NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 317

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORPHENIRAMINE MALEATE

(CAS NO. 113-92-8)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

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

September 1986

NTP TR 317

NIH Publication No. 86-2573

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NOTE TO THE READER

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 testing in the NTP Carcinogenesis Program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

Five categories of interpretative conclusions were adopted for use in June 1983 in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

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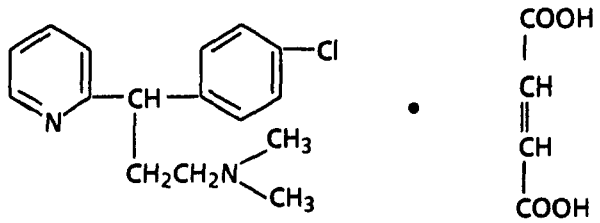


CHLORPHENIRAMINE MALEATE

(2-[*p*-chloro-α-(2-dimethylaminoethyl)benzyl]pyridine maleate; 2-pyridinepropanamine, γ-[4-chlorophenyl]-N,N-dimethyl-[z]-2-butenedioate)

CAS No. 113-92-8

$C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$ Molecular weight: 390.9

Trade Names: Allerclor, Allergisan, Antagonate, Chlormene, Chlorprophenpyridamine maleate, Chlor-Trimeton, Chlor-Tripolon, Chloropiril, C-Meton, Histadur, Histaspan, Lorphen, M.P. Chlorcaps T.D., Piriton, Pyridamal-100, Teldrin

ABSTRACT

Toxicology and carcinogenesis studies of chlorpheniramine maleate (99% pure), a widely used antihistaminic drug in human and veterinary medicine, were conducted by administering this chemical in deionized water by gavage to groups of 50 male and 50 female F344/N rats and B6C3F$_1$ mice, 5 days per week for 103 weeks. The doses used were: male rats--0, 15, or 30 mg/kg; female rats--0, 30, or 60 mg/kg; male mice--0, 25, or 50 mg/kg; female mice--0, 100, or 200 mg/kg. The selection of these doses was based largely on data from 14-day or 16-day studies and 13-week studies in which reduced body weight gain and reduced survival occurred at higher doses. Doses used in the 2-week studies ranged from 40 to 640 mg/kg in rats and 25 to 800 mg/kg in mice; in the 13-week studies, doses ranged from 3.75 to 60 mg/kg in rats and 12.5 to 200 mg/kg in mice. The recommended human adult daily oral dose of chlorpheniramine maleate is up to 0.32 mg/kg.

Doses originally selected for male mice in the 2-year study were 0, 100, or 200 mg/kg; however, because of poor survival, that study was stopped and a new study was started at doses of 0, 25, or 50 mg/kg. At the termination of the study (week 104), survival of high dose female rats (6/50) and high dose male mice (15/50) was lower than that of the vehicle controls (29/50 and 39/50, respectively). Survival of all other dosed groups was comparable to that of respective vehicle control groups. Mean body weights of dosed rats were about 10%-15% (male) or about 10%-25% (female) lower than those of the vehicle controls. Mean body weights of dosed male mice were 5%-10% lower than those of vehicle controls; mean body weights of female mice were generally 20%-35% lower than those of vehicle controls.

No compound-related gross or microscopic pathologic effects were observed in either species in the 16-day or 13-week studies. Hyperactivity and hyperexcitability associated with dosing were frequently noted in the 13-week and 2-year studies. There were no significant positive trends or increases in the incidences of neoplasms in either male or female rats dosed with chlorpheniramine maleate for 103 weeks. Marginal increases in the incidences of adrenal gland capsule adenomas in male mice (vehicle

control, 2/50; low dose, 7/49; high dose, 4/49) were not considered to be compound related, since there was not a corresponding increase in the incidence of adrenal gland capsule hyperplasia (46/50; 33/49; 22/49). A positive trend was seen for subcutaneous tissue tumors in male mice (4/50; 5/49; 8/50); this marginal effect was not considered to be compound related.

The incidences of thyroid gland follicular cell cysts (2/48; 10/49; 13/47), thyroid gland follicular cell hyperplasia (3/48; 29/49; 36/47), and thyroid gland follicular cell adenomas (0/48; 4/49; 2/47) were greater in dosed female mice than in vehicle controls. This finding is toxicologically important, since thyroid gland neoplasms are uncommon in mice and are often preceded by hyperplasia of the follicular epithelium.

The major route of excretion of chlorpheniramine or its metabolites is in the urine. In male F344 rats orally administered ^{14}C-chlorpheniramine maleate at doses of 2 or 20 mg/kg, there was essentially no difference in the percentage of urinary or fecal excretion of radioactivity between these dose levels.

Chlorpheniramine maleate was not mutagenic to Salmonella strains TA98, TA100, TA1535, or T1537 in the presence or absence of S9 metabolic activation systems prepared from the liver of Aroclor 1254-treated male Sprague-Dawley rats or male Syrian hamsters. Chlorpheniramine maleate did not induce forward mutations at the TK locus of L5178Y mouse lymphoma cells with or without metabolic activation. In Chinese hamster ovary cells in culture, chlorpheniramine maleate induced a weak but reproducible increase in sister-chromatid exchanges in the absence of exogenous metabolic activation. Chromosomal aberrations were induced at the highest dose tested but only in the presence of S9 from Aroclor 1254-induced Sprague-Dawley male rat liver.

An audit of the experimental data was conducted for these 2-year carcinogenesis studies on chlorpheniramine maleate. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** for F344/N rats or B6C3F$_1$ mice of either sex administered chlorpheniramine maleate in deionized water, 5 days per week for 2 years. Due to high mortality in high dose female rats and high dose male mice, the sensitivity of these groups to detect a carcinogenic response was reduced. Chlorpheniramine maleate had a proliferative effect on the thyroid gland of female mice, as shown by the increased incidences of follicular cell cysts and hyperplasia in both low dose and high dose groups.

*Categories of evidence of carcinogenicity are defined in the Note to Reader on page 2. The discussion regarding the interpretative conclusions is summarized on pages 13 and 14.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chlorpheniramine Maleate is based on the 13-week studies that began in February 1980 and ended in May 1980 and on the 2-year studies that began in October 1980 (rats), February 1981 (female mice), and October 1981 (male mice) and ended in October 1982 (rats), February 1983 (female mice), and October 1983 (male mice) at Battelle Columbus Laboratories.

National Toxicology Program
(Evaluated Experiment, Interpreted Results, and Reported Findings)

R.L. Melnick, Ph.D., Chemical Manager

Charles J. Alden, Ph.D.
Gary A. Boorman, D.V.M., Ph.D.
M. Elwell, D.V.M., Ph.D.
S. Eustis, D.V.M., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
C.W. Jameson, Ph.D.
E.E. McConnell, D.V.M.
J.H. Mennear, Ph.D.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
Raymond W. Tennant, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report for Rats on 2/265)

Paul Hildebrandt, D.V.M. (Chair)
PATHCO
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Melvin Hamlin, D.V.M.
Experimental Pathology Laboratories
Gaymen Helman, D.V.M., Ph.D.
University of Tennessee
Joe Mahler, D.V.M. (NTP)
Ronald Persing, D.V.M.
Battelle Columbus Laboratories

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report for Mice on 4/11/85)

Roger Alison, M.R.C.V.S (Chair) (NTP)
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Bhola Gupta, B.V.Sc., Ph.D. (NTP)
Ronald Persing, D.V.M.
Battelle Columbus Laboratories
James Popp, D.V.M., Ph.D.
Chemical Industry Institute of Toxicology
George Szczech, D.V.M., Ph.D.
Burroughs Wellcome Laboratories

Principal Contributors at Battelle Columbus Laboratories
(Conducted Studies and Evaluated Tissues)

A. Peters, D.V.M.
Principal Investigator
A. Killmeyer, B.S., Chemist
E. Leighty, Ph.D., Chemist
R. Persing, D.V.M., Pathologist
R. Wilson, B.S., Chemist

Principal Contributors at Experimental Pathology Laboratories
(Provided Pathology Quality Assurance)

Melvin Hamlin, D.V.M.
Jenece Gauchat, Pathology Coordinator

Principal Contributors at Carltech Associates, Inc.
(Contractor for Technical Report Preparation)

William D. Theriault, Ph.D.
Project Manager
Abigail C. Jacobs, Ph.D.
Senior Scientist
John Warner, M.S.
Chemist/Statistician

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on chlorpheniramine maleate on December 9, 1985, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors
Technical Reports Review Subcommittee

Jerry B. Hook, Ph.D. (Chair)
Vice President, Preclinical Research and Development
Smith Kline & French Laboratories, Philadelphia, Pennsylvania

Frederica Perera, Dr. P.H.
Division of Environmental Sciences
School of Public Health
Columbia University
New York, New York

James Swenberg, D.V.M., Ph.D.
Head, Department of Biochemical Toxicology and Pathobiology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Ad Hoc Subcommittee Panel of Experts

John J. Crowley, Ph.D.
Division of Public Health Services
The Fred Hutchinson Cancer Research Center
Seattle, Washington

Kim Hooper, Ph.D.
Hazard Evaluation System and Information Services
Department of Health Services, State of California
Berkeley, California

Thomas C. Jones, D.V.M.
Professor, Comparative Pathology
New England Regional Primate Research Center
Harvard Medical School
Southborough, Massachusetts

Richard J. Kociba, D.V.M., Ph.D.
Dow Chemical USA
Midland, Michigan

David Kotelchuck, Ph.D.*
Environmental Health Science Program
Hunter School of Health Sciences
New York, New York

Franklin E. Mirer, Ph.D.
Director, Health and Safety Department
International Union, United Auto Workers
Detroit, Michigan

I.F.H. Purchase, Ph.D. (Principal Reviewer)
Director, Central Toxicology Laboratory
Imperial Chemical Industries, PLC
Alderley Park, England

Robert A. Scala, Ph.D.
Senior Scientific Advisor, Medicine and Environmental Health Department
Exxon Corporation
East Millstone, New Jersey

Steven R. Tannenbaum, Ph.D.
(Principal Reviewer) Professor
Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts

Bruce W. Turnbull, Ph.D.
(Principal Reviewer)
Professor and Associate Director
College of Engineering, Cornell University
Ithaca, New York

*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORPHENIRAMINE MALEATE

On December 9, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of chlorpheniramine maleate received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held in the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. R. Melnick, NTP Chemical Manager, introduced the toxicology and carcinogenesis studies of chlorpheniramine maleate by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenicity in rats or mice). Dr. Turnbull, a principal reviewer, agreed in general with the conclusions as stated, although he expressed concern about whether the study had enough power to detect an effect, primarily because of the decreased survival in high dose female rats and male mice. He said that the estimated maximum tolerated dose (EMTD) was exceeded in both groups and possibly at both dose levels in female mice. Dr. Turnbull noted that it is much more difficult to substantiate a negative result than a positive result when there is reduced statistical power and that some consideration should be given to classifying the conclusions in female rats and male and female mice as inadequate studies of carcinogenicity.

As a second principal reviewer, Dr. Purchase agreed with the conclusions but also agreed with Dr. Turnbull that there be some debate and consideration given to categorizing the studies in mice as inadequate. He said that the importance of high mortality and reduced body weight in some of the groups on interpretation of the studies should be given more emphasis in the report. Dr. Purchase noted that considerable information for this chemical is available on metabolism and pharmacokinetics in humans and animals and should have been used in choosing the dose levels; this information also could aid in the discussion by putting the results of the animal studies into the context of human hazard. Dr. Melnick said that there would be additional discussion on the possibility of metabolism in mice being altered as a function of administration, as well as on a comparison of what is known about chlorpheniramine pharmacokinetics in rodents versus that in humans.

As a third principal reviewer, Dr. Tannenbaum agreed with the conclusions. He commented that no attempt was made to analyze for nitrosamine contamination and, had this been a positive study, this omission could have compromised interpretation. Further, unlike humans, rats lack the capacity for endogenous nitrosation. Dr. Melnick said that nitrosation studies had been considered but were not performed.

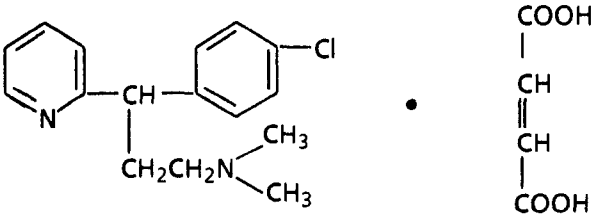
Discussion was focused on the issue of adequacy of the high dose studies in female rats and male mice. Excessive mortality in the original groups of male mice had required starting another study at lower dose levels. Dr. Melnick stated that survival in low dose groups of male mice and female rats was considered to be adequate to detect a carcinogenic response. Dr. Perera and Dr. Hooper supported a designation of inadequate study for both groups. In particular, Dr. Hooper commented on the marginally significant increases in adrenal gland capsular adenomas in male mice, lesions he opined might have been more pronounced had there been an intermediate dose group between the low and high doses. Dr. Swenberg mentioned that as a guideline, if there is 50% survival after 78 weeks, the study is considered to be adequate. Dr. J. Huff, NTP, indicated that most organizations suggest that survival in all groups should be 50% at the end of the studies to be considered adequate for negative (no evidence) studies.

Dr. Turnbull moved that the findings in male mice be considered an inadequate study of carcinogenicity based on the conduct of the study, e.g., the two starts, and the exceeding of the EMTD. Dr. Hooper seconded the motion. In discussion after the motion, Dr. Purchase stated that he now felt the available information supported the study's being adequate to assess a carcinogenic response. The motion was defeated by eight negative votes to three affirmative votes (Dr. Crowley, Dr. Perera, and Dr. Turnbull). Dr. Hooper then moved that the study in male mice be considered equivocal evidence of carcinogenicity based on the increases in adrenal gland capsular adenomas. Dr. Swenberg seconded the motion, and it was defeated by 10 negative votes to 1 affirmative vote (Dr. Hooper). Dr. Purchase moved that the conclusions as written for male mice, no evidence of carcinogenicity, be accepted. Dr. Jones seconded the motion, and it was approved by eight affirmative votes to three negative votes (Dr. Crowley, Dr. Perera, and Dr. Turnbull). Dr. Purchase moved that the conclusions as written for male and female rats and female mice, no evidence of carcinogenicity, be accepted. Dr. Kociba seconded the motion, and it was approved unanimously with 11 affirmative votes.

I. INTRODUCTION

Animal Toxicity Studies
Metabolism and Pharmacokinetics
Developmental Toxicity
Genotoxicity
Carcinogenicity
Human Effects
Study Rationale

I. INTRODUCTION



CHLORPHENIRAMINE MALEATE

(2-[*p*-chloro-α-(2-dimethylaminoethyl)benzyl]pyridine maleate; 2-pyridinepropanamine, γ-[4-chlorophenyl]-N,N-dimethyl-[z]-2-butenedioate)

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Chlorpheniramine maleate is a white crystalline solid commonly used as an antihistamine in human and veterinary medicine (Douglas, 1980; Merck, 1983). Preparations of chlorpheniramine maleate are available in tablet, injectable, or syrup forms. The recommended therapeutic dosage for adults is 2-4 mg four times a day (Modell, 1980; Douglas, 1980). Chlorpheniramine maleate has a relatively high melting point (130°-135° C) and therefore poses little exposure potential from vapor inhalation.

Chlorpheniramine maleate has been approved by the Food and Drug Administration for use as an over-the-counter drug (Fed. Reg., 1976). U.S. production of all antihistamine products in 1983 was 229,000 pounds (USITC, 1984a). Domestic production for chlorpheniramine maleate was 47,000 pounds in 1978, the last year in which production data on this drug were reported (USITC, 1979). In 1983, 28,633 pounds of chlorpheniramine maleate was imported into the United States (USITC, 1984b).

Chlorpheniramine maleate is an H_1-receptor antihistamine in which the substituted ethylamine moiety is connected by a carbon atom to the remainder of the molecule. It has been widely used in the symptomatic treatment of the common cold and allergic responses of the skin or mucous membranes. Chlorpheniramine maleate is effective in blocking the constrictor action of histamine on respiratory smooth muscle and in antagonizing the increase in capillary permeability and edema formation caused by histamine (Cirillo and Tempero, 1976; Douglas, 1980; Schachter et al., 1982). However, H_1-receptor antagonists may also stimulate or depress the central nervous system, and undesirable side effects such as drowsiness, dryness of the mouth, and dizziness have been associated with the use of chlorpheniramine maleate.

Animal Toxicity Studies

The toxic profile of chlorpheniramine maleate in rats and mice includes excitation, muscle tremor, ataxia, and convulsive seizures followed by respiratory depression and death (Smith et al., 1974). LD_{50} values reported for chlorpheniramine maleate in rats, mice, and guinea pigs are presented in Table 1. Beliles (1972) found no difference in the acute toxicity of chlorpheniramine maleate in pregnant and nonpregnant CD-1 mice. Adult Holtzman and Wistar rats are more resistant to chlorpheniramine maleate than are newborn rats (Lee, 1966; Goldenthal, 1971).

