System				
None				
Genital System				
Preputial gland	(48)	(50)	(48)	(50)
Hyperplasia		2 (4%)	1 (2%)	1 (2%)
Necrosis	1 (2%)	1 (2%)	2 (4%)	
Prostate	(48)	(50)	(50)	(48)
Hyperplasia			3 (6%)	
Inflammation, chronic active	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Mineralization			1 (2%)	
Seminal vesicle	(49)	(50)	(49)	(51)
Inflammation, acute	1 (2%)	1 (2%)		
Testes	(50)	(50)	(50)	(51)
Interstitial cell, hyperplasia	4 (8%)	10 (20%)	9 (18%)	5 (10%)
Seminiferous tubule, atrophy	13 (26%)	5 (10%)	3 (6%)	8 (16%)
Hematopoietic System				
Lymph node	(15)	(16)	(15)	(5)
Mediastinal, angiectasis	1 (7%)		1 (7%)	
Pancreatic, pigmentation	1 (7%)			
Renal, angiectasis		1 (6%)		
Lymph node, mesenteric	(49)	(50)	(50)	(50)
Degeneration	1 (2%)			
Infiltration cellular, histiocyte		1 (2%)		
Spleen	(50)	(50)	(49)	(51)
Cyst				1 (2%)
Fibrosis	2 (4%)	6 (12%)	4 (8%)	4 (8%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)	2 (4%)	
Infarct	1 (2%)	1 (2%)	2 (4%)	
Thymus	(42)	(45)	(46)	(46)
Cyst	1 (2%)			
Ectopic parathyroid gland			1 (2%)	
Epithelial cell, hyperplasia	3 (7%)			
Integumentary System				
Mammary gland	(49)	(45)	(38)	(42)
Galactocele				2 (5%)
Acinus, hyperplasia				1 (2%)
Skin	(50)	(50)	(50)	(51)
Abscess	1 (2%)			
Acanthosis				1 (2%)
Cyst epithelial inclusion	1 (2%)	1 (2%)		
Hyperkeratosis	2 (4%)			1 (2%)
Necrosis		1 (2%)		

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Musculoskeletal System				
Skeletal muscle	(1)	(6)		(1)
Edema				1 (100%)
Hemorrhage				1 (100%)
Necrosis		1 (17%)		
Nervous System				
Brain	(50)	(50)	(50)	(51)
Hemorrhage	2 (4%)			
Mineralization	1 (2%)			
Thrombosis	1 (2%)			
Peripheral nerve	(1)		(2)	
Degeneration	1 (100%)			
Inflammation, chronic active	1 (100%)			
Respiratory System				
Lung	(50)	(50)	(49)	(51)
Edema		4 (8%)	3 (6%)	5 (10%)
Fibrosis		1 (2%)	1 (2%)	
Hemorrhage	3 (6%)	11 (22%)	3 (6%)	1 (2%)
Infiltration cellular, histiocyte	2 (4%)	4 (8%)		1 (2%)
Inflammation, acute	1 (2%)	2 (4%)	2 (4%)	4 (8%)
Alveolar epithelium, hyperplasia	2 (4%)			
Artery, inflammation, chronic active		1 (2%)		
Bronchiole, inflammation, acute	1 (2%)			
Mediastinum, inflammation, chronic active			1 (2%)	1 (2%)
Nose	(50)	(50)	(50)	(51)
Fungus	7 (14%)	4 (8%)		4 (8%)
Hyperkeratosis	1 (2%)	1 (2%)		
Inflammation, acute	12 (24%)	9 (18%)	7 (14%)	8 (16%)
Trachea	(50)	(50)	(50)	(51)
Erosion				1 (2%)
Inflammation, acute				1 (2%)
Special Senses System				
Eye	(2)	(2)	(2)	(2)
Atrophy	1 (50%)			
Lens, cataract		1 (50%)	2 (100%)	

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Urinary System				
Kidney	(50)	(50)	(50)	(51)
Cyst	3 (6%)	3 (6%)	2 (4%)	4 (8%)
Developmental malformation	1 (2%)			
Hemorrhage		1 (2%)		1 (2%)
Hydronephrosis			2 (4%)	
Mineralization	2 (4%)	6 (12%)	5 (10%)	1 (2%)
Nephropathy	49 (98%)	46 (92%)	48 (96%)	47 (92%)
Pelvis, transitional epithelium, hyperplasia	1 (2%)			
Pelvis, transitional epithelium, inflammation	1 (2%)			
Renal tubule, hyperplasia		5 (10%)		1 (2%)
Urinary bladder	(49)	(48)	(49)	(48)
Calculus gross observation	1 (2%)			1 (2%)
Calculus microscopic observation only	1 (2%)			1 (2%)
Dilatation				1 (2%)
Hemorrhage	1 (2%)			
Hyperplasia			1 (2%)	

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

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR GAVAGE STUDY OF PROMETHAZINE HYDROCHLORIDE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride [a]

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	7
Early deaths				
Accidental deaths	1			2
Moribund	12	12	10	11
Natural deaths	5	4	9	16
Survivors				
Died last week of study	3	1		
Terminal sacrifice	29	33	31	24
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
None				
Cardiovascular System				
None				
Endocrine System				
Pituitary gland	(10)	(10)	(10)	(7)
Pars distalis, adenoma	2 (20%)	2 (20%)	1 (10%)	1 (14%)
General Body System				
None				
Genital System				
Uterus	(10)	(10)	(10)	(7)
Polyp stromal	2 (20%)	1 (10%)	1 (10%)	
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
15-Month Interim Evaluation (continued)				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(7)
Alveolar/bronchiolar adenoma	1 (10%)			
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Intestine large, colon	(49)	(47)	(43)	(42)
Sarcoma				1 (2%)
Intestine large, rectum	(48)	(47)	(44)	(39)
Sarcoma stromal, metastatic, uterus	1 (2%)			
Intestine small, ileum	(48)	(47)	(43)	(37)
Liver	(50)	(49)	(50)	(52)
Hepatocellular adenoma			1 (2%)	1 (2%)
Pancreas	(50)	(49)	(50)	(49)
Salivary glands	(50)	(49)	(49)	(52)
Stomach, forestomach	(49)	(49)	(50)	(50)
Squamous cell papilloma		1 (2%)	1 (2%)	1 (2%)
Stomach, glandular	(50)	(48)	(44)	(44)
Cardiovascular System				
Heart	(50)	(50)	(50)	(52)
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(51)
Adenoma		1 (2%)		
Adrenal medulla	(50)	(49)	(50)	(51)
Pheochromocytoma benign	4 (8%)	1 (2%)	2 (4%)	3 (6%)
Islets, pancreatic	(50)	(49)	(50)	(48)
Adenoma	1 (2%)	1 (2%)		
Adenoma, multiple	1 (2%)			
Pituitary gland	(49)	(48)	(48)	(51)
Pars distalis, adenoma	22 (45%)	23 (48%)	18 (38%)	16 (31%)
Pars distalis, adenoma, multiple	4 (8%)	1 (2%)	4 (8%)	1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Thyroid gland	(49)	(49)	(45)	(47)
Bilateral, C-cell, adenoma		1 (2%)		1 (2%)
C-cell, adenoma	4 (8%)	3 (6%)	10 (22%)	1 (2%)
C-cell, carcinoma				1 (2%)
Follicular cell, adenoma	2 (4%)	2 (4%)	2 (4%)	
Follicular cell, carcinoma			1 (2%)	
General Body System				
None				
Genital System				
Clitoral gland	(46)	(45)	(48)	(50)
Adenoma	3 (7%)	9 (20%)	1 (2%)	2 (4%)
Carcinoma				1 (2%)
Ovary	(50)	(49)	(50)	(51)
Arrhenoblastoma benign	1 (2%)			
Granulosa cell tumor benign		1 (2%)		
Uterus	(49)	(50)	(50)	(50)
Polyp stromal	10 (20%)	6 (12%)	4 (8%)	1 (2%)
Sarcoma	1 (2%)			1 (2%)
Sarcoma stromal	1 (2%)		1 (2%)	
Vagina		(1)		
Squamous cell papilloma		1 (100%)		
Hematopoietic System				
Blood	(5)	(5)	(3)	(5)
Bone marrow	(49)	(50)	(48)	(52)
Lymph node	(12)	(4)	(5)	(5)
Lymph node, mandibular	(50)	(49)	(50)	(52)
Lymph node, mesenteric	(50)	(49)	(50)	(51)
Spleen	(50)	(49)	(50)	(49)
Hemangioma		1 (2%)		
Thymus	(45)	(48)	(48)	(48)
Integumentary System				
Mammary gland	(50)	(46)	(50)	(46)
Adenoma	3 (6%)	3 (7%)		
Fibroadenoma	11 (22%)	9 (20%)	10 (20%)	6 (13%)
Fibroadenoma, multiple	3 (6%)	4 (9%)		
Skin	(50)	(48)	(50)	(51)
Basal cell adenoma		1 (2%)		
Squamous cell papilloma		1 (2%)		
Subcutaneous tissue, fibroma	1 (2%)			
Subcutaneous tissue, hemangiopericytoma				1 (2%)
Subcutaneous tissue, hemangiosarcoma	1 (2%)			
Subcutaneous tissue, sarcoma				1 (2%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Musculoskeletal System				
Skeletal muscle			(2)	
Sarcoma			1 (50%)	
Nervous System				
Brain	(50)	(50)	(50)	(52)
Respiratory System				
Lung	(50)	(49)	(50)	(52)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)		
Alveolar/bronchiolar carcinoma			1 (2%)	
Schwannoma malignant, metastatic, ear			1 (2%)	
Squamous cell carcinoma, metastatic, uncertain primary site				1 (2%)
Special Senses System				
Ear			(3)	
Schwannoma malignant			1 (33%)	
Squamous cell papilloma			1 (33%)	
Zymbal's gland				(1)
Carcinoma				1 (100%)
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Urinary bladder	(49)	(47)	(46)	(46)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(53)
Leukemia mononuclear	17 (34%)	18 (36%)	13 (26%)	9 (17%)
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	4	2	2	1
2-Year study	46	42	39	32
Total primary neoplasms				
15-Month interim evaluation	5	3	2	1
2-Year study	91	89	72	49
Total animals with benign neoplasms				
15-Month interim evaluation	4	2	2	1
2-Year study	39	35	38	23
Total benign neoplasms				
15-Month interim evaluation	5	3	2	1
2-Year study	71	71	54	34

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Neoplasm Summary (continued)				
Total animals with malignant neoplasms				
2-Year study	19	18	16	15
Total malignant neoplasms				
2-Year study	20	18	18	15
Total animals with metastatic neoplasms				
2-Year study	1		1	1
Total metastatic neoplasms				
2-Year study	1		1	1
Total animals with malignant neoplasms of uncertain primary site				
2-Year study				1

[a] Number of animals examined microscopically at site and number of animals with lesion
[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 Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control

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

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 5 5 2	0 5 8 1	0 5 8 2	0 5 8 3	0 5 7 1	0 5 7 2	0 5 7 3	0 5 7 4	0 5 9 1	0 6 0 1	0 6 0 2	0 6 0 3	0 6 1 1	0 6 1 2	0 6 1 3	0 6 2 1	0 6 2 2	0 6 3 1	0 6 3 2	0 6 3 3	0 6 3 4	0 6 4 1	0 6 4 2	0 6 4 3	0 6 5 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma stromal, metastatic, uterus																										1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery						+																				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue		+																								1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign													X				X	X					X			4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Adenoma, multiple													X													1
Parathyroid gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X			X	X	X		X								X		X	X	X	X	X	X		22
Pars distalis, adenoma, multiple											X			X		X									X	4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma						X									X											4
Follicular cell, adenoma												X														2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+		+	+	+	+	+	+	+	+	+	+	M	46
Adenoma						X																X	X			3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Arrhenoblastoma benign																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	0 2 3	4 1 2	4 1 3	4 6 2	4 7 3	4 7 7	5 1 3	5 4 6	5 4 7	5 7 4	6 2 9	6 3 6	6 4 5	6 7 3	6 7 4	6 8 4	7 1 7	7 2 2	7 2 9	7 3 4	7 3 5	7 3 5	7 3 5	7 3 6	7 3 6
Carcass ID Number	0 5 4 5	0 5 4 4	0 6 1 5	0 5 6 2	0 5 5 3	0 5 9 4	0 5 4 3	0 6 2 5	0 5 9 3	0 6 4 5	0 5 8 5	0 6 2 4	0 6 2 3	0 6 1 4	0 5 9 2	0 6 5 2	0 5 4 2	0 6 0 5	0 6 4 4	0 5 6 1	0 5 8 4	0 6 0 4	0 6 3 5	0 5 4 1	0 5 5 1
Genital System (continued)																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Polyp stromal					X				X	X						X		X	X		X				
Sarcoma																									
Sarcoma stromal			X																						
Hematopoietic System																									
Blood								+										+	+						
Bone marrow	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+	+	+				+		+		+			+	+		+				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Fibroadenoma									X										X					X	X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X		X			X		X		X		X	X	X		X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 5 5 2	0 5 8 1	0 5 8 2	0 5 8 3	0 5 7 1	0 5 7 2	0 5 7 3	0 5 7 4	0 5 9 1	0 6 0 1	0 6 0 2	0 6 0 3	0 6 1 1	0 6 1 2	0 6 1 3	0 6 2 1	0 6 2 2	0 6 3 1	0 6 3 2	0 6 3 3	0 6 3 4	0 6 4 1	0 6 4 2	0 6 4 3	0 6 5 1	Total Tissues/ Tumors
Genital System (continued)																											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal				X										X												X	10
Sarcoma							X																				1
Sarcoma stromal																											1
Hematopoietic System																											
Blood								+														+					5
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node								+													+						12
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+		45
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma									X																	X	3
Fibroadenoma	X			X	X	X										X	X					X					11
Fibroadenoma, multiple									X		X															X	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibroma																								X			1
Subcutaneous tissue, hemangiosarcoma																		X									1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																	1
Nose	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
None																											
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X							X										X		X		X	X				17

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 8.3 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 8.3 mg/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 6 7 1	0 6 7 2	0 6 7 3	0 6 7 4	0 6 8 1	0 6 8 2	0 6 8 3	0 6 8 4	0 6 9 1	0 6 9 2	0 6 9 3	0 7 0 1	0 7 0 2	0 7 1 1	0 7 1 2	0 7 1 3	0 7 3 1	0 7 3 2	0 7 4 4	0 7 4 5	0 7 5 1	0 7 5 2	0 7 6 2	0 7 7 1	0 7 7 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery		+																								2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma										X																1
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma					X	X	X		X	X	X	X			X		X	X			X		X		X	23
Pars distalis, adenoma, multiple								X																		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bilateral, C-cell, adenoma																										1
C-cell, adenoma									X			X														3
Follicular cell, adenoma	X																	X								2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	45
Adenoma	X	X						X		X																9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor benign		X																								1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X													X			X					6
Vagina											+															1
Squamous cell papilloma											X															1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 8.3 mg/kg (continued)

Number of Days on Study	4 7 9	5 6 1	5 9 1	5 9 7	5 9 7	5 9 7	6 1 6	6 2 4	6 3 2	6 3 2	6 3 9	6 5 7	6 7 6	6 9 2	7 0 4	7 1 7	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 6
Carcass ID Number	0 7 1 4	0 7 3 4	0 7 2 5	0 6 6 3	0 7 2 3	0 7 2 4	0 6 8 5	0 7 0 3	0 7 3 3	0 7 4 3	0 6 6 2	0 7 5 4	0 6 9 5	0 7 6 4	0 7 6 3	0 7 4 1	0 7 5 3	0 6 9 4	0 7 2 1	0 7 2 2	0 7 4 2	0 7 6 1	0 7 7 3	0 7 7 4	0 6 6 1
Hematopoietic System																								
Blood				+					+			+		+										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+											+	+	+										
Lymph node, mandibular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma								X																
Thymus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Integumentary System																								
Mammary gland	+	A	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X					X				
Fibroadenoma														X		X	X			X			X	
Fibroadenoma, multiple																		X	X					
Skin	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Basal cell adenoma																	X							
Squamous cell papilloma						X																		
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye				+																				
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	A	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X		X			X		X	X	X	X				X		X	X			X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 8.3 mg/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 6 7 1	0 6 7 2	0 6 7 3	0 6 7 4	0 6 8 1	0 6 8 2	0 6 8 3	0 6 8 4	0 6 9 1	0 6 9 2	0 6 9 3	0 7 0 1	0 7 0 2	0 7 1 1	0 7 1 2	0 7 1 3	0 7 3 1	0 7 3 2	0 7 4 4	0 7 4 5	0 7 5 1	0 7 5 2	0 7 6 2	0 7 7 1	0 7 7 2	Total Tissues/ Tumors
Hematopoietic System																											
Blood																			+								5
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																											4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																							X				3
Fibroadenoma													X				X			X						X	9
Fibroadenoma, multiple										X												X					4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Basal cell adenoma																											1
Squamous cell papilloma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																											
Eye																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X							X		X	X							X	X								18

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 16.6 mg/kg

Number of Days on Study	3 0 6	3 6 0	4 5 7	4 7 5	4 7 9	5 4 7	5 5 0	5 5 0	5 7 6	6 0 4	6 1 4	6 4 3	6 4 4	6 5 2	6 6 6	6 7 5	6 8 5	6 8 6	6 8 9	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4
Carcass ID Number	0 8 9 5	0 8 3 5	0 8 1 4	0 7 8 5	0 8 7 4	0 8 3 3	0 8 5 4	0 8 8 4	0 8 6 5	0 8 0 4	0 8 7 3	0 8 2 5	0 8 5 3	0 8 8 3	0 7 8 4	0 8 6 4	0 8 9 3	0 8 2 4	0 8 5 2	0 8 1 1	0 8 1 2	0 8 1 3	0 8 2 1	0 8 2 2	0 8 2 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	A	A	A	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	A	A	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	A	A	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																						X			
Stomach, glandular	+	A	+	+	A	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign												X													
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X					X		X	X			X		X	X	X			X		X	X
Pars distalis, adenoma, multiple													X												
Thyroid gland	+	+	+	+	A	A	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									X
Follicular cell, adenoma																									
Follicular cell, carcinoma																								X	
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Adenoma																			X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oviduct	+																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																									
Sarcoma stromal																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 16.6 mg/kg (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 8 3 1	0 8 3 2	0 8 4 1	0 8 4 2	0 8 4 3	0 8 4 4	0 8 7 1	0 8 7 2	0 8 8 1	0 8 8 2	0 8 9 1	0 8 9 2	0 8 7 1	0 7 8 2	0 7 8 3	0 7 9 1	0 7 9 2	0 7 9 3	0 8 0 1	0 8 0 2	0 8 0 3	0 8 5 1	0 8 6 1	0 8 6 2	0 8 6 3	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																			X							1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																							X			2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma		X		X		X	X		X		X						X									18
Pars distalis, adenoma, multiple																X					X	X				4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
C-cell, adenoma	X							X	X		X				X	X		X			X		X			10
Follicular cell, adenoma				X									X													2
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oviduct																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X						X				X	X											4
Sarcoma stromal										X																1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 16.6 mg/kg (continued)

Number of Days on Study	3	3	4	4	4	5	5	5	5	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7
	0	6	5	7	7	4	5	5	7	0	1	4	4	5	6	7	8	8	8	3	3	3	3	3
	6	0	7	5	9	7	0	0	6	4	4	3	4	2	6	5	5	6	9	4	4	4	4	4
Carcass ID Number	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	8	8	8	7	8	8	8	8	8	8	8	8	8	8	7	8	8	8	8	8	8	8	8	8
	9	3	1	8	7	3	5	8	6	0	7	2	5	8	8	6	9	2	5	1	1	1	2	2
	5	5	4	5	4	3	4	4	5	4	3	5	3	3	4	4	3	4	2	1	2	3	1	2	2	3
Hematopoietic System																								
Blood												+		+										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+
Lymph node										+		+	+	+										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma														X		X	X			X	X		X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle														+				+						
Sarcoma																		X						
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																								
Schwannoma malignant, metastatic, ear												X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear												+												
Schwannoma malignant												X												
Squamous cell papilloma																								
Eye	+																							+
Urinary System																								
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X	X	X		X								

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 16.6 mg/kg (continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 8 3 1	0 8 3 2	0 8 4 1	0 8 4 2	0 8 4 3	0 8 4 4	0 8 7 1	0 8 7 2	0 8 8 1	0 8 8 2	0 8 9 1	0 8 9 2	0 8 8 1	0 7 8 2	0 7 8 3	0 7 9 1	0 7 9 2	0 7 9 3	0 8 0 1	0 8 0 2	0 8 0 3	0 8 5 1	0 8 6 1	0 8 6 2	0 8 6 3	Total Tissues/ Tumors
Hematopoietic System																											
Blood																			+							3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node																					+					5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma			X					X				X														10
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Sarcoma																										1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma													X													1
Schwannoma malignant, metastatic, ear																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Ear													+										+			3
Schwannoma malignant																										1
Squamous cell papilloma																								X		1
Eye												+														3
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X			X								X	X	X			X	X		X	X				13

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 33.3 mg/kg

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 33.3 mg/kg (continued)

Number of Days on Study	6 8 9	7 0 2	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	
Carcass ID Number	0 9 3 3	0 9 7 2	0 9 6 2	0 9 1 1	0 9 2 1	0 9 2 2	0 9 3 1	0 9 3 2	0 9 4 1	0 9 4 2	0 9 5 1	0 9 5 2	0 9 5 3	0 9 5 4	0 9 6 1	0 9 7 1	0 9 9 1	1 0 1 1	0 9 0 1	0 9 8 1	0 9 8 2	0 9 9 1	0 9 9 2	1 0 0 1	0 1 0 0	0 1 0 1	0 0 9 8	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Sarcoma							X																				1
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	37
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Hepatocellular adenoma																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma	X																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pheochromocytoma benign							X			X																X	3
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Pars distalis, adenoma					X	X	X		X							X				X			X		X	X	16
Pars distalis, adenoma, multiple																			X								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Bilateral, C-cell, adenoma																										X	1
C-cell, adenoma						X																					1
C-cell, carcinoma																									X		1
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X					2
Carcinoma																				X							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal									X																		1
Sarcoma																											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 33.3 mg/kg (continued)

Number of Days on Study	0 2 9	0 3 0	0 8 3	2 5 9	2 5 9	3 1 1	3 1 1	3 7 1	3 9 3	3 9 3	4 2 1	4 4 1	4 4 2	4 7 0	4 9 9	5 5 0	5 5 0	5 5 2	5 6 2	5 7 5	5 8 7	5 9 0	5 9 1	6 2 9	6 4 0	6 5 1	6 6 6
Carcass ID Number	1 0 0 5	0 9 2 5	0 9 6 5	0 9 2 4	1 0 0 4	0 9 5 5	0 9 7 5	0 9 9 5	0 9 0 5	0 9 8 5	0 9 1 5	0 9 7 4	0 9 9 4	0 9 3 5	1 0 0 3	0 9 0 4	0 9 6 4	0 9 8 4	0 9 6 3	0 9 1 3	1 0 1 4	0 9 4 3	0 9 3 4	0 9 0 3	1 0 1 3	0 9 1 2	0 9 0 2
Hematopoietic System																											
Blood																		+									+
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+			+						+			+
Lymph node, mandibular	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	A	+	+	+	M	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																											
Mammary gland	+	M	A	+	+	+	M	+	M	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Fibroadenoma											X								X								X
Skin	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiopericytoma																											
Subcutaneous tissue, sarcoma																								X			
Musculoskeletal System																											
Bone	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																											
Brain	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																											
Lung	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, uncertain primary site											X																
Nose	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																											
Eye	+							+																			
Zymbal's gland																					+						
Carcinoma																					X						
Urinary System																											
Kidney	+	+	A	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	A	A	+	+	+	M	+	+	A	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X			X									X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride: 33.3 mg/kg (continued)

Number of Days on Study	6 8 9	7 0 2	7 2 9	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 5	
Carcass ID Number	0 9 3 3	0 9 7 2	0 9 6 2	0 9 1 1	0 9 2 1	0 9 2 2	0 9 3 1	0 9 3 2	0 9 4 1	0 9 4 2	0 9 5 1	0 9 5 2	0 9 5 3	0 9 5 4	0 9 6 1	0 9 7 1	0 9 7 1	1 0 1 1	0 9 0 1	0 9 8 1	0 9 8 2	0 9 9 1	0 9 9 2	1 0 0 1	0 0 0 0	1 0 1 1	0 0 9 8	Total Tissues/
Hematopoietic System																											
Blood	+		+													+											5
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node														+													5
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	48
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Fibroadenoma						X		X	X																		6
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Subcutaneous tissue, hemangiopericytoma																										X	1
Subcutaneous tissue, sarcoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Squamous cell carcinoma, metastatic, uncertain primary site																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	52
Special Senses System																											
Eye								+																			3
Zymbal's gland																											1
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear	X		X					X			X							X				X					9