Chlorpheniramine maleate was administered by gavage to groups of 12 female Sprague-Dawley

TABLE 1. LD_{50} VALUES OF CHLORPHENIRAMINE MALEATE IN RATS, MICE, AND GUINEA PIGS (a)

Species	Route of Administration				Reference
	Oral	Subcutaneous	Intraperitoneal	Intravenous	
Rat	118		89		Roth and Govier, 1958
	198 (1 day old)	182 (4 days old)			Lee, 1966
	540 (40 days old)	365 (40 days old)			Lee, 1966
	284 (1 day old)				Goldenthal, 1971
	680 (adult)				Goldenthal, 1971
Mouse	121		73	20	Roth and Govier, 1958
	162				Smith et al., 1974
	142	104	76.7	39.6	Labelle and Tislow, 1955
				26.1	Beliles, 1972
Guinea pig	186				Roth and Govier, 1958
	198	101.1			Labelle and Tislow, 1955

(a) LD_{50} values are given in milligrams per kilogram body weight (mg/kg).

rats for 29 days at doses of 0, 2, 5, 10, or 25 mg/kg body weight and in feed (average daily dose, 1 mg/kg) for three successive generations to male and female Sprague-Dawley rats (Labelle and Tislow, 1955). No clinical, hematologic, or pathologic alterations were apparent in either study.

No compound-related effects were reported after chlorpheniramine maleate was administered by gavage to groups of eight male and eight female rats (strain not specified) 5 days per week for 6 weeks at doses of 5 or 10 mg/kg per day. Similar experiments in which two rhesus monkeys were administered 20 mg/kg per day 5 days per week for 7 weeks resulted in no apparent adverse effects (Roth and Govier, 1958). Groups of four male and four female rhesus monkeys were administered chlorpheniramine maleate, dissolved in distilled water, by gavage at doses of 0, 5, 10, or 15 mg/kg, 6-7 days per week for 105 weeks (Schering Corp., 1975a, unpublished). Deaths of 5/8 high dose monkeys were attributed to cardiac failure. No compound-related gross or microscopic effects were observed in this study. Heart rates were decreased and the duration of electrical systole was prolonged in monkeys in the 10 and 15 mg/kg dose groups. Cardiac arrhythmias and fainting episodes occurred in the 15 mg/kg dose group.

Metabolism and Pharmacokinetics

Chlorpheniramine is rapidly and completely absorbed from the gastrointestinal tract of rats, dogs, and humans (Kamm et al., 1969; Peets et al., 1972a,b; Appendix N). The low bioavailability of chlorpheniramine maleate reported in New Zealand rabbits (Huang et al., 1981) was attributed to a saturable presystemic elimination pathway in this species.

Peak plasma levels of chlorpheniramine are achieved within 2-4 hours following ingestion in humans (Peets et al., 1972a; Huang et al., 1982), 30-60 minutes in rats and dogs (Kamm et al., 1969; Athanikar and Chiou, 1979), and 1.3 hours in rabbits (Huang et al., 1981). The plasma half-life of chlorpheniramine in adult humans receiving tablets containing 8-12 mg of chlorpheniramine maleate ranges from 12 to 43 hours (Peets et al., 1972a; Huang et al., 1982; Chiou et al., 1979; Yacobi et al., 1980; Kotzan et al., 1982).

The elimination half-life of chlorpheniramine is shorter in children than in adults (Thompson et al., 1981). The mean half-life of elimination of chlorpheniramine was 2.57 hours in rabbits (Huang and Chiou, 1981) and 1.7-3 hours in dogs (Athanikar and Chiou, 1979; Peets et al., 1972b). The decline in serum or plasma concentrations

of chlorpheniramine in humans or experimental animals has been described by bi- or triexponential equations (Peets et al., 1972a; Huang and Chiou, 1981; Athanikar and Chiou, 1979; Huang et al., 1982; Appendix N). The initial declining phase suggests that there is rapid and extensive distribution of chlorpheniramine to tissues and organs, whereas the secondary phase reflects the re-entry of chlorpheniramine or its metabolites into the blood from these compartments and elimination from the body.

Extensive tissue distribution of chlorpheniramine has been demonstrated in rabbits (Huang and Chiou, 1981) and male F344 rats (Appendix N). The liver, lung, and kidney appear to be the major sites of deposition of chlorpheniramine or its metabolites (Kamm et al., 1969). The large volume of distribution for chlorpheniramine maleate (5-11 liters/kg) suggests extensive tissue binding (Simons et al., 1982; Athanikar and Chiou, 1979; Huang and Chiou, 1981). The prolonged presence of chlorpheniramine or metabolites in the plasma may be due to enterohepatic circulation or plasma protein binding. Biliary secretion of radioactivity was demonstrated in rats administered ^{3}H-chlorpheniramine maleate (Kamm et al., 1969), and binding of chlorpheniramine to plasma proteins was demonstrated in humans and dogs (Peets et al., 1972a,b).

Chlorpheniramine maleate is extensively metabolized in humans and in laboratory animals. After oral administration of chlorpheniramine maleate, 1%-12% of the administered dose was excreted unchanged in the urine from humans (Kabasakalian et al., 1968; Peets et al., 1972a) and from rats and dogs (Kamm et al., 1969; Peets et al., 1972b; Osterloh et al., 1980). In these urine samples, mono- and didesmethylated metabolites of chlorpheniramine were identified and generally accounted for about 2% and 15%, respectively, of the administered dose. The additional metabolites are not believed to include glucuronide or sulfate conjugates, since metabolic profiles were not affected by incubation of urine samples with β-glucuronidase or aryl sulfatase (Kamm et al., 1969; Peets et al., 1972b; Osterloh et al., 1980). A metabolite of chlorpheniramine, which accounted for about 18% of the urinary radioactivity of [methylene-^{14}C]-chlorpheniramine maleate, was isolated from dog urine and identified after hydrolysis in concentrated hydrochloric acid as 3-(*p*-chlorobenzyl)-3-(2-pyridyl)propionic acid (Osterloh et al., 1980). The conjugating substance of this metabolite was not determined. Two less polar metabolites, accounting for about 30% of the radioactive dose recovered in the urine, were isolated; one was identified as 3-(*p*-chlorobenzyl)-3-(2-pyridyl)propanol. Thus, in addition to N-dealkylation, chlorpheniramine maleate also appears to be metabolized by an oxidative deamination mechanism (Figure 1). Metabolism of chlorpheniramine maleate was demonstrated in homogenates prepared from the small intestine, kidney, and liver of New Zealand White rabbits (Huang et al., 1981).

Male F344 rats were orally administered ^{14}C-chlorpheniramine maleate at doses of 2 or 20 mg/kg (Appendix N). The urine was the major route of excretion, containing 65%-70% of the dose; about 30%-35% was excreted in the feces. About 50% of the dose was excreted in the first 24 hours after dosing, 70% after 2 days, and about 90% after 4 days. There was essentially no difference between the two doses in the percentage of urinary or fecal excretion of the radioactivity.

Developmental Toxicity

Injection of 4 or 8 mg of chlorpheniramine maleate into fertilized chick embryos produced defects in digits and reductions in body weight and crown-rump length in embryos (King et al., 1973). Pregnant Swiss-Webster mice were provided with drinking water solutions containing 0.1, 0.5, or 1.0 g chlorpheniramine maleate per liter for the duration of pregnancy (Naranjo and de Naranjo, 1968). The starting day was the day when the spermatic plug in the vagina was observed. The initial daily doses of chlorpheniramine maleate were 20, 100, or 200 mg/kg. However, as the study progressed, consumption of the dosed water solutions decreased; doses at the end of pregnancy were 18, 80, or 142 mg/kg. After parturition, the mothers continued to drink the chlorpheniramine maleate solutions, as did the newborn mice after weaning. In the highest dose group, there was 100% abortion or

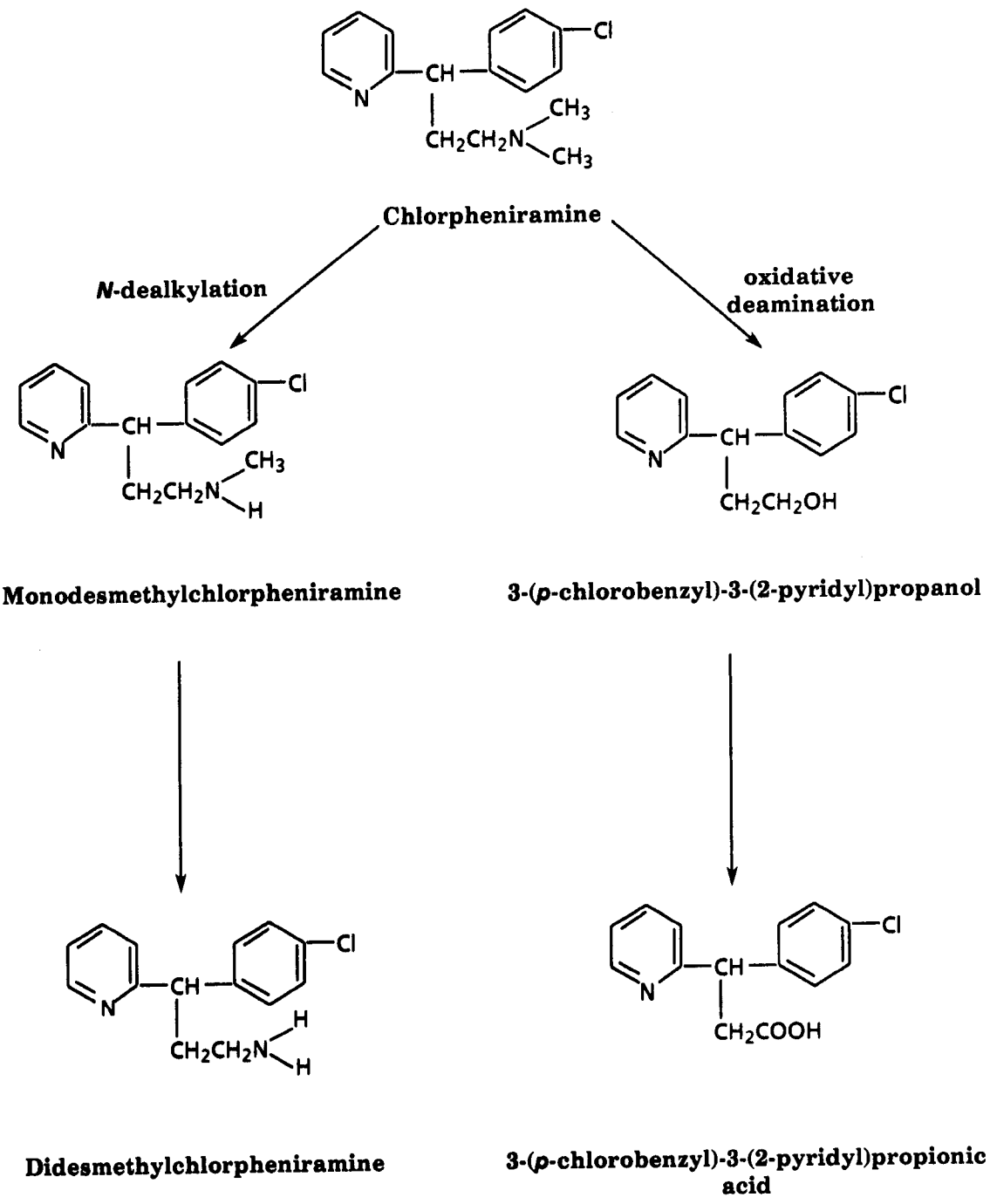

FIGURE 1. PATHWAYS OF CHLORPHENIRAMINE METABOLISM

resorption. There were marked decreases in survival in the offspring of the two lower dose groups at the end of pregnancy and at 60 hours and 42 days after delivery. Although the significance of these findings is somewhat confounded by the decreased water consumption, the results indicate that chlorpheniramine maleate is more toxic in the embryo, fetus, and newborn than in the adult animal (Naranjo and de Naranjo, 1968).

A series of reproduction studies of chlorpheniramine maleate in CD albino rats and New Zealand White rabbits was conducted by the Schering Corporation. Brief summaries of these studies follow.

1. Chlorpheniramine maleate, dissolved in distilled water, was administered by gavage to groups of 25 or 40 (controls) CD rats at doses of 0, 5, 10, or 20 mg/kg per day (Schering Corp., 1975b, unpublished). Males were dosed from 63 days before mating through the 3-week mating period; females were dosed from 21 days before mating until they were killed either at 14 days of gestation or 21 days after parturition. Administration of chlorpheniramine maleate did not affect mating behavior, pregnancy rates, length of gestation, number of implantations, number of dead implantations, litter size, or sex distribution of the offspring. The frequency of fetal abnormalities was not affected. The percentage of pups that died during lactation was greater in the 20 mg/kg dose group than in the vehicle controls. Mean body weights of offspring in the 20 mg/kg dose group were lower than those of vehicle controls on day 4 of lactation but not at birth or on day 21 of lactation.

2. Groups of 25 or 35 (vehicle controls) female CD rats were administered chlorpheniramine maleate dissolved in water at doses of 0, 5, 15, or 25 mg/kg per day on days 6 through 15 of gestation (Schering Corp., 1973, unpublished). The administration of chlorpheniramine maleate did not produce any major abnormalities in the offspring or affect the number of resorptions, litter size, sex distribution, or survival of offspring. There was a minor decrease in mean body weight (approximately 4%) of offspring in the dose groups relative to vehicle controls.

3. Chlorpheniramine maleate, dissolved in distilled water, was administered by gavage to groups of 25 or 40 (vehicle controls) female CD rats at doses of 0, 5, 10, or 20 mg/kg from day 14 of gestation to day 21 after parturition (Schering Corp., 1974a, unpublished). Administration of chlorpheniramine did not affect the length of gestation, the mean number of implantation sites per rat, litter size, or sex distribution of the offspring. There was a decrease in postnatal survival of pups in the 10 and 20 mg/kg dose groups relative to that of vehicle controls, and the mean body weight of pups in the 20 mg/kg dose group was lower than that of vehicle controls on the day of birth and on day 4 but not on day 21 after birth.

4. Groups of 14-16 New Zealand White rabbits were administered chlorpheniramine maleate dissolved in distilled water at doses of 0, 3, 6, or 15 mg/kg per day, from days 6 through 18 of gestation (Schering Corp., 1974b, unpublished). Dosing with chlorpheniramine maleate did not affect body weight gain during pregnancy, percentage of resorptions, litter size, sex distribution, body weight of offspring, or 24-hour survival rates of the offspring. No major malformations or minor variations were associated with the dosing.

Genotoxicity

Chlorpheniramine maleate was not mutagenic to *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of S9 metabolic activation systems prepared from the livers of Aroclor 1254-treated male Sprague-Dawley rats or male Syrian hamsters (Andrews et al., 1980; Mortelmans et al., 1986; Appendix G, Table G1). Since chlorpheniramine is a tertiary amine that could potentially react with nitrite to form nitrosamines in vivo, it was treated with sodium nitrite in acetic acid, and the products of this reaction were tested for mutagenicity in the Ames Salmonella/mammalian-microsome mutagenicity test (Andrews et al., 1980). Nitrosation of chlorpheniramine did not produce a mutagenic response in Salmonella; however, nitrosation of methapyrilene, a carcinogenic antihistaminic drug, did yield mutagenic products.

In studies on the induction of DNA repair (unscheduled DNA synthesis) by antihistamines in primary cultures of rat hepatocytes, chlorpheniramine maleate and methapyrilene hydrochloride were inactive, whereas pyrilamine maleate and tripelennamine hydrochloride produced positive responses (Probst and Neal, 1980; McQueen and Williams, 1981).

Chlorpheniramine maleate was not mutagenic when tested by the NTP in the mouse lymphoma L5178Y/TK$^{+/-}$ forward mutation assay with or without metabolic activation from Aroclor 1254-induced F344 male rat liver S9 (Table G2). Probst et al. (1981) reported in an abstract that chlorpheniramine maleate, methapyrilene hydrochloride, pyrilamine maleate, and tripelennamine hydrochloride were negative in the S9-activated L5178Y/TK$^{+/-}$ assay and also in in vitro assays for sister-chromatid exchanges (SCEs) in Chinese hamster ovary cells activated by cocultivation with rat hepatocytes. NTP-sponsored cytogenetic tests with cultured Chinese hamster ovary cells revealed weak mutagenic activity for chlorpheniramine maleate. Induction of SCEs was observed in the absence of any exogenous metabolic activation; in the presence of S9 from Aroclor 1254-induced male Sprague-Dawley rat liver, the level of SCEs remained unaltered (Table G3). The conditions for induction of chromosomal aberrations were reversed. Without metabolic activation, chlorpheniramine maleate did not cause an increase in chromosomal aberrations; however, in the presence of S9, an increase in chromosomal aberrations was observed at toxic or nearly toxic doses (Table G4).