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	4/50 (8%)	1/50 (2%)	2/50 (4%)	3/53 (6%)
Adjusted rate[b]	12.5%	2.6%	5.7%	12.5%
Terminal rate[c]	4/32 (13%)	0/34 (0%)	1/31 (3%)	3/24 (13%)
First incidence (days)	729 (T)	676	643	729 (T)
Life table test[d]	P=0.487	P=0.162N	P=0.348N	P=0.657
Logistic regression test[d]	P=0.502	P=0.157N	P=0.344N	P=0.657
Cochran-Armitage test[d]	P=0.515N			
Fisher exact test[d]		P=0.181N	P=0.339N	P=0.467N
Clitoral Gland: Adenoma				
Overall rate	3/46 (7%)	9/45 (20%)	1/48 (2%)	2/50 (4%)
Adjusted rate	10.7%	24.6%	3.1%	6.7%
Terminal rate	3/28 (11%)	5/30 (17%)	0/29 (0%)	1/24 (4%)
First incidence (days)	729 (T)	597	689	550
Life table test	P=0.201N	P=0.085	P=0.302N	P=0.563N
Logistic regression test	P=0.144N	P=0.074	P=0.293N	P=0.536N
Cochran-Armitage test	P=0.102N			
Fisher exact test		P=0.055	P=0.292N	P=0.460N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	3/46 (7%)	9/45 (20%)	1/48 (2%)	3/50 (6%)
Adjusted rate	10.7%	24.6%	3.1%	10.7%
Terminal rate	3/28 (11%)	5/30 (17%)	0/29 (0%)	2/24 (8%)
First incidence (days)	729 (T)	597	689	550
Life table test	P=0.349N	P=0.085	P=0.302N	P=0.597
Logistic regression test	P=0.275N	P=0.074	P=0.293N	P=0.620
Cochran-Armitage test	P=0.198N			
Fisher exact test		P=0.055	P=0.292N	P=0.621N
Mammary Gland: Adenoma				
Overall rate	3/50 (6%)	3/50 (6%)	0/50 (0%)	0/53 (0%)
Adjusted rate	8.4%	8.5%	0.0%	0.0%
Terminal rate	2/32 (6%)	2/34 (6%)	0/31 (0%)	0/24 (0%)
First incidence (days)	513	704	)[e]	)
Life table test	P=0.052N	P=0.629N	P=0.125N	P=0.168N
Logistic regression test	P=0.039N	P=0.651N	P=0.121N	P=0.124N
Cochran-Armitage test	P=0.032N			
Fisher exact test		P=0.661N	P=0.121N	P=0.111N
Mammary Gland: Fibroadenoma				
Overall rate	14/50 (28%)	13/50 (26%)	10/50 (20%)	6/53 (11%)
Adjusted rate	42.0%	36.1%	29.0%	20.1%
Terminal rate	13/32 (41%)	11/34 (32%)	7/31 (23%)	3/24 (13%)
First incidence (days)	547	692	652	421
Life table test	P=0.100N	P=0.421N	P=0.260N	P=0.132N
Logistic regression test	P=0.070N	P=0.412N	P=0.247N	P=0.085N
Cochran-Armitage test	P=0.016N			
Fisher exact test		P=0.500N	P=0.241N	P=0.029N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Mammary Gland: Fibroadenoma or Adenoma				
Overall rate	15/50 (30%)	15/50 (30%)	10/50 (20%)	6/53 (11%)
Adjusted rate	43.4%	40.5%	29.0%	20.1%
Terminal rate	13/32 (41%)	12/34 (35%)	7/31 (23%)	3/24 (13%)
First incidence (days)	513	692	652	421
Life table test	P=0.059N	P=0.502N	P=0.195N	P=0.095N
Logistic regression test	P=0.033N	P=0.485N	P=0.176N	P=0.049N
Cochran-Armitage test	P=0.007N			
Fisher exact test		P=0.586N	P=0.178N	P=0.017N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	26/49 (53%)	24/48 (50%)	22/48 (46%)	17/51 (33%)
Adjusted rate	69.6%	59.2%	54.5%	53.2%
Terminal rate	20/31 (65%)	18/34 (53%)	13/31 (42%)	10/24 (42%)
First incidence (days)	547	591	475	442
Life table test	P=0.307N	P=0.266N	P=0.295N	P=0.303N
Logistic regression test	P=0.100N	P=0.287N	P=0.259N	P=0.130N
Cochran-Armitage test	P=0.022N			
Fisher exact test		P=0.461N	P=0.306N	P=0.036N
Thyroid Gland (C-cell): Adenoma				
Overall rate	4/49 (8%)	4/49 (8%)	10/45 (22%)	2/47 (4%)
Adjusted rate	12.5%	11.3%	32.3%	8.3%
Terminal rate	4/32 (13%)	3/34 (9%)	10/31 (32%)	2/24 (8%)
First incidence (days)	729 (T)	692	729 (T)	729 (T)
Life table test	P=0.551	P=0.608N	P=0.058	P=0.475N
Logistic regression test	P=0.539	P=0.606N	P=0.058	P=0.475N
Cochran-Armitage test	P=0.409N			
Fisher exact test		P=0.643N	P=0.052	P=0.359N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	4/49 (8%)	4/49 (8%)	10/45 (22%)	3/47 (6%)
Adjusted rate	12.5%	11.3%	32.3%	12.5%
Terminal rate	4/32 (13%)	3/34 (9%)	10/31 (32%)	3/24 (13%)
First incidence (days)	729 (T)	692	729 (T)	729 (T)
Life table test	P=0.389	P=0.608N	P=0.058	P=0.657
Logistic regression test	P=0.375	P=0.606N	P=0.058	P=0.657
Cochran-Armitage test	P=0.552N			
Fisher exact test		P=0.643N	P=0.052	P=0.524N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	2/49 (4%)	2/49 (4%)	3/45 (7%)	0/47 (0%)
Adjusted rate	6.3%	5.9%	9.7%	0.0%
Terminal rate	2/32 (6%)	2/34 (6%)	3/31 (10%)	0/24 (0%)
First incidence (days)	729 (T)	729 (T)	729 (T)	)
Life table test	P=0.279N	P=0.674N	P=0.485	P=0.303N
Logistic regression test	P=0.279N	P=0.674N	P=0.485	P=0.303N
Cochran-Armitage test	P=0.214N			
Fisher exact test		P=0.691N	P=0.459	P=0.258N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Uterus: Stromal Polyp				
Overall rate	10/50 (20%)	6/50 (12%)	4/50 (8%)	1/53 (2%)
Adjusted rate	25.9%	16.0%	12.9%	4.2%
Terminal rate	5/32 (16%)	4/34 (12%)	4/31 (13%)	1/24 (4%)
First incidence (days)	473	566	729 (T)	729 (T)
Life table test	P=0.010N	P=0.174N	P=0.087N	P=0.020N
Logistic regression test	P=0.004N	P=0.207N	P=0.073N	P=0.007N
Cochran-Armitage test	P=0.002N			
Fisher exact test		P=0.207N	P=0.074N	P=0.003N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	11/50 (22%)	6/50 (12%)	4/50 (8%)	1/53 (2%)
Adjusted rate	27.5%	16.0%	12.9%	4.2%
Terminal rate	5/32 (16%)	4/34 (12%)	4/31 (13%)	1/24 (4%)
First incidence (days)	413	566	729 (T)	729 (T)
Life table test	P=0.006N	P=0.122N	P=0.057N	P=0.012N
Logistic regression test	P=0.002N	P=0.169N	P=0.047N	P=0.003N
Cochran-Armitage test	P=0.001N			
Fisher exact test		P=0.143N	P=0.045N	P=0.001N
All Organs: Mononuclear Cell Leukemia				
Overall rate	17/50 (34%)	18/50 (36%)	13/50 (26%)	9/53 (17%)
Adjusted rate	40.4%	41.8%	36.4%	30.6%
Terminal rate	8/32 (25%)	10/34 (29%)	9/31 (29%)	5/24 (21%)
First incidence (days)	412	479	643	499
Life table test	P=0.157N	P=0.557N	P=0.300N	P=0.221N
Logistic regression test	P=0.036N	P=0.446	P=0.252N	P=0.073N
Cochran-Armitage test	P=0.015N			
Fisher exact test		P=0.500	P=0.257N	P=0.039N
All Organs: Benign Neoplasms				
Overall rate	39/50 (78%)	36/50 (72%)	39/50 (78%)	24/53 (45%)
Adjusted rate	92.8%	81.5%	90.6%	67.0%
Terminal rate	29/32 (91%)	26/34 (76%)	27/31 (87%)	13/24 (54%)
First incidence (days)	473	566	306	259
Life table test	P=0.212N	P=0.198N	P=0.507	P=0.149N
Logistic regression test	P=0.011N	P=0.113N	P=0.571N	P=0.008N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.322N	P=0.595N	P<0.001N
All Organs: Malignant Neoplasms				
Overall rate	19/50 (38%)	18/50 (36%)	16/50 (32%)	16/53 (30%)
Adjusted rate	44.0%	41.8%	44.0%	47.6%
Terminal rate	9/32 (28%)	10/34 (29%)	11/31 (35%)	8/24 (33%)
First incidence (days)	412	479	643	371
Life table test	P=0.397	P=0.412N	P=0.384N	P=0.479
Logistic regression test	P=0.313N	P=0.583N	P=0.333N	P=0.345N
Cochran-Armitage test	P=0.213N			
Fisher exact test		P=0.500N	P=0.338N	P=0.265N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	46/50 (92%)	43/50 (86%)	40/50 (80%)	33/53 (62%)
Adjusted rate	95.8%	87.7%	93.0%	81.8%
Terminal rate	30/32 (94%)	28/34 (82%)	28/31 (90%)	17/24 (71%)
First incidence (days)	412	479	306	259
Life table test	P=0.413N	P=0.204N	P=0.241N	P=0.367N
Logistic regression test	P=0.004N	P=0.167N	P=0.043N	P=0.004N
Cochran-Armitage test	P<0.001N			
Fisher exact test		P=0.262N	P=0.074N	P<0.001N

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

TABLE B4a
Historical Incidence of Uterine Neoplasms in Untreated Female F344/N Rats [a]

Study	Incidence in Controls		
	Stromal Polyp	Stromal Sarcoma	Stromal Polyp or Stromal Sarcoma
Overall Historical Incidence: Water Gavage			
Total	54/368 (14.7%)	2/368 (0.5%)	56/368 (15.2%)
Standard deviation	6.7%	1.0%	6.5%
Range	2%-22%	0%-2%	4%-24%
Overall Historical Incidence: Feed			
Total	205/1,251 (16.4%)	9/1,251 (0.7%)	213/1,251 (17.0%)
Standard deviation	6.6%	1.5%	6.9%
Range	2%-30%	0%-6%	8%-30%

[a] Data as of 20 August 1992

TABLE B4b
Historical Incidence of Mammary Gland Neoplasms in Untreated Female F344/N Rats [a]

Study	Incidence in Controls		
	Fibroadenoma	Adenoma	Fibroadenoma or Adenoma
Overall Historical Incidence: Water Gavage			
Total	143/368 (38.9%)	5/368 (1.4%)	145/368 (39.4%)
Standard deviation	13.6%	1.3%	12.9%
Range	16%-53%	0%-3%	18%-53%
Overall Historical Incidence: Feed			
Total	484/1,251 (38.7%)	22/1,251 (1.8%)	500/1,251 (40.0%)
Standard deviation	13.5%	2.3%	13.7%
Range	8%-58%	0%-8%	8%-62%

[a] Data as of 20 August 1992

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride[a]

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	7
Early deaths				
Accidental deaths	1			2
Moribund	12	12	10	11
Natural deaths	5	4	9	16
Survivors				
Died last week of study	3	1		
Terminal sacrifice	29	33	31	24
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(7)
Basophilic focus	4 (40%)	6 (60%)	6 (60%)	4 (57%)
Clear cell focus	1 (10%)			
Fatty change, focal	1 (10%)			
Hepatodiaphragmatic nodule	1 (10%)	2 (20%)	2 (20%)	
Bile duct, hyperplasia		1 (10%)		
Salivary glands	(10)	(10)	(10)	(7)
Duct, metaplasia, squamous	1 (10%)			1 (14%)
Stomach, forestomach	(10)	(10)	(10)	(7)
Hyperplasia, basal cell		1 (10%)		
Stomach, glandular	(10)	(10)	(10)	(7)
Hyperplasia				1 (14%)
Cardiovascular System				
Heart	(10)	(10)	(10)	(7)
Cardiomyopathy	1 (10%)	1 (10%)	2 (20%)	1 (14%)
Endocrine System				
Adrenal cortex	(10)	(10)	(10)	(7)
Accessory adrenal cortical nodule			1 (10%)	
Pituitary gland	(10)	(10)	(10)	(7)
Pars distalis, angiectasis	3 (30%)		2 (20%)	
Pars distalis, cyst	1 (10%)	1 (10%)		
Pars distalis, hyperplasia	4 (40%)	2 (20%)	4 (40%)	3 (43%)
Pars intermedia, hyperplasia				1 (14%)
Thyroid gland	(10)	(10)	(10)	(7)
C-cell, hyperplasia	1 (10%)	1 (10%)		
General Body System				
None				

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
15-Month Interim Evaluation (continued)				
Genital System				
Ovary	(10)	(10)	(10)	(7)
Cyst	1 (10%)	1 (10%)	1 (10%)	
Uterus	(10)	(10)	(10)	(7)
Inflammation, acute	1 (10%)			
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(7)
Alveolar epithelium, hyperplasia	1 (10%)	1 (10%)		
Nose	(10)	(9)	(10)	(7)
Inflammation, acute			2 (20%)	1 (14%)
Special Senses System				
Eye	(1)			
Lens, cataract	1 (100%)			
Urinary System				
Kidney	(10)	(10)	(10)	(7)
Nephropathy	9 (90%)	7 (70%)	5 (50%)	4 (57%)
Cortex, mineralization	8 (80%)	6 (60%)	8 (80%)	4 (57%)
Pelvis, inflammation, chronic active		1 (10%)		
2-Year Study				
Alimentary System				
Esophagus	(50)	(49)	(50)	(51)
Erosion		1 (2%)		
Hyperkeratosis		1 (2%)	1 (2%)	
Inflammation, acute		1 (2%)		

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Intestine small, duodenum	(49)	(47)	(44)	(40)
Necrosis			1 (2%)	
Intestine small, ileum	(48)	(47)	(43)	(37)
Necrosis			1 (2%)	
Liver	(50)	(49)	(50)	(52)
Basophilic focus	24 (48%)	26 (53%)	17 (34%)	16 (31%)
Clear cell focus	1 (2%)			1 (2%)
Fatty change, diffuse	2 (4%)			
Fatty change, focal	4 (8%)			1 (2%)
Fibrosis			2 (4%)	
Hemorrhage	1 (2%)			
Hepatodiaphragmatic nodule		4 (8%)	3 (6%)	10 (19%)
Inflammation, granulomatous	6 (12%)	1 (2%)	2 (4%)	1 (2%)
Mixed cell focus	3 (6%)	1 (2%)	2 (4%)	7 (13%)
Necrosis	1 (2%)		1 (2%)	
Pigmentation	2 (4%)			1 (2%)
Mesentery	(1)	(2)		
Fat, mineralization	1 (100%)			
Fat, necrosis	1 (100%)	2 (100%)		
Pancreas	(50)	(49)	(50)	(49)
Acinus, atrophy	1 (2%)			1 (2%)
Acinus, hyperplasia		1 (2%)		
Salivary glands	(50)	(49)	(49)	(52)
Atrophy		1 (2%)		
Duct, metaplasia, squamous			2 (4%)	1 (2%)
Stomach, forestomach	(49)	(49)	(50)	(50)
Hyperkeratosis		2 (4%)		1 (2%)
Hyperplasia, basal cell		2 (4%)	1 (2%)	2 (4%)
Necrosis			2 (4%)	
Ulcer				1 (2%)
Stomach, glandular	(50)	(48)	(44)	(44)
Hyperplasia		1 (2%)		
Mineralization				1 (2%)
Necrosis	2 (4%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(52)
Cardiomyopathy	28 (56%)	28 (56%)	26 (52%)	26 (50%)
Inflammation, chronic active				1 (2%)
Mineralization		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(49)	(49)	(51)
Accessory adrenal cortical nodule		2 (4%)		
Hemorrhage		1 (2%)		
Hyperplasia	1 (2%)	1 (2%)	1 (2%)	2 (4%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal medulla	(50)	(49)	(50)	(51)
Hyperplasia	2 (4%)	4 (8%)	3 (6%)	1 (2%)
Islets, pancreatic	(50)	(49)	(50)	(48)
Hyperplasia		2 (4%)		
Pituitary gland	(49)	(48)	(48)	(51)
Craniopharyngeal duct, cyst				1 (2%)
Pars distalis, angiectasis	24 (49%)	24 (50%)	18 (38%)	16 (31%)
Pars distalis, cyst	6 (12%)	6 (13%)	3 (6%)	
Pars distalis, hyperplasia	17 (35%)	18 (38%)	14 (29%)	14 (27%)
Pars intermedia, hyperplasia		1 (2%)		
Pars nervosa, angiectasis	3 (6%)			
Pars nervosa, cyst	1 (2%)			
Thyroid gland	(49)	(49)	(45)	(47)
C-cell, hyperplasia	9 (18%)	5 (10%)	8 (18%)	7 (15%)
Follicle, cyst	2 (4%)		1 (2%)	1 (2%)
Follicular cell, hyperplasia				1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(46)	(45)	(48)	(50)
Dilatation				1 (2%)
Hyperplasia	1 (2%)			
Inflammation, acute	1 (2%)			1 (2%)
Necrosis		2 (4%)		
Ovary	(50)	(49)	(50)	(51)
Cyst	2 (4%)		1 (2%)	
Uterus	(49)	(50)	(50)	(50)
Cyst				1 (2%)
Decidual reaction			1 (2%)	
Hemorrhage	1 (2%)			1 (2%)
Metaplasia, osseous	1 (2%)			
Cervix, fibrosis	1 (2%)			
Cervix, inflammation, acute	1 (2%)			
Cervix, pigmentation	1 (2%)			
Hematopoietic System				
Lymph node	(12)	(4)	(5)	(5)
Mediastinal, angiectasis				1 (20%)
Mediastinal, pigmentation				1 (20%)
Pancreatic, angiectasis	1 (8%)			
Pancreatic, hemorrhage			1 (20%)	
Pancreatic, infiltration cellular, histiocyte	2 (17%)			

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(50)	(49)	(50)	(52)
Angiectasis			1 (2%)	
Hemorrhage		1 (2%)		
Lymph node, mesenteric	(50)	(49)	(50)	(51)
Angiectasis	1 (2%)		1 (2%)	
Hemorrhage			1 (2%)	
Hyperplasia			1 (2%)	
Infiltration cellular, histiocyte	2 (4%)			
Spleen	(50)	(49)	(50)	(49)
Fibrosis	2 (4%)	2 (4%)	1 (2%)	
Hematopoietic cell proliferation	3 (6%)		2 (4%)	1 (2%)
Hemorrhage		1 (2%)		
Infarct	1 (2%)			1 (2%)
Infiltration cellular, histiocyte	2 (4%)			
Thymus	(45)	(48)	(48)	(48)
Fibrosis			1 (2%)	
Hemorrhage	1 (2%)			
Epithelial cell, ectopic parathyroid gland				1 (2%)
Epithelial cell, hyperplasia			1 (2%)	
Integumentary System				
Mammary gland	(50)	(46)	(50)	(46)
Galactocele	14 (28%)	5 (11%)	5 (10%)	5 (11%)
Skin	(50)	(48)	(50)	(51)
Cyst epithelial inclusion	2 (4%)			
Musculoskeletal System				
Bone	(49)	(50)	(50)	(52)
Fibrous osteodystrophy			1 (2%)	
Nervous System				
Brain	(50)	(50)	(50)	(52)
Degeneration				1 (2%)
Hemorrhage	1 (2%)			
Hydrocephalus			1 (2%)	
Respiratory System				
Lung	(50)	(49)	(50)	(52)
Edema		1 (2%)	2 (4%)	
Hemorrhage	1 (2%)			1 (2%)
Infiltration cellular, histiocyte		2 (4%)	1 (2%)	1 (2%)
Inflammation, acute			2 (4%)	
Alveolar epithelium, hyperplasia	3 (6%)	1 (2%)	1 (2%)	

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
2-Year Study (continued)				
Respiratory System (continued)				
Nose	(49)	(50)	(49)	(52)
Fungus	1 (2%)	1 (2%)		
Inflammation, acute	2 (4%)	3 (6%)	4 (8%)	6 (12%)
Special Senses System				
Eye		(1)	(3)	(3)
Lens, cataract		1 (100%)	1 (33%)	1 (33%)
Retina, atrophy			1 (33%)	
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Inflammation, acute			1 (2%)	
Mineralization		2 (4%)	1 (2%)	
Nephropathy	43 (86%)	45 (90%)	45 (92%)	37 (74%)
Pigmentation	1 (2%)			
Artery, inflammation, chronic active	1 (2%)			
Bilateral, papilla, necrosis			1 (2%)	
Urinary bladder	(49)	(47)	(46)	(46)
Hemorrhage			1 (2%)	
Necrosis			1 (2%)	

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

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR GAVAGE STUDY OF PROMETHAZINE HYDROCHLORIDE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride [a]

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	8	4	6	6
Natural deaths	3	2	4	
Survivors				
Terminal sacrifice	39	44	40	44
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(10)	(10)
Hepatocellular carcinoma		1 (10%)		
Hepatocellular adenoma	1 (10%)	2 (20%)	1 (10%)	
Hepatocellular adenoma, multiple		1 (10%)		1 (10%)
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
None				
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar/bronchiolar carcinoma		1 (10%)		
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Gallbladder	(48)	(48)	(45)	(45)
Intestine large, colon	(49)	(49)	(49)	(50)
Intestine small, duodenum	(45)	(49)	(46)	(50)
Adenocarcinoma				1 (2%)
Intestine small, jejunum	(48)	(50)	(47)	(50)
Adenocarcinoma			2 (4%)	
Intestine small, ileum	(49)	(49)	(49)	(50)
Adenocarcinoma		1 (2%)		
Liver	(50)	(50)	(49)	(50)
Hemangioma			1 (2%)	
Hemangiosarcoma				1 (2%)
Hemangiosarcoma, multiple		2 (4%)		
Hepatoblastoma				1 (2%)
Hepatocellular carcinoma	8 (16%)	8 (16%)	5 (10%)	8 (16%)
Hepatocellular carcinoma, multiple				1 (2%)
Hepatocellular adenoma	13 (26%)	10 (20%)	11 (22%)	11 (22%)
Hepatocellular adenoma, multiple	3 (6%)	2 (4%)	3 (6%)	9 (18%)
Hepatocholangiocarcinoma		1 (2%)		
Histiocytic sarcoma	1 (2%)		1 (2%)	
Mast cell tumor malignant			1 (2%)	
Pancreas	(50)	(50)	(49)	(50)
Salivary glands	(48)	(50)	(50)	(50)
Stomach, forestomach	(50)	(50)	(49)	(50)
Squamous cell papilloma	1 (2%)			
Stomach, glandular	(50)	(50)	(49)	(50)
Hemangiosarcoma, metastatic, liver		1 (2%)		
Tongue	(1)	(2)		(2)
Squamous cell papilloma		1 (50%)		1 (50%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(48)	(50)	(48)	(49)
Adenoma	1 (2%)	1 (2%)	3 (6%)	
Capsule, adenoma	1 (2%)	1 (2%)	2 (4%)	
Adrenal medulla	(46)	(46)	(46)	(46)
Islets, pancreatic	(50)	(50)	(49)	(50)
Adenoma	1 (2%)			3 (6%)
Pituitary gland	(48)	(50)	(45)	(46)
Sarcoma, metastatic, nose	1 (2%)			
Thyroid gland	(48)	(50)	(48)	(50)
Follicular cell, adenoma		1 (2%)		
Follicular cell, carcinoma			1 (2%)	
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(14)	(22)	(16)	(19)
Adenoma		1 (5%)		
Prostate	(45)	(46)	(48)	(46)
Seminal vesicle	(50)	(50)	(50)	(50)
Testes	(50)	(49)	(50)	(50)
Interstitial cell, adenoma	1 (2%)			
Hematopoietic System				
Bone marrow	(49)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma	1 (2%)			
Mast cell tumor malignant			1 (2%)	
Lymph node	(1)	(1)	(3)	(1)
Axillary, mast cell tumor malignant			1 (33%)	
Mediastinal, mast cell tumor malignant			1 (33%)	
Lymph node, mandibular	(44)	(44)	(46)	(47)
Mast cell tumor malignant			1 (2%)	
Lymph node, mesenteric	(43)	(47)	(43)	(46)
Spleen	(49)	(48)	(50)	(50)
Hemangioma		1 (2%)		
Hemangiosarcoma		1 (2%)		2 (4%)
Histiocytic sarcoma	1 (2%)			
Mast cell tumor malignant			1 (2%)	
Thymus	(38)	(40)	(42)	(41)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Squamous cell carcinoma				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
2-Year Study (continued)				
Integumentary System (continued)				
Skin (continued)	(50)	(50)	(50)	(50)
Subcutaneous tissue, hemangioma				1 (2%)
Subcutaneous tissue, hemangiosarcoma				1 (2%)
Musculoskeletal System				
Skeletal muscle	(1)	(3)	(1)	(1)
Hepatocholangiocarcinoma, metastatic, liver		1 (33%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Meningioma benign			1 (2%)	
Sarcoma, metastatic, nose	1 (2%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	8 (16%)	6 (12%)	6 (12%)	7 (14%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma	2 (4%)	5 (10%)	1 (2%)	1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)			
Carcinoma, metastatic, thyroid gland			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)	3 (6%)	3 (6%)	2 (4%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Mediastinum, hemangioma				1 (2%)
Nose	(49)	(47)	(50)	(46)
Sarcoma	1 (2%)			
Special Senses System				
Harderian gland	(1)	(4)	(2)	(3)
Adenoma		2 (50%)	2 (100%)	2 (67%)
Carcinoma	1 (100%)			
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Renal tubule, adenoma	1 (2%)			1 (2%)
Urinary bladder	(49)	(50)	(48)	(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Lymphoma malignant histiocytic			2 (4%)	
Lymphoma malignant lymphocytic		2 (4%)	2 (4%)	3 (6%)
Lymphoma malignant mixed	3 (6%)	6 (12%)	2 (4%)	1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[§]				
15-Month interim evaluation	1	5	1	1
2-Year study	31	35	29	37
Total primary neoplasms				
15-Month interim evaluation	1	5	1	1
2-Year study	47	53	51	58
Total animals with benign neoplasms				
15-Month interim evaluation	1	3	1	1
2-Year study	25	22	23	29
Total benign neoplasms				
15-Month interim evaluation	1	3	1	1
2-Year study	31	26	29	36
Total animals with malignant neoplasms				
15-Month interim evaluation		2		
2-Year study	15	21	14	19
Total malignant neoplasms				
15-Month interim evaluation		2		
2-Year study	16	27	22	22
Total animals with metastatic neoplasms				
2-Year study	3	5	4	2
Total metastatic neoplasms				
2-Year study	4	7	4	2

[a] Number of animals examined microscopically at site and number of animals with lesion
[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 Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control

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

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	
Carcass ID Number	0 1 7 1	0 1 8 1	0 1 9 1	0 2 0 1	0 2 1 1	0 2 3 1	0 2 5 1	0 2 9 1	0 3 1 1	0 3 2 1	0 3 4 1	0 3 5 1	0 3 7 1	0 5 7 1	0 5 8 1	0 3 9 1	0 4 0 1	0 4 3 1	0 4 4 1	0 4 5 1	0 4 6 1	0 4 7 1	0 4 8 1	0 4 9 1	0 5 9 1	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																											8
Hepatocellular adenoma							X		X								X				X						13
Hepatocellular adenoma, multiple													X														3
Histiocytic sarcoma																											1
Mesentery																											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma							X																				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																											1
Tooth																											1
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																											1
Capsule, adenoma																			X								1
Adrenal medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																											1
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M		43
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		48
Sarcoma, metastatic, nose																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
General Body System																											
None																											
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Preputial gland										+									+								14
Prostate	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Interstitial cell, adenoma																							X				1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	2 8 3	3 6 2	5 1 6	5 8 0	5 8 4	6 2 7	6 3 3	6 7 4	6 7 6	6 9 8	7 2 2	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6
Carcass ID Number	0 4 2 1	0 5 5 1	0 0 6 1	0 3 3 1	0 2 2 1	0 4 1 1	0 5 3 1	0 2 8 1	0 6 0 1	0 5 4 1	0 5 1 1	0 0 2 1	0 0 3 1	0 0 4 1	0 0 5 1	0 0 7 1	0 0 8 1	0 1 9 1	0 1 0 1	0 1 1 1	0 1 2 1	0 1 3 1	0 1 4 1	0 1 5 1	0 1 6 1
Hematopoietic System																									
Blood					+																				
Bone marrow	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Lymph node																	+								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																+									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, nose	X																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X														X	X	X					
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma									X																
Carcinoma, metastatic, harderian gland											X														
Hepatocellular carcinoma, metastatic, liver																			X						
Histiocytic sarcoma										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma	X																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye				+																					
Harderian gland											+														
Carcinoma											X														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																X									
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Lymphoma malignant mixed														X			X						X		

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	737	737	737	737	737	737	737	737	737	
Carcass ID Number	01717	01818	01919	02201	02211	02231	02251	02291	03111	03211	03411	03511	03711	05711	05811	03901	04011	04311	04411	04511	04611	04711	04811	04911	05911	Total Tissues/ Tumors
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node																										1
Lymph node, mandibular	+	M	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Thymus	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	M	M	+	M	+	M	+	M	M	+	38
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
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, nose																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X			X		X			X				8
Alveolar/bronchiolar adenoma, multiple						X																				1
Alveolar/bronchiolar carcinoma								X																		2
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye				+																						2
Harderian gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant mixed																										3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 11.25 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 11.25 mg/kg (continued)

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	736	736	736	
Carcass ID Number	08331	08341	09331	09941	09951	09971	09981	10001	10021	10031	10041	10051	10071	10081	10091	10111	10121	10141	10161	10171	10201	10731	10891	10901		Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+		49
Adenocarcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma, multiple				X																						2
Hepatocellular carcinoma			X					X	X												X	X				8
Hepatocellular adenoma					X						X													X		10
Hepatocellular adenoma, multiple														X					X							2
Hepatocholangiocarcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma, metastatic, liver				X																						1
Tongue																										2
Squamous cell papilloma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma																										1
Capsule, adenoma								X																		1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		46
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Parathyroid gland	+	+	+	M	+	+	+	M	M	+	M	+	+	+	M	+	+	M	+	+	M	+	M	+		35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Preputial gland	+				+		+				+				+	+	+		+	+	+	+	+	+		22
Adenoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+		46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Testes	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+		49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 11.25 mg/kg (continued)

Number of Days on Study	12 28	21 11	56 18	60 00	64 09	71 13	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11	73 11
Carcass ID Number	10 15 11	11 19 11	09 99 11	09 92 11	09 96 11	06 64 11	06 63 11	06 65 11	06 66 11	06 67 11	06 68 11	06 69 11	07 01 11	07 02 11	07 04 11	07 06 11	07 07 11	07 09 11	08 00 11	08 01 11	08 02 11	08 05 11	08 07 11	08 08 11	09 01 11
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+																							
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Hemangioma																X									
Hemangiosarcoma																		X							
Thymus	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	M	M	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+	+	+																						
Hepatocholangiocarcinoma, metastatic, liver			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X													X				
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver						X																			
Hepatocholangiocarcinoma, metastatic, liver			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+			+											+										
Harderian gland	+	+		+											+										
Adenoma				X											X										
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic	X	X																							
Lymphoma malignant mixed												X												X	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 11.25 mg/kg (continued)

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 6	7 3 6	7 3 6	
Carcass ID Number	0 8 3 1	0 8 4 1	0 9 3 1	0 9 4 1	0 9 5 1	0 9 7 1	0 9 8 1	1 0 0 1	1 0 2 1	1 0 3 1	1 0 4 1	1 0 5 1	1 0 7 1	1 0 8 1	1 0 9 1	1 1 0 1	1 1 0 1	1 1 2 1	1 1 4 1	1 1 6 1	1 1 7 1	1 2 0 1	0 7 3 1	0 8 9 1	0 9 0 1	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	44
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma																											1
Hemangiosarcoma																											1
Thymus	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	40
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	M	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																											3
Hepatocholangiocarcinoma, metastatic, liver																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X								X							X		X								6
Alveolar/bronchiolar carcinoma		X	X						X								X				X						5
Hepatocellular carcinoma, metastatic, liver																							X	X			3
Hepatocholangiocarcinoma, metastatic, liver																											1
Nose	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye																											3
Harderian gland																											4
Adenoma																											2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																											2
Lymphoma malignant mixed									X	X			X								X						6

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 22.5 mg/kg

Number of Days on Study	4 4 4	4 5 3	5 2 2	5 2 6	5 2 7	5 2 8	6 6 6	6 9 3	7 1 0	7 2 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	1 6 1 1	1 3 8 1	1 4 4 1	1 6 8 1	1 5 9 1	1 5 0 1	1 3 2 1	1 2 7 1	1 4 2 1	1 4 6 1	1 2 1 1	1 2 2 1	1 2 3 1	1 2 5 1	1 2 6 1	1 2 9 1	1 3 0 1	1 3 1 1	1 3 3 1	1 3 4 1	1 3 5 1	1 3 6 1	1 3 7 1	1 4 3 1	1 4 7 1
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Gallbladder	M	+	+	A	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma									X															
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma							X																	
Hepatocellular carcinoma			X	X	X																			
Hepatocellular adenoma	X			X									X			X			X					
Hepatocellular adenoma, multiple																						X	X	
Histiocytic sarcoma										X														
Mast cell tumor malignant									X															
Pancreas	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X														
Capsule, adenoma																								
Adrenal medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	M	M	+	+	+	+	+	M	+	+	M	+	M	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+
Follicular cell, carcinoma										X														
General Body System																								
Tissue NOS																								
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland			+		+	+				+	+					+		+		+				+
Prostate	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 22.5 mg/kg (continued)

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	
Carcass ID Number	14481	14491	15111	15121	15131	15411	15611	15711	15811	16001	16021	16031	16041	16051	16061	16691	17011	17113	17313	17411	17515	17611	17711	17911	18001	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma																						X				2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Hepatocellular carcinoma						X			X																	5
Hepatocellular adenoma	X										X		X			X				X	X					11
Hepatocellular adenoma, multiple									X																	3
Histiocytic sarcoma																										1
Mast cell tumor malignant																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Adenoma									X				X													3
Capsule, adenoma				X																				X		2
Adrenal medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	M	+	M	38
Pituitary gland	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	45
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, carcinoma																										1
General Body System																										
Tissue NOS															+											1
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland									+		+							+	+	+			+	+		16
Prostate	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 22.5 mg/kg (continued)

Number of Days on Study	4 4 4	4 5 3	5 2 2	5 2 6	5 2 7	5 2 8	6 6 6	6 9 3	7 1 0	7 2 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 4 0	7 3 0
Carcass ID Number	1 6 1 1	1 3 8 1	1 4 4 1	1 6 8 1	1 5 9 1	1 5 0 1	1 3 2 1	1 2 7 1	1 4 2 1	1 4 6 1	1 2 1 1	1 2 2 1	1 2 3 1	1 2 5 1	1 2 6 1	1 2 9 1	1 3 0 1	1 3 1 1	1 3 3 1	1 3 4 1	1 3 5 1	1 3 6 1	1 3 7 1	1 4 3 1	1 4 7 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant									X																
Lymph node							+	+	+																
Axillary, mast cell tumor malignant									X																
Mediastinal, mast cell tumor malignant									X																
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+
Mast cell tumor malignant									X																
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant									X																
Thymus	+	+	+	+	+	+	+	M	+	M	+	+	M	+	M	+	+	+	+	+	M	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma benign						X																			
Spinal cord						+																			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X												X					
Alveolar/bronchiolar carcinoma																X									
Carcinoma, metastatic, thyroid gland										X															
Hepatocellular carcinoma, metastatic, liver			X	X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Harderian gland																				+					
Adenoma																				X					
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Lymphoma malignant histiocytic																									
Lymphoma malignant lymphocytic							X	X																	
Lymphoma malignant mixed																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 22.5 mg/kg (continued)

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	1 4 8 1	1 4 9 1	1 5 1 1	1 5 2 1	1 5 3 1	1 5 4 1	1 5 6 1	1 5 7 1	1 5 8 1	1 6 0 1	1 6 2 1	1 6 3 1	1 6 4 1	1 6 5 1	1 6 6 1	1 6 9 1	7 0 1	7 1 1	7 3 1	7 4 1	7 5 1	7 6 1	7 7 1	7 9 1	8 0 1	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																										1
Lymph node																										3
Axillary, mast cell tumor malignant																										1
Mediastinal, mast cell tumor malignant																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Mast cell tumor malignant																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	42
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	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma benign																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X										X		X				X									6
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, thyroid gland																										1
Hepatocellular carcinoma, metastatic, liver									X																	3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear													+													1
Harderian gland					+																					2
Adenoma					X																					2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant histiocytic																					X	X				2
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																		X						X		2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 45 mg/kg

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 45 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	20071	20091	20101	20111	20131	20151	20161	20171	20181	20191	20201	20221	20231	20251	20261	20281	20311	20321	20341	20351	20361	20371	20381	20391	20401	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																		1
Hepatoblastoma																			X							1
Hepatocellular carcinoma						X	X						X		X							X				8
Hepatocellular carcinoma, multiple																		X								1
Hepatocellular adenoma		X												X	X	X										11
Hepatocellular adenoma, multiple			X				X	X											X	X						9
Mesentery															+											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																+										2
Squamous cell papilloma																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X	X												3
Parathyroid gland	+	+	+	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	37
Pituitary gland	+	+	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland		+	+					+	+	+			+			+					+			+	+	19
Prostate	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 45 mg/kg (continued)

Number of Days on Study	5 6 8	6 3 1	6 6 9	6 9 6	7 0 3	7 1 3	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	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 0 8 1	1 9 2 1	2 3 3 1	2 2 7 1	2 2 1 1	1 9 5 1	1 8 3 1	1 8 4 1	1 8 5 1	1 8 6 1	1 9 0 1	1 9 1 1	1 9 3 1	1 9 4 1	1 9 6 1	1 9 7 1	1 9 8 1	1 9 9 1	2 0 0 1	2 0 1 1	2 0 2 1	2 0 3 1	2 0 4 1	2 0 5 1	2 0 6 1
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																						
Lymph node					+																				
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymph node, mesenteric	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma			X																						
Thymus	+	+	M	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, hemangiosarcoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X					X				X	X						
Alveolar/bronchiolar carcinoma																									
Hepatocellular carcinoma, metastatic, liver		X																							
Mediastinum, hemangioma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland					+			+					+												
Adenoma					X			X																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic	X				X																X				
Lymphoma malignant mixed																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 45 mg/kg (continued)

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	300	300	300	300	300	300	300	300	300	300	300	300	300	300	
Carcass ID Number	20771	20791	21011	21131	21351	21551	21661	21771	21881	21991	22001	22021	22311	22351	22661	22811	23111	23211	23411	23511	23611	23711	23811	23911	24001	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph node																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	47
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X										2
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	M	+	+	+	+	+	M	+	41
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
Squamous cell carcinoma																	X									1
Subcutaneous tissue, hemangioma						X																				1
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X											X			X	7
Alveolar/bronchiolar carcinoma												X														1
Hepatocellular carcinoma, metastatic, liver																		X								2
Mediastinum, hemangioma																X										1
Nose	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										3
Adenoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed					X																					1

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
Adrenal Cortex: Adenoma				
Overall rate[a]	2/50 (4%)	2/50 (4%)	5/50 (10%)	0/50 (0%)
Adjusted rate[b]	4.7%	4.5%	12.2%	0.0%
Terminal rate[c]	1/39 (3%)	2/44 (5%)	4/40 (10%)	0/44 (0%)
First incidence (days)	627	729 (T)	725	)[e]
Life table test[d]	P=0.236N	P=0.659N	P=0.229	P=0.217N
Logistic regression test[d]	P=0.245N	P=0.694N	P=0.218	P=0.265N
Cochran-Armitage test[d]	P=0.263N			
Fisher exact test[d]		P=0.691N	P=0.218	P=0.247N
Liver: Hepatocellular Adenoma				
Overall rate	16/50 (32%)	12/50 (24%)	14/49 (29%)	20/50 (40%)
Adjusted rate	35.4%	26.1%	32.9%	42.6%
Terminal rate	10/39 (26%)	10/44 (23%)	12/40 (30%)	17/44 (39%)
First incidence (days)	584	600	444	696
Life table test	P=0.228	P=0.179N	P=0.396N	P=0.431
Logistic regression test	P=0.156	P=0.246N	P=0.439N	P=0.305
Cochran-Armitage test	P=0.137			
Fisher exact test		P=0.252N	P=0.440N	P=0.266
Liver: Hepatocellular Carcinoma				
Overall rate	8/50 (16%)	8/50 (16%)	5/49 (10%)	9/50 (18%)
Adjusted rate	17.6%	17.4%	10.9%	19.4%
Terminal rate	3/39 (8%)	6/44 (14%)	2/40 (5%)	7/44 (16%)
First incidence (days)	362	600	522	631
Life table test	P=0.540	P=0.530N	P=0.283N	P=0.589
Logistic regression test	P=0.383	P=0.608	P=0.305N	P=0.361
Cochran-Armitage test	P=0.471			
Fisher exact test		P=0.607N	P=0.290N	P=0.500
Liver: Hepatoblastoma or Hepatocellular Carcinoma				
Overall rate	8/50 (16%)	8/50 (16%)	5/49 (10%)	10/50 (20%)
Adjusted rate	17.6%	17.4%	10.9%	21.6%
Terminal rate	3/39 (8%)	6/44 (14%)	2/40 (5%)	8/44 (18%)
First incidence (days)	362	600	522	631
Life table test	P=0.430	P=0.530N	P=0.283N	P=0.496
Logistic regression test	P=0.277	P=0.608	P=0.305N	P=0.273
Cochran-Armitage test	P=0.357			
Fisher exact test		P=0.607N	P=0.290N	P=0.398
Liver: Hepatoblastoma, Hepatocellular Adenoma or Carcinoma				
Overall rate	18/50 (36%)	18/50 (36%)	17/49 (35%)	25/50 (50%)
Adjusted rate	38.9%	39.1%	38.0%	52.1%
Terminal rate	11/39 (28%)	16/44 (36%)	13/40 (33%)	21/44 (48%)
First incidence (days)	362	600	444	631
Life table test	P=0.162	P=0.436N	P=0.475N	P=0.261
Logistic regression test	P=0.073	P=0.580N	P=0.541N	P=0.096
Cochran-Armitage test	P=0.076			
Fisher exact test		P=0.582N	P=0.530N	P=0.113

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	9/50 (18%)	6/50 (12%)	6/50 (12%)	7/50 (14%)
Adjusted rate	22.2%	13.6%	14.5%	15.9%
Terminal rate	8/39 (21%)	6/44 (14%)	5/40 (13%)	7/44 (16%)
First incidence (days)	580	729 (T)	693	729 (T)
Life table test	P=0.326N	P=0.213N	P=0.275N	P=0.299N
Logistic regression test	P=0.336N	P=0.265N	P=0.283N	P=0.337N
Cochran-Armitage test	P=0.391N			
Fisher exact test		P=0.288N	P=0.288N	P=0.393N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	1/50 (2%)
Adjusted rate	4.9%	11.4%	2.5%	2.3%
Terminal rate	1/39 (3%)	5/44 (11%)	1/40 (3%)	1/44 (2%)
First incidence (days)	676	729 (T)	729 (T)	729 (T)
Life table test	P=0.170N	P=0.266	P=0.491N	P=0.459N
Logistic regression test	P=0.173N	P=0.232	P=0.499N	P=0.494N
Cochran-Armitage test	P=0.194N			
Fisher exact test		P=0.218	P=0.500N	P=0.500N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	11/50 (22%)	9/50 (18%)	7/50 (14%)	8/50 (16%)
Adjusted rate	26.5%	20.5%	17.0%	18.2%
Terminal rate	9/39 (23%)	9/44 (20%)	6/40 (15%)	8/44 (18%)
First incidence (days)	580	729 (T)	693	729 (T)
Life table test	P=0.196N	P=0.299N	P=0.207N	P=0.216N
Logistic regression test	P=0.204N	P=0.373N	P=0.213N	P=0.255N
Cochran-Armitage test	P=0.254N			
Fisher exact test		P=0.402N	P=0.218N	P=0.306N
Pancreatic Islets: Adenoma				
Overall rate	1/50 (2%)	0/50 (0%)	0/49 (0%)	3/50 (6%)
Adjusted rate	2.2%	0.0%	0.0%	6.8%
Terminal rate	0/39 (0%)	0/44 (0%)	0/40 (0%)	3/44 (7%)
First incidence (days)	627	)	)	729 (T)
Life table test	P=0.099	P=0.496N	P=0.504N	P=0.347
Logistic regression test	P=0.085	P=0.490N	P=0.523N	P=0.291
Cochran-Armitage test	P=0.086			
Fisher exact test		P=0.500N	P=0.505N	P=0.309
All Organs: Hemangiosarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	3/50 (6%)
Adjusted rate	0.0%	6.8%	0.0%	6.5%
Terminal rate	0/39 (0%)	3/44 (7%)	0/40 (0%)	2/44 (5%)
First incidence (days)	)	729 (T)	)	669
Life table test	P=0.187	P=0.143	)	P=0.145
Logistic regression test	P=0.178	P=0.143	)	P=0.117
Cochran-Armitage test	P=0.163			
Fisher exact test		P=0.121	)	P=0.121

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	0/50 (0%)	3/50 (6%)	1/50 (2%)	4/50 (8%)
Adjusted rate	0.0%	6.8%	2.3%	8.8%
Terminal rate	0/39 (0%)	3/44 (7%)	0/40 (0%)	3/44 (7%)
First incidence (days)	)	729 (T)	666	669
Life table test	P=0.089	P=0.143	P=0.505	P=0.081
Logistic regression test	P=0.077	P=0.143	P=0.494	P=0.065
Cochran-Armitage test	P=0.072			
Fisher exact test		P=0.121	P=0.500	P=0.059
All Organs: Lymphocytic Malignant Lymphoma				
Overall rate	3/50 (6%)	8/50 (16%)	6/50 (12%)	4/50 (8%)
Adjusted rate	7.7%	17.1%	14.1%	8.5%
Terminal rate	3/39 (8%)	6/44 (14%)	4/40 (10%)	2/44 (5%)
First incidence (days)	729 (T)	128	666	568
Life table test	P=0.461N	P=0.137	P=0.259	P=0.562
Logistic regression test	P=0.499	P=0.100	P=0.244	P=0.481
Cochran-Armitage test	P=0.516N			
Fisher exact test		P=0.100	P=0.243	P=0.500
All Organs: Malignant Lymphoma or Histiocytic Sarcoma				
Overall rate	4/50 (8%)	8/50 (16%)	7/50 (14%)	4/50 (8%)
Adjusted rate	9.9%	17.1%	16.2%	8.5%
Terminal rate	3/39 (8%)	6/44 (14%)	4/40 (10%)	2/44 (5%)
First incidence (days)	698	128	666	568
Life table test	P=0.373N	P=0.234	P=0.285	P=0.577N
Logistic regression test	P=0.530N	P=0.179	P=0.264	P=0.626
Cochran-Armitage test	P=0.426N			
Fisher exact test		P=0.178	P=0.262	P=0.643N
All Organs: Benign Neoplasms				
Overall rate	25/50 (50%)	23/50 (46%)	23/50 (46%)	29/50 (58%)
Adjusted rate	54.2%	47.9%	49.8%	61.7%
Terminal rate	18/39 (46%)	19/44 (43%)	17/40 (43%)	26/44 (59%)
First incidence (days)	580	211	444	696
Life table test	P=0.351	P=0.268N	P=0.399N	P=0.510
Logistic regression test	P=0.210	P=0.418N	P=0.418N	P=0.358
Cochran-Armitage test	P=0.195			
Fisher exact test		P=0.421N	P=0.421N	P=0.274
All Organs: Malignant Neoplasms				
Overall rate	15/50 (30%)	22/50 (44%)	14/50 (28%)	19/50 (38%)
Adjusted rate	31.7%	44.8%	29.7%	38.6%
Terminal rate	7/39 (18%)	17/44 (39%)	7/40 (18%)	14/44 (32%)
First incidence (days)	283	128	522	568
Life table test	P=0.519	P=0.215	P=0.479N	P=0.414
Logistic regression test	P=0.249	P=0.064	P=0.511N	P=0.106
Cochran-Armitage test	P=0.401			
Fisher exact test		P=0.107	P=0.500N	P=0.263

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	31/50 (62%)	35/50 (70%)	29/50 (58%)	37/50 (74%)
Adjusted rate	63.2%	70.0%	59.2%	74.0%
Terminal rate	21/39 (54%)	29/44 (66%)	20/40 (50%)	31/44 (70%)
First incidence (days)	283	128	444	568
Life table test	P=0.401	P=0.519	P=0.400N	P=0.422
Logistic regression test	P=0.121	P=0.208	P=0.424N	P=0.084
Cochran-Armitage test	P=0.182			
Fisher exact test		P=0.263	P=0.419N	P=0.142

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

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride[a]

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	10	10
Early deaths				
Moribund	8	4	6	6
Natural deaths	3	2	4	
Survivors				
Terminal sacrifice	39	44	40	44
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, cecum	(10)	(10)	(10)	(10)
Hyperplasia		1 (10%)		
Liver	(10)	(10)	(10)	(10)
Eosinophilic focus				1 (10%)
Fatty change, diffuse		1 (10%)	1 (10%)	
Fatty change, focal	3 (30%)	2 (20%)	2 (20%)	6 (60%)
Inflammation, focal, necrotizing		1 (10%)		
Mixed cell focus	1 (10%)	1 (10%)		1 (10%)
Necrosis, focal				2 (20%)
Centrilobular, hypertrophy			1 (10%)	
Stomach, forestomach	(10)	(10)	(10)	(10)
Acanthosis			1 (10%)	
Hyperkeratosis			1 (10%)	
Stomach, glandular	(10)	(10)	(10)	(10)
Hyperplasia		1 (10%)	1 (10%)	
Cardiovascular System				
None				
Endocrine System				
Islets, pancreatic	(10)	(10)	(10)	(10)
Hyperplasia	1 (10%)			
General Body System				
None				
Genital System				
None				
Hematopoietic System				
Lymph node			(1)	
Mediastinal, angiectasis			1 (100%)	

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
15-Month Interim Evaluation (continued)				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(10)	(10)
Alveolar epithelium, hyperplasia	1 (10%)	1 (10%)		
Nose	(10)	(10)	(10)	(9)
Inflammation, acute			2 (20%)	1 (11%)
Special Senses System				
None				
Urinary System				
Kidney	(10)	(10)	(10)	(10)
Cyst	1 (10%)			
Renal tubule, regeneration	6 (60%)	2 (20%)	6 (60%)	3 (30%)
2-Year Study				
Alimentary System				
Esophagus	(50)	(50)	(48)	(50)
Hyperkeratosis	1 (2%)			
Liver	(50)	(50)	(49)	(50)
Basophilic focus	1 (2%)	6 (12%)	2 (4%)	2 (4%)
Clear cell focus	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Eosinophilic focus	3 (6%)	9 (18%)	10 (20%)	11 (22%)
Eosinophilic focus, multiple				1 (2%)
Fatty change				1 (2%)
Fatty change, diffuse				1 (2%)
Fatty change, focal	1 (2%)			
Fibrosis				1 (2%)
Hematopoietic cell proliferation			1 (2%)	
Inflammation, chronic active			1 (2%)	
Inflammation, focal, necrotizing	1 (2%)			1 (2%)
Inflammation, granulomatous	1 (2%)			
Mixed cell focus	2 (4%)	4 (8%)	1 (2%)	6 (12%)
Necrosis	2 (4%)			
Centrilobular, hypertrophy			5 (10%)	6 (12%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Mesentery	(1)			(1)
Inflammation, chronic active				1 (100%)
Fat, necrosis	1 (100%)			
Pancreas	(50)	(50)	(49)	(50)
Duct, cyst				1 (2%)
Stomach, forestomach	(50)	(50)	(49)	(50)
Hyperkeratosis	2 (4%)	1 (2%)		
Hyperplasia, basal cell	3 (6%)	1 (2%)		
Inflammation, chronic active	2 (4%)	1 (2%)		
Necrosis	1 (2%)			
Stomach, glandular	(50)	(50)	(49)	(50)
Inflammation, chronic active			1 (2%)	
Mineralization	1 (2%)			
Necrosis		1 (2%)		
Tongue	(1)	(2)		(2)
Mineralization	1 (100%)			1 (50%)
Tooth	(1)			
Developmental malformation	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	1 (2%)		2 (4%)	1 (2%)
Mineralization			1 (2%)	
Artery, inflammation, chronic active	1 (2%)		1 (2%)	
Endocrine System				
Adrenal cortex	(48)	(50)	(48)	(49)
Accessory adrenal cortical nodule	2 (4%)		1 (2%)	
Hyperplasia				3 (6%)
Hypertrophy	3 (6%)	6 (12%)	8 (17%)	2 (4%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Hyperplasia	3 (6%)	1 (2%)	3 (6%)	
Pituitary gland	(48)	(50)	(45)	(46)
Pars distalis, cyst		1 (2%)	1 (2%)	
Pars distalis, hyperplasia	1 (2%)		1 (2%)	2 (4%)
Thyroid gland	(48)	(50)	(48)	(50)
Artery, inflammation, chronic active			1 (2%)	
Follicular cell, hyperplasia			3 (6%)	3 (6%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	1 (2%)			
Mineralization	1 (2%)			

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
2-Year Study (continued)				
Genital System (continued)				
Preputial gland	(14)	(22)	(16)	(19)
Abscess		2 (9%)		
Dilatation	8 (57%)	19 (86%)	16 (100%)	18 (95%)
Prostate	(45)	(46)	(48)	(46)
Hyperplasia		1 (2%)		
Hematopoietic System				
Lymph node, mandibular	(44)	(44)	(46)	(47)
Hematopoietic cell proliferation		1 (2%)		
Lymph node, mesenteric	(43)	(47)	(43)	(46)
Hyperplasia, lymphoid	1 (2%)			
Infiltration cellular, histiocyte			1 (2%)	
Thrombosis		1 (2%)		
Artery, inflammation, chronic active			1 (2%)	
Spleen	(49)	(48)	(50)	(50)
Angiectasis		4 (8%)	1 (2%)	
Hematopoietic cell proliferation	2 (4%)	9 (19%)	6 (12%)	3 (6%)
Hyperplasia		4 (8%)		
Necrosis			1 (2%)	
Thymus	(38)	(40)	(42)	(41)
Depletion lymphoid	1 (3%)			
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Necrosis				2 (4%)
Musculoskeletal System				
Skeletal muscle	(1)	(3)	(1)	(1)
Artery, inflammation, chronic active	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Edema	1 (2%)			
Hemorrhage	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Infiltration cellular, histiocyte	6 (12%)	3 (6%)		1 (2%)
Alveolar epithelium, hyperplasia		1 (2%)	2 (4%)	1 (2%)
Nose	(49)	(47)	(50)	(46)
Inflammation, acute	1 (2%)			1 (2%)

TABLE C4
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
2-Year Study (continued)				
Special Senses System				
Eye	(2)	(3)		
Cornea, inflammation, acute		1 (33%)		
Lens, cataract	1 (50%)			
Harderian gland	(1)	(4)	(2)	(3)
Hyperplasia				1 (33%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst		4 (8%)		2 (4%)
Infarct			1 (2%)	
Infiltration cellular, plasma cell		1 (2%)		
Nephropathy	7 (14%)	8 (16%)	9 (18%)	6 (12%)
Artery, inflammation, chronic active			1 (2%)	
Cortex, mineralization			2 (4%)	
Papilla, mineralization			1 (2%)	
Urinary bladder	(49)	(50)	(48)	(49)
Calculus gross observation				1 (2%)
Calculus microscopic observation only				2 (4%)

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

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR GAVAGE STUDY OF PROMETHAZINE HYDROCHLORIDE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride [a]

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	9
Early deaths				
Accidental deaths			2	1
Moribund	10	7	9	6
Natural deaths	1	1	1	3
Survivors				
Died last week of study	2			
Terminal sacrifice	37	42	39	41
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Liver	(10)	(10)	(9)	(9)
Hepatocellular adenoma				1 (11%)
Cardiovascular System				
None				
Endocrine System				
None				
General Body System				
None				
Genital System				
Uterus	(10)	(10)	(9)	(9)
Polyp stromal			1 (11%)	2 (22%)
Hematopoietic System				
None				
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
15-Month Interim Evaluation (continued)				
Respiratory System				
Lung	(10)	(10)	(9)	(9)
Alveolar/bronchiolar adenoma	2 (20%)			
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Esophagus	(50)	(49)	(49)	(50)
Squamous cell papilloma				1 (2%)
Gallbladder	(46)	(49)	(47)	(49)
Intestine large, colon	(50)	(49)	(51)	(51)
Intestine large, cecum	(49)	(49)	(50)	(49)
Intestine small, duodenum	(48)	(49)	(51)	(50)
Intestine small, jejunum	(46)	(49)	(49)	(48)
Intestine small, ileum	(49)	(49)	(51)	(49)
Liver	(50)	(50)	(51)	(51)
Hemangiosarcoma			1 (2%)	
Hepatocellular carcinoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Hepatocellular adenoma	2 (4%)	4 (8%)	6 (12%)	8 (16%)
Hepatocellular adenoma, multiple	1 (2%)			
Histiocytic sarcoma		2 (4%)	1 (2%)	2 (4%)
Mesentery	(4)	(1)	(3)	(2)
Fibroma	1 (25%)			
Sarcoma		1 (100%)		1 (50%)
Pancreas	(50)	(49)	(51)	(50)
Sarcoma, metastatic, skin		1 (2%)		
Salivary glands	(49)	(50)	(51)	(50)
Stomach, forestomach	(50)	(50)	(51)	(51)
Mast cell tumor benign	1 (2%)			
Squamous cell papilloma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Stomach, glandular	(49)	(49)	(51)	(50)
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Carcinoma, metastatic, harderian gland			1 (2%)	
Histiocytic sarcoma		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
2-Year Study (continued)				
Endocrine System				
Adrenal cortex	(50)	(50)	(51)	(51)
Capsule, adenoma	2 (4%)		1 (2%)	
Islets, pancreatic	(49)	(49)	(51)	(50)
Adenoma	1 (2%)			
Pituitary gland	(46)	(49)	(50)	(49)
Carcinoma			1 (2%)	
Pars distalis, adenoma	5 (11%)	2 (4%)	4 (8%)	3 (6%)
Pars distalis, adenoma, multiple		1 (2%)		
Pars intermedia, adenoma			1 (2%)	
Thyroid gland	(50)	(50)	(48)	(51)
Carcinoma				1 (2%)
Bilateral, follicular cell, adenoma				1 (2%)
Follicular cell, adenoma	4 (8%)	2 (4%)	1 (2%)	
General Body System				
None				
Genital System				
Ovary	(49)	(49)	(49)	(49)
Adenoma, tubular				1 (2%)
Cystadenoma		2 (4%)	2 (4%)	1 (2%)
Hemangioma			1 (2%)	
Histiocytic sarcoma				1 (2%)
Luteoma		1 (2%)		
Uterus	(50)	(50)	(51)	(51)
Adenoma			1 (2%)	
Histiocytic sarcoma			1 (2%)	1 (2%)
Leiomyosarcoma			1 (2%)	1 (2%)
Polyp stromal	1 (2%)	3 (6%)	2 (4%)	
Hematopoietic System				
Bone marrow	(50)	(49)	(51)	(51)
Lymph node	(4)	(7)	(3)	(2)
Lymph node, mandibular	(48)	(48)	(49)	(48)
Lymph node, mesenteric	(46)	(49)	(49)	(46)
Hemangioma		1 (2%)		
Histiocytic sarcoma		1 (2%)	1 (2%)	1 (2%)
Sarcoma, metastatic, skin		1 (2%)		
Spleen	(49)	(49)	(50)	(51)
Hemangioma			1 (2%)	
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma		1 (2%)	1 (2%)	2 (4%)
Thymus	(42)	(48)	(46)	(48)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
2-Year Study (continued)				
Integumentary System				
Mammary gland	(39)	(40)	(42)	(45)
Adenocarcinoma		1 (3%)		
Adenoma	1 (3%)		1 (2%)	
Skin	(50)	(50)	(51)	(50)
Basosquamous tumor benign	1 (2%)			
Subcutaneous tissue, fibrosarcoma	1 (2%)			
Subcutaneous tissue, sarcoma	1 (2%)	2 (4%)		1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(51)	(51)
Osteosarcoma	1 (2%)			
Skeletal muscle		(1)	(2)	
Nervous System				
Brain	(50)	(49)	(51)	(51)
Carcinoma, metastatic, pituitary gland			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(51)
Alveolar/bronchiolar adenoma	6 (12%)	2 (4%)		2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)			
Carcinoma, metastatic, harderian gland	1 (2%)		1 (2%)	
Carcinoma, metastatic, thyroid gland				1 (2%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)		1 (2%)	
Histiocytic sarcoma		2 (4%)		2 (4%)
Osteosarcoma, metastatic, uncertain primary site	1 (2%)			
Mediastinum, carcinoma, metastatic, lung	1 (2%)			
Nose	(47)	(49)	(49)	(48)
Carcinoma, metastatic, harderian gland			1 (2%)	
Special Senses System				
Ear			(1)	
Sarcoma			1 (100%)	
Harderian gland	(3)	(5)	(1)	(1)
Adenoma	2 (67%)	4 (80%)		1 (100%)
Carcinoma			1 (100%)	
Bilateral, carcinoma	1 (33%)			
Urinary System				
Kidney	(50)	(50)	(51)	(51)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Histiocytic sarcoma		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride
(continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
2-Year Study (continued)				
Urinary System (continued)				
Kidney (continued)	(50)	(50)	(51)	(51)
Osteosarcoma, metastatic, uncertain primary site	1 (2%)			
Urinary bladder	(50)	(48)	(51)	(49)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(51)	(51)
Histiocytic sarcoma		2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant lymphocytic	1 (2%)	3 (6%)	4 (8%)	3 (6%)
Lymphoma malignant mixed	7 (14%)	12 (24%)	9 (18%)	7 (14%)
Lymphoma malignant undifferentiated cell		1 (2%)	1 (2%)	
Neoplasm Summary				
Total animals with primary neoplasms[c]				
15-Month interim evaluation	2		1	3
2-Year study	31	33	29	26
Total primary neoplasms				
15-Month interim evaluation	2		1	3
2-Year study	44	46	43	39
Total animals with benign neoplasms				
15-Month interim evaluation	2		1	3
2-Year study	24	20	16	15
Total benign neoplasms				
15-Month interim evaluation	2		1	3
2-Year study	29	23	22	20
Total animals with malignant neoplasms				
2-Year study	15	21	19	17
Total malignant neoplasms				
2-Year study	15	23	21	19
Total animals with metastatic neoplasms				
2-Year study	5	1	3	1
Total metastatic neoplasms				
2-Year study	7	2	5	1
Total animals with malignant neoplasms of uncertain primary site				
2-Year study	1			