Carcinogenicity

A 2-year oncogenicity study of chlorpheniramine maleate was conducted in which groups of 50 male and 50 female CD albino rats were fed diets containing SCH 190 (Chlor-trimeton®) for 103 weeks (Schering-Plough Research Division, 1978, unpublished). The doses (approximately 2, 10, or 20 mg/kg per day) were formulated based on group mean values for body weight and feed consumption. There were no reported increases in the incidences of neoplastic lesions attributed to dosing with chlorpheniramine maleate; however, the tissues examined microscopically were limited to gross lesions, liver, spleen, lung, urinary bladder, mammary tissue (in females), and kidney. The tumor incidence data were based on the evaluations of two pathologists.

Interest in the potential carcinogenicity of antihistaminic drugs increased as a result of the finding that liver neoplasia was induced in male and female Sprague-Dawley and F344 rats dosed with methapyrilene hydrochloride (Lijinsky and Taylor, 1977; Lijinsky et al., 1980). Liver neoplasms (hepatocellular carcinomas and cholangiocarcinomas) developed in nearly all (94%-98%) male or female F344 rats (50 animals per group) administered 0.1% methapyrilene in feed with or without 0.2% sodium nitrite for 64 weeks (Lijinsky et al., 1980). In subsequent studies, 0.025% methapyrilene hydrochloride in the diet resulted in increased incidences of hepatocellular carcinomas or neoplastic nodules of the liver in male and female F344 rats, and incorporation of 0.2% pyrilamine maleate in the diet produced increases in the incidences of liver neoplasms in female rats but not in male rats (Lijinsky, 1984a). Methapyrilene was also shown to enhance the hepatocarcinogenicity of *N*-2-fluorenylacetamide and the development of liver preneoplastic foci in male F344 rats (Furuya et al., 1983). However, since methapyrilene alone also produced altered liver foci, it was concluded that the hepatocarcinogencity of this chemical must involve effects other than just promoting activity.

Chlorpheniramine maleate was administered in feed at a concentration of 1,000 ppm with or without 2,000 ppm sodium nitrite to groups of 24 male and 24 female F344 rats for 106 weeks (Lijinsky, 1984b). Dosing with chlorpheniramine maleate alone did not produce any increases in tumor incidences in comparison with untreated controls. However, simultaneous feeding of chlorpheniramine maleate with sodium nitrite resulted in a threefold to fivefold increase in the incidence of liver neoplasms in male rats in comparison with untreated or nitrite-dosed control animals. Thus, nitrosation of chlorpheniramine maleate may produce a carcinogenic compound.

Human Effects

In the preliminary screening for carcinogenicity of commonly used medicinal drugs, no positive associations were found for orally administered chlorpheniramine maleate and cancers at any of 56 primary cancer sites in 13,481 users (Friedman and Ury, 1980). In this study, drug-dispensing records at the San Francisco medical offices of the Kaiser-Permanente Medical Care Program were used to identify outpatients who had at least one recorded prescription between July 1969 and August 1973. Cancer occurrence was detected primarily from hospital records that usually included a histologic examination of tissue. The authors recognized shortcomings in this study, including inadequate duration of followup for cancers with long latency periods and confounding variables that may have concealed associations.

Adult volunteers dosed twice daily for 4 days with 4 mg of chlorpheniramine maleate showed no significant adverse effects in tests measuring performance on tasks of attention, reasoning, and memory (Millet et al., 1982). Case reports have associated the use of chlorpheniramine maleate with oral and facial dyskinesia (Thach et al., 1975), thrombocytopenic purpura (Eisner et al., 1975), bone marrow suppression (Deringer and Maniatis, 1976), and aplastic anemia (Kanoh et al., 1977).

Study Rationale

Chlorpheniramine maleate was selected for 2-year oral toxicity and carcinogenicity studies because of its widespread human use as an antihistamine and because there were insufficient carcinogenicity data on this drug. In addition, chlorpheniramine maleate was selected as a representative aryl chloride.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CHLORPHENIRAMINE MALEATE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FOURTEEN-DAY STUDIES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CHLORPHENIRAMINE MALEATE

USP-grade chlorpheniramine maleate was obtained in two lots from Hexagon Laboratory, Inc. (Bronx, New York) (Table 2). The supplier provided documentation that these lots conformed to USP specifications and that the material was 99.7%-99.8% pure. Purity and identity determinations were conducted by Midwest Research Institute on both lots (Appendix H). Chemical identity was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectroscopic data were consistent with the structure of chlorpheniramine maleate. The purity of the two lots was determined to be approximately 99% by elemental analysis, water analysis, nonaqueous titrations of amine and carboxyl groups, thin-layer chromatography, and high-performance liquid chromatography relative to a USP standard. Both lots of study material were determined to meet USP specifications.

Chlorpheniramine maleate was determined to be stable on storage for 2 weeks at 60° C (Appendix H). Chlorpheniramine maleate was stored at room temperature during the study. Periodic characterization of chlorpheniramine maleate by infrared spectroscopy and nonaqueous amine titration detected no deterioration over the course of the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Chlorpheniramine maleate was mixed with deionized water to give the desired concentrations (Table 3; Appendix I). There was no measurable loss of chlorpheniramine maleate from an 0.1% aqueous solution stored for 7 days at room temperature (Appendix I). In a 14-day stability study of chlorpheniramine maleate dissolved in water at a concentration of 2.5 mg/ml, there was a decrease of 1% or less in recovery of the study chemical when the mixture was stored in the dark at 5° C or at room temperature. The dose mixtures used for the toxicology studies were stored at 23° C for no longer than 2 weeks.

Periodic analyses for chlorpheniramine maleate in water were performed by the study and analytical chemistry laboratories to confirm that chlorpheniramine maleate at the correct concentrations was administered to the animals (Appendix J). Because 95/101 mixtures analyzed were within ± 10% of the target concentrations, it is estimated that the mixtures were prepared within specifications 94% of the time (Table 4; Appendix K).

TABLE 2. IDENTITY AND SOURCE OF LOTS USED IN THE GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Fourteen-Day Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers			
2189ME	2189ME	2189ME	2189ME, 21-110-1
Date of Initial Use			
Rats--7/26/79; mice--6/5/79	10/29/79	2/11/80	Lot no. 2189ME--rats, 10/20/80; male mice, 10/27/81; female mice, 2/2/81; lot no. 21-110-1--5/20/81
Supplier			
Hexagon Laboratory, Inc. (Bronx, NY)	Same as 14-d studies	Same as 14-d studies	Same as 14-d studies

TABLE 3. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Fourteen-Day Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
Weighed portion of chlorpheniramine maleate mixed in a graduated cylinder with deionized water by shaking vigorously for 10 sec to prepare highest concentration; lower concentrations obtained by serial dilution with deionized water	Same as 14-d studies	Same as 14-d studies except prepared with distilled water	Weighed portion of chlorpheniramine maleate mixed with deionized water in a graduated cylinder by inverting approximately 20 times; lower concentrations obtained by serial dilution with deionized water
Maximum Time Stored			
2 wk	7 d	2 wk	2 wk
Storage Conditions			
23° C in foil-wrapped bottles	Same as 14-d studies	23° C in the dark	23° C in amber glass bottles

TABLE 4. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

	Concentration of Chlorpheniramine Maleate in Deionized Water (mg/ml)						
	2.5	3	5	6	10	12	20
Mean (mg/ml)	2.43	2.90	4.92	5.96	10.02	12.13	20.06
Standard deviation	0.227	0.289	0.237	0.269	0.375	0.459	0.699
Coefficient of variation (percent)	9.3	10.0	4.8	4.5	3.7	3.8	3.5
Range (mg/ml)	1.93-2.79	2.42-3.30	4.57-5.37	5.55-6.37	9.52-10.80	11.20-12.80	19.20-21.20
Number of samples	14	15	14	15	14	15	14

FOURTEEN-DAY STUDIES

Fourteen-day studies were conducted to assist in selecting doses for the 13-week studies. Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 13 days (rats) or 24 days (mice) before the studies began. Rats were 6 weeks old and mice were 7-8 weeks old when placed on study. Groups of five rats of each sex were administered 40, 80, 160, 320, or 640 mg/kg chlorpheniramine maleate in water by gavage for 14 consecutive days. Groups of five mice of each sex were given 12, 25, 50, 100, or 200 mg/kg. Controls were untreated. Animals were housed five per cage. Feed and water were available ad libitum. Rats and mice were observed twice per day. Rats were weighed on days 1, 7, and 15, and mice were weighed on days 1 and 15. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 5.

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Fourteen-Day Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 males and 5 females (mice only)	10 males and 10 females of each species	50 males and 50 females of each species
Doses			
Rats--40, 80, 160, 320, or 640 mg/kg chlorpheniramine maleate in deionized water by gavage (controls were untreated); mice--12, 25, 50, 100, or 200 mg/kg chlorpheniramine maleate in deionized water by gavage (controls were untreated); dose vol--5 ml/kg	0, 25, 50, 100, 200, 400, or 800 mg/kg chlorpheniramine maleate in deionized water by gavage; dose vol--5 ml/kg	Rats--0, 3.75, 7.5, 15, 30, or 60 mg/kg chlorpheniramine maleate in distilled water by gavage; mice--0, 12.5, 25, 50, 100, or 200 mg/kg chlorpheniramine maleate in distilled water by gavage; dose vol--rats, 5 ml/kg; mice, 10 ml/kg	Rats--male: 0, 15, or 30 mg/kg; female: 0, 30, or 60 mg/kg chlorpheniramine maleate in deionized water by gavage; dose vol--5 ml/kg; mice--male: 0, 25, or 50 mg/kg; female: 0, 100, or 200 mg/kg chlorpheniramine maleate in deionized water by gavage; dose vol--10 ml/kg
Date of First Dose			
Rats--7/26/79; mice--6/5/79	10/29/79	2/11/80	Rats--10/20/80; mice--male: 10/27/81; female: 2/2/81
Date of Last Dose			
Rats--8/8/79; mice--6/18/79	11/13/79	5/9/80	Rats--10/8/82; mice--male: 10/14/83; female: 1/21/83
Duration of Dosing			
14 consecutive d	Administered on 12 d over a 16-d period	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation			
Observed 2 × d; rats--weighed on d 1, 7, and 15; mice--weighed on d 1 and 15	Observed 2 × d; weighed on d 1, 8, and 16	Observed 2 × d; weighed 1 × wk	Observed 2 × d; weighed 1 × wk for 12 or 13 wk and monthly thereafter
Necropsy and Histologic Examination			
Necropsy performed on all animals; histologic exam not performed	Same as 14-d studies	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups: skin, mandibular lymph node, mammary gland, salivary gland, skeletal muscle, sciatic nerve, bone marrow, thymus, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, small intestine, large intestine, mesenteric lymph node, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, prostate/testes or ovaries/uterus, brain, pituitary gland, and spinal cord	Necropsy and histologic examination performed on all animals; the following tissues were examined: gross lesions and tissue masses, mesenteric lymph node, salivary gland, femur including marrow, thyroid gland, parathyroids, small intestine, colon, liver, gallbladder (mice), esophagus, stomach, prostate/testes or ovaries/uterus, heart, brain, pituitary gland, thymus, trachea, pancreas, spleen, skin, lungs and mainstem bronchi, kidneys, urinary bladder, adrenal glands, eyes, and mammary gland

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE (Continued)

Fourteen-Day Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species			
F344/N rats; B6C3F$_1$ mice	B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Same as 14-d studies	Rats--Harlan Industries (Indianapolis, IN); mice--Charles River Breeding Laboratories (Portage, MI)	Same as 14-d studies
Study Laboratory			
Battelle Columbus Laboratories	Same as 14-d studies	Same as 14-d studies	Same as 14-d studies
Method of Animal Identification			
Rats--none; mice--toe mark	Same as 14-d studies	Rats--toe clip; mice--toe mark	Toe and ear clip
Time Held Before Study			
Rats--13 d; mice--24 d	17 d	Rats--14 d; mice--17 d	Rats--17 d; mice--male, 26 d; female, 17 d
Age When Placed on Study			
Rats--6 wk; mice--7-8 wk	7 wk	Rats--9 wk; mice--7 wk	Rats--7 wk; mice--male, 9 wk; female, 8 wk
Age When Killed			
Rats--8 wk; mice--9-10 wk	10 wk	Rats--23 wk; mice--21 wk	Rats--111 wk; mice--male, 113 wk; female, 112 wk
Necropsy Dates			
Rats--8/9/79; mice--6/20/79	11/15/79	Rats--5/12/80-5/13/80; mice--5/13/80-5/14/80	Rats--10/18/82-10/21/82; mice--male, 10/24/82-10/25/82; female, 1/31/83-2/2/83
Method of Animal Distribution			
Animals assigned from weight classes to cages according to a table of random numbers; cages assigned to study groups according to another table of random numbers	Same as 14-d studies	Same as 14-d studies	Same as 14-d studies
Feed			
Purina 5001 Lab Chow, pelleted (Ralston Purina, St. Louis, MO)	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 16-d studies	Same as 16-d studies except for 1 wk when pelleted Purina Certified Rodent Chow was used
Bedding			
Absorb-dri hardwood chips (Absorb-Dri, Inc., Garfield, NJ)	Same as 14-d studies	Same as 14-d studies	Same as 14-d studies
Water			
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 14-d studies	Same as 14-d studies	Same as 14-d studies

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE (Continued)

Fourteen-Day Studies	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Cages			
Polycarbonate (Lab Products, Garfield, NJ)	Same as 14-d studies	Same as 14-d studies	Same as 14-d studies
Cage Filters			
Reemay® spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 14-d studies	Same as 14-d studies	Same as 14-d studies
Animals per Cage			
5	5	5	5
Other Chemicals on Study in the Same Room			
None	None	None	None
Animal Room Environment			
Temp--21°-23° C; humidity--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Same as 14-d studies	Same as 14-d studies	Same as 14-d studies

SIXTEEN-DAY STUDIES

Because there were no deaths in mice in the 14-day studies even at 200 mg/kg (a dose greater than the reported oral LD_{50} values of chlorpheniramine maleate in mice), a second repeated-dose study (16 days) was conducted to assist in selection of doses for the 13-week studies. Male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories and held for 17 days before the studies began. Mice were 7 weeks old when placed on study. Groups of five mice of each sex were administered 0, 25, 50, 100, 200, 400, or 800 mg/kg chlorpheniramine maleate in water by gavage for 12 days over a 16-day period. Mice were observed twice daily and were weighed on days 1, 8, and 16. A necropsy was performed on all animals. Mice were housed five per cage. Feed and water were available ad libitum. Details of animal maintenance are presented in Table 5.

THIRTEEN-WEEK STUDIES

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

Seven-week-old male and female F344/N rats were obtained from Harlan Industries and 5-week-old $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories. Animals were observed for 14 days (rats) and 17 days (mice) before being placed on study. Groups of 10 rats of each sex were administered 0, 3.75, 7.5, 15, 30, or 60 mg/kg chlorpheniramine maleate in distilled water by gavage, 5 days per week for 13 weeks. During week 2, one rat in the 60 mg/kg dose group of males was discovered to be a female and was removed from the study. Groups of 10 mice of each sex were administered 0, 12.5, 25, 50, 100, or 200 mg/kg on the same schedule.

Animals were housed five per cage. Feed and water were available ad libitum. Further experimental details are summarized in Table 5.

Animals were checked two times per day; moribund animals were killed. Individual animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 male rats were administered 0, 15, or 30 mg/kg chlorpheniramine maleate in deionized water by gavage, 5 days per week for 103 weeks. Groups of 50 female rats were administered 0, 30, or 60 mg/kg on the same schedule. Initially, groups of 50 male mice and groups of 50 female mice were administered 0, 100, or 200 mg/kg. Because of a high incidence of deaths in dosed male mice during week 1, the studies in mice were restarted (at the same doses). However, due to high rates of early deaths in the dosed male mice, the study in male mice was restarted again at doses of 0, 25, or 50 mg/kg with 50 animals per group. The same dosing schedule was followed.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female, × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age; male mice were shipped at 5 weeks and female mice, at 5-6 weeks. The animals were quarantined at the study laboratory for 17 days (rats and female mice) and 26 days (male mice). Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7 weeks of age; the male mice, at 9 weeks; and the female mice, at 8 weeks. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix L).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

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

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 5.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12 weeks (rats) or 13 weeks (mice) of the studies and once per month thereafter. Mean body weights were calculated for

each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 5. When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those for which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless lesions in question are subtle or unless there is inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g.,

skin or mammary tumors) prior to histologic sampling or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. All reported P values for tumor analyses are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals on which a necropsy was actually performed during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendix containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

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

III. RESULTS

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III. RESULTS: RATS

FOURTEEN-DAY STUDIES

Doses selected for these studies were based on data available in the literature on the acute toxicity of chlorpheniramine maleate in rats (see Table 1). All rats that received 320 or 640 mg/kg chlorpheniramine maleate, 3/5 males and 5/5 females that received 160 mg/kg, and 2/5 males and 2/5 females that received 80 mg/kg died before the end of the studies (Table 6). Convulsions preceded these deaths. Tremors were observed in rats that received 160 mg/kg. Hyperactivity was noted in animals in the 80 mg/kg and 40 mg/kg dose groups. There were dose-related depressions in mean body weight gain in both male and female rats. Final mean body weights of the dosed male groups were about 10%-40% lower than those of the controls, whereas final mean body weights of the dosed female groups were about 12%-17% lower than those of the controls.