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control

Number of Days on Study	4 4 2	5 2 9	5 8 2	6 0 1	6 2 2	6 9 3	7 0 7	7 1 5	7 1 8	7 2 0	7 2 8	7 3 8	7 4 2	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3
Carcass ID Number	3 0 6 1	2 6 0 1	2 8 9 1	3 0 3 1	2 9 1 1	3 1 5 1	2 9 4 1	2 8 0 1	2 9 2 1	2 2 8 1	2 9 7 1	2 7 0 1	2 6 2 1	2 6 3 1	2 7 5 1	2 7 6 1	2 7 7 1	2 8 2 1	2 8 3 1	2 8 6 1	2 8 7 1	2 9 0 1	2 9 3 1	2 9 5 1	2 9 8 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	M	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma													X												
Hepatocellular adenoma																								X	
Hepatocellular adenoma, multiple																		X							
Mesentery					+						+												+		
Fibroma											X														
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor benign																									
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung						X																			
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma															X										
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	M	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M
Pars distalis, adenoma					X										X			X					X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma			X									X													
General Body System																									
None																									
Genital System																									
Clitoral gland				+																					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																					X				

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	2 9 9 1	3 0 1 1	3 0 2 1	3 0 4 1	3 0 9 1	3 1 4 1	2 5 6 1	2 5 7 1	2 6 1 1	2 6 4 1	2 6 6 1	2 6 8 1	2 6 9 1	2 7 1 1	2 7 2 1	2 7 3 1	2 7 4 1	2 8 5 1	2 8 8 1	3 0 7 1	3 0 8 1	3 1 0 1	3 1 1 1	3 1 2 1	3 1 3 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Hepatocellular adenoma							X																			2
Hepatocellular adenoma, multiple																										1
Mesentery										+																4
Fibroma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor benign																									X	1
Squamous cell papilloma					X																					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma											X															2
Adrenal medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	+	M	+	+	M	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Pars distalis, adenoma	X																									5
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																	X			X						4
General Body System																										
None																										
Genital System																										
Clitoral gland																						+				2
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	4	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	4	2	8	0	2	9	0	1	1	2	2	3	4	4	4	4	4	4	4	4	4	4	4	4
	2	9	2	1	2	3	7	5	8	0	8	8	2	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	3	2	2	3	2	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	0	6	8	0	9	1	9	8	9	5	9	7	6	6	7	7	8	8	8	8	9	9	9	9
	6	0	9	3	1	5	4	0	2	8	7	0	2	3	5	6	7	2	3	6	7	0	3	5	8
	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
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node															+										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Lymph node, mesenteric	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Thymus	+	+	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	M
Adenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor benign	X																								
Subcutaneous tissue, fibrosarcoma			X																						
Subcutaneous tissue, sarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord		+																							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X		X					X											
Alveolar/bronchiolar carcinoma						X					X														
Carcinoma, metastatic, harderian gland										X															
Hepatocellular carcinoma, metastatic, liver													X												
Osteosarcoma, metastatic, uncertain primary site								X																	
Mediastinum, carcinoma, metastatic, lung											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland										+															
Adenoma																									
Bilateral, carcinoma										X															
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung						X																			
Osteosarcoma, metastatic, uncertain primary site								X																	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	2 9 9 1	3 0 1 1	3 0 2 1	3 0 4 1	3 0 9 1	3 1 4 1	2 5 6 1	2 5 7 1	2 6 1 1	2 6 4 1	2 6 6 1	2 6 8 1	2 6 9 1	2 7 1 1	2 7 2 1	2 7 3 1	2 7 4 1	2 8 5 1	2 8 8 1	3 0 7 1	3 0 8 1	3 1 0 1	3 1 1 1	3 1 2 1	3 1 3 1	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node							+									+			+							4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	42
Integumentary System																										
Mammary gland	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	M	M	39
Adenoma				X																						1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor benign																										1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma				X																						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X		X									X								6
Alveolar/bronchiolar carcinoma																										2
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										1
Osteosarcoma, metastatic, uncertain primary site																										1
Mediastinum, carcinoma, metastatic, lung																										1
Nose	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																			+					+		3
Adenoma																			X					X		2
Bilateral, carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Osteosarcoma, metastatic, uncertain primary site																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	4	5	5	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
	4	2	8	0	2	9	0	1	1	2	2	3	4	4	4	4	4	4	4	4	4	4	4	4	4
	2	9	2	1	2	3	7	5	8	0	8	8	2	3	3	3	3	3	3	3	3	3	3	3	3
Carcass ID Number	3	2	2	3	2	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	0	6	8	0	9	1	9	8	9	5	9	7	6	6	7	7	7	8	8	8	8	9	9	9	9
	6	0	9	3	1	5	4	0	2	8	7	0	2	3	5	6	7	2	3	6	7	0	3	5	8
	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
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed									X						X										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: Vehicle Control (continued)

Number of Days on Study	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	7 4 4	
Carcass ID Number	2 9 9 1	3 0 1 1	3 0 2 1	3 0 4 1	3 0 9 1	3 1 4 1	2 5 6 1	2 5 7 1	2 6 1 1	2 6 4 1	2 6 6 1	2 6 8 1	2 6 9 1	2 7 1 1	2 7 2 1	2 7 3 1	2 7 4 1	2 8 5 1	2 8 8 1	3 0 7 1	3 0 8 1	3 1 0 1	3 1 1 1	3 1 2 1	3 1 3 1	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic														X												1
Lymphoma malignant mixed		X					X									X			X			X				7

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 3.75 mg/kg

Number of Days on Study	5 5 4	6 7 7	6 9 3	6 9 4	7 1 0	7 2 2	7 2 5	7 3 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2
Carcass ID Number	3 1 8 1	3 4 6 1	3 5 6 1	3 2 1 1	3 6 3 1	3 6 8 1	3 4 9 1	3 2 3 1	3 1 7 1	3 1 9 1	3 2 0 1	3 2 2 1	3 2 4 1	3 2 6 1	3 2 8 1	3 2 9 1	3 3 0 1	3 3 1 1	3 3 3 1	3 3 4 1	3 3 5 1	3 3 6 1	3 3 7 1	3 3 8 1	3 3 9 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																									
Hepatocellular adenoma							X								X										
Histiocytic sarcoma		X						X																	
Mesentery																		+							
Sarcoma																		X							
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin						X																			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue							+																		
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																		X							
Pars distalis, adenoma, multiple											X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																X		X							
General Body System																									
None																									
Genital System																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma			X																						
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal							X			X															

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 3.75 mg/kg (continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	3 4 0 1	3 4 1 1	3 4 2 1	3 4 3 1	3 4 4 1	3 4 5 1	3 4 7 1	3 4 8 1	3 5 0 1	3 5 1 1	3 5 2 1	3 5 3 1	3 5 7 1	3 6 0 1	3 6 4 1	3 6 5 1	3 7 4 1	3 6 1 1	3 6 2 1	3 6 6 1	3 6 7 1	3 6 9 1	3 7 1 1	3 7 2 1	3 7 3 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X																							1
Hepatocellular adenoma			X																			X				4
Histiocytic sarcoma																										2
Mesentery																										1
Sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, skin																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X																								1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	M	+	M	+	+	+	+	+	+	40
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X																								2
Pars distalis, adenoma, multiple																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										2
General Body System																										
None																										
Genital System																										
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																		X								2
Luteoma	X																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal								X																		3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 3.75 mg/kg (continued)

Number of Days on Study	5 5 4	6 7 7	6 9 3	6 9 4	7 1 0	7 2 2	7 2 5	7 3 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2
Carcass ID Number	3 1 8 1	3 4 6 1	3 5 6 1	3 2 1 1	3 6 3 1	3 6 8 1	3 4 9 1	3 2 3 1	3 1 7 1	3 1 9 1	3 2 0 1	3 2 2 1	3 2 4 1	3 2 6 1	3 2 8 1	3 2 9 1	3 3 0 1	3 3 1 1	3 3 3 1	3 3 4 1	3 3 5 1	3 3 6 1	3 3 7 1	3 3 8 1	3 3 9 1
Hematopoietic System																									
Blood	+																								
Bone marrow	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+	+	+										+										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Histiocytic sarcoma								X																	
Sarcoma, metastatic, skin						X																			
Spleen	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Thymus	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+
Adenocarcinoma											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma						X																X			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X						
Histiocytic sarcoma		X						X																	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+																								
Harderian gland	+																								+
Adenoma	X																								X
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Urinary bladder	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X						X																	
Lymphoma malignant lymphocytic			X	X											X									
Lymphoma malignant mixed													X									X	X		
Lymphoma malignant undifferentiated cell type					X																				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 3.75 mg/kg (continued)

Number of Days on Study	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	7 4 3	
Carcass ID Number	3 4 0 1	3 4 1 1	3 4 2 1	3 4 3 1	3 4 4 1	3 4 5 1	3 4 7 1	3 4 8 1	3 5 0 1	3 5 1 1	3 5 2 1	3 5 3 1	3 5 7 1	3 6 0 1	3 6 4 1	3 6 5 1	3 7 4 1	3 6 1 1	3 6 2 1	3 6 6 1	3 6 7 1	3 6 9 1	3 7 1 1	3 7 2 1	3 7 3 1	Total Tissues/ Tumors
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node									+		+										+					7
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma													X													1
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	M	+	+	40
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X																			2
Histiocytic sarcoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland				+							+					+										5
Adenoma											X					X										4
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed	X		X						X		X	X		X		X					X			X		12
Lymphoma malignant undifferentiated cell type																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 7.5 mg/kg

Number of Days on Study	371	388	569	626	629	632	640	701	707	723	731	732	738	738	738	738	738	738	738	738	738	738	741	741	741	741
Carcass ID Number	4321	3811	4061	4141	4301	4021	3881	4081	3931	4181	4251	4191	3831	3841	3851	3861	3871	3891	3911	3921	3941	3951	3791	3801	3821	3961
Alimentary System																										
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X																						
Hepatocellular carcinoma			X																							
Hepatocellular adenoma					X										X						X					
Histiocytic sarcoma								X																		
Mesentery																										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																										
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland									X																	
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																										
Adrenal medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	M	+	+	+	+	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																				
Pars distalis, adenoma					X		X														X				X	
Pars intermedia, adenoma																										
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																										X
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Cystadenoma																					X					
Hemangioma								X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																										
Histiocytic sarcoma								X																		
Leiomyosarcoma																										
Polyp stromal																									X	

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 7.5 mg/kg (continued)

Number of Days on Study	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	
Carcass ID Number	3 9 7 1	3 9 8 1	3 9 9 1	4 0 0 1	4 0 1 1	4 0 3 1	4 0 4 1	4 0 5 1	4 0 9 1	4 1 1 1	4 1 2 1	4 1 3 1	4 1 5 1	4 1 6 1	4 1 7 1	4 2 0 1	4 2 1 1	4 2 2 1	4 2 3 1	4 2 6 1	4 2 7 1	4 2 8 1	4 3 1 1	4 3 3 1	4 3 5 1	Total Tissues/ Tumors	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Hemangiosarcoma																									1	
Hepatocellular carcinoma																									1	
Hepatocellular adenoma	X															X						X			6	
Histiocytic sarcoma																									1	
Mesentery				+	+														+						3	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Squamous cell papilloma											X														1	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma, metastatic, harderian gland																									1	
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Capsule, adenoma										X															1	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	42	
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Carcinoma																									1	
Pars distalis, adenoma																									4	
Pars intermedia, adenoma		X																							1	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	48	
Follicular cell, adenoma																									1	
General Body System																										
None																										
Genital System																										
Ovary	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49	
Cystadenoma																X									2	
Hemangioma																									1	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51	
Adenoma				X																					1	
Histiocytic sarcoma																										1
Leiomyosarcoma							X																		1	
Polyp stromal						X																				2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 7.5 mg/kg (continued)

Number of Days on Study	3 7 1	3 8 8	5 6 9	6 2 6	6 2 9	6 3 2	6 4 0	7 0 1	7 0 7	7 2 3	7 3 1	7 3 2	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 4 1	7 4 1	7 4 1	7 4 1
Carcass ID Number	4 3 2 1	3 8 1 1	4 0 6 1	4 1 4 1	4 3 0 1	4 0 2 1	3 8 8 1	4 0 8 1	3 9 3 1	4 1 8 1	4 2 5 1	4 1 9 1	3 8 3 1	3 8 4 1	3 8 5 1	3 8 6 1	3 8 7 1	3 8 9 1	3 9 1 1	3 9 2 1	3 9 4 1	3 9 5 1	3 7 9 1	3 8 0 1	3 8 2 1	3 9 6 1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node												+														
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Hemangioma																										
Histiocytic sarcoma								X																		
Thymus	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	M	+	+	+
Adenoma					X																					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+																
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland						X																				
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland									X																	
Hepatocellular carcinoma, metastatic, liver			X																							
Nose	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland									X																	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Ear							+																			
Sarcoma							X																			
Harderian gland									+																	
Carcinoma									X																	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 7.5 mg/kg (continued)

Number of Days on Study	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	
Carcass ID Number	3 9 7 1	3 9 8 1	3 9 9 1	4 0 0 1	4 0 1 1	4 0 3 1	4 0 4 1	4 0 5 1	4 0 9 1	4 1 1 1	4 1 2 1	4 1 3 1	4 1 5 1	4 1 6 1	4 1 7 1	4 2 0 1	4 2 1 1	4 2 2 1	4 2 3 1	4 2 6 1	4 2 7 1	4 2 8 1	4 3 1 1	4 3 3 1	4 3 5 1	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node																		+				+					3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma												X															1
Histiocytic sarcoma																											1
Thymus	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																											
Mammary gland	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	M		42
Adenoma																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Skeletal muscle																						+					2
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma, metastatic, pituitary gland																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, harderian gland																											1
Hepatocellular carcinoma, metastatic, liver																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, harderian gland																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Ear																											1
Sarcoma																											1
Harderian gland																											1
Carcinoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 7.5 mg/kg (continued)

Number of Days on Study	3 7 1	3 8 8	5 6 9	6 2 6	6 2 9	6 3 2	6 4 0	7 0 1	7 0 7	7 2 3	7 3 1	7 3 2	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 3 8	7 4 1	7 4 1	7 4 1	7 4 1
Carcass ID Number	4 3 2 1	3 8 1 1	4 0 6 1	4 1 4 1	4 3 0 1	4 0 2 1	3 8 8 1	4 0 8 1	3 9 3 1	4 1 8 1	4 2 5 1	4 1 9 1	3 8 3 1	3 8 4 1	3 8 5 1	3 8 6 1	3 8 7 1	3 8 9 1	3 9 1 1	3 9 2 1	3 9 4 1	3 9 5 1	3 7 9 1	3 8 0 1	3 8 2 1	3 9 6 1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																		
Lymphoma malignant lymphocytic													X					X								
Lymphoma malignant mixed				X																	X		X			
Lymphoma malignant undifferentiated cell type												X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 7.5 mg/kg (continued)

Number of Days on Study	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	741	
Carcass ID Number	39771	39881	39911	40011	40111	40131	40141	40151	40191	41121	41121	41131	41151	41161	41171	42011	42111	42211	42311	42611	42711	42811	43111	43311	43511	Total Tissues/ Tumors
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic												X										X				4
Lymphoma malignant mixed		X		X			X											X	X						X	9
Lymphoma malignant undifferentiated cell type																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 15 mg/kg

Number of Days on Study	0 0 5 5 5 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	0 6 1 5 6 4 5 7 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3
	6 6 7 4 1 3 0 9 2 4 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6
Carcass ID Number	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4
	4 4 9 6 9 3 4 7 8 8 3 3 3 4 4 4 4 4 5 5 5 5 5 5 5
	8 6 4 3 1 6 1 1 2 1 7 8 9 0 2 3 4 7 9 0 1 4 6 7 8 9
	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
Alimentary System	
Esophagus	+ +
Squamous cell papilloma	X
Gallbladder	+ A +
Intestine large, colon	+ +
Intestine large, rectum	+ M + + + M + + + + + + + + + + + + + + + + + + +
Intestine large, cecum	+ + + + A M + + + + + + + + + + + + + + + + + + +
Intestine small, duodenum	+ + + + + M + + + + + + + + + + + + + + + + + + +
Intestine small, jejunum	+ + + + A M + + + + + + M + + + + + + + + + + + +
Intestine small, ileum	+ + + + A M + + + + + + + + + + + + + + + + + + +
Liver	+ +
Hepatocellular carcinoma	X X
Hepatocellular adenoma	X X X X
Histiocytic sarcoma	X X
Mesentery	+
Sarcoma	
Pancreas	+ + + + + M + + + + + + + + + + + + + + + + + + +
Salivary glands	+ +
Stomach, forestomach	+ +
Squamous cell papilloma	
Stomach, glandular	+ + + + + A + + + + + + + + + + + + + + + + + + +
Cardiovascular System	
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Adrenal medulla	+ + + + + M + + + + + + + + + + + + + + + + + + +
Islets, pancreatic	+ + + + + M + + + + + + + + + + + + + + + + + + +
Parathyroid gland	M + M + M + + + + M + M + + M M + + M + M + + + + M
Pituitary gland	+ +
Pars distalis, adenoma	X X
Thyroid gland	+ +
Carcinoma	X
Bilateral, follicular cell, adenoma	X
General Body System	
None	
Genital System	
Clitoral gland	+
Ovary	+ + M +
Adenoma, tubular	
Cystadenoma	X
Histiocytic sarcoma	X
Uterus	+ +
Histiocytic sarcoma	X
Leiomyosarcoma	

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 15 mg/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	
Carcass ID Number	4 6 0 1	4 6 1 1	4 6 2 1	4 6 4 1	4 6 5 1	4 6 6 1	4 6 7 1	4 6 8 1	4 6 9 1	4 7 2 1	4 7 3 1	4 7 5 1	4 7 8 1	4 8 0 1	4 8 3 1	4 8 4 1	4 8 6 1	4 8 7 1	4 8 8 1	4 9 0 1	4 9 2 1	4 9 3 1	4 9 5 1	4 7 4 1	4 8 9 1	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hepatocellular carcinoma																										2
Hepatocellular adenoma			X		X													X				X			8
Histiocytic sarcoma																										2
Mesentery																		+								2
Sarcoma																		X								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Squamous cell papilloma			X												X											2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	M	+	M	+	+	M	M	+	+	M	+	+	+	+	+	+	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	49
Pars distalis, adenoma								X																		3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Carcinoma																										1
Bilateral, follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland				+														+								3
Ovary	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, tubular																									X	1
Cystadenoma																										1
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										1
Leiomyosarcoma										X																1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 15 mg/kg (continued)

Number of Days on Study	0 0 5 5 5 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7
	0 6 1 5 6 4 5 7 2 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3
	6 6 7 4 1 3 0 9 2 4 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6
Carcass ID Number	4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4
	4 4 9 6 9 3 4 7 8 8 3 3 3 4 4 4 4 4 4 5 5 5 5 5 5 5 5
	8 6 4 3 1 6 1 1 2 1 7 8 9 0 2 3 4 7 9 0 1 1 4 6 7 8 9
	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 1 1
Hematopoietic System	
Blood	+
Bone marrow	+ +
Lymph node	+ +
Lymph node, mandibular	+ + + + + + + + M + + + + M + + + + + + + + + + + + + +
Lymph node, mesenteric	+ + + + + M + + M + + + M + + + + + + + + + + + + + +
Histiocytic sarcoma	X
Spleen	+ +
Hemangiosarcoma	
Histiocytic sarcoma	X X
Thymus	+ + + + M + + + M + + + + + + + + + + + + + + + + + + +
Integumentary System	
Mammary gland	+ + + + + + + + + + + M + + + + + + + + + M + + + + +
Skin	+ + + + + + + + + + + M + + + + + + + + + + + + + + +
Subcutaneous tissue, sarcoma	X
Musculoskeletal System	
Bone	+ +
Nervous System	
Brain	+ +
Spinal cord	+
Respiratory System	
Lung	+ +
Alveolar/bronchiolar adenoma	
Carcinoma, metastatic, thyroid gland	X
Histiocytic sarcoma	X X
Nose	+ + + + + M + + + + + + + + + + + M + + + + M + + + +
Trachea	+ +
Special Senses System	
Harderian gland	
Adenoma	
Urinary System	
Kidney	+ +
Urinary bladder	+ M + + + A +
Systemic Lesions	
Multiple organs	+ +
Histiocytic sarcoma	X X
Lymphoma malignant lymphocytic	X
Lymphoma malignant mixed	X X X X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride: 15 mg/kg (continued)

Number of Days on Study	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 7	7 3 8	7 3 8	
Carcass ID Number	4 6 0 1	4 6 1 1	4 6 2 1	4 6 4 1	4 6 5 1	4 6 6 1	4 6 7 1	4 6 8 1	4 6 9 1	4 7 2 1	4 7 3 1	4 7 5 1	4 7 8 1	4 8 0 1	4 8 3 1	4 8 4 1	4 8 6 1	4 8 7 1	4 8 8 1	4 9 0 1	4 9 2 1	4 9 3 1	4 9 5 1	4 7 4 1	4 8 9 1	Total Tissues/ Tumors
Hematopoietic System																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Lymph node																										2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Hemangiosarcoma														X												1
Histiocytic sarcoma																										2
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	M	45
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Alveolar/bronchiolar adenoma													X												X	2
Carcinoma, metastatic, thyroid gland																										1
Histiocytic sarcoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Special Senses System																										
Harderian gland																								+		1
Adenoma																								X		1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	51
Histiocytic sarcoma																										2
Lymphoma malignant lymphocytic					X		X																			3
Lymphoma malignant mixed			X											X						X						7

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	2/50 (4%)	4/50 (8%)	0/51 (0%)	1/51 (2%)
Adjusted rate[b]	5.1%	9.0%	0.0%	2.4%
Terminal rate[c]	2/39 (5%)	3/42 (7%)	0/39 (0%)	1/41 (2%)
First incidence (days)	736 (T)	554	)[e]	736 (T)
Life table test[d]	P=0.194N	P=0.370	P=0.238N	P=0.483N
Logistic regression test[d]	P=0.190N	P=0.285	P=0.238N	P=0.483N
Cochran-Armitage test[d]	P=0.193N			
Fisher exact test[d]		P=0.339	P=0.243N	P=0.492N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	3/50 (6%)	4/50 (8%)	1/51 (2%)	1/51 (2%)
Adjusted rate	7.4%	9.0%	2.3%	2.4%
Terminal rate	2/39 (5%)	3/42 (7%)	0/39 (0%)	1/41 (2%)
First incidence (days)	720	554	707	736 (T)
Life table test	P=0.136N	P=0.539	P=0.308N	P=0.289N
Logistic regression test	P=0.129N	P=0.450	P=0.303N	P=0.305N
Cochran-Armitage test	P=0.131N			
Fisher exact test		P=0.500	P=0.301N	P=0.301N
Liver: Hepatocellular Adenoma				
Overall rate	3/50 (6%)	4/50 (8%)	6/51 (12%)	8/51 (16%)
Adjusted rate	7.7%	9.3%	14.7%	19.5%
Terminal rate	3/39 (8%)	3/42 (7%)	5/39 (13%)	8/41 (20%)
First incidence (days)	736 (T)	725	629	736 (T)
Life table test	P=0.060	P=0.542	P=0.246	P=0.115
Logistic regression test	P=0.049	P=0.540	P=0.245	P=0.115
Cochran-Armitage test	P=0.060			
Fisher exact test		P=0.500	P=0.254	P=0.106
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	7/51 (14%)	10/51 (20%)
Adjusted rate	10.3%	9.3%	16.4%	23.8%
Terminal rate	4/39 (10%)	3/42 (7%)	5/39 (13%)	9/41 (22%)
First incidence (days)	736 (T)	725	569	734
Life table test	P=0.032	P=0.600N	P=0.268	P=0.090
Logistic regression test	P=0.025	P=0.604N	P=0.273	P=0.079
Cochran-Armitage test	P=0.031			
Fisher exact test		P=0.643N	P=0.274	P=0.080
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	6/50 (12%)	2/50 (4%)	0/50 (0%)	2/51 (4%)
Adjusted rate	14.4%	4.8%	0.0%	4.9%
Terminal rate	4/39 (10%)	2/42 (5%)	0/38 (0%)	2/41 (5%)
First incidence (days)	707	736 (T)	)	736 (T)
Life table test	P=0.077N	P=0.117N	P=0.021N	P=0.127N
Logistic regression test	P=0.080N	P=0.118N	P=0.019N	P=0.135N
Cochran-Armitage test	P=0.074N			
Fisher exact test		P=0.134N	P=0.013N	P=0.128N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	8/50 (16%)	2/50 (4%)	0/50 (0%)	2/51 (4%)
Adjusted rate	18.4%	4.8%	0.0%	4.9%
Terminal rate	4/39 (10%)	2/42 (5%)	0/38 (0%)	2/41 (5%)
First incidence (days)	693	736 (T)	)	736 (T)
Life table test	P=0.023N	P=0.042N	P=0.007N	P=0.048N
Logistic regression test	P=0.023N	P=0.042N	P=0.005N	P=0.049N
Cochran-Armitage test	P=0.021N			
Fisher exact test		P=0.046N	P=0.003N	P=0.043N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	5/46 (11%)	3/49 (6%)	4/50 (8%)	3/49 (6%)
Adjusted rate	13.4%	7.3%	9.3%	7.7%
Terminal rate	4/35 (11%)	3/41 (7%)	2/38 (5%)	3/39 (8%)
First incidence (days)	622	736 (T)	629	736 (T)
Life table test	P=0.316N	P=0.280N	P=0.461N	P=0.306N
Logistic regression test	P=0.320N	P=0.317N	P=0.440N	P=0.335N
Cochran-Armitage test	P=0.312N			
Fisher exact test		P=0.322N	P=0.447N	P=0.322N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	5/46 (11%)	3/49 (6%)	5/50 (10%)	3/49 (6%)
Adjusted rate	13.4%	7.3%	11.3%	7.7%
Terminal rate	4/35 (11%)	3/41 (7%)	2/38 (5%)	3/39 (8%)
First incidence (days)	622	736 (T)	629	736 (T)
Life table test	P=0.337N	P=0.280N	P=0.589N	P=0.306N
Logistic regression test	P=0.330N	P=0.317N	P=0.563N	P=0.335N
Cochran-Armitage test	P=0.332N			
Fisher exact test		P=0.322N	P=0.575N	P=0.322N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	4/50 (8%)	2/50 (4%)	1/48 (2%)	1/51 (2%)
Adjusted rate	9.6%	4.8%	2.7%	2.4%
Terminal rate	3/39 (8%)	2/42 (5%)	1/37 (3%)	1/41 (2%)
First incidence (days)	582	736 (T)	736 (T)	736 (T)
Life table test	P=0.111N	P=0.309N	P=0.194N	P=0.172N
Logistic regression test	P=0.112N	P=0.368N	P=0.188N	P=0.173N
Cochran-Armitage test	P=0.110N			
Fisher exact test		P=0.339N	P=0.194N	P=0.175N
Uterus: Stromal Polyp				
Overall rate	1/50 (2%)	3/50 (6%)	2/51 (4%)	0/51 (0%)
Adjusted rate	2.6%	6.9%	5.1%	0.0%
Terminal rate	1/39 (3%)	2/42 (5%)	2/39 (5%)	0/41 (0%)
First incidence (days)	736 (T)	725	736 (T)	)
Life table test	P=0.236N	P=0.335	P=0.500	P=0.490N
Logistic regression test	P=0.244N	P=0.329	P=0.500	P=0.490N
Cochran-Armitage test	P=0.236N			
Fisher exact test		P=0.309	P=0.508	P=0.495N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/51 (6%)	1/51 (2%)
Adjusted rate	0.0%	2.4%	6.8%	2.4%
Terminal rate	0/39 (0%)	1/42 (2%)	1/39 (3%)	1/41 (2%)
First incidence (days)	)	736 (T)	626	736 (T)
Life table test	P=0.354	P=0.515	P=0.128	P=0.510
Logistic regression test	P=0.362	P=0.515	P=0.130	P=0.510
Cochran-Armitage test	P=0.358			
Fisher exact test		P=0.500	P=0.125	P=0.505
All Organs: Malignant Lymphoma (Lymphocytic, Mixed, or Undifferentiated Cell Type)				
Overall rate	8/50 (16%)	16/50 (32%)	14/51 (27%)	10/51 (20%)
Adjusted rate	19.9%	35.3%	33.9%	23.7%
Terminal rate	7/39 (18%)	13/42 (31%)	12/39 (31%)	9/41 (22%)
First incidence (days)	718	693	626	679
Life table test	P=0.522N	P=0.081	P=0.118	P=0.438
Logistic regression test	P=0.517	P=0.067	P=0.113	P=0.395
Cochran-Armitage test	P=0.518N			
Fisher exact test		P=0.050	P=0.124	P=0.416
All Organs: Malignant Lymphoma or Histiocytic Sarcoma				
Overall rate	8/50 (16%)	18/50 (36%)	15/51 (29%)	12/51 (24%)
Adjusted rate	19.9%	38.1%	35.4%	27.0%
Terminal rate	7/39 (18%)	13/42 (31%)	12/39 (31%)	9/41 (22%)
First incidence (days)	718	677	626	643
Life table test	P=0.426	P=0.041	P=0.083	P=0.265
Logistic regression test	P=0.380	P=0.026	P=0.077	P=0.220
Cochran-Armitage test	P=0.432			
Fisher exact test		P=0.020	P=0.085	P=0.243
All Organs: Benign Neoplasms				
Overall rate	24/50 (48%)	20/50 (40%)	16/51 (31%)	18/51 (35%)
Adjusted rate	53.0%	44.2%	37.7%	41.7%
Terminal rate	18/39 (46%)	17/42 (40%)	13/39 (33%)	16/41 (39%)
First incidence (days)	442	554	629	66
Life table test	P=0.126N	P=0.200N	P=0.092N	P=0.132N
Logistic regression test	P=0.117N	P=0.320N	P=0.068N	P=0.139N
Cochran-Armitage test	P=0.112N			
Fisher exact test		P=0.273N	P=0.066N	P=0.137N
All Organs: Malignant Neoplasms				
Overall rate	16/50 (32%)	21/50 (42%)	19/51 (37%)	17/51 (33%)
Adjusted rate	34.7%	43.6%	40.9%	36.8%
Terminal rate	9/39 (23%)	15/42 (36%)	12/39 (31%)	12/41 (29%)
First incidence (days)	582	677	569	561
Life table test	P=0.493N	P=0.314	P=0.359	P=0.542
Logistic regression test	P=0.504N	P=0.210	P=0.364	P=0.500
Cochran-Armitage test	P=0.474N			
Fisher exact test		P=0.204	P=0.365	P=0.528

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	32/50 (64%)	33/50 (66%)	29/51 (57%)	28/51 (55%)
Adjusted rate	66.6%	66.0%	61.4%	59.4%
Terminal rate	23/39 (59%)	25/42 (60%)	21/39 (54%)	22/41 (54%)
First incidence (days)	442	554	569	66
Life table test	P=0.198N	P=0.478N	P=0.365N	P=0.241N
Logistic regression test	P=0.151N	P=0.459	P=0.304N	P=0.242N
Cochran-Armitage test	P=0.142N			
Fisher exact test		P=0.500	P=0.298N	P=0.233N

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

TABLE D4a
Historical Incidence of Liver Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Hepatocellular Adenoma	Hepatocellular Carcinoma	Hepatocellular Adenoma or Carcinoma
Overall Historical Incidence: Water Gavage			
Total	13/315 (4.1%)	8/315 (2.5%)	21/315 (6.7%)
Standard deviation	3.2%	2.1%	4.2%
Range	2%-10%	0%-6%	2%-12%
Overall Historical Incidence: Feed			
Total	159/1,363 (11.7%)	80/1,363 (5.9%)	223/1,363 (16.4%)
Standard deviation	8.3%	5.5%	10.7%
Range	0%-33%	0%-20%	3%-42%

[a] Data as of 20 August 1992

TABLE D4b
Historical Incidence of Lung Neoplasms in Untreated Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Alveolar/bronchiolar Adenoma	Alveolar/bronchiolar Carcinoma	Alveolar/bronchiolar Adenoma or Carcinoma
Overall Historical Incidence: Water Gavage			
Total	14/315 (4.4%)	5/315 (1.6%)	19/315 (6.0%)
Standard deviation	4.1%	1.5%	5.4%
Range	0%-10%	0%-4%	0%-12%
Overall Historical Incidence: Feed			
Total	78/1,371 (5.7%)	30/1,371 (2.2%)	106/1,371 (7.7%)
Standard deviation	4.9%	2.3%	5.0%
Range	0%-24%	0%-8%	2%-26%

[a] Data as of 20 August 1992

TABLE D4c
Historical Incidence of Malignant Lymphomas and Histiocytic Sarcomas in Untreated Female B6C3F $_1$ Mice[a]

Study	Incidence in Controls		
	Malignant Lymphoma[b]	Histiocytic Sarcoma	Malignant Lymphoma or Histiocytic Sarcoma
Overall Historical Incidence: Water Gavage			
Total	121/315 (38.4%)	3/315 (1.0%)	124/315 (39.4%)
Standard deviation	11.8%	2.0%	12.8%
Range	18%-50%	0%-5%	18%-53%
Overall Historical Incidence: Feed			
Total	353/1,371 (25.7%)	10/1,371 (0.7%)	363/1,371 (26.5%)
Standard deviation	10.8%	1.4%	10.2%
Range	8%-44%	0%-4%	10%-44%

[a] Data as of 20 August 1992
[b] Malignant lymphomas include histiocytic, lymphocytic, mixed, NOS, or undifferentiated cell types.

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride[a]

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
Disposition Summary				
Animals initially in study	60	60	60	60
15-Month interim evaluation	10	10	9	9
Early deaths				
Accidental deaths			2	1
Moribund	10	7	9	6
Natural deaths	1	1	1	3
Survivors				
Died last week of study	2			
Terminal sacrifice	37	42	39	41
Animals examined microscopically	60	60	60	60
15-Month Interim Evaluation				
Alimentary System				
Intestine large, colon	(10)	(10)	(9)	(9)
Artery, inflammation, acute				1 (11%)
Intestine large, cecum	(10)	(10)	(9)	(9)
Hyperplasia		1 (10%)		1 (11%)
Epithelium, hyperplasia			2 (22%)	2 (22%)
Liver	(10)	(10)	(9)	(9)
Basophilic focus				1 (11%)
Inflammation, focal, necrotizing			1 (11%)	
Mixed cell focus			1 (11%)	
Necrosis, focal				1 (11%)
Sinusoid, centrilobular, ectasia				1 (11%)
Stomach, forestomach	(10)	(10)	(9)	(9)
Acanthosis		2 (20%)	3 (33%)	1 (11%)
Hyperkeratosis		1 (10%)	3 (33%)	2 (22%)
Hyperplasia, basal cell				1 (11%)
Stomach, glandular	(10)	(10)	(9)	(9)
Hyperplasia		1 (10%)	1 (11%)	1 (11%)
Artery, inflammation, acute				1 (11%)
Cardiovascular System				
Heart	(10)	(10)	(9)	(9)
Artery, inflammation, acute				1 (11%)
Endocrine System				
Pituitary gland	(10)	(10)	(9)	(9)
Pars distalis, hyperplasia			1 (11%)	
General Body System				
None				

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
15-Month Interim Evaluation (continued)				
Genital System				
Ovary	(10)	(10)	(9)	(9)
Cyst		1 (10%)	2 (22%)	2 (22%)
Uterus	(10)	(10)	(9)	(9)
Endometrium, hyperplasia	2 (20%)	3 (30%)	9 (100%)	7 (78%)
Hematopoietic System				
Lymph node, mesenteric	(10)	(10)	(9)	(8)
Artery, inflammation, acute				1 (13%)
Integumentary System				
None				
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(10)	(10)	(9)	(9)
Alveolar epithelium, hyperplasia	1 (10%)			
Special Senses System				
None				
Urinary System				
None				
2-Year Study				
Alimentary System				
Intestine large, cecum	(49)	(49)	(50)	(49)
Epithelium, hyperplasia			1 (2%)	
Intestine small, jejunum	(46)	(49)	(49)	(48)
Diverticulum		1 (2%)		
Erosion	1 (2%)			
Inflammation, chronic active	1 (2%)			
Intestine small, ileum	(49)	(49)	(51)	(49)
Lymphoid tissue, hyperplasia			1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
2-Year Study (continued)				
Alimentary System (continued)				
Liver	(50)	(50)	(51)	(51)
Basophilic focus	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Clear cell focus		1 (2%)	1 (2%)	
Eosinophilic focus	6 (12%)	3 (6%)	5 (10%)	3 (6%)
Fatty change, focal	1 (2%)			
Hematopoietic cell proliferation				1 (2%)
Hematopoietic cell proliferation granulocytic		1 (2%)		
Infiltration cellular, lymphocyte		2 (4%)	1 (2%)	
Inflammation, granulomatous	1 (2%)			
Mixed cell focus	4 (8%)		3 (6%)	3 (6%)
Necrosis	2 (4%)	3 (6%)	5 (10%)	1 (2%)
Vacuolization cytoplasmic, focal	1 (2%)			1 (2%)
Centrilobular, hypertrophy			1 (2%)	
Mesentery	(4)	(1)	(3)	(2)
Inflammation, chronic active			1 (33%)	
Inflammation, granulomatous	1 (25%)			
Fat, necrosis	2 (50%)		1 (33%)	1 (50%)
Pancreas	(50)	(49)	(51)	(50)
Acinus, atrophy		1 (2%)		
Artery, inflammation, chronic active	1 (2%)			
Duct, cyst		1 (2%)	1 (2%)	
Duct, ectasia		1 (2%)		
Salivary glands	(49)	(50)	(51)	(50)
Artery, inflammation, chronic active	1 (2%)			
Stomach, forestomach	(50)	(50)	(51)	(51)
Hyperkeratosis		1 (2%)		1 (2%)
Hyperplasia, basal cell	1 (2%)	2 (4%)	1 (2%)	
Hyperplasia, squamous			1 (2%)	1 (2%)
Inflammation, chronic active		1 (2%)	1 (2%)	
Stomach, glandular	(49)	(49)	(51)	(50)
Hyperplasia			1 (2%)	
Inflammation, chronic active	2 (4%)			
Necrosis				1 (2%)
Ulcer	2 (4%)			
Tongue		(1)		
Congestion		1 (100%)		
Hemorrhage		1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(51)
Mineralization	1 (2%)	1 (2%)		3 (6%)
Artery, mineralization	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(51)	(51)
Accessory adrenal cortical nodule	1 (2%)	1 (2%)		
Hyperplasia	1 (2%)			
Hypertrophy		1 (2%)	2 (4%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
2-Year Study (continued)				
Endocrine System (continued)				
Adrenal cortex (continued)	(50)	(50)	(51)	(51)
Capsule, hyperplasia	1 (2%)			
Islets, pancreatic	(49)	(49)	(51)	(50)
Hyperplasia	2 (4%)	1 (2%)		1 (2%)
Parathyroid gland	(40)	(40)	(42)	(36)
Infiltration cellular, lymphocyte			1 (2%)	
Pituitary gland	(46)	(49)	(50)	(49)
Pars distalis, angiectasis	3 (7%)	1 (2%)	1 (2%)	6 (12%)
Pars distalis, cyst				1 (2%)
Pars distalis, hyperplasia	9 (20%)	14 (29%)	8 (16%)	11 (22%)
Thyroid gland	(50)	(50)	(48)	(51)
Follicle, cyst	3 (6%)	1 (2%)		1 (2%)
Follicular cell, hyperplasia	3 (6%)	5 (10%)	1 (2%)	4 (8%)
General Body System				
None				
Genital System				
Clitoral gland	(2)			(3)
Dilatation	2 (100%)			3 (100%)
Ovary	(49)	(49)	(49)	(49)
Amyloid deposition				1 (2%)
Angiectasis	2 (4%)		1 (2%)	1 (2%)
Atrophy			1 (2%)	
Cyst	10 (20%)	12 (24%)	4 (8%)	10 (20%)
Hemorrhage	1 (2%)			
Hyperplasia	1 (2%)			
Mineralization	1 (2%)			
Pigmentation	1 (2%)			
Thrombosis	2 (4%)			
Uterus	(50)	(50)	(51)	(51)
Angiectasis			1 (2%)	1 (2%)
Hemorrhage	1 (2%)			
Hyperplasia				1 (2%)
Inflammation, acute			1 (2%)	
Mineralization				1 (2%)
Pigmentation				1 (2%)
Thrombosis				1 (2%)
Endometrium, hyperplasia, cystic			2 (4%)	
Hematopoietic System				
Bone marrow	(50)	(49)	(51)	(51)
Angiectasis				1 (2%)
Myelofibrosis			1 (2%)	
Lymph node	(4)	(7)	(3)	(2)
Mediastinal, hematopoietic cell proliferation		1 (14%)		

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
2-Year Study (continued)				
Hematopoietic System (continued)				
Lymph node, mandibular	(48)	(48)	(49)	(48)
Hematopoietic cell proliferation		1 (2%)		
Inflammation, granulomatous	1 (2%)			
Lymph node, mesenteric	(46)	(49)	(49)	(46)
Hemorrhage	1 (2%)			
Inflammation, granulomatous	1 (2%)			
Spleen	(49)	(49)	(50)	(51)
Amyloid deposition	1 (2%)			
Angiectasis			1 (2%)	
Hematopoietic cell proliferation	5 (10%)	7 (14%)	5 (10%)	6 (12%)
Infarct			1 (2%)	
Thymus	(42)	(48)	(46)	(48)
Hyperplasia				1 (2%)
Integumentary System				
Skin	(50)	(50)	(51)	(50)
Erosion			1 (2%)	
Necrosis			1 (2%)	1 (2%)
Subcutaneous tissue, inflammation, chronic active			1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(51)	(51)
Fracture				1 (2%)
Skeletal muscle		(1)	(2)	
Inflammation, chronic active			1 (50%)	
Nervous System				
Brain	(50)	(49)	(51)	(51)
Mineralization			1 (2%)	
Spinal cord	(1)			(1)
Hemorrhage				1 (100%)
Respiratory System				
Lung	(50)	(50)	(50)	(51)
Hemorrhage	1 (2%)	4 (8%)	4 (8%)	1 (2%)
Infiltration cellular, histiocyte	1 (2%)			
Alveolar epithelium, hyperplasia		3 (6%)	1 (2%)	1 (2%)
Mediastinum, inflammation, granulomatous	1 (2%)			
Nose	(47)	(49)	(49)	(48)
Glands, cytoplasmic alteration			2 (4%)	
Mucosa, cytoplasmic alteration			2 (4%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
2-Year Study (continued)				
Special Senses System				
Eye		(1)		
Cornea, inflammation, acute		1 (100%)		
Urinary System				
Kidney	(50)	(50)	(51)	(51)
Glomerulosclerosis				1 (2%)
Inflammation, granulomatous	1 (2%)			
Metaplasia, osseous		1 (2%)		
Nephropathy	2 (4%)		4 (8%)	2 (4%)
Artery, inflammation, chronic active	1 (2%)			
Papilla, mineralization			1 (2%)	

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

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Mortelmans *et al.* (1986). Promethazine hydrochloride was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. 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 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and at least five doses of promethazine hydrochloride. The high dose was limited by toxicity. All negative 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 of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There was no minimum percentage or fold increase required for a chemical to the judged positive or weakly positive.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Promethazine hydrochloride 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 promethazine hydrochloride; the high dose was limited by toxicity. A single flask per dose was used.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 26 hours with promethazine hydrochloride in McCoy's 5A medium supplemented with fetal bovine serum, *l*-glutamine, and antibiotics. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing promethazine hydrochloride 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 promethazine hydrochloride, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no promethazine hydrochloride and incubation proceeded for an additional 26 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. 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.

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 ($P<0.05$) 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 promethazine hydrochloride for 12 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with promethazine hydrochloride and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 12 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

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

Chromosomal aberration data are presented as percentage of cells with aberrations. Statistical analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) are considered weak evidence for a positive response; significant differences for two or more doses indicate the trial is positive. A positive trend test in the absence of a statistically significant increase at any one dose results in an equivocal call (Galloway*et al*., 1987).

DROSOPHILA MELANOGASTER TEST PROTOCOL

The assays for induction of sex-linked recessive lethal (SLRL) mutations were performed with adult flies as described by Yoon *et al*. (1985). Promethazine hydrochloride was supplied as a coded aliquot by Radian Corporation. It 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 response was obtained, promethazine hydrochloride was retested by injection into adult males.

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

Toxicity tests were performed to set concentrations of promethazine hydrochloride 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. For the SLRL test, oral exposure was achieved by allowing Canton-S males to feed for 72 hours on a solution of promethazine hydrochloride in 5% sucrose. In the injection experiments, 24- to 72-hour old Canton-S males were treated with a solution of promethazine hydrochloride dissolved in saline or peanut oil and allowed to recover for 24 hours. A concurrent saline/peanut oil control group was also included. In the adult exposures, treated males were mated to three *Basc* females for 3 days and 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 post-meiotic 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 results 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, using a normal approximation to the binomial test (Margolin *et al.*, 1983). A test result is considered positive if the P value is less than 0.01 and the mutation frequency in the tested group is greater than 0.10%, or if the P value is less than 0.05 and the frequency in the treatment group is greater than 0.15%. A test is considered to be inconclusive if (a) the P value is between 0.05 and 0.01 but the frequency in the treatment group is between 0.10% and 0.15% or (b) the P value is between 0.10 and 0.05 but the frequency in the treatment group is greater than 0.10%. A test is considered negative if the P value is greater than 0.10 or if the frequency in the treatment group is less than 0.10%.

RESULTS

Promethazine hydrochloride (1 to 666 µg/plate), tested at two laboratories with a preincubation protocol in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9, did not induce gene mutations in *S. typhimurium* strains TA97, TA98, TA100, TA1535, or TA1537 (Table E1; Mortelmans *et al.*, 1986). In cytogenetic tests with cultured Chinese hamster ovary (CHO) cells, promethazine hydrochloride did not induce sister chromatid exchanges (SCEs) or chromosomal aberrations (Abs) in the absence of S9 activation (Tables E2 and E3; Galloway *et al.*, 1987). When tested in the presence of Aroclor 1254-induced male Sprague-Dawley rat liver S9, promethazine hydrochloride did not induce a significant increase in the percent cells with Abs, but a small dose-related increase in SCEs occurred. This increase was of insufficient magnitude to be considered positive, and the SCE test with S9 was concluded to be equivocal. Promethazine hydrochloride did not induce sex-linked recessive lethal mutations in germ cells of male *D. melanogaster* administered the chemical by feeding (1,000 ppm) or by injection (2,500 ppm) (Table E4; Yoon *et al.*, 1985).

TABLE E1
Mutagenicity of Promethazine Hydrochloride in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2	+10% rat S9 Trial 3
Study performed at EG&G Mason Research Institute								
TA100	0	164 ± 9.4	192 ± 12.3	171 ± 3.9	199 ± 5.5	141 ± 6.1	210 ± 2.9	133 ± 10.7
	1	143 ± 10.8	200 ± 16.3					
	3.3	167 ± 8.0	186 ± 11.0	145 ± 9.5	214 ± 18.8	141 ± 20.4	207 ± 4.0	144 ± 1.9
	10	150 ± 6.4	190 ± 0.6	155 ± 3.2	215 ± 19.5	168 ± 3.0	224 ± 20.3	163 ± 11.7
	33	154 ± 8.1	188 ± 3.5	163 ± 11.3	196 ± 5.2	170 ± 9.8	231 ± 4.7	137 ± 9.2
	100	103 ± 8.6[c]	115 ± 5.2[c]	168 ± 6.7	196 ± 11.3	166 ± 2.3	222 ± 6.4	143 ± 9.8
	333			110 ± 3.8[c]	150 ± 6.2[c]	125 ± 3.2[c]	197 ± 4.4[c]	133 ± 5.0[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		1,175 ± 9.9	1,143 ± 42.2	1,188 ± 33.7	2,234 ± 63.0	934 ± 3.7	294 ± 0.7	854 ± 34.4
TA1535	0	33 ± 2.1	39 ± 2.6	13 ± 2.4	21 ± 2.7	12 ± 0.3	22 ± 2.7	18 ± 1.0
	1	39 ± 3.5	33 ± 7.4					
	3.3	36 ± 3.7	30 ± 3.1	11 ± 2.6	18 ± 1.5	16 ± 1.2	19 ± 3.8	22 ± 3.2
	10	25 ± 3.5	30 ± 3.2	13 ± 2.3	14 ± 0.0	14 ± 0.9	15 ± 2.0	17 ± 0.9
	33	37 ± 0.6	28 ± 0.9	16 ± 0.7	19 ± 2.7	13 ± 2.5	18 ± 2.3	15 ± 0.9
	100	21 ± 5.4[c]	13 ± 0.9[c]	12 ± 2.1	14 ± 3.3	14 ± 2.6	17 ± 3.5	13 ± 2.0
	333			8 ± 2.2[c]	11 ± 2.0[c]	6 ± 1.5[c]	10 ± 1.3[c]	10 ± 1.8[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,062 ± 15.0	944 ± 25.5	112 ± 2.9	171 ± 10.8	108 ± 5.1	32 ± 0.6	89 ± 2.7
TA1537	0	6 ± 1.2	6 ± 1.9	5 ± 0.6	6 ± 1.8	8 ± 0.3	8 ± 1.2	7 ± 0.9
	1	7 ± 0.9	4 ± 0.6					
	3.3	6 ± 1.7	5 ± 1.2	5 ± 1.9	7 ± 2.4	7 ± 1.2	8 ± 2.1	4 ± 0.3
	10	8 ± 0.3	7 ± 1.2	6 ± 0.3	4 ± 0.3	6 ± 1.3	9 ± 0.9	7 ± 1.8
	33	9 ± 1.5	7 ± 1.5	7 ± 1.3	7 ± 0.7	4 ± 0.7	5 ± 0.6	6 ± 1.2
	100	6 ± 2.3[c]	)[e]	10 ± 1.2	6 ± 0.0	6 ± 0.9	6 ± 1.2	6 ± 2.3
	333			4 ± 0.6[c]	3 ± 0.6[c]	4 ± 1.2[c]	6 ± 1.0[c]	5 ± 1.7[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		364 ± 22.3	518 ± 71.8	88 ± 1.2	273 ± 10.2	60 ± 7.1	16 ± 0.6	64 ± 4.1
TA98	0	23 ± 3.8	16 ± 2.4	31 ± 2.2	22 ± 3.7	30 ± 3.2	22 ± 4.3	25 ± 2.3
	1	18 ± 0.0	16 ± 2.0					
	3.3	21 ± 1.9	16 ± 2.1	25 ± 2.9	29 ± 3.2	30 ± 6.4	29 ± 4.7	28 ± 2.6
	10	19 ± 1.2	20 ± 2.7	26 ± 3.2	26 ± 1.2	32 ± 4.4	24 ± 3.8	29 ± 2.1
	33	25 ± 2.2	15 ± 2.5	28 ± 1.9	28 ± 0.3	31 ± 0.3	33 ± 3.8	29 ± 0.9
	100	13 ± 3.4[c]	14 ± 0.3[c]	31 ± 2.7	19 ± 2.2	37 ± 3.2	21 ± 1.8	27 ± 1.2
	333			26 ± 3.6[c]	19 ± 3.2[c]	21 ± 2.2[c]	19 ± 2.0[c]	21 ± 1.5[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative	Negative
Positive control		1,430 ± 30.1	1,409 ± 46.7	983 ± 7.1	1,218 ± 21.8	621 ± 16.1	71 ± 1.2	327 ± 13.5

TABLE E1
Mutagenicity of Promethazine Hydrochloride in *Salmonella typhimurium* (continued)