THIRTEEN-WEEK STUDIES

All the rats survived to the end of the studies (Table 7). Final mean body weights of males that received 15, 30, or 60 mg/kg chlorpheniramine maleate were 8%, 9%, or 13% lower than that of the vehicle controls. Final mean body weights of female rats were not related to dose. Piloerection was observed in male and female rats at 60 mg/kg. Hyperactivity during the early weeks of the study (generally between weeks 2 and 6) and postgavage lethargy during the latter weeks of the study (weeks 6 through 10) were noted in male and female rats at the 60 mg/kg dose. No compound-related gross or microscopic pathologic effects were observed. Pulmonary lesions in vehicle control and dosed animals were attributed to Sendai infection.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Controls (percent)
MALE					
(c) 0	5/5	112	192	+ 80	--
40	5/5	113	170	+ 57	88.5
80	(d) 3/5	108	146	+ 38	76.0
160	(e) 2/5	112	114	+ 2	59.4
320	(f) 0/5	110	(g)	(g)	(g)
640	(h) 0/5	109	(g)	(g)	(g)
FEMALE					
(c) 0	5/5	98	138	+ 40	--
40	5/5	98	121	+ 23	87.7
80	(i) 3/5	98	115	+ 17	83.3
160	(j) 0/5	96	(g)	(g)	(g)
320	(k) 0/5	96	(g)	(g)	(g)
640	(h) 0/5	96	(g)	(g)	(g)

(a) Number surviving/number initially in group
(b) Mean body weight change of the group
(c) Controls were untreated.
(d) Day of death: 2, 9
(e) Day of death: 4, 5, 5
(f) Day of death: 2, 4, 4, 4, 4
(g) No data are reported due to the 100% mortality in this group.
(h) Day of death: 1, 2, 2, 2, 2
(i) Day of death: 8, 9
(j) Day of death: 2, 3, 4, 6, 9
(k) Day of death: all 2

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	125 ± 4	334 ± 7	+ 209 ± 8	--
3.75	10/10	126 ± 3	331 ± 7	+ 205 ± 5	99
7.5	10/10	124 ± 4	328 ± 9	+ 204 ± 9	98
15	10/10	121 ± 3	307 ± 7	+ 186 ± 7	92
30	10/10	122 ± 3	304 ± 8	+ 182 ± 8	91
60	(d) 9/9	125 ± 4	289 ± 4	+ 164 ± 4	87
FEMALE					
0	10/10	97 ± 2	182 ± 3	+ 85 ± 4	--
3.75	10/10	100 ± 2	183 ± 2	+ 83 ± 3	101
7.5	10/10	95 ± 2	170 ± 3	+ 75 ± 3	93
15	10/10	97 ± 2	180 ± 2	+ 83 ± 2	99
30	10/10	99 ± 2	182 ± 3	+ 83 ± 4	100
60	10/10	94 ± 3	172 ± 3	+ 78 ± 2	95

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change ± standard error of the mean
(d) During week 2, one member of the group was found to be female and was removed from the study.

Dose Selection Rationale: Based mainly on weight gain depression in the 14-day and 13-week studies and on the incidence of deaths in the 14-day studies, doses of chlorpheniramine maleate selected for rats for the 2-year studies were 15 and 30 mg/kg for males and 30 and 60 mg/kg for females administered in deionized water by gavage, 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Initial mean body weights of dosed male rats and low dose female rats were 7% lower than those of the vehicle controls, and that of high dose female rats was 9% lower than that of the vehicle controls (Table 8 and Figure 2). The data reported for week 0 were obtained on day 2 of the study. When the animals were weighed and toe clipped 2 days before the first dosing, there was no discrepancy between the mean body weights of the vehicle control and dosed groups. Mean body weights of high dose male rats were 7%-19% lower than those of the vehicle controls throughout the studies; mean body weights of low dose male rats were 7%-11% lower than those of the vehicle controls throughout most of the studies. Mean body weights of high dose female rats were more than 10% lower than those of the vehicle controls after week 8 and 20%-28% lower after week 54; mean body weights of low dose female rats were 10%-19% lower than those of the vehicle controls after week 33.

Most high dose male and high dose female rats were hyperexcitable for approximately 1 hour after dosing. High dose male and high dose female rats had an increased incidence of nasal discharge relative to that of the vehicle controls.

TABLE 8. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE				**15 mg/kg**			**30 mg/kg**	
0	163	50	152	93	50	152	93	50
1	200	50	190	95	50	184	92	50
2	227	50	211	93	50	205	90	50
3	250	50	226	90	50	224	90	50
4	275	50	245	89	50	243	88	49
5	290	50	260	90	50	251	87	49
6	305	50	273	90	50	262	86	49
7	316	50	283	90	50	269	85	49
8	330	50	297	90	50	279	85	49
9	343	50	309	90	50	289	84	49
10	350	50	315	90	50	294	84	49
11	357	50	322	90	50	301	84	49
12	369	50	335	91	50	308	83	49
16	393	50	354	90	50	329	84	49
20	414	50	379	92	50	348	84	49
24	432	50	393	91	50	358	83	49
28	441	50	404	92	50	371	84	49
33	457	50	420	92	50	374	82	49
37	467	50	424	91	50	383	82	48
41	469	49	423	90	50	380	81	48
46	472	49	424	90	50	386	82	46
50	476	49	426	89	50	386	81	46
54	481	49	427	89	48	397	83	43
59	479	49	431	90	48	390	81	40
63	494	49	445	90	47	405	82	40
68	497	49	442	89	46	405	81	39
72	503	48	453	90	46	419	83	39
76	499	48	456	91	43	415	83	39
80	488	47	449	92	42	414	85	38
85	480	46	441	92	42	415	86	34
89	485	43	438	90	40	407	84	32
93	482	43	441	91	36	420	87	31
97	485	39	442	91	33	425	88	28
103	457	33	429	94	29	417	91	24
FEMALE				**30 mg/kg**			**60 mg/kg**	
0	121	50	113	93	50	110	91	50
1	140	50	130	93	50	125	89	49
2	151	50	138	91	50	133	88	49
3	162	50	150	93	50	141	87	49
4	175	50	158	90	50	155	89	48
5	179	50	161	90	50	157	88	48
6	182	50	166	91	49	163	90	47
7	187	50	171	91	49	168	90	47
8	193	50	177	92	49	173	90	46
9	200	50	181	91	49	175	88	46
10	203	50	183	90	47	179	88	45
11	205	50	186	91	47	180	88	45
12	209	50	192	92	47	186	89	44
16	217	50	196	90	47	190	88	43
20	224	50	204	91	47	200	89	41
24	232	50	209	90	47	204	88	38
28	240	50	217	90	47	210	88	35
33	249	50	222	89	47	212	85	34
37	260	50	228	88	47	218	84	31
41	259	50	227	88	46	216	83	26
46	261	49	230	88	45	218	84	21
50	269	49	231	86	44	220	82	19
54	279	49	238	85	43	224	80	16
59	291	49	244	84	41	227	78	16
63	305	48	248	81	40	231	76	12
68	316	47	257	81	37	228	72	10
72	323	46	266	82	36	241	75	10
76	325	44	267	82	34	238	73	10
80	318	44	268	84	33	236	74	9
85	326	42	280	86	30	243	75	7
89	331	41	273	82	27	248	75	9
93	340	40	279	82	27	262	77	8
97	339	39	283	83	26	252	74	6
103	338	31	291	86	24	270	80	6

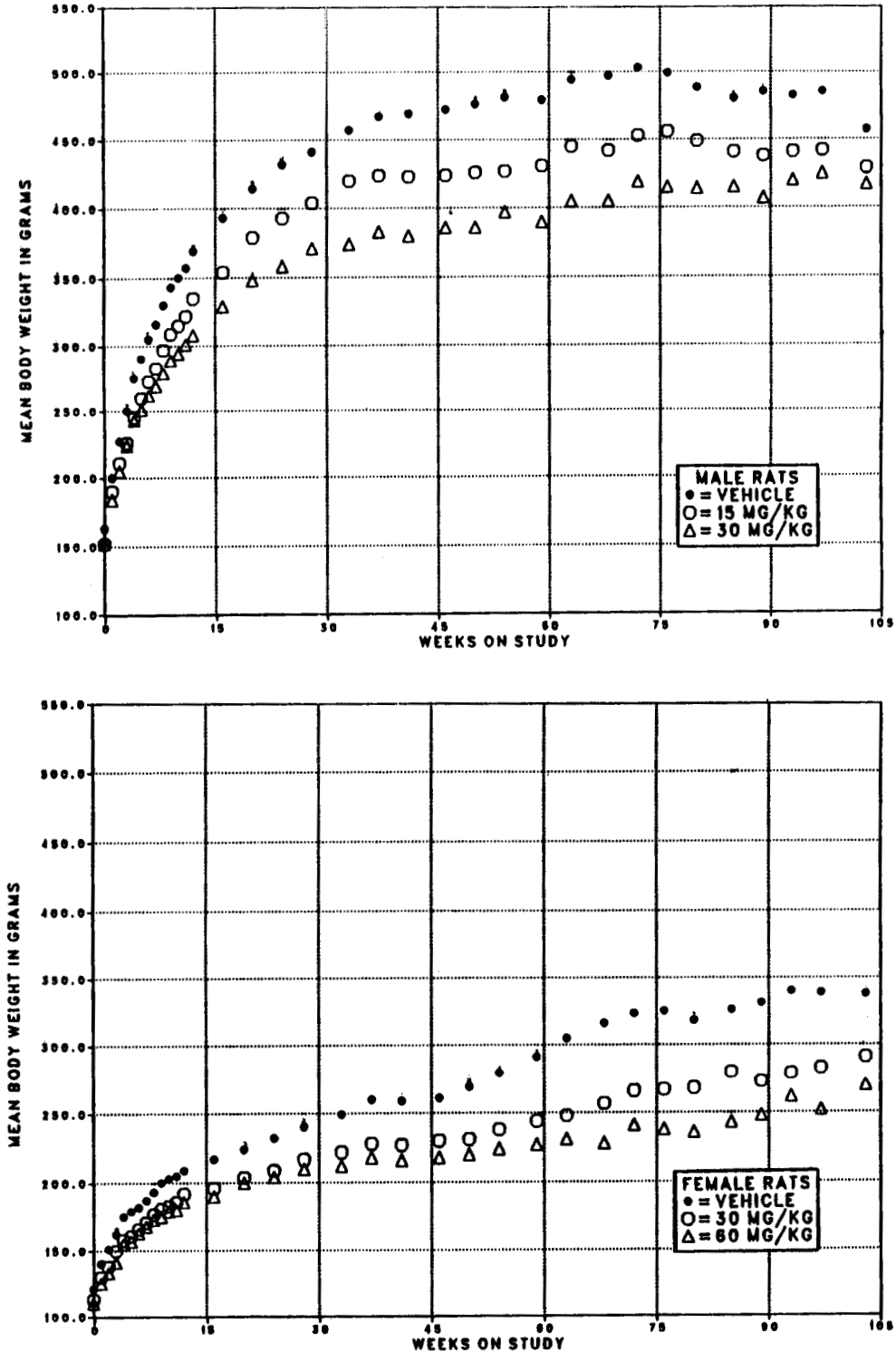

FIGURE 2. GROWTH CURVES FOR RATS ADMINISTERED CHLORPHENIRAMINE MALEATE IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered chlorpheniramine maleate at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 3. The survival of the high dose group of female rats was significantly lower than that of the vehicle control group after week 15 (Table 9). Survival rates of the low dose group of female rats and of the low dose and high dose groups of male rats were not significantly different from those of the respective vehicle control groups. In male rats, 31/50 (62%) of the vehicle controls, 28/50 (56%) of the low dose group, and 24/50 (48%) of the high dose group survived until the termination of the study. Two deaths in the high dose males were attributed to gavage dosing accidents. In female rats, 29/50 (58%) of the vehicle controls and 24/50 (48%) of the low dose group survived until the termination of the study. One death in the vehicle control group and three deaths in the low dose females were attributed to gavage dosing accidents.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the hematopoietic system, adrenal gland (medulla), and clitoral gland. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1 and E2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in control animals are listed in Appendix F.

TABLE 9. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

	Vehicle Control	Low Dose	High Dose
MALE (a)		**15 mg/kg**	**30 mg/kg**
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	19	21	24
Accidentally killed	0	0	2
Killed at termination	31	28	24
Died during termination period	0	1	0
Survival P values (c)	0.127	0.601	0.152
FEMALE (a)		**30 mg/kg**	**60 mg/kg**
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	23	43
Accidentally killed	1	3	1
Killed at termination	29	24	6
Survival P values (c)	<0.001	0.243	<0.001

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

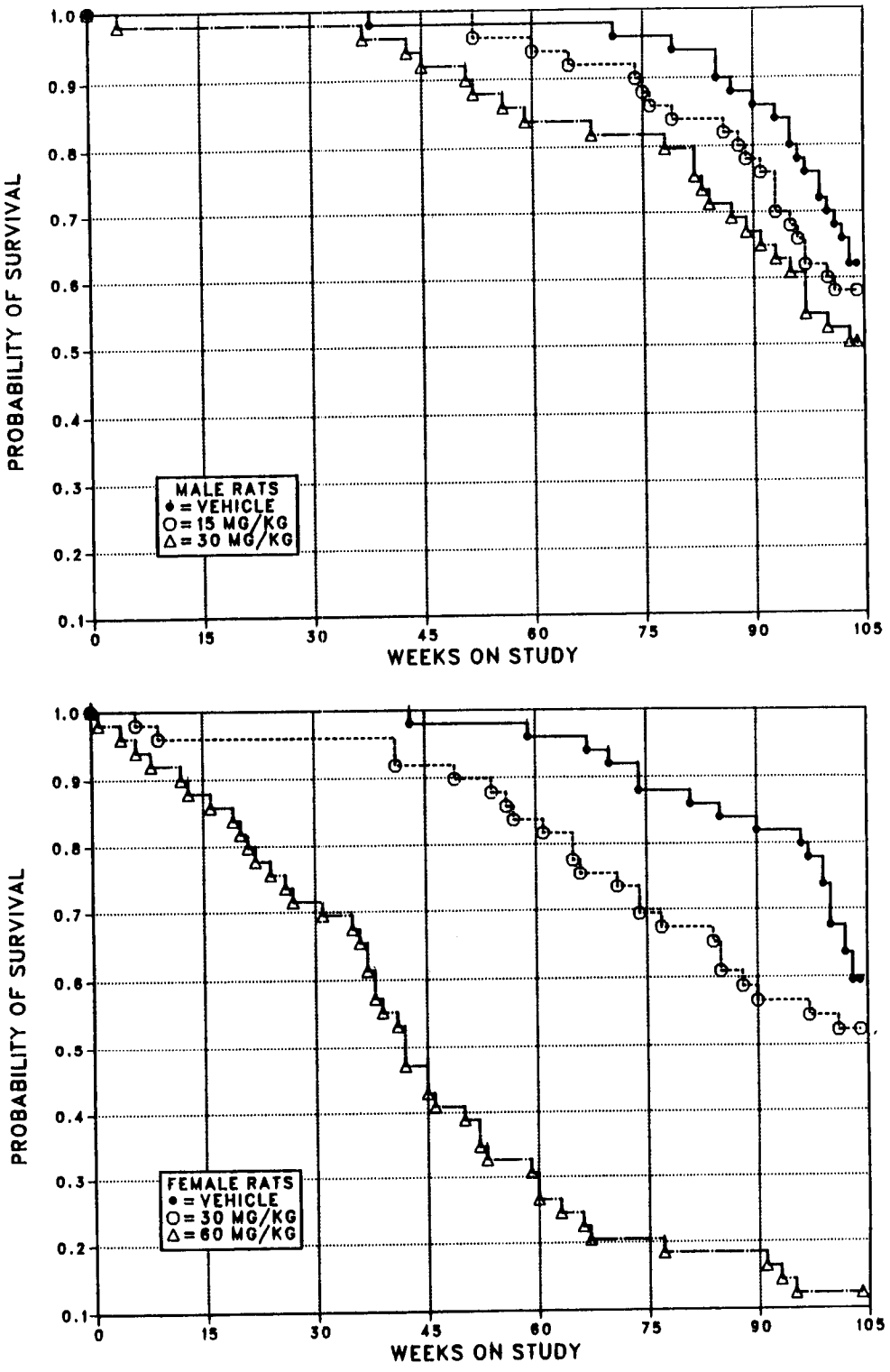

FIGURE 3. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED CHLORPHENIRAMINE MALEATE IN WATER BY GAVAGE FOR TWO YEARS

There were no significant positive trends or increases in the incidences of primary tumors in male or female rats dosed with chlorpheniramine maleate in comparison to the vehicle controls. There were instances of significant negative trends and decreases in the incidences of primary tumors (Table 10). Because of the high mortality rate in female rats at the 60 mg/kg dose, entries for female rats in Table 10 were made only if there were significant differences in the incidences of neoplasms between the vehicle controls and the low dose group.

Hematopoietic System: Mononuclear cell leukemia in male rats occurred with a significant negative trend, and the incidences in the dosed groups were significantly ($P<0.05$) lower than that in the vehicle controls by the incidental tumor test but not by life table analysis (Table 10).

Adrenal Gland Medulla: Pheochromocytomas in male rats occurred with a significant negative trend, and the incidences in the dosed groups were significantly lower than that in the vehicle controls (Table 10).

Clitoral Gland: The incidence of adenomas in female rats was significantly lower in the low dose group (15 mg/kg) than that in the vehicle controls by the incidental tumor test (Table 10).

TABLE 10. ANALYSIS OF SELECTED TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE (a)

	Vehicle Control	Low Dose	High Dose
MALE		**15 mg/kg**	**30 mg/kg**
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates	25/50 (50%)	14/50 (28%)	11/50 (22%)
Adjusted Rates	58.1%	37.3%	32.7%
Terminal Rates	14/31 (45%)	7/29 (24%)	2/24 (8%)
Week of First Observation	71	76	84
Life Table Tests	P=0.049N	P=0.075N	P=0.078N
Incidental Tumor Tests	P=0.011N	P=0.031N	P=0.018N
Adrenal Gland Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates	21/49 (43%)	9/50 (18%)	5/49 (10%)
Adjusted Rates	56.0%	30.0%	21.7%
Terminal Rates	15/31 (48%)	8/29 (28%)	5/23 (22%)
Week of First Observation	87	101	104
Life Table Tests	P=0.002N	P=0.018N	P=0.005N
Incidental Tumor Tests	P=0.001N	P=0.017N	P=0.004N
FEMALE		**30 mg/kg**	**60 mg/kg**
Clitoral Gland: Adenoma			
Overall Rates	5/50 (10%)	0/50 (0%)	0/50 (0%)
Adjusted Rates	14.7%	0.0%	0.0%
Terminal Rates	3/29 (10%)	0/24 (0%)	0/6 (0%)
Week of First Observation	67		
Life Table Tests	P=0.045N	P=0.060N	P=0.338N
Incidental Tumor Tests	P=0.030N	P=0.049N	P=0.186N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).

FOURTEEN-DAY STUDIES

Doses selected for these studies were based on data available in the literature on the acute toxicity of chlorpheniramine maleate in mice (see Table 1). All the mice survived to the end of the studies (Table 11). The final mean body weight of male mice that received 200 mg/kg was 93% that of the controls. Male mice that received 200 mg/kg had tremors for about 2 hours after dosing until day 3. Hunched posture and hyperactivity were observed for mice that received 200 mg/kg throughout the study. No compound-related effects were observed at necropsy. Because there were no deaths or gross lesions that could be definitively attributed to the administration of chlorpheniramine maleate in male or female mice, a 2-week study was performed at higher doses (up to 800 mg/kg) to assist in the selection of doses for the 13-week studies.

SIXTEEN-DAY STUDIES

All the mice that received 800 mg/kg, 4/5 males and 4/5 females that received 400 mg/kg, and 1/5 in all other groups (except the 25 mg/kg male and female groups and the male vehicle controls) died before the end of the studies (Table 12). Final mean body weights were not adversely affected by administration of chlorpheniramine maleate. Tremors and loss of coordination were observed in the four highest dose groups, primarily during the first 4 days of the studies. Hyperactivity was observed in the 50, 100, 200, and 400 mg/kg groups throughout the studies; the severity appeared to be dose related. No compound-related gross or microscopic lesions were observed.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Controls (percent)
MALE					
(c) 0	5/5	28.4	30.4	+ 2.0	--
12	5/5	29.8	32.4	+ 2.6	106.6
25	5/5	28.6	30.6	+ 2.0	100.7
50	5/5	29.0	31.2	+ 2.2	102.6
100	5/5	28.4	30.6	+ 2.2	100.7
200	5/5	28.2	28.2	0.0	92.8
FEMALE					
(c) 0	5/5	20.8	23.4	+ 2.6	--
12	5/5	20.4	21.2	+ 0.8	90.6
25	5/5	20.6	22.2	+ 1.6	94.9
50	5/5	20.2	22.2	+ 2.0	94.9
100	5/5	20.8	23.6	+ 2.8	100.9
200	5/5	20.8	22.8	+ 2.0	97.4

(a) Number surviving/number initially in group
(b) Mean body weight change of the group
(c) Controls were untreated.

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	24.0 ± 0.5	27.0 ± 0.5	+ 3.0 ± 0.4	--
25	5/5	23.8 ± 0.4	29.0 ± 0.4	+ 5.2 ± 0.5	107.4
50	(d) 4/5	24.6 ± 0.5	24.5 ± 0.6	+ 0.3 ± 0.9	90.7
100	(e) 4/5	25.2 ± 0.5	27.5 ± 0.3	+ 2.0 ± 0.7	101.9
200	(f) 4/5	25.2 ± 0.5	25.8 ± 0.3	+ 0.5 ± 0.6	95.6
400	(g) 1/5	25.2 ± 0.7	26.0	+ 1.0	96.3
800	(h) 0/5	25.2 ± 0.4	(i)	(i)	
FEMALE					
0	(j) 4/5	17.6 ± 0.5	19.5 ± 1.0	+ 2.0 ± 1.1	--
25	5/5	18.6 ± 1.0	22.6 ± 0.9	+ 4.0 ± 0.3	115.9
50	(k) 4/5	19.6 ± 0.9	21.8 ± 0.8	+ 2.0 ± 0.6	111.8
100	(e) 4/5	18.8 ± 0.6	21.0 ± 0.4	+ 2.5 ± 0.5	107.7
200	(k) 4/5	19.2 ± 0.4	21.3 ± 0.5	+ 2.3 ± 0.3	109.2
400	(l) 1/5	19.2 ± 0.7	21.0	+ 1.0	107.7
800	(m) 0/5	18.2 ± 0.7	(i)	(i)	

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean; susbsequent calculations are based on those animals surviving to the end of the study.
(c) Mean weight change of the survivors of the group ± standard error of the mean
(d) Day of death: 4
(e) Day of death: 11
(f) Day of death: 10
(g) Day of death: 1, 1, 2, 2
(h) Day of death: 1, 1, 1, 1, 2
(i) No data are reported due to the 100% mortality in this group.
(j) Day of death: 12
(k) Day of death: 8
(l) Day of death: 2, 3, 3, 4
(m) Day of death: 1, 1, 1, 2, 3

THIRTEEN-WEEK STUDIES

Two of 10 males that received 200 mg/kg chlorpheniramine maleate died before the end of the studies (Table 13). One death was attributed to Sendai infection; the cause of the other death was undetermined. During week 1, male mice that received 200 mg/kg lost weight (about 5 g per animal). Final mean body weights were not adversely affected by administration of chlorpheniramine maleate. Hyperactivity was observed in the 200 mg/kg dose groups between week 2 and week 5 for male mice and week 2 and week 10 for female mice. Piloerection and thinness, which occurred during weeks 5 through 8 in various dose groups and in the vehicle control, were attributed to a Sendai infection. No compound-related gross or microscopic pathologic effects were observed.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	24.8 ± 0.7	32.8 ± 0.9	+ 8.0 ± 0.5	--
12.5	10/10	25.4 ± 0.8	35.7 ± 1.1	+10.3 ± 0.7	108.8
25	10/10	25.3 ± 0.8	36.0 ± 1.3	+10.7 ± 0.8	109.8
50	10/10	25.2 ± 0.7	35.3 ± 1.2	+10.1 ± 1.0	107.6
100	10/10	23.8 ± 0.9	34.6 ± 1.2	+10.8 ± 1.2	105.5
200	(d) 8/10	26.7 ± 0.5	36.0 ± 1.0	+ 8.9 ± 0.7	109.8
FEMALE					
0	10/10	19.1 ± 0.3	24.6 ± 0.6	+ 5.5 ± 0.4	--
12.5	10/10	18.9 ± 0.5	26.0 ± 0.6	+ 7.1 ± 0.6	105.7
25	10/10	20.4 ± 0.2	26.9 ± 0.6	+ 6.5 ± 0.5	109.3
50	10/10	20.1 ± 0.6	25.5 ± 0.7	+ 5.4 ± 0.4	103.7
100	10/10	19.8 ± 0.4	25.5 ± 0.5	+ 5.7 ± 0.4	103.7
200	10/10	19.3 ± 0.3	25.9 ± 0.4	+ 6.6 ± 0.3	105.3

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Week of death: 8, 15

Dose Selection Rationale: Doses selected for the 2-year studies of chlorpheniramine maleate in mice were 0, 100, and 200 mg/kg for each sex. This selection was based on the high mortality rates in the 16-day studies at 400 mg/kg and the lack of any clear toxicity in the 13-week studies at doses of 200 mg/kg. In week 1 of the 2-year study, 18 male mice in the 200 mg/kg group died. Due to this unusually high early mortality rate, the entire study was stopped. The discrepancy between this result and the absence of life-threatening toxicity in the 13-week study was never resolved. The 2-year study was restarted at the same doses (0, 100, and 200 mg/kg) based on the assumption that the 13-week studies provided more reliable data on the toxicologic potential of this chemical. In the first restarted study, there was also a high mortality rate in male mice (Figure 4); however, it was not nearly as high as that in the previously started study. Since the high rate of early deaths might have compromised interpretations on the carcinogenic potential of chlorpheniramine maleate, the male mouse study was terminated and restarted for a second time but at doses of 0, 25, and 50 mg/kg. Survival of the female mice was not adversely affected by doses of 100 or 200 mg/kg, and the female mouse study was continued until the week-104 termination date.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were generally 5%-11% lower than those of the vehicle controls after week 24; mean body weights of low dose male mice generally differed by less than 5% from those of the vehicle controls throughout the study (Table 14 and Figure 5). Mean body weights of high dose female mice were 13%-40% lower than those of the vehicle controls after week 33; mean body weights of low dose female mice were 12%-33% lower than those of the vehicle controls after week 33. Most of the dosed female mice (94% of the 100 mg/kg group and 98% of the 200 mg/kg group) exhibited transient hyperexcitability and hyperactivity immediately following dosing.

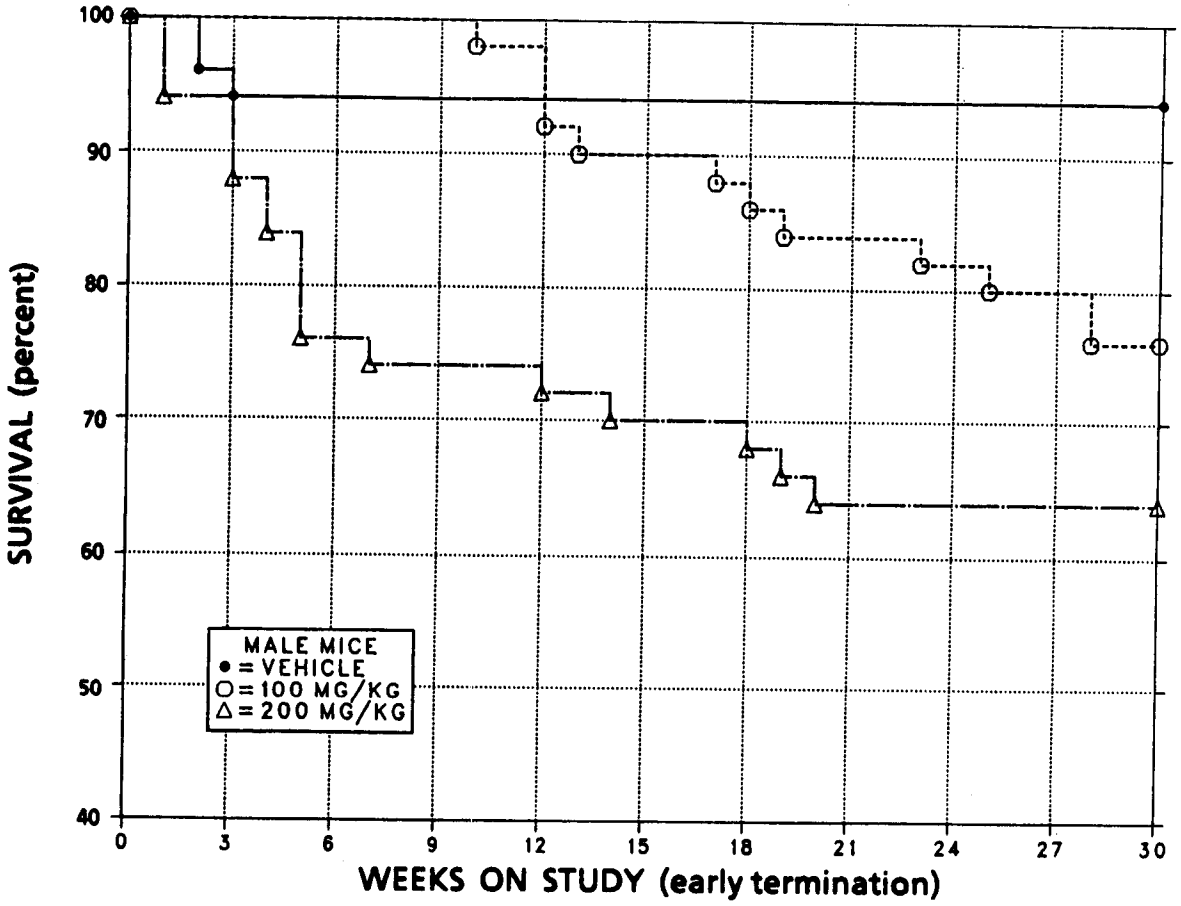

FIGURE 4. SURVIVAL CURVES FOR MALE MICE IN THE FIRST RESTARTED TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

TABLE 14. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE				**25 mg/kg**			**50 mg/kg**	
0	24.5	50	24.5	100	50	24.6	100	50
1	26.8	50	27.1	101	50	26.0	97	50
2	27.7	50	27.8	100	50	28.4	103	41
3	27.6	50	29.0	105	50	28.4	103	41
4	28.7	50	29.3	102	50	29.6	103	41
5	30.8	50	31.0	101	50	30.5	99	41
6	29.2	50	31.0	106	50	29.6	101	41
7	31.6	50	32.3	102	50	31.7	100	41
8	31.6	50	31.9	101	50	32.1	102	40
9	32.1	50	33.2	103	50	32.2	100	40
10	33.5	50	34.6	103	50	33.4	100	39
11	33.7	50	34.1	101	50	33.3	99	38
12	34.4	50	34.8	101	50	33.7	98	38
13	33.1	50	33.2	100	50	32.5	98	38
16	34.9	50	34.7	99	50	33.7	97	37
20	36.3	50	36.7	101	49	35.1	97	35
24	38.1	50	37.5	98	44	35.3	93	35
28	38.9	50	37.7	97	43	35.7	92	32
33	41.6	50	40.2	97	43	37.7	91	31
37	43.1	50	41.3	96	43	39.4	91	31
41	43.0	50	40.5	94	42	39.4	92	30
45	44.7	50	43.4	97	42	40.5	91	29
49	44.7	50	43.5	97	42	41.1	92	29
54	45.7	50	44.6	98	41	40.8	89	27
58	45.8	50	45.0	98	41	40.9	89	27
62	45.5	50	44.5	98	40	41.7	92	27
67	44.8	50	44.2	99	39	41.1	92	27
71	46.0	50	45.1	98	39	43.4	94	27
77	46.5	50	44.7	96	38	43.2	93	25
79	45.3	48	--	--	--	41.1	91	24
80	--	--	44.2	--	37	--	--	--
83	44.5	47	43.8	98	37	41.6	93	24
88	46.7	46	45.9	98	34	42.9	92	23
95	43.7	45	43.3	99	33	42.5	97	21
98	45.8	41	44.0	96	32	43.5	95	20
102	44.9	39	42.8	95	32	43.2	96	17
FEMALE				**100 mg/kg**			**200 mg/kg**	
0	19.7	50	18.9	96	50	19.7	100	50
1	20.3	50	20.4	100	48	20.7	102	50
2	21.3	50	21.0	99	48	20.9	98	49
3	21.6	50	22.2	103	48	22.3	103	49
4	22.8	50	21.6	95	48	22.9	100	49
5	22.6	50	22.5	100	48	23.4	104	49
6	23.5	50	23.1	98	48	23.6	100	49
7	23.5	50	23.3	99	48	24.0	102	49
8	23.9	50	24.3	102	48	24.3	102	49
9	24.4	50	23.9	98	48	24.3	100	48
10	24.6	50	24.0	98	48	24.7	100	48
11	25.0	50	24.5	98	48	25.1	100	48
12	25.6	50	24.5	96	48	25.8	101	48
15	26.2	50	25.0	95	48	25.3	97	48
20	28.1	50	25.7	91	48	25.6	91	46
24	29.5	50	26.7	91	48	25.6	87	46
28	29.3	50	27.6	94	48	27.0	92	46
33	31.1	50	27.4	88	48	27.1	87	46
37	34.3	50	29.1	85	48	27.2	79	46
42	34.6	50	27.5	79	48	26.6	77	46
46	35.0	50	29.5	84	47	29.4	84	46
50	36.7	50	29.5	80	47	29.9	81	45
55	35.6	50	29.3	82	47	28.0	79	44
59	36.7	50	29.0	79	47	28.2	77	44
63	37.1	50	29.1	78	47	25.8	70	44
67	38.7	50	29.3	76	47	27.1	70	43
72	41.5	46	30.5	73	47	27.8	67	42
76	43.6	46	31.1	71	45	26.9	66	42
80	43.8	46	30.2	69	45	26.6	61	41
84	43.8	46	29.5	67	44	26.9	61	39
87	47.0	46	31.7	67	43	28.7	61	39
92	44.3	46	29.9	67	43	27.0	61	38
96	44.2	43	30.6	69	42	27.3	62	37
100	44.2	39	30.7	69	40	26.4	60	37
103	44.1	38	31.7	72	39	29.1	66	37