Strain	Dose (µg/plate)	Revertants/plate -S9 Trial 1	-S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
Study performed at SRI, International							
TA100	0	126 ± 5.6	104 ± 9.9	145 ± 12.9	102 ± 10.2	131 ± 10.1	102 ± 10.2
	10	122 ± 9.8	94 ± 11.2	150 ± 6.2	118 ± 12.3	153 ± 7.6	128 ± 7.5
	33	122 ± 7.8	83 ± 12.2	145 ± 3.2	132 ± 5.7	153 ± 15.5	126 ± 5.8
	100	123 ± 6.6	89 ± 2.3	140 ± 14.6	139 ± 0.0	121 ± 15.7	116 ± 22.4
	333	89 ± 11.3	67 ± 6.0	132 ± 14.3	104 ± 4.6	118 ± 13.9	102 ± 6.4
	666	5 ± 1.0[c]	5 ± 5.0[c]	60 ± 9.3[c]	90 ± 17.2	79 ± 10.0[c]	83 ± 8.3
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		368 ± 42.0	481 ± 5.8	1,182 ± 18.8	927 ± 16.3	802 ± 7.8	433 ± 30.0
TA1535	0	27 ± 2.5	38 ± 1.7	13 ± 0.7	11 ± 0.3	12 ± 2.8	11 ± 0.6
	10	31 ± 2.6	20 ± 1.2	12 ± 1.8	7 ± 2.2	10 ± 0.7	8 ± 0.9
	33	32 ± 4.3	17 ± 0.9	10 ± 2.0	12 ± 2.5	8 ± 1.8	10 ± 1.5
	100	36 ± 7.8	18 ± 1.7	12 ± 1.5	8 ± 0.9	12 ± 1.2	10 ± 1.0
	333	37 ± 2.5	17 ± 1.2	8 ± 0.9[c]	8 ± 3.2	7 ± 1.7	6 ± 0.3
	666	4 ± 2.0[c]	3 ± 0.6[c]	3 ± 1.2[c]	4 ± 0.9[c]	2 ± 0.7[c]	4 ± 1.7[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		387 ± 9.0	509 ± 24.1	292 ± 27.0	538 ± 21.8	236 ± 17.7	167 ± 10.1
TA97	0	159 ± 0.6	113 ± 5.3	219 ± 5.4	147 ± 7.8	226 ± 10.9	151 ± 13.0
	10	182 ± 8.3	138 ± 14.5	220 ± 5.1	171 ± 16.8	254 ± 2.3	154 ± 15.0
	33	165 ± 3.7	136 ± 21.7	222 ± 5.8	197 ± 2.9	243 ± 14.4	144 ± 22.6
	100	189 ± 12.1	122 ± 8.2	219 ± 18.9	186 ± 10.3	233 ± 2.8	163 ± 4.0
	333	84 ± 14.7	31 ± 15.8	194 ± 14.3	165 ± 1.2	216 ± 4.0	150 ± 11.7
	666	1 ± 1.3[c]	2 ± 1.5[c]	29 ± 13.0[c]	88 ± 13.0	84 ± 50.5	98 ± 22.5
Trial summary		Negative	Negative	Negative	Equivocal	Negative	Negative
Positive control		843 ± 14.5	1,135 ± 91.1	1,241 ± 77.4	1,311 ± 28.9	1,270 ± 7.6	687 ± 3.7
TA98	0	27 ± 2.9	19 ± 4.0	43 ± 2.9	23 ± 1.8	32 ± 3.7	41 ± 0.9
	10	19 ± 2.0	18 ± 2.8	45 ± 2.0	25 ± 2.0	40 ± 4.2	42 ± 0.9
	33	26 ± 1.8	15 ± 1.0	37 ± 3.7	25 ± 5.5	38 ± 2.8	45 ± 0.3
	100	21 ± 1.9	18 ± 2.2	36 ± 2.7	21 ± 1.5	37 ± 4.8	30 ± 8.0
	333	31 ± 3.5	17 ± 1.8	40 ± 3.3	25 ± 4.9	44 ± 0.3	25 ± 2.5
	666	9 ± 9.0[c]	4 ± 2.0[c]	23 ± 3.0[c]	19 ± 2.3	25 ± 4.6[c]	26 ± 3.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		743 ± 6.4	801 ± 26.3	1,743 ± 181.9	331 ± 24.3	409 ± 11.9	179 ± 14.2

[a] The detailed protocol is presented in Mortelmans *et al.* (1986).
[b] Revertants are presented as mean ± standard error from three plates.
[c] Slight toxicity
[d] 2-Aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-o-phenylenediamine was tested on TA98, sodium azide was tested on TA100 and TA1535, and 9-aminoacridine was tested on TA1537 and TA97.
[e] Toxic

TABLE E2
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Promethazine Hydrochloride[a]

Compound	Dose µg/mL	Total Cells	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative SCEs/ Chromosome (%)[b]
-S9								
Trial 1								
Summary: Negative								
Distilled water		50	1,051	489	0.46	9.8	26.0	
Mitomycin-C	0.005	50	1,050	1,174	1.11	23.5	26.0	140.31
Promethazine hydrochloride	0.500	50	1,047	444	0.42	8.9	26.0	-8.86
	1.600	50	1,050	412	0.39	8.2	26.0	-15.67
	5.000	50	1,043	400	0.38	8.0	26.0	-17.58
								P=0.999[c]
+S9								
Trial 1								
Summary: Equivocal								
Distilled water		100	2,093	1,023	0.48	10.2	26.0	
Cyclophosphamide	1	100	2,086	1,492	0.71	14.9	26.0	46.33
Promethazine hydrochloride	5	50	1,045	561	0.53	11.2	26.0	9.83
	16	50	1,049	570	0.54	11.4	26.0	11.17
	50	50	1,046	606	0.57	12.1	26.0	18.53
								P<0.001

[a] Study performed at Columbia University. The detailed protocol and these data are presented in Galloway *et al.* (1987). SCE = sister chromatid exchange; BrdU = bromodeoxyuridine.
[b] SCEs/chromosome of culture exposed to promethazine hydrochloride relative to those of culture exposed to solvent
[c] Significance of relative SCEs/chromosome tested by the linear regression trend test vs. log of the dose

TABLE E3
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Promethazine Hydrochloride[a]

-S9					+S9				
Dose (µg/mL)	**Total Cells**	**No. of Abs**	**Abs/ Cell**	**Percent Cells with Abs**	**Dose (µg/mL)**	**Total Cells**	**No. of Abs**	**Abs/ Cell**	**Percent Cells with Abs**
Trial 1 - Harvest time: 14.0 hours Summary: Negative					**Trial 1** - Harvest time: 14.0 hours Summary: Negative				
Distilled water					Distilled water				
	100	7	0.07	7.0		100	8	0.08	8.0
Mitomycin-C					Cyclophosphamide				
0.15	50	23	0.46	30.0	15	100	28	0.28	23.0
Promethazine hydrochloride					Promethazine hydrochloride				
1.6	100	10	0.10	10.0	5	100	5	0.05	5.0
5.0	100	4	0.04	4.0	16	100	13	0.13	11.0
16.0	100	12	0.12	11.0	50	100	9	0.09	7.0
				P=0.308[b]					P=0.399
Trial 2 - Harvest time: 14.0 hours Summary: Negative					**Trial 2** - Harvest time: 14.0 hours Summary: Negative				
Distilled water					Distilled water				
	100	4	0.04	4.0		100	3	0.03	3.0
Mitomycin-C					Cyclophosphamide				
0.15	50	26	0.52	40.0	15	100	21	0.21	18.0
Promethazine hydrochloride					Promethazine hydrochloride				
5.0	100	10	0.10	8.0	10	100	5	0.05	5.0
10.0	100	8	0.08	7.0	20	100	11	0.11	10.0
15.0	100	7	0.07	6.0	30	100	8	0.08	8.0
20.0	100	10	0.10	8.0	40	100	7	0.07	7.0
					50	100	7	0.07	7.0
				P=0.234					P=0.079

[a] Study performed at Columbia University. Abs = aberrations. A detailed presentation of the technique and these data are presented in Galloway *et al.* (1987).
[b] Significance of percent cells with aberrations tested by the linear regression trend test vs. log of the dose

TABLE E4
Induction of Sex-Linked Recessive Lethal Mutations in *Drosophila melanogaster* by Promethazine Hydrochloride[a]

Route of Exposure	Dose (ppm)	Incidence of Deaths (%)	Incidence of Sterility (%)	No. of Lethal/No. of X Chromosomes Tested			
				Mating 1	Mating 2	Mating 3	Total[b]
Feeding	1,000	13	6	3/2,180	1/2,298	2/2,277	6/6,755 (0.09%)
	0			2/2,170	7/3,081	2/1,498	11/6,749 (0.16%)
Injection	2,500	9	13	1/1,917	1/2,563	0/2,044	2/6,524 (0.03%)
	0			1/2,143	0/2,530	0/1,790	1/6,463 (0.02%)

[a] Study performed at Brown University. A detailed protocol of the sex-linked recessive lethal assay and these data are presented in Yoon *et al.* (1985).
[b] Combined total number of lethal mutations/number of X chromosomes tested for three mating trials

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

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Study of Promethazine Hydrochloride[a]

	Vehicle Control	18.5 mg/kg	55.5 mg/kg	166.5 mg/kg	500 mg/kg
Male					
n	5	5	5	4	1[b]
Necropsy body wt	203 ± 5	202 ± 3	182 ± 5	154 ± 16**	136
Brain					
Absolute	1.823 ± 0.050	1.828 ± 0.026	1.775 ± 0.038	1.802 ± 0.030	1.696
Relative	8.96 ± 0.16	9.08 ± 0.23	9.76 ± 0.12	12.09 ± 1.17**	12.47
Heart					
Absolute	0.943 ± 0.064	0.920 ± 0.029	0.811 ± 0.022	0.751 ± 0.074*	0.585
Relative	4.62 ± 0.22	4.57 ± 0.18	4.47 ± 0.17	4.90 ± 0.03	4.30
R. Kidney					
Absolute	0.926 ± 0.027	0.922 ± 0.037	0.871 ± 0.025	0.840 ± 0.087	0.828
Relative	4.55 ± 0.10	4.57 ± 0.16	4.78 ± 0.05	5.48 ± 0.11**	6.09
Liver					
Absolute	9.201 ± 0.269	9.855 ± 0.160	9.792 ± 0.327	10.523 ± 1.228	11.389
Relative	45.27 ± 1.20	48.89 ± 0.58*	53.84 ± 1.56**	68.20 ± 1.40**	83.74
Lungs					
Absolute	1.652 ± 0.066	1.631 ± 0.073	1.609 ± 0.047	1.454 ± 0.080	1.120
Relative	8.12 ± 0.22	8.09 ± 0.34	8.84 ± 0.05	9.70 ± 0.88*	8.24
R. Testis					
Absolute	1.212 ± 0.048	1.210 ± 0.037	1.150 ± 0.020	1.077 ± 0.092	1.020
Relative	5.96 ± 0.18	6.00 ± 0.10	6.33 ± 0.14	7.06 ± 0.28**	7.50
Thymus					
Absolute	0.417 ± 0.016	0.411 ± 0.028	0.331 ± 0.018*	0.242 ± 0.045**	0.109
Relative	2.06 ± 0.12	2.05 ± 0.16	1.82 ± 0.11	1.53 ± 0.15*	0.80

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 16-Day Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	18.5 mg/kg	55.5 mg/kg	166.5 mg/kg	500 mg/kg
Female					
n	5	5	5	4	1[b]
Necropsy body wt	142 ± 3	141 ± 3	132 ± 3	125 ± 6**	107
Brain					
Absolute	1.735 ± 0.009	1.754 ± 0.008	1.702 ± 0.023	1.670 ± 0.045	1.671
Relative	12.25 ± 0.30	12.50 ± 0.33	12.91 ± 0.26	13.39 ± 0.45*	15.62
Heart					
Absolute	0.661 ± 0.027	0.661 ± 0.026	0.645 ± 0.022	0.589 ± 0.029	0.638
Relative	4.67 ± 0.28	4.72 ± 0.24	4.90 ± 0.25	4.70 ± 0.07	5.96
R. Kidney					
Absolute	0.654 ± 0.026	0.659 ± 0.022	0.652 ± 0.013	0.658 ± 0.040	0.605
Relative	4.60 ± 0.09	4.69 ± 0.10	4.94 ± 0.05*	5.25 ± 0.15**	5.65
Liver					
Absolute	5.632 ± 0.218	5.520 ± 0.316	6.153 ± 0.258	6.543 ± 0.368	7.837
Relative	39.61 ± 0.75	39.16 ± 1.57	46.60 ± 1.54**	52.19 ± 0.67**	73.24
Lungs					
Absolute	1.381 ± 0.056	1.320 ± 0.060	1.231 ± 0.047	1.221 ± 0.120	1.174
Relative	9.73 ± 0.30	9.41 ± 0.50	9.33 ± 0.34	9.68 ± 0.52	10.97
Thymus					
Absolute	0.323 ± 0.028	0.342 ± 0.036	0.273 ± 0.010	0.211 ± 0.016*	0.105
Relative	2.26 ± 0.15	2.42 ± 0.21	2.06 ± 0.04	1.68 ± 0.05*	0.98

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No organ weights or organ-weight-to-body-weight ratios were calculated for males or females administered 1,500 mg/kg due to 100% mortality in these groups.
[b] No standard error was calculated due to high mortality in males and females administered 500 mg/kg.

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Study of Promethazine Hydrochloride[a]

	Vehicle Control	3.7 mg/kg	11.1 mg/kg	33.3 mg/kg	100 mg/kg	300 mg/kg
Male						
n	10	10	10	10	10	3
Necropsy body wt	313 ± 6	309 ± 8	319 ± 8	302 ± 7	254 ± 9**	248 ± 29**
Brain						
Absolute	2.057 ± 0.024	2.019 ± 0.035	1.994 ± 0.017	1.985 ± 0.020	1.989 ± 0.026	1.949 ± 0.077
Relative	6.58 ± 0.12	6.56 ± 0.09	6.28 ± 0.16	6.60 ± 0.15	7.90 ± 0.22**	8.13 ± 1.14**
Heart						
Absolute	1.147 ± 0.042	1.147 ± 0.047	1.100 ± 0.037[b]	1.051 ± 0.029	1.061 ± 0.044	1.080 ± 0.076
Relative	3.66 ± 0.11	3.72 ± 0.15	3.49 ± 0.14[b]	3.49 ± 0.11	4.17 ± 0.08*	4.48 ± 0.64**
R. Kidney						
Absolute	1.089 ± 0.039	1.073 ± 0.027	1.190 ± 0.024	1.084 ± 0.030	1.026 ± 0.035	1.244 ± 0.151
Relative	3.47 ± 0.08	3.49 ± 0.08	3.74 ± 0.08	3.59 ± 0.07	4.05 ± 0.10**	5.02 ± 0.04**
Liver						
Absolute	10.155 ± 0.203	10.235 ± 0.334	12.082 ± 0.344*	11.480 ± 0.410*	11.319 ± 0.509*	19.249 ± 2.459**
Relative	32.43 ± 0.25	33.22 ± 0.93	37.86 ± 0.65**	37.92 ± 0.74**	44.51 ± 1.18**	77.57 ± 2.37**
Lungs						
Absolute	2.221 ± 0.088	2.262 ± 0.086	2.252 ± 0.042	2.216 ± 0.103	1.961 ± 0.106	2.597 ± 0.291
Relative	7.09 ± 0.25	7.33 ± 0.18	7.08 ± 0.17	7.35 ± 0.34	7.69 ± 0.24	10.70 ± 1.52**
R. Testis						
Absolute	1.467 ± 0.045	1.393 ± 0.039	1.519 ± 0.021	1.425 ± 0.063	1.357 ± 0.022	1.415 ± 0.012
Relative	4.69 ± 0.12	4.52 ± 0.07	4.78 ± 0.12	4.75 ± 0.25	5.39 ± 0.18**	5.86 ± 0.62**
Thymus						
Absolute	0.323 ± 0.033	0.320 ± 0.021	0.307 ± 0.013[b]	0.260 ± 0.010*	0.233 ± 0.017**	0.179 ± 0.022**
Relative	1.03 ± 0.10	1.04 ± 0.06	0.98 ± 0.05[b]	0.86 ± 0.03	0.91 ± 0.05	0.73 ± 0.06*

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 13-Week Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	3.7 mg/kg	11.1 mg/kg	33.3 mg/kg	100 mg/kg	300 mg/kg
Female						
n	10	10	10	10	9	1[c]
Necropsy body wt	169 ± 3	180 ± 3*	184 ± 2**	175 ± 3	165 ± 3	117
Brain						
Absolute	1.791 ± 0.030	1.855 ± 0.015	1.833 ± 0.021	1.805 ± 0.019	1.785 ± 0.012	0.423
Relative	10.61 ± 0.23	10.36 ± 0.22	9.99 ± 0.18	10.35 ± 0.12	10.88 ± 0.22	3.62
Heart						
Absolute	0.680 ± 0.027	0.708 ± 0.016	0.718 ± 0.017	0.683 ± 0.016	0.660 ± 0.018	0.492
Relative	4.02 ± 0.15	3.94 ± 0.06	3.92 ± 0.12	3.91 ± 0.06	4.02 ± 0.14	4.21
R. Kidney						
Absolute	0.653 ± 0.026	0.680 ± 0.016[b]	0.688 ± 0.012	0.689 ± 0.018	0.667 ± 0.017	0.688
Relative	3.88 ± 0.19	3.80 ± 0.07[b]	3.75 ± 0.05	3.95 ± 0.09	4.05 ± 0.05	5.88
Liver						
Absolute	5.334 ± 0.114	5.419 ± 0.106	5.996 ± 0.101**	5.991 ± 0.115**	6.635 ± 0.157**	9.235
Relative	31.54 ± 0.52	30.19 ± 0.52	32.65 ± 0.57	34.36 ± 0.68**	40.31 ± 0.63**	78.93
Lungs						
Absolute	1.528 ± 0.051	1.514 ± 0.115	1.633 ± 0.048	1.460 ± 0.038	1.518 ± 0.064	1.324
Relative	9.03 ± 0.24	8.48 ± 0.68	8.91 ± 0.31	8.37 ± 0.22	9.20 ± 0.27	11.32
Thymus						
Absolute	0.227 ± 0.017	0.255 ± 0.020	0.245 ± 0.015	0.197 ± 0.013	0.191 ± 0.019	0.044
Relative	1.33 ± 0.09	1.42 ± 0.11	1.34 ± 0.09	1.12 ± 0.07	1.16 ± 0.12	0.38

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=9
[c] No standard error was calculated due to high mortality in females administered 300 mg/kg.

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Promethazine Hydrochloride [a]

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Male				
n	10	10	10	9
Necropsy body wt	475 ± 8	470 ± 5	446 ± 10*	421 ± 10**
Brain				
Absolute	2.141 ± 0.015	2.122 ± 0.019	2.088 ± 0.019	2.064 ± 0.021**
Relative	4.52 ± 0.08	4.51 ± 0.05	4.70 ± 0.12	4.91 ± 0.07**
R. Kidney				
Absolute	1.516 ± 0.032	1.534 ± 0.047	1.507 ± 0.044	1.497 ± 0.059
Relative	3.19 ± 0.04	3.26 ± 0.08	3.38 ± 0.10	3.55 ± 0.12**
Liver				
Absolute	16.846 ± 0.435	17.447 ± 0.580	17.061 ± 0.579	17.504 ± 0.469
Relative	35.42 ± 0.54	37.04 ± 1.02	38.22 ± 0.86*	41.55 ± 0.72**
Female				
n	10	10	10	7
Necropsy body wt	292 ± 11	276 ± 6	264 ± 5*	261 ± 8*
Brain				
Absolute	1.904 ± 0.026	1.878 ± 0.015	1.905 ± 0.017	1.896 ± 0.030
Relative	6.58 ± 0.21	6.83 ± 0.16	7.23 ± 0.14*	7.31 ± 0.26*
R. Kidney				
Absolute	0.859 ± 0.018	0.843 ± 0.013	0.874 ± 0.022	0.882 ± 0.025
Relative	2.96 ± 0.08	3.06 ± 0.05	3.31 ± 0.05**	3.39 ± 0.05**
Liver				
Absolute	8.357 ± 0.160	8.823 ± 0.198	9.079 ± 0.231*	9.433 ± 0.272**
Relative	28.81 ± 0.77	32.00 ± 0.60**	34.34 ± 0.44**	36.19 ± 0.46**

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

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Study of Promethazine Hydrochloride[a]

	Vehicle Control	18.8 mg/kg	37.5 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Male						
n	5	5	5	5	4	5
Necropsy body wt	18.0 ± 0.3	20.2 ± 0.4	19.8 ± 0.6	19.6 ± 0.8	19.0 ± 0.4	18.8 ± 0.8
Brain						
Absolute	0.477 ± 0.018	0.456 ± 0.010	0.466 ± 0.011	0.465 ± 0.008	0.455 ± 0.003	0.453 ± 0.017
Relative	26.51 ± 0.95	22.59 ± 0.48*	23.68 ± 1.18	23.80 ± 0.63	23.97 ± 0.61	24.19 ± 0.91
Heart						
Absolute	0.127 ± 0.009	0.124 ± 0.005	0.128 ± 0.007	0.124 ± 0.005	0.123 ± 0.005	0.118 ± 0.008[b]
Relative	7.05 ± 0.43	6.14 ± 0.16	6.46 ± 0.29	6.37 ± 0.39	6.49 ± 0.25	6.41 ± 0.39[b]
R. Kidney						
Absolute	0.165 ± 0.008	0.180 ± 0.007	0.159 ± 0.009	0.172 ± 0.008	0.158 ± 0.005	0.174 ± 0.014
Relative	9.16 ± 0.39	8.91 ± 0.29	8.07 ± 0.59	8.78 ± 0.24	8.31 ± 0.23	9.19 ± 0.42
Liver						
Absolute	0.858 ± 0.034	1.047 ± 0.026**	1.046 ± 0.032**	1.193 ± 0.044**	1.200 ± 0.037**	1.229 ± 0.076**
Relative	47.64 ± 1.20	51.81 ± 0.57	52.87 ± 1.23*	61.06 ± 2.23**	63.11 ± 0.72**	65.22 ± 2.28**
Lungs						
Absolute	0.218 ± 0.016	0.235 ± 0.013	0.235 ± 0.012	0.224 ± 0.007	0.230 ± 0.015	0.228 ± 0.012
Relative	12.08 ± 0.70	11.62 ± 0.56	11.90 ± 0.67	11.52 ± 0.68	12.08 ± 0.71	12.16 ± 0.47
R. Testis						
Absolute	0.104 ± 0.003	0.103 ± 0.003	0.143 ± 0.034	0.107 ± 0.004	0.098 ± 0.005	0.105 ± 0.007
Relative	5.77 ± 0.20	5.09 ± 0.09	7.19 ± 1.67	5.46 ± 0.10	5.16 ± 0.21	5.60 ± 0.24
Thymus						
Absolute	0.042 ± 0.008	0.051 ± 0.007	0.038 ± 0.011	0.036 ± 0.005	0.040 ± 0.002	0.033 ± 0.006
Relative	2.32 ± 0.45	2.53 ± 0.41	1.88 ± 0.51	1.88 ± 0.27	2.11 ± 0.13	1.76 ± 0.32

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 16-Day Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	18.8 mg/kg	37.5 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Female						
n	5	5	5	3	4	1[c]
Necropsy body wt	14.4 ± 0.2	14.0 ± 0.6	14.4 ± 0.2	15.0 ± 0.0	15.3 ± 0.3	13.0
Brain						
Absolute	0.468 ± 0.011	0.438 ± 0.013	0.455 ± 0.006	0.460 ± 0.008	0.454 ± 0.009	0.448
Relative	32.53 ± 0.77	31.41 ± 0.72	31.68 ± 0.84	30.64 ± 0.52	29.76 ± 0.74*	34.46
Heart						
Absolute	0.092 ± 0.006	0.095 ± 0.005	0.092 ± 0.005	0.086 ± 0.003	0.089 ± 0.006	0.084
Relative	6.37 ± 0.42	6.81 ± 0.44	6.40 ± 0.42	5.73 ± 0.20	5.85 ± 0.41	6.46
R. Kidney						
Absolute	0.139 ± 0.006	0.127 ± 0.013	0.119 ± 0.008	0.134 ± 0.001	0.124 ± 0.007	0.111
Relative	9.66 ± 0.33	8.98 ± 0.62	8.25 ± 0.55	8.91 ± 0.08	8.17 ± 0.56	8.54
Liver						
Absolute	0.751 ± 0.033	0.810 ± 0.035	0.852 ± 0.030*	0.871 ± 0.019*	1.027 ± 0.028**	0.789
Relative	52.12 ± 1.75	57.92 ± 0.86*	59.14 ± 1.77**	58.04 ± 1.26*	67.36 ± 1.77**	60.69
Lungs						
Absolute	0.224 ± 0.007	0.220 ± 0.019	0.198 ± 0.007	0.205 ± 0.030	0.191 ± 0.017	0.186
Relative	15.55 ± 0.49	15.67 ± 0.93	13.79 ± 0.59	13.69 ± 1.98	12.53 ± 1.04*	14.31
Thymus						
Absolute	0.054 ± 0.005	0.048 ± 0.005	0.052 ± 0.003	0.050 ± 0.005	0.053 ± 0.005	0.021
Relative	3.79 ± 0.42	3.40 ± 0.28	3.58 ± 0.21	3.33 ± 0.33	3.45 ± 0.29	1.62

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error).
[b] n=4
[c] No standard error calculated due to high mortality in females administered 300 mg/kg.

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Study of Promethazine Hydrochloride[a]

	Vehicle Control	5 mg/kg	15 mg/kg	45 mg/kg	135 mg/kg
Male					
n	10	10	10	10	10
Necropsy body wt	26.5 ± 0.9	26.4 ± 0.7	25.6 ± 0.3	25.8 ± 0.6	25.4 ± 0.3
Brain					
Absolute	0.461 ± 0.008	0.452 ± 0.010	0.469 ± 0.007	0.455 ± 0.008	0.465 ± 0.010
Relative	17.61 ± 0.72	17.22 ± 0.58	18.33 ± 0.32	17.69 ± 0.34	18.33 ± 0.52
Heart					
Absolute	0.156 ± 0.004	0.144 ± 0.005	0.164 ± 0.004	0.147 ± 0.004	0.149 ± 0.005
Relative	5.97 ± 0.27	5.47 ± 0.16	6.40 ± 0.16	5.69 ± 0.11	5.87 ± 0.18
R. Kidney					
Absolute	0.230 ± 0.007	0.230 ± 0.011	0.220 ± 0.005	0.219 ± 0.007	0.209 ± 0.006
Relative	8.69 ± 0.14	8.71 ± 0.34	8.61 ± 0.22	8.49 ± 0.21	8.24 ± 0.19
Liver					
Absolute	1.216 ± 0.039	1.236 ± 0.040	1.287 ± 0.032	1.386 ± 0.040**	1.388 ± 0.018**
Relative	45.94 ± 0.37	46.86 ± 1.17	50.30 ± 1.36**	53.74 ± 1.02**	54.70 ± 0.80**
Lungs					
Absolute	0.256 ± 0.013	0.261 ± 0.008	0.306 ± 0.026	0.263 ± 0.007	0.265 ± 0.008
Relative	9.63 ± 0.21	9.90 ± 0.23	11.97 ± 1.08	10.22 ± 0.31	10.44 ± 0.29
R. Testis					
Absolute	0.109 ± 0.003	0.110 ± 0.003	0.112 ± 0.002	0.114 ± 0.003	0.111 ± 0.003
Relative	4.12 ± 0.13	4.20 ± 0.19	4.37 ± 0.09	4.43 ± 0.11	4.38 ± 0.11
Thymus					
Absolute	0.029 ± 0.002	0.034 ± 0.002	0.040 ± 0.006	0.032 ± 0.003	0.030 ± 0.002
Relative	1.10 ± 0.07	1.30 ± 0.09	1.54 ± 0.22*	1.24 ± 0.10	1.17 ± 0.07

TABLE F5
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 13-Week Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	5 mg/kg	15 mg/kg	45 mg/kg	135 mg/kg
Female					
n	9	9	10	8	6
Necropsy body wt	19.1 ± 0.4	20.0 ± 0.6	20.4 ± 0.6	19.5 ± 0.5	20.2 ± 0.8
Brain					
Absolute	0.477 ± 0.008	0.473 ± 0.009	0.468 ± 0.011	0.461 ± 0.011	0.460 ± 0.012
Relative	25.01 ± 0.54	23.81 ± 0.83	23.13 ± 0.84	23.69 ± 0.45	23.00 ± 1.04
Heart					
Absolute	0.117 ± 0.004	0.111 ± 0.004	0.122 ± 0.004	0.121 ± 0.006	0.108 ± 0.005
Relative	6.12 ± 0.25	5.56 ± 0.16	6.01 ± 0.22	6.19 ± 0.29	5.38 ± 0.11
R. Kidney					
Absolute	0.165 ± 0.003	0.159 ± 0.005	0.175 ± 0.004	0.163 ± 0.007	0.154 ± 0.010
Relative	8.64 ± 0.13	8.00 ± 0.28	8.59 ± 0.22	8.33 ± 0.25	7.59 ± 0.22*
Liver					
Absolute	0.923 ± 0.028	0.956 ± 0.036	1.113 ± 0.039**	1.043 ± 0.024**	1.247 ± 0.048**
Relative	48.34 ± 1.14	47.90 ± 1.43	54.53 ± 0.83**	53.56 ± 0.79**	61.97 ± 1.74**
Lungs					
Absolute	0.275 ± 0.004	0.265 ± 0.013	0.273 ± 0.017	0.286 ± 0.019	0.269 ± 0.017
Relative	14.43 ± 0.43	13.27 ± 0.65	13.43 ± 0.88	14.68 ± 0.92	13.32 ± 0.64
Thymus					
Absolute	0.034 ± 0.002	0.038 ± 0.004	0.036 ± 0.003	0.038 ± 0.004	0.034 ± 0.006
Relative	1.76 ± 0.10	1.86 ± 0.19	1.74 ± 0.14	1.94 ± 0.21	1.64 ± 0.27

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). No organ weights or organ-weight-to-body-weight ratios were calculated for males or females administered 405 mg/kg due to 100% mortality in these groups.

TABLE F6
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Promethazine Hydrochloride [a]

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
Male				
n	10	10	9	10
Necropsy body wt	44.2 ± 1.4	44.0 ± 1.3	43.5 ± 1.2	42.6 ± 1.4
Brain				
Absolute	0.463 ± 0.007	0.450 ± 0.006	0.459 ± 0.003	0.466 ± 0.003
Relative	10.55 ± 0.38	10.31 ± 0.27	10.61 ± 0.29	11.05 ± 0.42
R. Kidney				
Absolute	0.369 ± 0.022	0.362 ± 0.011	0.361 ± 0.016	0.368 ± 0.017
Relative	8.35 ± 0.37	8.25 ± 0.12	8.29 ± 0.20	8.67 ± 0.42
Liver				
Absolute	1.969 ± 0.222	2.013 ± 0.144	1.855 ± 0.111	2.048 ± 0.131
Relative	44.31 ± 4.52	46.17 ± 3.96	42.43 ± 1.48	47.80 ± 2.01
Female	**Vehicle Control**	**3.75 mg/kg**	**7.5 mg/kg**	**15 mg/kg**
n	10	10	9	9
Necropsy body wt	42.2 ± 1.7	41.6 ± 1.7	41.6 ± 1.5	40.0 ± 1.9
Brain				
Absolute	0.473 ± 0.006	0.462 ± 0.006	0.465 ± 0.004	0.472 ± 0.004
Relative	11.35 ± 0.45	11.22 ± 0.37	11.28 ± 0.40	12.09 ± 0.79
R. Kidney				
Absolute	0.230 ± 0.007	0.215 ± 0.005	0.213 ± 0.007	0.218 ± 0.006
Relative	5.49 ± 0.22	5.20 ± 0.14	5.15 ± 0.21	5.56 ± 0.30
Liver				
Absolute	1.563 ± 0.036	1.492 ± 0.036	1.511 ± 0.047	1.602 ± 0.066
Relative	37.31 ± 1.17	36.14 ± 0.92	36.40 ± 0.69	40.34 ± 1.35

[a] Organ weights and body weights are given in grams; organ-weight-to-body-weight ratios are given as mg organ weight/g body weight (mean ± standard error). Differences from the control group were not significant by Williams' or Dunnett's test.

APPENDIX G
HEMATOLOGY AND CLINICAL CHEMISTRY RESULTS

TABLE G1
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Promethazine Hydrochloride [a]

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Male				
Hematology				
n	10	10	10	9
Hematocrit (%)	45.1 ± 0.4	45.4 ± 0.3	45.7 ± 0.5	46.2 ± 1.0
Hemoglobin (g/dL)	15.9 ± 0.2	16.0 ± 0.1	16.3 ± 0.1	16.4 ± 0.4
Erythrocytes (10^6/µL)	8.85 ± 0.05	8.83 ± 0.07	8.92 ± 0.09	8.96 ± 0.16
Mean cell volume (fL)	50.9 ± 0.3	51.5 ± 0.2	51.3 ± 0.4	51.6 ± 0.5
Mean cell hemoglobin (pg)	18.0 ± 0.2	18.1 ± 0.2	18.3 ± 0.2	18.3 ± 0.2
Mean cell hemoglobin concentration (g/dL)	35.35 ± 0.32	35.26 ± 0.39	35.72 ± 0.48	35.49 ± 0.35
Leukocytes (10^3/µL)	7.30 ± 0.48	7.57 ± 0.36	7.18 ± 0.20	7.27 ± 0.52
Segmented neutrophils (10^3/µL)	2.33 ± 0.25	2.11 ± 0.24	1.93 ± 0.09	2.75 ± 0.33
Lymphocytes (10^3/µL)	4.42 ± 0.27	4.98 ± 0.35	4.77 ± 0.22	3.99 ± 0.25
Monocytes (10^3/µL)	0.41 ± 0.06	0.34 ± 0.08	0.35 ± 0.06	0.39 ± 0.05
Eosinophils (10^3/µL)	0.10 ± 0.03	0.13 ± 0.03	0.10 ± 0.03	0.13 ± 0.05
Nucleated erythrocytes (10^3/µL)	0.05 ± 0.02	0.08 ± 0.03	0.02 ± 0.01	0.01 ± 0.01
Clinical Chemistry				
n	10	10	10	9
Alanine aminotransferase (IU/L)	89 ± 5	101 ± 9	92 ± 4	86 ± 7
Aspartate aminotransferase (IU/L)	120 ± 10	126 ± 10	117 ± 4	111 ± 8
Lactate dehydrogenase (IU/L)	907 ± 139	875 ± 88	799 ± 96	1,137 ± 125
Sorbitol dehydrogenase (IU/L)	17 ± 1	17 ± 2	15 ± 1	16 ± 1
5'-Nucleotidase (IU/L)	38.50 ± 1.49	38.00 ± 1.10	35.80 ± 0.76	34.22 ± 1.46

TABLE G1
Hematology and Clinical Chemistry Data for Rats at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	8.3 mg/kg	16.6 mg/kg	33.3 mg/kg
Female				
Hematology				
n	10	8	9	4
Hematocrit (%)	44.8 ± 0.6	44.6 ± 0.5	44.9 ± 0.4	45.8 ± 0.4
Hemoglobin (g/dL)	15.7 ± 0.1	15.7 ± 0.2	15.8 ± 0.1	16.2 ± 0.2
Erythrocytes (10^3/µL)	7.89 ± 0.12	7.86 ± 0.10	7.91 ± 0.08	8.05 ± 0.06
Mean cell volume (fL)	56.8 ± 0.3	56.8 ± 0.5	56.7 ± 0.3	57.0 ± 0.0
Mean cell hemoglobin (pg)	20.0 ± 0.3	20.0 ± 0.2	19.9 ± 0.3	20.1 ± 0.2
Mean cell hemoglobin concentration (g/dL)	35.2 ± 0.4	35.3 ± 0.2	35.1 ± 0.4	35.2 ± 0.2
Leukocytes (10^3/µL)	3.80 ± 0.31	4.49 ± 0.43	4.49 ± 0.23	4.95 ± 0.37*
Segmented neutrophils (10^3/µL)	0.99 ± 0.12	1.18 ± 0.23	0.95 ± 0.13	1.21 ± 0.19
Lymphocytes (10^3/µL)	2.62 ± 0.25	3.07 ± 0.24	3.34 ± 0.14*	3.43 ± 0.17*
Monocytes (10^3/µL)	0.11 ± 0.03	0.17 ± 0.04	0.17 ± 0.05	0.21 ± 0.02
Eosinophils (10^3/µL)	0.03 ± 0.01	0.04 ± 0.01	0.02 ± 0.01	0.04 ± 0.04
Nucleated erythrocytes (10^3/µL)	0.04 ± 0.02	0.04 ± 0.02	0.02 ± 0.01	0.05 ± 0.03
Clinical Chemistry				
n	10	10	10	7
Alanine aminotransferase (IU/L)	59 ± 6	60 ± 4	62 ± 4	58 ± 5
Aspartate aminotransferase (IU/L)	80 ± 6	84 ± 6	79 ± 5	68 ± 2
Lactate dehydrogenase (IU/L)	707 ± 79	672 ± 71	744 ± 98	483 ± 41
Sorbitol dehydrogenase (IU/L)	8 ± 0[b]	9 ± 1	9 ± 1	11 ± 1
5'-Nucleotidase (IU/L)	34.80 ± 1.03	30.10 ± 0.89**	30.40 ± 1.17**	29.00 ± 0.98**

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

TABLE G2
Hematology Data for Mice in the 16-Day Gavage Study of Promethazine Hydrochloride [a]

	Vehicle Control	18.8 mg/kg	37.5 mg/kg	75 mg/kg	150 mg/kg	300 mg/kg
Male						
n	5	5	5	5	3	5
Hematocrit (%)	53.4 ± 0.5	54.9 ± 0.7	53.7 ± 0.3	52.9 ± 0.7	53.3 ± 0.3[b]	52.9 ± 0.7
Hemoglobin (g/dL)	16.7 ± 0.4	15.9 ± 0.9	16.1 ± 0.6	16.8 ± 0.2	16.1 ± 0.6	15.7 ± 0.6
Erythrocytes (10^6/µL)	9.67 ± 0.21	9.11 ± 0.52	9.06 ± 0.30	9.33 ± 0.12	8.97 ± 0.22[b]	8.97 ± 0.29
Reticulocytes (10^6/µL)	0.06 ± 0.03	0.15 ± 0.04	0.09 ± 0.04	0.15 ± 0.05	0.12 ± 0.07[b]	0.12 ± 0.06
Leukocytes (10^3/µL)	4.20 ± 0.30	3.48 ± 0.46	3.08 ± 0.33	3.56 ± 0.14	4.03 ± 0.67	3.14 ± 0.15
Segmented neutrophils (10^3/µL)	1.08 ± 0.14	0.64 ± 0.18	0.59 ± 0.19	0.62 ± 0.11	0.76 ± 0.31	0.88 ± 0.42
Lymphocytes (10^3/µL)	3.10 ± 0.25	2.76 ± 0.31	2.44 ± 0.20	2.83 ± 0.19	3.14 ± 0.36	2.21 ± 0.33
Monocytes (10^3/µL)	0.05 ± 0.01[c]	0.07 ± 0.02[b]	0.06 ± 0.02[b]	0.10 ± 0.02	0.16 ± 0.08[c]	0.07 ± 0.03[b]
Eosinophils (10^3/µL)	)[d]	0.04 ± 0.00[c]	)	0.04[e]	0.10[e]	)
Female						
n	5	5	5	3	4	1[e]
Hematocrit (%)	52.2 ± 0.7	52.0 ± 0.8	50.3 ± 0.8	51.8 ± 0.9	51.9 ± 0.8	54.0
Hemoglobin (g/dL)	16.3 ± 0.7	15.7 ± 0.7	15.8 ± 0.8	16.3 ± 1.0	15.2 ± 0.6	14.3
Erythrocytes (10^6/µL)	9.13 ± 0.39	8.73 ± 0.38	8.81 ± 0.42	9.02 ± 0.53	8.54 ± 0.34	8.41
Reticulocytes (10^6/µL)	0.10 ± 0.02	0.06 ± 0.02	0.10 ± 0.03	0.16 ± 0.08	0.11 ± 0.04	0.19
Leukocytes (10^3/µL)	4.78 ± 0.43	3.38 ± 0.19	3.96 ± 0.15	3.97 ± 0.54	11.18 ± 6.60	4.20
Segmented neutrophils (10^3/µL)	1.61 ± 0.26	1.34 ± 0.26	1.61 ± 0.42	1.24 ± 0.46	2.88 ± 1.75	2.39
Lymphocytes (10^3/µL)	3.05 ± 0.35	1.95 ± 0.23	2.29 ± 0.38	2.68 ± 0.14	8.05 ± 4.74	1.64
Monocytes (10^3/µL)	0.09 ± 0.04[b]	0.09 ± 0.01	0.10 ± 0.02[f]	0.09 ± 0.01[c]	0.25 ± 0.13	0.17

[a] Mean ± standard error. Differences from the control group are not significant by Dunn's or Shirley's test.
[b] n=4
[c] n=2
[d] Not examined
[e] No standard error was calculated due to high mortality.
[f] n=3

TABLE G3
Hematology Data for Mice in the 13-Week Gavage Study of Promethazine Hydrochloride [a]

	Vehicle Control	5 mg/kg	15 mg/kg	45 mg/kg	135 mg/kg
Male					
n	10	10	10	10	10
Hematocrit (%)	49.9 ± 0.7	50.2 ± 0.3	50.3 ± 0.3	50.9 ± 0.5*	50.7 ± 0.4
Hemoglobin (g/dL)	16.5 ± 0.3	16.5 ± 0.1	16.7 ± 0.2	16.8 ± 0.2	16.6 ± 0.1
Erythrocytes (10^6/µL)	9.39 ± 0.15	9.35 ± 0.06	9.32 ± 0.08	9.19 ± 0.14	9.17 ± 0.11
Reticulocytes (10^6/µ)	0.27 ± 0.20	0.31 ± 0.18	0.13 ± 0.12**	0.19 ± 0.12	0.28 ± 0.01
Leukocytes (10^3/µL)	5.67 ± 0.57	5.62 ± 0.22	3.93 ± 0.53*	4.90 ± 0.24	5.60 ± 0.29
Segmented neutrophils (10^3/µL)	1.46 ± 0.37	0.79 ± 0.10	0.98 ± 0.46**	0.89 ± 0.10	0.91 ± 0.15
Lymphocytes (10^3/µL)	4.17 ± 0.46	4.81 ± 0.20	2.95 ± 0.21	3.91 ± 0.24	4.57 ± 0.18
Female					
n	9	9	10	8	6
Hematocrit (%)	51.2 ± 0.3	50.5 ± 0.3	49.8 ± 0.7	51.6 ± 1.0	51.4 ± 0.7
Hemoglobin (g/dL)	16.9 ± 0.1	16.8 ± 0.2	16.8 ± 0.3	16.9 ± 0.2	16.9 ± 0.3
Erythrocytes (10^6/µL)	9.58 ± 0.07	9.37 ± 0.13	9.26 ± 0.13	9.51 ± 0.17	9.53 ± 0.19
Reticulocytes (10^6/µ)	0.27 ± 0.27	0.26 ± 0.16	0.10 ± 0.02**	0.20 ± 0.01	0.25 ± 0.02
Leukocytes (10^3/µL)	5.26 ± 0.37	4.52 ± 0.24	4.37 ± 0.47	4.83 ± 0.40	4.60 ± 0.46
Segmented neutrophils (10^3/µL)	1.33 ± 0.20	1.13 ± 0.17	0.80 ± 0.17*	1.09 ± 0.15	0.82 ± 0.18
Lymphocytes (10^3/µL)	3.93 ± 0.36	3.38 ± 0.30	3.55 ± 0.45	3.70 ± 0.38	3.69 ± 0.43

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. No hematology data were calculated for males or females administered 405 mg/kg due to 100% mortality in these groups.

TABLE G4
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Promethazine Hydrochloride [a]

	Vehicle Control	11.25 mg/kg	22.5 mg/kg	45 mg/kg
Male				
n	10	10	10	10
Hematology				
Hematocrit (%)	45.5 ± 0.7	45.3 ± 0.7	44.7 ± 0.5	44.7 ± 0.5
Hemoglobin (g/dL)	15.6 ± 0.2	15.6 ± 0.3	15.3 ± 0.2	15.4 ± 0.2
Erythrocytes (10^6/µL)	9.41 ± 0.10	9.38 ± 0.14	9.14 ± 0.13	9.14 ± 0.09
Mean cell volume (fL)	48.3 ± 0.4	48.2 ± 0.4	48.9 ± 0.4	48.9 ± 0.2
Mean cell hemoglobin (pg)	16.5 ± 0.1	16.6 ± 0.2	16.8 ± 0.1	16.9 ± 0.1
Mean cell hemoglobin concentration (g/dL)	34.3 ± 0.4	34.4 ± 0.3	34.3 ± 0.3	34.5 ± 0.3
Leukocytes (10^3/µL)	7.20 ± 0.37	6.22 ± 0.27	6.15 ± 0.46	6.45 ± 0.41
Segmented neutrophils (10^3/µL)	1.53 ± 0.11	1.62 ± 0.12	1.60 ± 0.19	1.52 ± 0.15
Lymphocytes (10^3/µL)	5.39 ± 0.33	4.30 ± 0.25	4.31 ± 0.36	4.69 ± 0.35
Monocytes (10^3/µL)	0.07 ± 0.03	0.05 ± 0.02	0.06 ± 0.02	0.07 ± 0.03
Eosinophils (10^3/µL)	0.21 ± 0.04	0.26 ± 0.04	0.18 ± 0.04	0.16 ± 0.03
Nucleated erythrocytes (10^3/µL)	0.03 ± 0.02	0.00 ± 0.00	0.01 ± 0.01	0.01 ± 0.01
Clinical Chemistry				
Alanine aminotransferase (IU/L)	38 ± 5	37 ± 7 [b]	34 ± 3	45 ± 2
Aspartate aminotransferase (IU/L)	57 ± 4	66 ± 8	64 ± 6	81 ± 9*
Lactate dehydrogenase (IU/L)	373 ± 43	393 ± 41	382 ± 42	383 ± 43
Sorbitol dehydrogenase (IU/L)	32 ± 2	33 ± 2	34 ± 1	32 ± 2
5'-Nucleotidase (IU/L)	17.22 ± 1.34 [b]	16.30 ± 1.14	16.30 ± 1.14	19.70 ± 1.19

TABLE G4
Hematology and Clinical Chemistry Data for Mice at the 15-Month Interim Evaluation in the 2-Year Gavage Study of Promethazine Hydrochloride (continued)

	Vehicle Control	3.75 mg/kg	7.5 mg/kg	15 mg/kg
Female				
Hematology				
n	10	10	8	9
Hematocrit (%)	46.3 ± 0.4	46.2 ± 0.5	46.5 ± 0.4	47.0 ± 0.2
Hemoglobin (g/dL)	16.7 ± 0.2	16.3 ± 0.2	16.4 ± 0.1	16.9 ± 0.2
Erythrocytes (10^6/µL)	9.63 ± 0.06	9.68 ± 0.07	9.66 ± 0.09	9.75 ± 0.07
Mean cell volume (fL)	48.0 ± 0.4	47.7 ± 0.3	48.1 ± 0.1	48.2 ± 0.4
Mean cell hemoglobin (pg)	17.3 ± 0.2	16.8 ± 0.1	17.0 ± 0.1	17.4 ± 0.1
Mean cell hemoglobin concentration (g/dL)	36.1 ± 0.5	35.3 ± 0.2	35.2 ± 0.3	36.0 ± 0.3
Leukocytes (10^3/µL)	6.49 ± 0.35	6.73 ± 0.46	6.48 ± 0.53	6.48 ± 0.61
Segmented neutrophils (10^3/µL)	1.74 ± 0.19	1.73 ± 0.19	1.85 ± 0.25	2.03 ± 0.43
Bands (10^3/µL)	0.01 ± 0.01	0.01 ± 0.01	0.03 ± 0.01	0.01 ± 0.01
Lymphocytes (10^3/µL)	4.55 ± 0.25	4.82 ± 0.44	4.41 ± 0.38	4.26 ± 0.31
Monocytes (10^3/µL)	0.06 ± 0.03	0.05 ± 0.02	0.04 ± 0.02	0.06 ± 0.02
Eosinophils (10^3/µL)	0.13 ± 0.02	0.12 ± 0.03	0.15 ± 0.04	0.13 ± 0.03
Nucleated erythrocytes (10^3/µL)	0.01 ± 0.01	0.01 ± 0.01	0.02 ± 0.02	0.02 ± 0.01
Clinical Chemistry				
n	10	10	9	8
Alanine aminotransferase (IU/L)	80 ± 29	34 ± 3	24 ± 2**	33 ± 7*
Aspartate aminotransferase (IU/L)	168 ± 59	88 ± 12	68 ± 7	83 ± 18[b]
Lactate dehydrogenase	576 ± 164	358 ± 50	316 ± 24	310 ± 23[b]
Sorbitol dehydrogenase (IU/L)	21 ± 3[b]	23 ± 1[c]	23 ± 1[c]	27 ± 2
5'-Nucleotidase (IU/L)	79.38 ± 6.48[d]	97.43 ± 5.98*[c]	106.67 ± 6.32*[e]	93.75 ± 7.30*

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error
[b] n=9
[c] n=7
[d] n=8
[e] n=6

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

PROCUREMENT AND CHARACTERIZATION OF PROMETHAZINE HYDROCHLORIDE

Promethazine hydrochloride was obtained from Napp Chemicals, Incorporated (Lodi, NJ) in one lot (31321), which was used throughout the studies. Identity, purity, and stability analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). The reports on analyses performed in support of the promethazine hydrochloride studies are on file at the National Institute of Environmental Health Sciences.

The chemical, a white to faint yellow crystalline powder, was identified as promethazine hydrochloride by infrared, ultraviolet/visible, and nuclear magnetic resonance (NMR) spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra of promethazine hydrochloride (*Sadtler Standard Spectra*) (Figures H1 and H2).

The purity of promethazine hydrochloride was determined by elemental analyses, Karl Fischer water analysis, titration of the amine group, ultraviolet spectroscopy, thin-layer chromatography (TLC), and gas chromatography. Titration of the amine group was performed by dissolving a sample in acetic acid, containing an excess of mercury (II) acetate, and titrated with 0.1 N perchloric acid. An ultraviolet spectrophotometric assay was performed by dissolving the sample in 95% ethanol, and the absorbance at 256 nm was compared to that of a similarly treated, dried United States Pharmacopeia XX (USP) reference standard. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: A) cyclohexane:diethylamine (90:10) and B) concentrated methanol:ammonium hydroxide (99:1). One µL of a 10 mg/mL solution of phenothiazine in methylene chloride and 30 µL of a 10 mg/mL solution of a USP promethazine hydrochloride reference standard in methylene chloride were used as internal standards. Visualization was accomplished with ultraviolet (254 and 366 nm) light and a spray of potassium iodoplatinate. Gas chromatography was performed on a methylene chloride solution of promethazine hydrochloride with a flame ionization detector, a nitrogen carrier gas at 70 mL/minute, and an oven temperature program consisting of 50° C for 5 minutes then 50° C to 250° C at increases of 10° C/minute with two columns: A) 3% SP-2100 (DB) on 100/120 Supelcoport column, and B) 3% SP-2401 on 100/120 Supelcoport column.

Elemental analyses for carbon, hydrogen, nitrogen, sulfur, and chlorine were in agreement with the theoretical values for promethazine hydrochloride. Karl Fischer analysis indicated 0.03 ± 0.01% water. Titration of one amine group with perchloric acid indicated a purity of 100.9 ± 0.5%. An ultraviolet spectrophotometric assay versus a USP promethazine hydrochloride reference standard indicated a relative purity of 99.4 ± 1.4%. TLC analysis using system A resolved a major spot, a minor spot, and five trace impurities (one at the origin); using system B, a major spot, a minor spot, and four trace impurities (one at the origin) were observed. Concurrent analyses of a USP standard of promethazine hydrochloride indicated a major spot, a minor spot, and three trace impurities (one at the origin) using system A, and one major spot, one minor spot, and two trace impurities (one at the origin) using system B. Gas chromatography using system A resolved a major peak and three impurities with a combined relative area of approximately 1%. Gas chromatography using system B indicated a major peak and a single impurity with an area 0.30% of the major peak area. Gas chromatographic major peak comparison between lot 31321 and a USP standard indicated a relative purity of 99.5 ± 1.2% using system B. The overall purity was determined to be greater than 99%.

Stability studies were performed by the analytical chemistry laboratory. Gas chromatography was performed using system A described above except with an isothermal oven temperature of 220° C. These studies indicated that promethazine hydrochloride was stable for 2 weeks at temperatures up to 60° C when stored in sealed containers in the dark. The stability of the bulk chemical was monitored periodically at the study laboratory with gas chromatography as described above and using titration of the amine group. No degradation of the bulk chemical was observed.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations were prepared by dissolving promethazine hydrochloride in deionized water (Table H1). The mixture was stored in labeled, amber-glass dosing bottles for no longer than 3 weeks at 0 ± 5° C.

Dose formulation stability analyses of the 0.5 mg/mL dose formulation were performed by the analytical chemistry laboratory. Aliquots were mixed with 6 mL of internal standard solution (*p*-terphenyl, 0.5 mg/mL in acetonitrile) and diluted to 50 mL with acetonitrile. After mixing, gas chromatographic analysis was performed using system A described above except with an isothermal oven temperature of 215° C and a flow rate of 30 mL/minute. The stability of the dose formulations was confirmed for at least 3 weeks when stored in the dark at room temperature and for at least 3 hours stored under simulated dosing room conditions.

Periodic analyses of the dose formulations of promethazine hydrochloride were conducted at the study laboratory using ultraviolet spectrophotometry for the 16-day and 13-week studies and using gas chromatography for the 2-year studies. Periodic analyses of the dose formulations of promethazine hydrochloride were conducted at the analytical chemistry laboratory using gas chromatography. During the 16-day studies, all dose formulations for rats and mice were within the acceptable range of ± 10% of target concentrations (Table H2). During the 13-week studies, 23 of the 28 dose formulations analyzed were within 10% of the target concentrations (Table H3). During the 2-year studies, dose formulations were analyzed approximately every 8 weeks; 122 of the 123 dose formulations analyzed were within 10% of the target concentrations. Results of the dose formulation analyses for the 2-year studies are presented in Table H4. Results of periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results obtained by the study laboratories (Table H5).

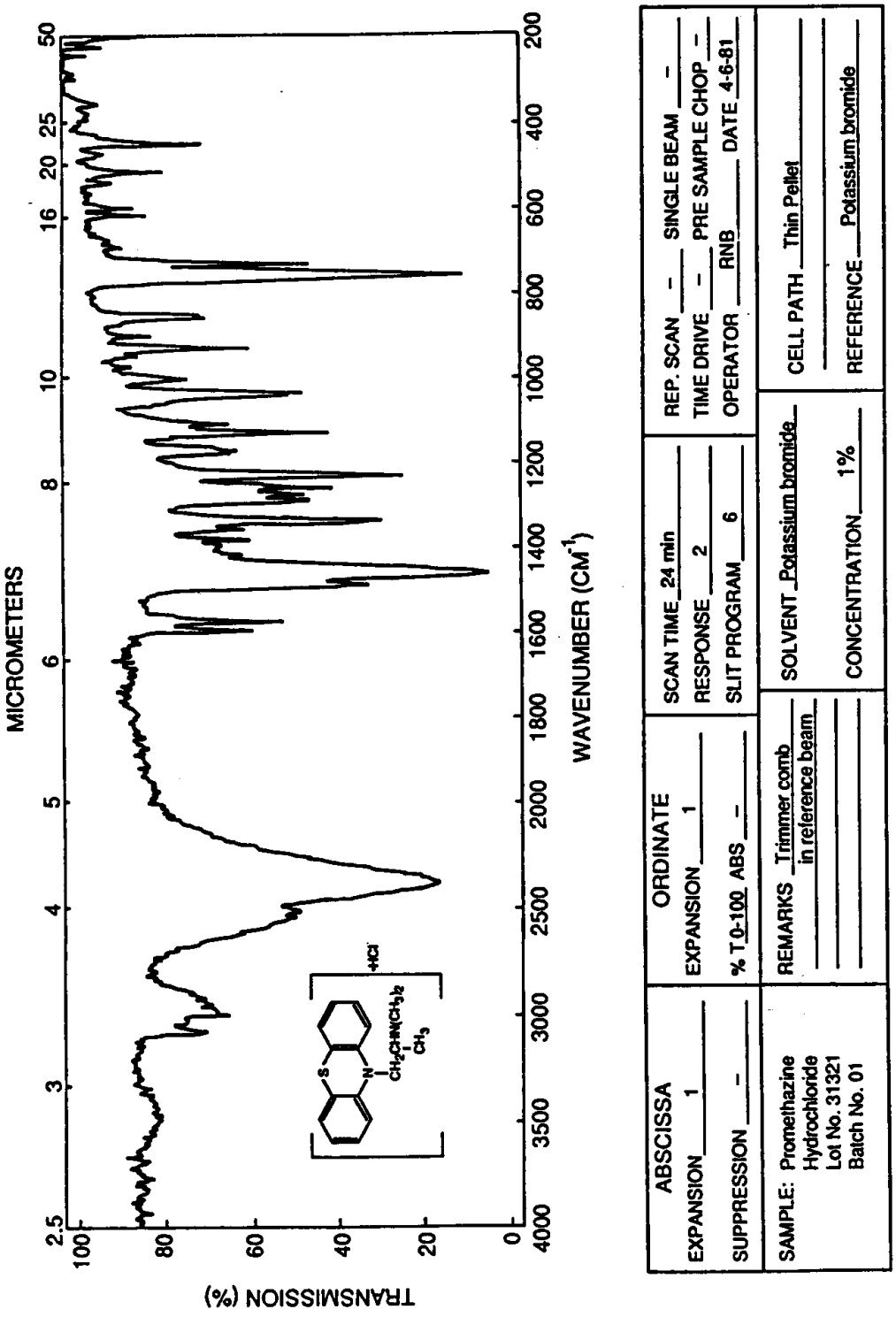

FIGURE H1
Infrared Absorption Spectrum of Promethazine Hydrochloride

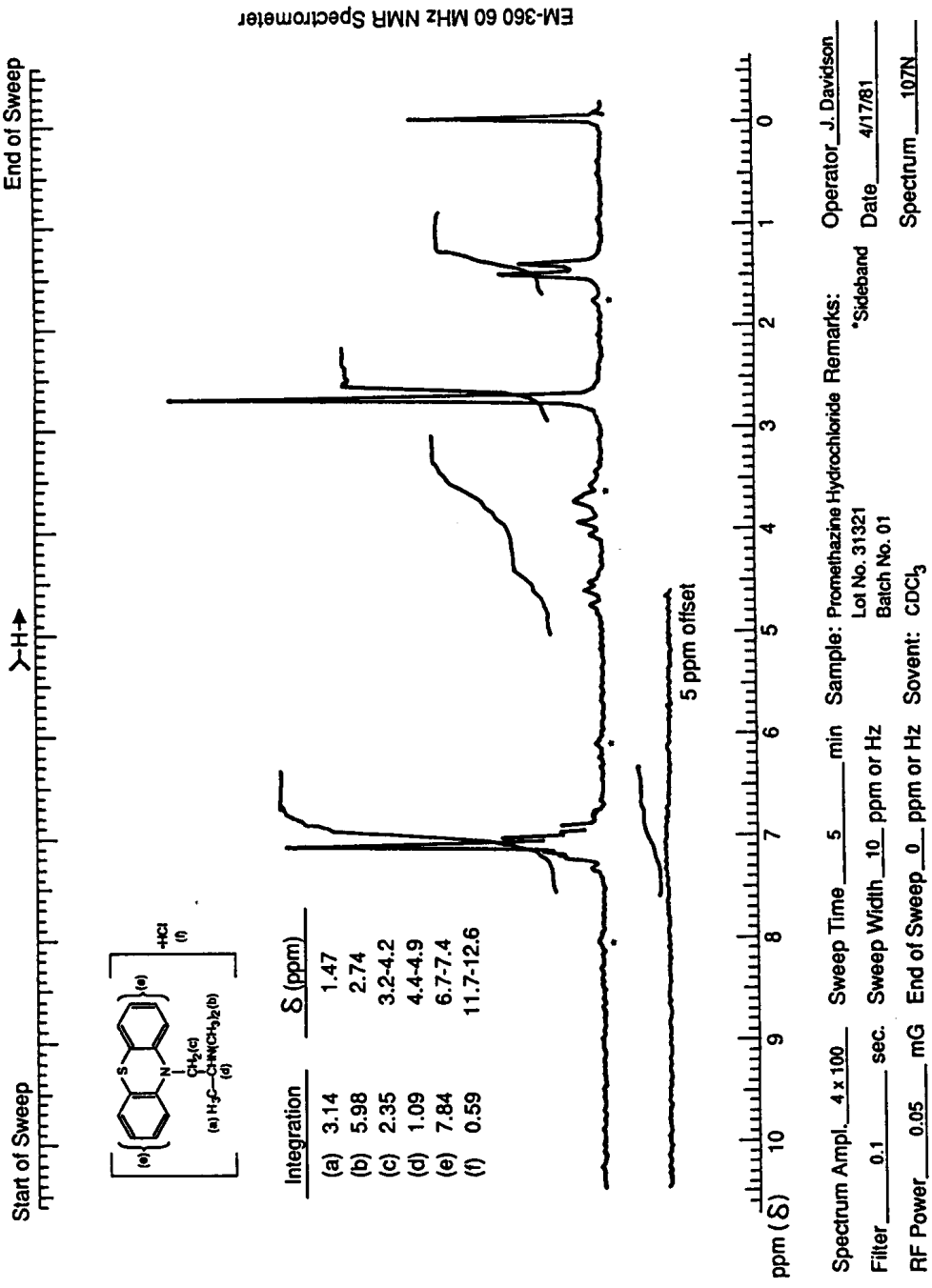

FIGURE H2
Nuclear Magnetic Resonance Spectrum of Promethazine Hydrochloride

TABLE H1
Preparation and Storage of Dose Formulations in the Gavage Studies of Promethazine Hydrochloride