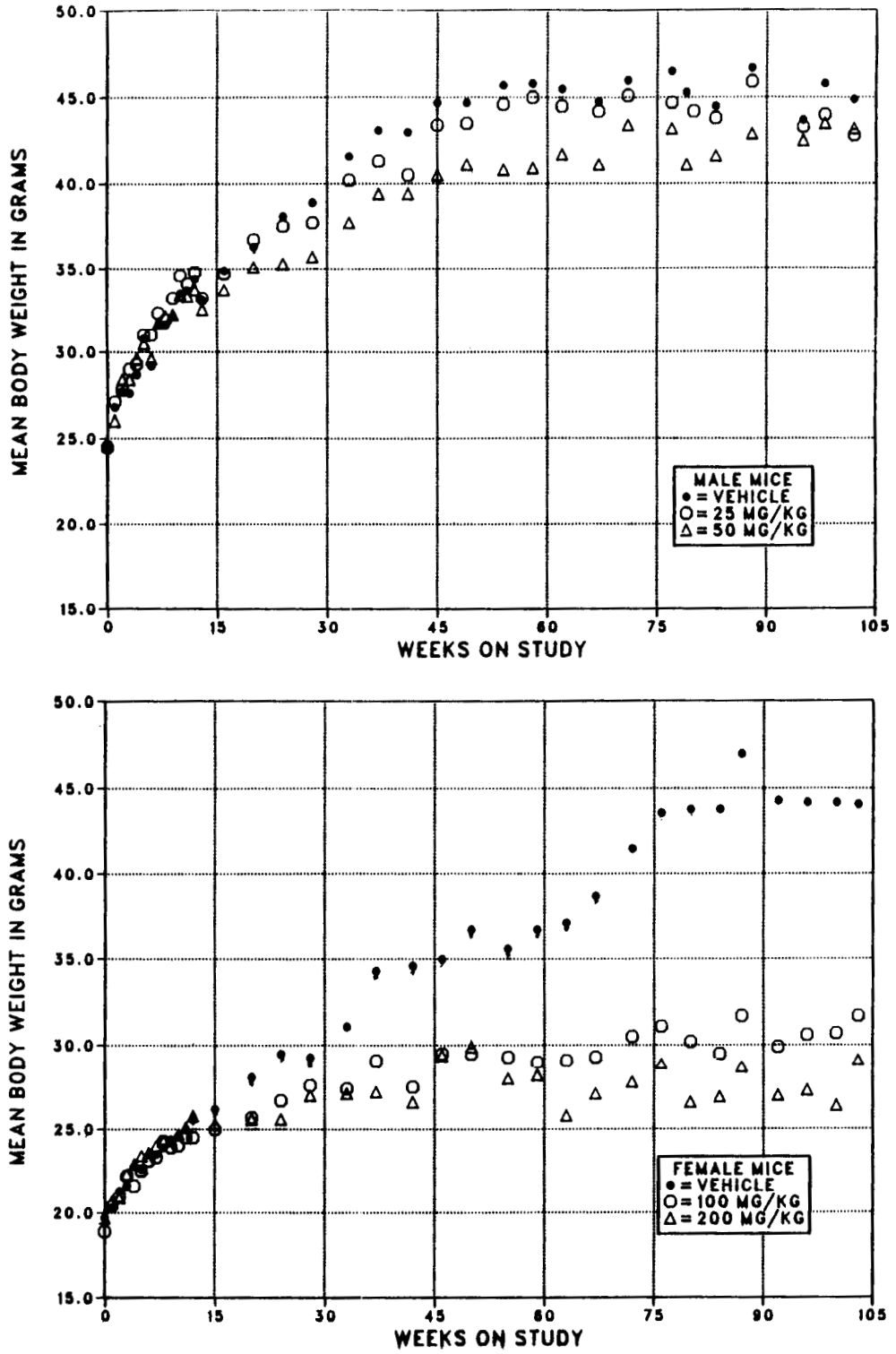

FIGURE 5. GROWTH CURVES FOR MICE ADMINISTERED CHLORPHENIRAMINE MALEATE IN WATER BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered chlorpheniramine maleate at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 6. The survival of the high dose group of male mice was significantly lower than that of the vehicle control after week 16 (Table 15). The survival of the low dose group of male mice was significantly ($P<0.05$) lower than that of the vehicle controls between weeks 23 and 97, but the overall (104 week) survival of the low dose group was not significantly different from that of vehicle controls. At the termination of the study (week 104), the survival rate was 39/50 (78%) for the vehicle control males and 31/49 (63%) for the low dose males. One low dose male was reported missing, and another died during the termination period. No significant differences in survival were observed between any groups of female mice.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the adrenal gland capsule, thyroid gland, subcutaneous tissue, kidney, lung, spleen, thymus, bone marrow, and brain. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in control animals are listed in Appendix F.

TABLE 15. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

	Vehicle Control	Low Dose	High Dose
MALE (a)		**25 mg/kg**	**50 mg/kg**
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	11	17	28
Accidentally killed	0	0	7
Animals missing	0	1	0
Killed at termination	39	31	15
Died during termination period	0	1	0
Survival P values (c)	<0.001	0.134	<0.001
FEMALE (a)		**100 mg/kg**	**200 mg/kg**
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	12	10	13
Accidentally killed	0	1	0
Killed at termination	38	39	37
Survival P values (c)	0.721	0.877	0.784

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

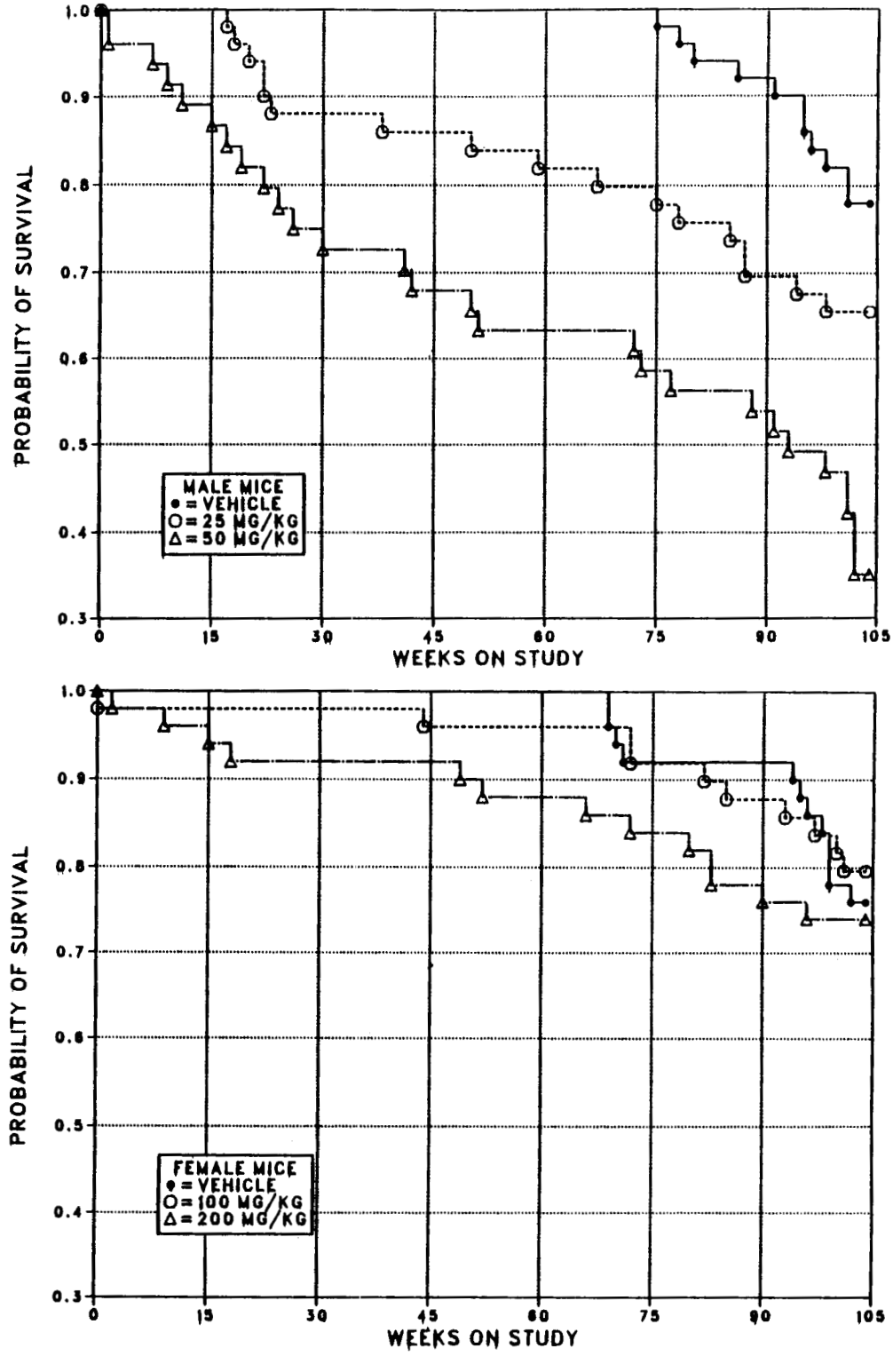

FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED CHLORPHENIRAMINE MALEATE IN WATER BY GAVAGE FOR TWO YEARS

Adrenal Gland Capsule: Adenomas in male mice occurred with a significant positive trend, and the incidences in the dosed groups were significantly greater than that in the vehicle controls (Table 16). There was a dose-related decrease in the incidences of focal hyperplasia of the adrenal gland capsule in male mice. This latter change largely reflects the increased rate of early deaths in the dosed groups; however, the negative trend and the decrease in the low dose group compared with the vehicle controls were marginally significant by the incidental tumor test. No malignant tumors of the adrenal gland capsule were observed in any group.

Thyroid Gland: Follicular cell cysts and follicular cell hyperplasia were observed at increased incidences in dosed female mice (Table 17). Incidences of follicular cell adenomas were slightly but not significantly increased in dosed female mice. No follicular cell carcinomas were observed in any of the groups of male or female mice.

TABLE 16. ANALYSIS OF ADRENAL GLAND CAPSULE LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (a)

	Vehicle Control	25 mg/kg	50 mg/kg
Hyperplasia, Focal			
Overall Rates	46/50 (92%)	33/49 (67%)	22/49 (45%)
Adjusted Rates	100.0%	89.1%	83.5%
Terminal Rates	39/39 (100%)	28/32 (88%)	11/15 (73%)
Week of First Observation	78	23	30
Life Table Tests	P=0.317	P=0.159N	P=0.245
Incidental Tumor Tests	P=0.042N	P=0.031N	P=0.082N
Adenoma (b)			
Overall Rates	2/50 (4%)	7/49 (14%)	4/49 (8%)
Adjusted Rates	5.1%	21.1%	26.7%
Terminal Rates	2/39 (5%)	6/32 (19%)	4/15 (27%)
Week of First Observation	104	94	104
Life Table Tests	P=0.022	P=0.042	P=0.040
Incidental Tumor Tests	P=0.031	P=0.030	P=0.040

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence of adrenal cortex or adrenal capsule tumors in vehicle controls in water gavage studies (mean ± SD): 8/198 (4% ± 0.5%); historical incidence in untreated controls: 43/1,716 (3% ± 3%)

TABLE 17. NUMBER OF MICE WITH THYROID GLAND FOLLICULAR CELL LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

	Male Dose (mg/kg)			Female Dose (mg/kg)		
	0	25	50	0	100	200
Number of mice examined	50	49	47	48	49	47
Cysts	2	2	0	2	10	13
Hyperplasia	4	3	3	3	29	36
Adenoma (b)	2	1	0	0	(a) 4	2

(a) P=0.070, incidental tumor test pairwise comparison with the vehicle controls; for a full statistical analysis of this lesion in female mice, see Appendix E, Table E4.
(b) Historical incidence of thyroid gland follicular cell tumors in vehicle control female B6C3F$_1$ mice in water gavage studies (mean ± SD): 3/193 (2% ± 1%); historical incidence in untreated controls: 43/1,661 (3% ± 3%)

Follicular cell cysts were diagnosed when cystic dilation of follicles lined by flattened epithelium was considered to exceed the normal limits of physiologic dilation of follicles by secretion. Follicular hyperplasia was diagnosed when single or multiple follicles were lined by enlarged follicular epithelial cells with prominent hyperchromatic nuclei. Proliferation of the affected epithelium resulted in the formation of small papillary invaginations into the follicular lumens. The follicular cell adenomas were well-differentiated expansible lesions that caused compression of the surrounding tissue. The epithelial cells resembled those seen in follicular cell hyperplasia but varied from cuboidal to columnar in shape, had more basophilic cytoplasm, and had an increased nucleus to cytoplasm ratio. Papillary patterns of growth in the adenomas were more extensive and complex than those seen in follicular hyperplasia and were accompanied by a delicate fibrovascular stroma.

Subcutaneous Tissue: Fibrosarcomas, sarcomas, fibrosarcomas, or neurofibrosarcomas (combined) and fibromas, sarcomas, fibrosarcomas, or neurofibrosarcomas (combined) occurred in male mice with significant positive trends (Table 18). The incidences in the high dose group were significantly greater than those in the vehicle controls by the life table test but not by the incidental tumor test in pairwise comparisons. Since these tumors are not lethal, the more appropriate analysis is provided by the incidental tumor test.

Kidney: A tubular cell adenoma was observed in one low dose male mouse, and a tubular cell adenocarcinoma was observed in one high dose male mouse. Three tubular cell adenomas and one adenocarcinoma have been observed in 1,780 untreated control male mice in NTP studies.

TABLE 18. ANALYSIS OF SUBCUTANEOUS TISSUE TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	Vehicle Control	25 mg/kg	50 mg/kg
Fibroma			
Overall Rates	1/50 (2%)	1/49 (2%)	0/50 (0%)
Fibrosarcoma			
Overall Rates	3/50 (6%)	3/49 (6%)	6/50 (12%)
Adjusted Rates	7.1%	9.1%	25.2%
Terminal Rates	2/39 (5%)	2/32 (6%)	0/15 (0%)
Week of First Observation	86	98	72
Life Table Tests	P=0.021	P=0.558	P=0.030
Incidental Tumor Tests	P=0.098	P=0.518	P=0.156
Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates	3/50 (6%)	4/49 (8%)	8/50 (16%)
Adjusted Rates	7.1%	11.6%	33.2%
Terminal Rates	2/39 (5%)	2/32 (6%)	0/15 (0%)
Week of First Observation	86	87	72
Life Table Tests	P=0.003	P=0.384	P=0.005
Incidental Tumor Tests	P=0.027	P=0.359	P=0.053
Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma (a)			
Overall Rates	4/50 (8%)	5/49 (10%)	8/50 (16%)
Adjusted Rates	9.7%	14.6%	33.2%
Terminal Rates	3/39 (8%)	3/32 (9%)	0/15 (0%)
Week of First Observation	86	87	72
Life Table Tests	P=0.007	P=0.370	P=0.010
Incidental Tumor Tests	P=0.047	P=0.349	P=0.088

(a) Historical incidence of integumentary system tumors in vehicle control male $B6C3F_1$ mice in water gavage studies (mean ± SD): 31/200 (16% ± 8%); historical incidence in untreated controls: 123/1,791 (7% ± 7%)

Lung: Alveolar/bronchiolar adenomas or carcinomas (combined) in male mice occurred with a significant negative trend, and the incidence of these lesions in low dose male mice was significantly lower than that in the vehicle controls (Table 19).