16-Day Studies	13-Week Studies	2-Year Studies
Preparation		
Solutions were mixed with deionized water in a graduated cylinder and inverted several times to produce a solution.	Same as 16-day studies	Same as 16-day studies
Chemical Lot Number		
31321	31321	31321
Maximum Storage Time		
3 weeks	3 weeks	3 weeks
Storage Conditions		
In amber glass, labeled dosing bottles; sealed and stored at 4° C	Same as 16-day studies	Same as 16-day studies
Study Laboratory		
Litton Bionetics, Inc. Kensington, MD	Same as 16-day studies	EG&G Mason Research Institute, Worcester, MA
Referee Laboratory		
Midwest Research Institute, Kansas City, MO	Same as 16-day studies	Same as 16-day studies

TABLE H2
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 16-Day Gavage Studies of Promethazine Hydrochloride

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	Difference from Target (%)
Rats				
17 February 1982	19 February 1982	3.70	3.68	0
		11.1	11.5	+4
		33.3	34.5	+4
		100	98.8	)1
		300	304	+1
	3 March 1982[c]	3.70	3.74	+1
		11.1	11.4	+3
		33.3	33.6	+1
		100	99.9	0
		300	310	+3
Mice				
17 February 1982	18 February 1982	1.88	1.76	)6
		3.75	3.82	+2
		7.50	7.48	0
		15.0	15.4	+3
		30.0	31.5	+5
	3 March 1982[c]	1.88	1.79	)5
		3.75	3.67	)2
		7.50	7.64	+2
		15.0	15.4	+3
		30.0	30.8	+3

[a] Rats: Dosing volume = 5 mL/kg; 18.5 mg/kg = 3.70 mg/mL, 55.5 mg/kg = 11.1 mg/mL, 166.5 mg/kg = 33.3 mg/mL, 500 mg/kg = 100 mg/mL, 1,500 mg/kg = 300 mg/mL
Mice: Dosing volume = 10 mL/kg; 18.8 mg/kg = 1.88 mg/mL, 37.5 mg/kg = 3.75 mg/mL, 75.0 mg/kg = 7.50 mg/mL, 150 mg/kg = 15 mg/mL, 300 mg/kg = 30 mg/mL.
[b] Results of duplicate analyses
[c] Animal-room samples

TABLE H3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Gavage Studies of Promethazine Hydrochloride

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	Difference from Target (%)
Rats				
10 June 1982	11 June 1982	0.74	0.72	)3
		2.22	2.28	+3
		6.66	6.78	+2
		20.0	19.8	)1
		60.0	59.8	0
	23 June 1982[c]	0.74	0.89	+20
		2.22	2.30	+4
		6.66	5.97	)10
		20.0	20.4	+2
		60.0	60.9	+2
15 July 1982	19 July 1982	0.74	)[d]	)
		2.22	)[d]	)
		6.66	)[d]	)
		20.0	)[d]	)
		60.0	)[d]	)
19 July 1982[e]	20 July 1982	0.74	0.71	)4
		2.22	2.25	+1
		6.66	6.55	)2
		20.0	19.6	)2
		60.0	58.5	)2
	28 July 1982[c]	0.74	0.68	)8
		2.22	2.18	)2
		6.66	6.59	)1
		20.0	19.7	)1
		60.0	54.8	)9
9 September 1982	9 September 1982	0.74	0.78	+5
		2.22	2.34	+5
		6.66	6.90	+4
		20.0	20.8	+4
		60.0	61.8	+3

TABLE H3
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 13-Week Gavage Studies of Promethazine Hydrochloride (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice				
3 June 1982	4 June 1982	0.5	0.52	+4
		1.5	1.48	)2
		4.5	4.40	)4
		13.5	13.6	+1
		40.5	41.0	+1
	15 June 1982[c]	0.5	0.52	+4
		1.5	1.50	0
		4.5	4.48	0
		13.5	13.4	)1
		40.5	40.0	)1
8 July 1982	12 July 1982	0.5	0.49	)2
		1.5	1.47	)2
		4.5	4.45	)1
		13.5	13.5	0
	23 July 1982[c]	0.5	0.47	)6
		1.5	1.51	+1
		4.5	4.46	)1
		13.5	13.4	)1
19 July 1982	20 July 1982	0.5	0.49	)2
		1.5	1.38	)8
		4.5	4.30	)4
		13.5	12.6	)7
2 September 1982	3 September 1982	0.5	0.47	)6
		1.5	1.50	0
		4.5	4.55	+1
		13.5	13.66	+1

[a] Rats: Dosing volume = 5 mL/kg; 3.7 mg/kg = 0.74 mg/mL, 11.1 mg/kg = 2.22 mg/mL, 33.3 mg/kg = 6.66 mg/mL, 100 mg/kg = 20 mg/mL, 300 mg/kg = 60 mg/mL.
Mice: Dosing volume = 10 mL/kg; 5 mg/kg = 0.5 mg/mL, 15 mg/kg = 1.5 mg/mL, 45 mg/kg = 4.5 mg/mL, 135 mg/kg = 13.5 mg/mL, 405 mg/kg = 40.5 mg/mL.
[b] Results of duplicate analyses
[c] Animal-room samples
[d] Off scale; sample remixed
[e] Analysis results of remix

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Promethazine Hydrochloride

Date Prepared	Date Analyzed	Target Concentration[a] (mg/mL)	Determined Concentration[b] (mg/mL)	Difference from Target (%)
Rats				
22 February 1985	26 February 1985	1.66	1.53	)8
		3.32	3.30	)1
		6.66	6.54	)2
	19 March 1985[c]	1.66	1.66	0
		3.32	3.34	0
		6.66	6.65	0
10 May 1985	13 May 1985	1.66	1.68	+1
		3.32	3.28	)1
		6.66	6.59	)1
14 June 1985	18 June 1985	1.66	1.68	+1
		3.32	3.28	)1
		6.66	6.63	)1
9 August 1985	14 August 1985	1.66	1.73	+5
		3.32	3.39	+2
		6.66	6.79	+2
	16 October 1985[c]	1.66	1.73	+4
		3.32	3.51	+6
		6.66	7.15	+7
11 October 1985	16 October 1985	1.66	1.80	+9
		3.32	3.46	+4
		6.66	6.87	+3
6 December 1985	9 December 1985	1.66	1.73	+4
		3.32	3.34	+1
		6.66	6.37	)4
24 January 1986	28 January 1986	1.66	1.91	+15
		3.32	3.51	+6
		6.66	6.96	+5
	4 March 1986[c]	1.66	1.61	)1
		3.32	3.30	)1
		6.66	6.57	)1
14 March 1986	18 March 1986	1.66	1.68	+1
		3.32	3.40	+2
		6.66	6.57	)1
16 May 1986	20 May 1986	1.66	1.51	)9
		3.32	3.27	)2
		6.66	6.84	+3

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Promethazine Hydrochloride (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Rats (continued)				
11 July 1986	14 July 1986	1.66	1.80	+8
		3.32	3.26	)2
		6.66	6.57	)13
31 October 1986	3 November 1986	1.66	1.60	)4
		3.32	3.21	)3
		6.66	6.45	)3
12 December 1986	16 December 1986	1.66	1.82	+9
		3.32	3.36	+1
		6.66	6.78	+2
	7 January 1987[c]	1.66	1.63	)2
		3.32	3.23	)3
		6.66	6.56	)2
20 February 1987	23 February 1987	1.66	1.65	)1
		3.32	3.16	)5
		6.66	6.25	)6
Mice				
19 April 1985	22 April 1985	0.375	0.396	+6
		0.75	0.75	0
		1.125	1.11	)1
		1.50	1.48	)1
		2.25	2.13	)5
		4.50	4.46	)1
	9 May 1985[c]	0.375	0.387	+3
		0.75	0.74	)1
		1.125	1.12	)1
		1.50	1.43	)5
		2.25	2.28	+1
		4.50	4.43	)2
10 May 1985	13 May 1985	2.25	2.23	)1
		4.50	4.37	)3
	14 May 1985	0.375	0.378	+1
		0.75	0.74	)2
		1.125	1.13	+1
		1.50	1.54	+3

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Promethazine Hydrochloride (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
14 June 1985	17 June 1985	0.375	0.364	)3
		0.75	0.69	)8
		1.125	1.098	)2
		1.50	1.49	)1
	18 June 1985	2.25	2.24	0
		4.50	4.42	)2
9 August 1985	13 August 1985	0.375	0.366	)2
		0.75	0.72	)4
		1.125	1.093	)3
		1.50	1.47	)2
	14 August 1985	2.25	2.30	+2
		4.50	4.58	+2
	15 October 1985[c]	0.375	0.362	)4
		0.75	0.73	)3
		1.125	1.113	)1
		1.50	1.45	)3
	16 October 1985[c]	2.25	2.23	)1
		4.50	4.88	+9
11 October 1985	15 October 1985	0.375	0.384	+2
		0.75	0.79	+5
		1.125	1.184	+5
		1.50	1.52	+1
	16 October 1985	2.25	2.33	+4
		4.50	4.70	+4
6 December 1985	9 December 1985	0.375	0.393	+5
		0.75	0.77	+3
		1.125	1.188	+6
		1.50	1.65	+10
		2.25	2.34	+4
		4.50	4.44	)1
24 January 1986	27 January 1986	0.375	0.359	)4
		0.75	0.71	)6
		1.125	1.15	+2
		1.50	1.45	)3
	28 January 1986	2.25	2.47	+10
		4.50	4.81	+7

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Promethazine Hydrochloride (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
24 January 1986	4 March 1986[c]	0.375	0.385	+3
		0.75	0.76	+1
		1.125	1.16	+3
		1.50	1.56	+4
		2.25	2.23	)1
		4.50	4.50	0
14 March 1986	18 March 1986	0.375	0.361	)4
		0.75	0.72	)4
		1.125	1.125	0
		1.50	1.52	+1
		2.25	2.30	+2
		4.50	4.45	)1
16 May 1986	19 May 1986	0.375	0.356	)5
		0.75	0.72	)4
		1.125	1.13	+1
		1.50	1.53	+2
	20 May 1986	2.25	2.05	)9
		4.50	4.56	+1
11 July 1986	14 July 1986	0.375	0.41	+9
		0.75	0.74	)1
		1.125	1.17	+4
		1.50	1.59	+6
		2.25	2.25	0
		4.50	4.43	)2
12 September 1986	15 September 1986	0.375	0.385	+3
		0.75	0.75	)1
		1.125	1.11	)1
		1.50	1.50	0
		2.25	2.17	)4
		4.50	4.45	)1
	6 October 1986[c]	0.375	0.357	)5
		0.75	0.71	)6
		1.125	1.09	)3
		1.50	1.50	0
		2.25	2.19	)3
		4.50	4.53	+1

TABLE H4
Results of Analysis of Dose Formulations Administered to Rats and Mice in the 2-Year Gavage Studies of Promethazine Hydrochloride (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	Difference from Target (%)
Mice (continued)				
31 October 1986	3 November 1986	0.375	0.381	+2
		0.75	0.74	)1
		1.125	1.118	)1
		1.50	1.51	+1
		2.25	2.20	)2
		4.50	4.40	)2
12 December 1986	16 December 1986	0.375	0.399	+6
		0.75	0.75	)1
		1.125	1.159	+3
		1.50	1.56	+4
		2.25	2.33	+3
		4.50	4.49	0
	7 January 1987[c]	0.375	0.337	)10
		0.75	0.68	)9
		1.125	1.075	)5
		1.50	1.48	)2
		2.25	2.28	+1
		4.50	4.34	)4
20 February 1987	23 February 1987	0.375	0.381	+2
		0.75	0.76	+1
		1.125	1.136	+1
		1.50	1.49	)1
		2.25	2.27	+1
		4.50	4.40	)2

[a] Rats: Dosing volume = 5 mL/kg; 8.3 mg/kg = 1.66 mg/mL, 16.6 mg/kg = 3.32 mg/mL, 33.3 mg/kg = 6.66 mg/mL
Mice: Dosing volume = 10 mL/kg; 11.25 mg/kg = 1.125 mg/mL, 22.5 mg/kg = 2.25 mg/mL, 45 mg/kg = 4.50 mg/mL (males); 3.75 mg/kg = 0.375 mg/mL, 7.5 mg/kg = 0.75 mg/mL, 15 mg/kg = 1.50 mg/mL (females)
[b] Results of duplicate analyses
[c] Animal-room samples

TABLE H5
Results of Referee Analysis of Dose Formulations Administered in the 13-Week and 2-Year Gavage Studies of Promethazine Hydrochloride

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
13-Week Studies (Litton Bionetics, Inc.)			
Mice			
3 June 1982	13.5	13.6	13.2 ± 0.0
2-Year Studies (EG&G Mason Research Institute)			
Rats			
22 February 1985	1.66	1.53	1.65 ± 0.01
9 August 1985	6.66	6.79	6.45 ± 0.03
Mice			
14 March 1986	0.38	0.36	0.35 ± 0.00
12 September 1986	4.50	4.45	4.35 ± 0.06
20 February 1987	1.13	1.14	1.10 ± 0.01

[a] Results of duplicate analysis
[b] Results of triplicate analysis; mean ± standard deviation

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

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

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

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

TABLE I2
Vitamins and Minerals in NIH-07 Rat and Mouse Ration[a]

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

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

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

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	22.25 ± 0.57	21.2) 23.2	23
Crude Fat (% by weight)	5.54 ± 0.28	4.8) 6.0	23
Crude Fiber (% by weight)	3.46 ± 0.54	2.8) 5.4	23
Ash (% by weight)	6.44 ± 0.97	2.1) 7.9	23
Amino Acids (% of total diet)			
Arginine	1.308 ± 0.606	1.210) 1.390	8
Cystine	0.306 ± 0.084	0.181) 0.400	8
Glycine	1.150 ± 0.047	1.060) 1.210	8
Histidine	0.576 ± 0.024	0.531) 0.607	8
Isoleucine	0.917 ± 0.029	0.881) 0.944	8
Leucine	1.946 ± 0.055	1.850) 2.040	8
Lysine	1.270 ± 0.058	1.200) 1.370	8
Methionine	0.448 ± 0.128	0.306) 0.699	8
Phenylalanine	0.987 ± 0.140	0.665) 1.110	8
Threonine	0.877 ± 0.042	0.824) 0.940	8
Tryptophan	0.236 ± 0.176	0.107) 0.671	8
Tyrosine	0.676 ± 0.105	0.564) 0.794	8
Valine	1.103 ± 0.040	1.050) 1.170	8
Essential Fatty Acids (% of total diet)			
Linoleic	2.393 ± 0.258	1.830) 2.570	7
Linolenic	0.280 ± 0.040	0.210) 0.320	7
Vitamins			
Vitamin A (IU/kg)	7,565 ± 3,295	4,500) 19,000	23
Vitamin D (IU/kg)	4,450 ± 1,382	3,000) 6,300	4
α-Tocopherol (ppm)	37.95 ± 9.406	22.50) 48.90	8
Thiamine (ppm)	21.96 ± 3.57	19.0) 37.0	23
Riboflavin (ppm)	7.92 ± 0.87	6.10) 9.00	8
Niacin (ppm)	103.38 ± 26.59	65.0) 150.0	8
Pantothenic acid (ppm)	29.54 ± 3.60	23.0) 34.0	8
Pyridoxine (ppm)	9.55 ± 3.48	5.60) 14.0	8
Folic acid (ppm)	2.25 ± 0.73	1.80) 3.70	8
Biotin (ppm)	0.254 ± 0.042	0.19) 0.32	8
Vitamin B_{12} (ppb)	38.45 ± 22.01	10.6) 65.0	8
Choline (ppm)	3,089 ± 328.69	2,400) 3,430	8
Minerals			
Calcium (%)	1.13 ± 0.12	0.90) 1.35	23
Phosphorus (%)	1.14 ± 0.13	0.90) 1.39	23
Potassium (%)	0.883 ± 0.078	0.772) 0.971	6
Chloride (%)	0.526 ± 0.092	0.380) 0.635	8
Sodium (%)	0.313 ± 0.390	0.258) 0.371	8
Magnesium (%)	0.168 ± 0.010	0.151) 0.181	8
Sulfur (%)	0.280 ± 0.064	0.208) 0.420	8
Iron (ppm)	360.54 ± 100	255.0) 523.0	8
Manganese (ppm)	91.97 ± 6.01	81.70) 99.40	8
Zinc (ppm)	54.72 ± 5.67	46.10) 64.50	8
Copper (ppm)	11.06 ± 2.50	8.090) 15.39	8
Iodine (ppm)	3.37 ± 0.92	1.52) 4.13	6
Chromium (ppm)	1.79 ± 0.36	1.04) 2.09	8
Cobalt (ppm)	0.681 ± 0.14	0.490) 0.780	4

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

	Mean ± Standard Deviation[a]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.651 ± 0.25	0.20) 0.98	26
Cadmium (ppm)	0.10 ± 0.02	<0.10) 0.20	26
Lead (ppm)	0.41 ± 0.21	0.05) 0.87	26
Mercury (ppm)	0.05 ± 0.01	0.05) 0.08	26
Selenium (ppm)	0.37 ± 0.08	0.17) 0.48	26
Aflatoxins (ppb)	<5.0		26
Nitrate nitrogen (ppm)	19.96 ± 7.34	11.0) 37.0	26
Nitrite nitrogen (ppm)	0.28 ± 0.45	<0.10) 2.10	26
BHA (ppm)[b]	2.39 ± 0.84	<2.00) 5.00	26
BHT (ppm)[b]	1.35 ± 0.71	<1.00) 13.00	26
Aerobic plate count (CFU/g)[c]	127,261 ± 126,935	20,000) 450,000	26
Coliform (MPN/g)[d]	140 ± 160	<3.00) 460	26
E. coli (MPN/g)[e]	4.91 ± 8.31	<3.00) 43.0	23
E. coli (MPN/g)[f]	3.18 ± 0.39	3.00) 4.00	22
Total nitrosamines (ppb)[g]	7.37 ± 2.64	3.30) 13.30	26
N-Nitrosodimethylamine (ppb)[g]	6.33 ± 2.52	3.00) 13.00	26
N-Nitrosopyrrolidine (ppb)[g]	1.04 ± 1.11	0.30) 4.30	26
Pesticides (ppm)			
α-BHC[h]	<0.01		26
β-BHC	<0.02		26
γ-BHC	<0.01		26
δ-BHC	<0.01		26
Heptachlor	<0.01		26
Aldrin	<0.01		26
Heptachlor epoxide	<0.01		26
DDE	<0.01		26
DDD	<0.01		26
DDT	<0.01		26
HCB	<0.01		26
Mirex	<0.01		26
Methoxychlor	<0.05		26
Dieldrin	<0.01		26
Endrin	<0.01		26
Telodrin	<0.01		26
Chlordane	<0.05		26
Toxaphene	<0.1		26
Estimated PCBs	<0.2		26
Ronnel	<0.01		26
Ethion	<0.02		26
Trithion	<0.05		26
Diazinon	<0.1		26
Methyl parathion	<0.02		26
Ethyl parathion	<0.02		26
Malathion[i]	0.28 ± 0.66	0.05) 3.20	26
Endosulfan I	<0.01		26
Endosulfan 2	<0.01		26
Endosulfan sulfate	<0.03		26

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

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

APPENDIX J
SENTINEL ANIMAL PROGRAM

SENTINEL ANIMAL PROGRAM

METHODS

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

Rats

For the 13-week study, samples were obtained from control animals at terminal sacrifice. These samples were processed appropriately and were submitted to Microbiological Associates (Bethesda, MD) for viral titer screening. The following tests were performed on the serum of five male and five female control rats:

Method of Analysis	Time of Analysis
Complement Fixation	
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus	Study termination
RCV (rat coronavirus)	Study termination
Sendai	Study termination
ELISA	
MHV (mouse hepatitis virus)	Study termination
Hemagglutination Inhibition	
Ectromelia virus	Study termination
GDVII (mouse encephalomyelitis virus)	Study termination
H-1 (Toolan's H-1 virus)	Study termination
KRV (Kilham rat virus)	Study termination
MVM (minute virus of mice)	Study termination
Polyoma virus	Study termination
PVM (pneumonia virus mice)	Study termination
Reovirus 3	Study termination

During the 2-year study, serum samples for viral screening were collected from five male and five female rats at 6-month intervals; however, to better evaluate the virological burden of the study, some rats were live-bled so that sera could be collected at additional time points. Serum from the 24-month screening was obtained from five control males and five females from the control, low-dose, and mid-dose groups. Blood from each collection was processed appropriately, shipped to Microbiological Associates (Bethesda, MD), and screened for the following:

Method of Analysis	Time of Analysis
ELISA	
Cilia-associated respiratory bacillus	18 months
Mycoplasma arthritidis	6, 9, 12, 13, 14, 18, and 24 months
Mycoplasma pulmonis	6, 9, 12, 13, 14, 18, and 24 months
PVM	6, 9, 12, 13, 14, 18, 19, 20, 21, and 24 months
Sendai	6, 9, 12, 13, 14, 18, 19, 20, 21, and 24 months
RCV/SDA (rat coronavirus/ sialodacryoadenitis virus)	6, 9, 12, 13, 14, 18, 19, 20, 21, and 24 months
Hemagglutination Inhibition	
KRV	6, 9, 12, 13, 14, 18, 19, 20, 21, and 24 months
H-1	6, 9, 12, 13, 14, 18, 19, 20, 21, and 24 months

Mice

For the 13-week study, samples were obtained from control animals at terminal sacrifice. These samples were processed appropriately and were submitted to Microbiological Associates (Bethesda, MD) for viral titer screening. The following tests were performed on the serum of five male and five female control mice:

Method of Analysis	Time of Analysis
Complement Fixation	
LCM	Study termination
Mouse adenoma virus	Study termination
RCV	Study termination
Sendai	Study termination
ELISA	
MHV	Study termination
Hemagglutination Inhibition	
Ectromelia virus	Study termination
GDVII	Study termination
H-1	Study termination
KRV	Study termination
MVM	Study termination
Polyoma virus	Study termination
PVM	Study termination
Reovirus 3	Study termination

During the 2-year study, serum samples for viral screening were collected from five male and five female mice at 6-month intervals; because of reduced survival in the sentinel animals, serum was collected from five male and two female mice at 18 months. To better evaluate the virological burden of the study, some mice were live-bled so that sera could be collected at additional time points. Serum from the 24-month screening was obtained from five control males and five control females. Blood from each collection was processed appropriately, shipped to Microbiological Associates (Bethesda, MD), and screened for the following:

Method of Analysis	Time of Analysis
Complement Fixation	
LCM	6, 11.5, 12.5, 13, and 18 months
ELISA	
Reovirus 3	6, 11.5, 12.5, 13, 18, 23, and 24 months
Ectromelia virus	6, 11.5, 12.5, 13, 18, 23, and 24 months
GDVII	6, 11.5, 12.5, 13, 18, 23, and 24 months
LCM	23 and 24 months
MHV	6, 11.5, 12.5, 13, 18, 23, and 24 months
Mouse adenoma virus	6, 11.5, 12.5, 13, 18, 23, and 24 months
MVM	23 and 24 months
M. arthritidis	6, 11.5, 12.5, 13, 18, 23, and 24 months
M. pulmonis	6, 11.5, 12.5, 13, 18, 23, and 24 months
PVM	6, 11.5, 12.5, 13, 18, 23, and 24 months
Sendai	6, 11.5, 12.5, 13, 18, 23, and 24 months
Hemagglutination Inhibition	
MVM	6, 11.5, 12.5, 13, and 18 months
Papovavirus	6, 11.5, 12.5, 13, 18, 23, and 24 months
Polyoma virus	6, 11.5, 12.5, 13, 18, 23, and 24 months
Immunofluorescence Assay	
Epizootic diarrhea of infant mice	6, 12.5, 13, 18, 23, and 24 months
Reovirus 3	11.5, 12.5, 13, and 18
Sendai	11.5

The serology results for rats and mice are presented in Table J1.

TABLE J1
Murine Virus Antibody Determinations for Rats and Mice in the 13-Week and 2-Year Gavage Studies of Promethazine Hydrochloride

Interval (months)	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
13-Week Studies		
Rats		
Study termination	0/20	None positive
Mice		
Study termination	0/20	None positive
2-Year Studies		
Male Rats		
6	0/5	None positive
12	3/3	Sendai
	2/2	Sendai
	5/5	Sendai
13	5/5	Sendai
14	5/5	Sendai
18	4/4	Sendai
20	1/1	Sendai
21	1/1	Sendai
24	5/5	Sendai
Female Rats		
6	1/5	KRV
9	1/2	KRV
12	5/5	Sendai
13	1/5	KRV
	5/5	Sendai
14	5/5	Sendai
18	4/4	Sendai
20	1/1	Sendai
24	3/3	Sendai
	5/5	Sendai
Mice (Male and Female)		
6	0/10	None positive
11.5	8/10	Reovirus 3
	1/10	Sendai
12.5	3/7	Reovirus 3
	1/6	*M. arthritidis*
	1/9	Sendai
13	1/10	MHV
18	1/7	Reovirus 3
23	0/1	None positive
24	0/5	None positive
	0/11	None positive