Spleen: Lymphoid depletion of the splenic follicles was observed at increased incidences in dosed male mice (vehicle control, 0/49; low dose, 9/49, 18%; high dose, 14/48, 29%).

Thymus: Lymphoid depletion of the thymus and necrosis of thymic lymphocytes were observed at increased incidences in dosed male mice (lymphoid depletion: vehicle control, 1/35, 3%; low dose, 4/38, 11%; high dose, 9/39, 23%; necrosis: vehicle control, 1/35, 3%; low dose, 6/38, 16%; high dose, 10/39, 26%).

Bone Marrow: Myelofibrosis was observed at an increased incidence in low dose female mice (vehicle control, 3/50, 6%; low dose, 15/48, 31%; high dose, 6/47, 13%).

Brain: Lymphocytic inflammatory infiltrates were observed at increased incidences in dosed female mice (vehicle control, 2/48, 4%; low dose, 9/49, 18%; high dose, 14/50, 28%).

TABLE 19. ANALYSIS OF LUNG LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	Vehicle Control	25 mg/kg	50 mg/kg
Epithelial Hyperplasia			
Overall Rates	2/50 (4%)	5/49 (10%)	3/48 (6%)
Alveolar/Bronchiolar Adenoma			
Overall Rates	12/50 (24%)	4/49 (8%)	2/48 (4%)
Adjusted Rates	28.8%	11.2%	13.3%
Terminal Rates	10/39 (26%)	2/32 (6%)	2/15 (13%)
Week of First Observation	86	75	104
Life Table Tests	P=0.058N	P=0.078N	P=0.166N
Incidental Tumor Tests	P=0.033N	P=0.060N	P=0.126N
Alveolar/Bronchiolar Carcinoma			
Overall Rates	5/50 (10%)	1/49 (2%)	1/48 (2%)
Adjusted Rates	12.4%	3.1%	6.7%
Terminal Rates	4/39 (10%)	1/32 (3%)	1/15 (7%)
Week of First Observation	101	104	104
Life Table Tests	P=0.203N	P=0.158N	P=0.420N
Incidental Tumor Tests	P=0.171N	P=0.194N	P=0.347N
Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates	16/50 (32%)	5/49 (10%)	3/48 (6%)
Adjusted Rates	37.8%	14.2%	20.0%
Terminal Rates	13/39 (33%)	3/32 (9%)	3/15 (20%)
Week of First Observation	86	75	104
Life Table Tests	P=0.035N	P=0.031N	P=0.131N
Incidental Tumor Tests	P=0.017N	P=0.027N	P=0.081N

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Chlorpheniramine maleate, an antihistaminic drug widely used in human and veterinary medicine, was studied by oral administration for toxicologic potential in male and female F344/N rats and B6C3F$_1$ mice. A feeding study was originally planned; however, because the recovery of the parent compound from a 100-ppm mixture in rodent feed stored for 2 weeks at 25° C was only 77%, chlorpheniramine maleate was administered by gavage with deionized water in the 13-week and 2-year toxicity studies.

In the 14-day studies in rats, compound-related deaths of males and females occurred at doses of 80 mg/kg and higher (see Table 6). In the 14-day studies in mice, no deaths or gross pathologic lesions occurred at doses up to 200 mg/kg (see Table 11). This finding was unexpected, since oral LD_{50} values of chlorpheniramine maleate in mice had been reported to vary from 121 to 162 mg/kg (Roth and Govier, 1958; Labelle and Tislow, 1955; Smith et al., 1974). Male Swiss-Webster mice were used in the study by Smith et al. (1974); the strains of mice in the other two studies (Roth and Govier, 1958; Labelle and Tislow, 1955) were not identified. Strain differences may account for the variable sensitivities of mice to chlorpheniramine maleate. A second 2-week study (12 doses over a 16-day period) was conducted in B6C3F$_1$ mice at doses up to 800 mg/kg. In this study, compound-related deaths of males and females occurred at 400 and 800 mg/kg (see Table 12). Hyperactivity was noted in rats and mice in the 14-day and 16-day studies at doses of 40 mg/kg and higher.

In the 13-week studies, chlorpheniramine maleate was administered to male and female rats 5 days per week at doses of 0 (vehicle control), 3.75, 7.5, 15, 30, or 60 mg/kg per day. No deaths or compound-related gross or microscopic lesions were observed in these studies. The final mean body weight of males in the 60 mg/kg dose group was 13% lower than that of the vehicle controls (see Table 7). Based on the mortality and body weight data from the 14-day and 13-week studies, the doses selected for rats in the 2-year studies were 0, 15, and 30 mg/kg per day for males and 0, 30, and 60 mg/kg per day for females. The therapeutic human adult daily oral dose of chlorpheniramine maleate varies up to 0.32 mg/kg.

In the 13-week studies of chlorpheniramine maleate in mice, doses of 0 (vehicle control), 12.5, 25, 50, 100, or 200 mg/kg per day were administered 5 days per week. Two males in the 200 mg/kg dose group died; however, one of those deaths was attributed to Sendai infection. No compound-related gross or microscopic lesions or adverse effects on mean body weight were observed at the end of the study. Because of the high mortality rates in the 16-day study at 400 mg/kg and the lack of a clear toxic effect at 200 mg/kg in the 13-week study, doses selected for mice in the 2-year studies were 0 (vehicle control), 100, and 200 mg/kg per day for males and females. In the 2-year studies, doses were administered to rats and mice 5 days per week.

The doses of chlorpheniramine maleate used in the 2-year studies did not significantly affect survival in male rats or female mice. Deaths not due to neoplasia were significantly increased in female rats in the 60 mg/kg dose group relative to vehicle controls (see Table 9). Because only 6/50 female rats in the 60 mg/kg dose group survived to the end of the study, this group was considered to be inadequate for an evaluation of the carcinogenic potential of chlorpheniramine maleate. Survival of female rats in the 30 mg/kg dose group was not significantly different from that of the vehicle controls.

During week 1 of the 2-year studies in mice, 18/50 (36%) males in the 200 mg/kg dose group died. Since this type of response was not observed in the 13-week studies, the 2-year studies were restarted at the same doses (0, 100, and 200 mg/kg per day). A high mortality rate was again observed in males in the second study: after 20 weeks the survival rates in the vehicle control, 100 mg/kg, and 200 mg/kg groups were 47/50 (94%), 42/50 (84%), and 32/50 (64%), respectively; consequently, the 2-year study in male mice was again restarted but at lower doses (0, 25, and 50 mg/kg). After 2 years, survival of male mice in the 50 mg/kg dose group (15/50) was significantly reduced relative to the vehicle controls (39/50; see Table 15). Survival of male mice in the 25 mg/kg dose group was lower than that of the vehicle control group for about 75% of the study; however, the overall survival at the end of the study (31/50) was not significantly different. After 78 weeks of the study, there

were 38 surviving low dose male mice, and at the termination of the study, there were 32 surviving low dose male mice. Since this level of survival is comparable to the mean historical control survival rate of 67% ± 14.6% for male B6C3F$_1$ mice in corn oil gavage studies (Haseman et al., 1985), it was considered adequate for the evaluation of chemically induced carcinogenesis.

The high mortality rates for male mice in the 2-year studies were not expected from the results from the 13-week studies. An audit of the data collected during the conduct of these studies did not reveal any environmental or dosing problems that might account for these mortality patterns (Appendix O). Although an explanation is not readily available, several possibilities are considered. First, body weight or age may affect the acute toxicity of chlorpheniramine maleate in mice as it does in rats (Lee, 1966; Goldenthal, 1971). The initial mean body weight of male mice dosed at 200 mg/kg was 26.7 g in the 13-week study, 21.9 g in the initial 2-year study, and 23.4 g in the first restarted 2-year study. The smaller mice in the 2-year studies may have been more sensitive to this dose of chlorpheniramine maleate. Variance in initial body weights was discounted as an important factor, since there was no clear relationship between initial body weight and day of death. Second, variation in the daily dosing schedule may have been a contributing factor, since the time of dosing during the day can influence peak blood levels. Third, hyperactivity associated with administration of chlorpheniramine maleate to rats or mice may have contributed to more dosing accidents than were reported, especially since confirmation of dosing accidents is difficult when water rather than oil is the vehicle. Fourth, the early deaths may reflect a toxicologic effect of high doses of chlorpheniramine in young male mice.

No organ or tissue sites were identified that would account for the toxicity and increased mortality of male mice dosed with chlorpheniramine maleate. H_1 receptor anatagonists are known to stimulate and depress the central nervous system (Douglas, 1980). Deaths of mice administered toxic levels of chlorpheniramine maleate were attributed to central nervous system (CNS) stimulation, muscle tremors, and convulsive seizures followed by postictal respiratory depression (Smith et al., 1974). Deaths of monkeys dosed with 15 mg/kg per day of chlorpheniramine maleate were attributed to cardiac failure (Schering Corp., 1975a). Deaths in the present studies may also have been related to CNS stimulation or cardiac failure. The decrease in body weight gain of dosed female mice in the 2-year study may also have reflected CNS stimulation, since hyperexcitability and hyperactivity were associated with the administration of chlorpheniramine maleate (see Figure 5).

No significant positive trends or increases in the incidences of neoplasia were observed in either male or female rats dosed with chlorpheniramine maleate in the 2-year studies. Negative trends and decreases in the incidences of mononuclear cell leukemia and of pheochromocytomas of the adrenal gland were observed in dosed male rats (see Table 10). However, the incidences of these tumors in the dosed groups were not very different from their historical incidences in untreated male F344/N rats (Appendix F, Tables F1 and F2). A decrease in the incidence of clitoral gland adenomas was observed in the 30 mg/kg dose group of female rats compared with that in the vehicle controls. The negative trend in female rats was not considered to be compound related because of the high mortality rate in the 60 mg/kg dose group. Although no clitoral gland adenomas occurred in the low dose female rat group, this difference may not represent a chemical effect, since the historical rate of clitoral gland adenomas or carcinomas (combined) in untreated female F344/N rats is 4% ± 3%.

The incidence of adrenal gland capsule adenomas in the 25 and 50 mg/kg dose groups of male mice was increased compared with that of the vehicle controls (see Table 16); however, the incidence of adrenal capsule hyperplasia was decreased. Neoplasms in the subcapsular area are thought to originate from areas of subcapsular hyperplasia which are frequently seen in older mice (Dunn, 1970). There is no clear morphologic distinction between hyperplasia and adenoma of the adrenal capsule; these lesions are generally distinguished by size (Dunn, 1970, 1979). Since proliferative lesions of the adrenal capsule are considered to be progressive, a

chemical-related effect would likely include increases in the incidence of both hyperplasia and adenomas. The rates of adenomas or hyperplasia (combined) (vehicle control, 46/50, 92%; 25 mg/kg, 35/49, 71%; 50 mg/kg, 25/49, 51%) indicate that chlorpheniramine maleate did not increase the frequency of these proliferative lesions in male mice. No malignant tumors of the adrenal gland capsule were observed in any group of mice.

The increases in the incidences of thyroid gland follicular cell hyperplasia and cysts in female mice were the most notable effects associated with administration of chlorpheniramine maleate. A slight but nonsignificant increase ($P=0.07$) in thyroid gland follicular cell adenomas was observed in the low dose group (see Table 17). Thyroid gland follicular cell carcinomas were not observed in any group of mice. Since the historical rate of thyroid gland follicular cell adenomas in untreated female $B6C3F_1$ mice is 2.2% ± 2% (Table F7), the rate (4/49, 8%) observed in the 100 mg/kg dose group of female mice might indicate a compound-related effect. The distinction between follicular cell hyperplasia and follicular cell adenoma of the thyroid gland is not always obvious (Biancifiori, 1979). Nevertheless, the increase in proliferative follicular cell lesions in female mice dosed with chlorpheniramine maleate raises a toxicologic concern, since thyroid gland neoplasms are uncommon in mice and are often preceded by hyperplasia of the follicular epithelium (Biancifiori, 1979).

The incidence of subcutaneous tissue tumors in the 50 mg/kg dose group of male mice was greater than that in the vehicle control group by life table analysis but not by the incidental tumor test in pairwise comparisons (see Table 18). There has been a marked variability in the historical incidence of integumentary system tumors in untreated control and water vehicle control groups of male $B6C3F_1$ mice (Table F4). The range for the historical incidence of fibromas, sarcomas, or fibrosarcomas (combined) in untreated control groups is 0%-38%, whereas the range of incidence of these tumors in four water vehicle control groups is 8%-26%. Since the incidence of these nonlethal tumors in dosed male mice was not significant compared with vehicle controls when analyzed by the incidental tumor test, and since the incidence of subcutaneous tumors in high dose male mice in the present study is comparable to the overall rates of subcutaneous tumors in water vehicle control groups from previous studies, the presence of these tumors is not considered to be related to the administration of chlorpheniramine maleate.

The incidence of alveolar/bronchiolar neoplasms in the 25 mg/kg dose group of male mice was significantly lower than that in the vehicle controls (see Table 19); however, this change may not be due to administration of chlorpheniramine maleate, since the rate in the dosed group is within the range of the historical rate of these tumors in untreated control male $B6C3F_1$ mice (Table F5). The role of chlorpheniramine maleate in causing this decrease is not understood.

Splenic and thymic lymphocyte depletion as well as lymphoid necrosis were observed at increased incidences in dosed male mice. All of the affected animals died before the termination of the study or were killed in a moribund condition due to the presence of metastatic tumors or severe infection. The lymphoid changes in the spleen and thymus are considered to be secondary to debilitation and illness in these mice and not to be chemically related effects.

Lymphocytic inflammatory cell infiltration of the meninges was observed at increased incidences in dosed female mice; however, this effect was not accompanied by toxic or proliferative lesions. The possible role of chlorpheniramine maleate in causing this change is not understood.

The metabolism and pharmacokinetic parameters for chlorpheniramine maleate in rats are slightly different from those in humans. In rats administered an oral dose of 2.5 mg/kg of radiolabeled chlorpheniramine, maximum blood levels of chlorpheniramine equivalents of about 0.7 µg/ml were observed 30-60 minutes after dosing (Kamm et al., 1969). About 40%-50% of orally administered chlorpheniramine maleate is excreted in the urine within 24 hours (Kamm et al., 1969; Peets et al., 1972b; Appendix N), with the mono- and didesmethylated metabolites

accounting for about 50% of the excreted dose (Kamm et al., 1969; Peets et al., 1972b). The plasma half-life of radiolabeled chlorpheniramine is about 24 hours in rats. In humans, peak plasma levels of chlorpheniramine were 17.9 ng/ml 2.8 hours after a single oral dose of 0.14 mg/kg (Huang et al., 1982). Peets et al. (1972a) observed peak plasma levels of chlorpheniramine to be 17.1 ng/ml 2 hours after dosing, whereas plasma levels of chlorpheniramine equivalents (parent compound and metabolites) reached a level of 48.3 ng/ml. With frequent daily dosing, the peak plasma concentration of chlorpheniramine in humans is about 35 ng/ml, which is indicative of accumulation of the drug (Yacobi et al., 1980; Huang et al., 1982). The plasma half-life of chlorpheniramine in humans is also about 24 hours but has been reported to vary from 12 to 43 hours (Peets et al., 1972a; Yacobi et al., 1980; Huang et al., 1982). Chlorpheniramine is extensively metabolized in humans; urinary excretion includes mono- and didesmethyl chlorpheniramine, chlorpheniramine, and unidentified polar metabolites (Kabasakalian et al., 1968; Peets et al., 1972a; Huang et al., 1982). Wide individual variations exist in the metabolism and urinary excretion of chlorpheniramine in humans.

The ratio of dose to peak plasma levels of chlorpheniramine in rats is equivalent to or about two times greater than that in humans. Based on this comparison, and because the plasma half-life in rats and humans is nearly identical and the elimination profile of chlorpheniramine in rats is unchanged between doses of 2 and 20 mg/kg, it was estimated that the dose of 15 mg/kg used in the 2-year studies in rats would result in a plasma level about 25-50 times greater than that which would result when humans received the recommended adult daily oral dose of 0.32 mg/kg of chlorpheniramine maleate. No data are available to make similar comparisons at higher doses in rats or mice. It should also be noted that metabolism and pharmacokinetic parameters may change as animals age or when continuous dosing produces a toxic effect. It is not known whether such changes occur for chlorpheniramine or what effect such changes would have on the development of neoplastic and nonneoplastic lesions.

The mutagenicity of chlorpheniramine maleate in in vitro tests with bacteria and cultured mammalian cells is limited in that positive responses were observed only at doses where there was concomitant cellular toxicity. There were no genotoxic effects associated with chlorpheniramine maleate in assays for mutagenicity in *Salmonella typhimurium* (Andrews et al., 1980; Mortelmans et al., 1986; Appendix G) or in mouse lymphoma L5178Y cells (Appendix G) or for induction of DNA repair in primary cultures of rat hepatocytes (Probst and Neal, 1980). The increase in sister-chromatid exchanges (SCEs) in Chinese hamster ovary cells treated in the absence of activation was observed only in the presence of cell cycle delay and was only marginally positive. In the presence of S9, no increase in SCEs was observed even when chlorpheniramine maleate was tested up to toxic dose levels. A high level of chromosomal aberrations was seen at levels just below the most toxic dose tested in the presence of S9. No increase in the frequency of chromosomal aberrations was observed in the absence of metabolic activation.

In 2-year feed studies of chlorpheniramine maleate in male and female CD rats at doses of 0, 2, 10, or 20 mg/kg per day, no increases in tumor rates were observed compared with controls (Schering-Plough Research Division, 1978, unpublished). In a 106-week study, there was no effect of feed mixtures containing 1,000 ppm chlorpheniramine maleate on tumor rates in male or female F344 rats (Lijinsky, 1984b). However, feed stability data acquired before the start of the NTP toxicology and carcinogenicity studies indicated that chlorpheniramine maleate was only 77% recoverable from rodent feed mixtures. In the NTP water gavage studies, no increases in neoplasia were associated with the administration of chlorpheniramine maleate; however, in dosed female mice an increase was observed in the incidence of thyroid gland follicular cell hyperplasia, a lesion that often precedes the appearance of thyroid gland follicular cell tumors. An increase in liver neoplasms was observed in male rats fed diets containing 1,000 ppm chlorpheniramine maleate plus 2,000 ppm sodium nitrite (Lijinsky, 1984b), indicating that nitrosation of chlorpheniramine maleate may produce a carcinogenic compound.

IV. DISCUSSION AND CONCLUSIONS

Interest in the potential carcinogenicity of antihistaminic drugs developed largely from the finding of a high incidence of hepatocellular neoplasms in male and female Sprague-Dawley and F344 rats fed diets containing 1,000 ppm methapyrilene hydrochloride (Lijinsky and Taylor, 1977; Lijinsky et al., 1980). In the present studies, significantly increased incidences of liver neoplasms were not observed in male or female F344/N rats. Other antihistaminic drugs being studied by the National Toxicology Program for toxicity and carcinogenicity include diphenhydramine, doxylamine, pyrilamine, tripelennamine, and triprolidine.

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** for F344/N rats or B6C3F$_1$ mice of either sex administered chlorpheniramine maleate in deionized water, 5 days per week for 2 years. Due to high mortality in high dose female rats and high dose male mice, the sensitivity of these groups to detect a carcinogenic response was reduced. Chlorpheniramine maleate had a proliferative effect on the thyroid gland of female mice, as shown by the increased incidences of follicular cell cysts and hyperplasia in both low dose and high dose groups.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2. The discussion regarding the interpretative conclusions is summarized on pages 13 and 14.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	3 (6%)	2 (4%)	1 (2%)
Trichoepithelioma	1 (2%)		
Keratoacanthoma	1 (2%)	2 (4%)	
*Subcutaneous tissue	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
Sarcoma, NOS		1 (2%)	
Fibroma	2 (4%)	2 (4%)	
Fibrosarcoma	1 (2%)		
Osteosarcoma		1 (2%)	
Neurofibroma			1 (2%)
RESPIRATORY SYSTEM			
None			
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	25 (50%)	14 (28%)	11 (22%)
#Axillary lymph node	(48)	(49)	(45)
C-cell carcinoma, metastatic	1 (2%)		
#Thymus	(44)	(43)	(44)
Thymoma, benign	1 (2%)		
CIRCULATORY SYSTEM			
*Subcut tissue	(50)	(50)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma			1 (2%)
#Splenic red pulp	(49)	(50)	(50)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
#Liver	(50)	(50)	(50)
Neoplastic nodule	4 (8%)	2 (4%)	5 (10%)
Hepatocellular carcinoma	1 (2%)	1 (2%)	1 (2%)
#Pancreas	(50)	(47)	(49)
Acinar cell adenoma	1 (2%)		
#Jejunum	(49)	(50)	(49)
Adenocarcinoma, NOS		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Transitional cell carcinoma	1 (2%)		
#Urinary bladder/mucosa	(49)	(48)	(49)
Papilloma, NOS			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(47)
Adenoma, NOS	12 (24%)	16 (32%)	8 (17%)
#Adrenal	(49)	(50)	(49)
Cortical adenoma			1 (2%)
#Adrenal medulla	(49)	(50)	(49)
Pheochromocytoma	21 (43%)	8 (16%)	5 (10%)
Pheochromocytoma, malignant		1 (2%)	
#Thyroid	(50)	(49)	(47)
Follicular cell carcinoma	1 (2%)		
C-cell adenoma	7 (14%)	6 (12%)	3 (6%)
C-cell carcinoma	2 (4%)	1 (2%)	
Papillary cystadenoma, NOS			1 (2%)
#Parathyroid	(42)	(44)	(45)
Adenoma, NOS		2 (5%)	
#Pancreatic islets	(50)	(47)	(49)
Islet cell adenoma	3 (6%)	1 (2%)	1 (2%)
Islet cell carcinoma	2 (4%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	
Fibroadenoma	3 (6%)		
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
Adenoma, NOS	1 (2%)		
#Prostate	(49)	(50)	(50)
Adenocarcinoma, NOS		1 (2%)	
#Testis	(49)	(50)	(50)
Interstitial cell tumor	44 (90%)	43 (86%)	38 (76%)
NERVOUS SYSTEM			
#Cerebrum	(50)	(50)	(50)
Granular cell tumor, benign	1 (2%)		
Oligodendroglioma		1 (2%)	
#Cerebellum	(50)	(50)	(50)
Granular cell tumor, benign		1 (2%)	
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		2 (4%)	
MUSCULOSKELETAL SYSTEM			
*Occipital bone	(50)	(50)	(50)
Osteosarcoma			1 (2%)
BODY CAVITIES			
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Osteosarcoma, metastatic		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	8	11	18
Moribund sacrifice	11	11	6
Terminal sacrifice	31	28	24
Dosing accident			2
TUMOR SUMMARY			
Total animals with primary tumors**	50	47	39
Total primary tumors	142	111	80
Total animals with benign tumors	47	46	38
Total benign tumors	103	84	60
Total animals with malignant tumors	30	22	15
Total malignant tumors	34	25	15
Total animals with secondary tumors##	1	1	
Total secondary tumors	1	1	
Total animals with tumors uncertain-- benign or malignant	5	2	5
Total uncertain tumors	5	2	5

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

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
Keratoacanthoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma		1 (2%)	1 (2%)
Fibrosarcoma	1 (2%)		
Lipoma	1 (2%)		
Neurofibroma	1 (2%)		
RESPIRATORY SYSTEM			
None			
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	11 (22%)	4 (8%)	2 (4%)
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(49)
Neoplastic nodule	2 (4%)		1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(48)	(45)
Adenoma, NOS	24 (50%)	13 (27%)	6 (13%)
Carcinoma, NOS	1 (2%)	1 (2%)	
#Adrenal	(50)	(49)	(47)
Cortical adenoma	1 (2%)	1 (2%)	1 (2%)
#Adrenal medulla	(50)	(49)	(47)
Pheochromocytoma	3 (6%)	2 (4%)	
#Thyroid	(47)	(46)	(45)
C-cell adenoma	4 (9%)	2 (4%)	
#Parathyroid	(33)	(34)	(32)
Adenoma, NOS		1 (3%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
Adenocarcinoma, NOS	3 (6%)	1 (2%)	
Fibroadenoma	14 (28%)	6 (12%)	
*Clitoral gland	(50)	(50)	(50)
Adenoma, NOS	5 (10%)		
#Uterus	(49)	(50)	(46)
Endometrial stromal polyp	10 (20%)	11 (22%)	1 (2%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Cervix uteri	(49)	(50)	(46)
Endometrial stromal polyp	1 (2%)		
NERVOUS SYSTEM			
#Cerebrum	(50)	(49)	(49)
Carcinoma, NOS, invasive	1 (2%)		
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Pelvis	(50)	(50)	(50)
Lipoma	1 (2%)		
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	15	41
Moribund sacrifice	11	8	2
Terminal sacrifice	29	24	6
Dosing accident	1	3	1
TUMOR SUMMARY			
Total animals with primary tumors**	42	30	8
Total primary tumors	87	43	12
Total animals with benign tumors	38	29	8
Total benign tumors	68	37	9
Total animals with malignant tumors	16	6	2
Total malignant tumors	17	6	2
Total animals with secondary tumors##	1		
Total secondary tumors	1		
Total animals with tumors uncertain--benign or malignant	2		1
Total uncertain tumors	2		1

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

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: VEHICLE CONTROL

ANIMAL NUMBER	01 17	04 49	03 34	01 15	02 23	03 31	00 07	03 32	00 05	01 11	02 22	00 01	01 13	03 37	02 27	04 47	03 36	00 04	01 14	00 02	00 03	00 06	00 08	00 09	01 10
WEEKS ON STUDY	03 38	07 71	07 79	08 85	08 85	08 87	09 00	09 93	09 95	09 95	09 96	09 97	09 99	09 99	10 00	10 01	10 02	10 03	10 03	10 04	10 04	10 04	10 04	10 04	10 04
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Trichoepithelioma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma	X																								
Fibroma												X									X				
Fibrosarcoma																									
Hemangioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma								X																	
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																			X						
Thymus	−	+	+	+	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																								X	
Hepatocellular carcinoma																									X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X			X		X										X	X				X	
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma						X			X		X	X					X		X						
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma																X	X						X		
C-cell carcinoma								X											X						
Parathyroid	−	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																	X								
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	N	+	+	+	+	N	N	N	N	N	+	N	+	+	+	N	N	+	+	N
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X		X	X		X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, benign																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X		X	X	X		X	X	X	X		X			X	X						X		X

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

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	012	016	018	019	020	021	024	025	026	028	029	030	033	035	038	039	040	041	042	043	044	045	046	048	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma		X										X														3
Trichoepithelioma																X										1
Keratoacanthoma							X																			1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Fibroma																										2
Fibrosarcoma														X												1
Hemangioma			X																							1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	48
C-cell carcinoma, metastatic																										1
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymoma, benign																X										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule			X					X						X												4
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma																								X		1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma																									X	1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS			X				X	X					X				X							X		12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma		X	X	X		X	X	X	X		X		X	X	X	X		X	X				X			21
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																									X	1
C-cell adenoma							X								X			X					X			7
C-cell carcinoma																										2
Parathyroid	–	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma						X											X									3
Islet cell carcinoma			X																X							2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	N	N	+	N	N	N	+	+	+	N	+	+	+	N	N	+	+	N	N	+	*50
Fibroadenoma	X				X																X					3
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	44
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS	X																									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, benign																					X					1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS				X																						1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell		X	X		X	X	X			X		X	X			X	X						X	X		25

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: LOW DOSE

ANIMAL NUMBER	0008	0022	0092	0244	0337	0066	0334	0110	0440	0122	0339	0355	0091	0166	0333	0447	0004	0111	0455	0227	0003	0005	0007	0009	0113
WEEKS ON STUDY	052	052	060	065	074	075	076	079	086	088	089	091	093	093	093	095	096	097	097	100	101	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																						X			
Keratoacanthoma																									X
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																		X							
Fibroma																									X
Osteosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	−	+	+	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma					X																				
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule													X												
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS										X															
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS								X	X	X							X			X	X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																					X				
Pheochromocytoma, malignant																									
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																		X				X			
C-cell carcinoma																									
Parathyroid	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+
Adenoma, NOS														X											
Pancreatic islets	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	N	+	+	N	N	+	+	N	N	+	N	+	+	N	+	+	+	N	N	+	N	+
Adenocarcinoma, NOS																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor				X		X	X		X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS				X																					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, benign																	X								
Oligodendroglioma																									X
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS						X	X																		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma, metastatic																									
Leukemia, mononuclear cell							X					X	X	X	X	X			X						

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0 1 4	0 1 5	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 3	0 2 5	0 2 6	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 6	0 3 8	0 4 1	0 4 2	0 4 3	0 4 4	0 4 6	0 4 8	0 4 9	0 5 0	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma				X																						2
Keratoacanthoma										X																2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma											X															2
Osteosarcoma									X																	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																					X					2
Hepatocellular carcinoma																									X	1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X	X				X	X				X				X	X			X			X			16
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X		X						X		X	X	X							X					8
Pheochromocytoma, malignant																								X		1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma						X										X				X			X			6
C-cell carcinoma					X																					1
Parathyroid	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	44
Adenoma, NOS																					X					2
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell adenoma								X																		1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	N	+	+	+	+	+	+	N	+	N	N	+	+	+	+	N	+	N	N	+	N	*50
Adenocarcinoma, NOS													X													1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	43
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, benign																										1
Oligodendroglioma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma, metastatic									X																	1
Leukemia, mononuclear cell												X	X	X		X		X		X					X	14

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: HIGH DOSE

ANIMAL NUMBER	038	004	019	029	008	002	020	016	033	035	001	017	005	043	007	022	023	003	027	026	024	025	040	042	039
WEEKS ON STUDY	004	037	043	045	051	052	052	056	056	059	068	078	082	082	083	084	087	089	091	093	095	097	097	097	100
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Neurofibroma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	−	+	+	+	−	+	+	−	−	+	+	+	−	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																							X		
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																		X							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																								X	
Pheochromocytoma																									
Thyroid	−	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									X
Papillary cystadenoma, NOS																									
Parathyroid	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma														X											
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	+	+	+	+	N	N	N	+	N	N	N	N	N	N	+	+	N	N	N	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor										X			X	X	X	X	X	X	X		X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma														X											
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																X	X		X	X	X	X		X	X

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	0014	0006	0009	0110	0111	0112	0113	0115	0118	0121	0128	0130	0131	0132	0134	0136	0137	0141	0144	0145	0146	0147	0148	0149	0150	TOTAL:
WEEKS ON STUDY	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma									X																	1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Hemangiosarcoma																		X								1
Neurofibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	45
Thymus	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule			X	X	X														X							5
Hepatocellular carcinoma																					X					1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma, NOS															X											1
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS							X	X						X		X	X			X		X				8
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																										1
Pheochromocytoma					X	X		X					X						X							5
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell adenoma										X								X								3
Papillary cystadenoma, NOS		X																								1
Parathyroid	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	+	+	+	N	+	N	N	+	+	+	+	N	N	N	+	N	N	N	+	+	N	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	38
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS						X																				1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X															X					X					11

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: VEHICLE CONTROL

ANIMAL NUMBER	0013	0007	0045	0009	0027	0049	0050	0112	0118	0035	0042	0110	0114	0116	0023	0030	0037	0024	0043	0002	0019	0001	0003	0004	0005
WEEKS ON STUDY	043	059	067	070	074	074	081	085	088	090	096	097	099	099	100	100	100	102	102	103	103	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																			X						
Lipoma																									
Neurofibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
Thymus	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule															X										
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS			X		X	X	X		X	X	X			X	X	X		X		X		X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma													X												
Pheochromocytoma														X											
Thyroid	+	−	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma														X											X
Parathyroid	+	+	−	+	+	−	+	+	−	−	−	+	−	+	+	−	−	−	+	+	−	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	N	N	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N
Adenoma, NOS																									
Adenocarcinoma, NOS				X												X									
Fibroadenoma								X				X				X		X				X			
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS			X												X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp						X	X			X			X							X					X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																X									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Lipoma																	X								
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell			X								X			X						X	X		X		

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

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0006	0008	0011	0015	0017	0020	0021	0022	0025	0026	0028	0029	0031	0032	0033	0034	0036	0038	0039	0040	0041	0044	0046	0047	0048	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma		X																								1
Keratoacanthoma																			X							1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
Lipoma												X														1
Neurofibroma																	X									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	−	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule													X													2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS								X																		1
Adenoma, NOS			X	X					X		X		X						X	X	X			X	X	24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma					X												X									3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell adenoma												X									X					4
Parathyroid	+	−	+	+	+	+	−	−	+	+	+	−	+	+	+	+	+	−	+	+	+	−	+	+	−	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	N	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	N	+	*50
Adenoma, NOS		X																								1
Adenocarcinoma, NOS																		X								3
Fibroadenoma	X	X					X		X				X	X				X		X				X		14
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X			X																				X	5
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Endometrial stromal polyp			X											X		X				X			X			11
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive								X																		1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Lipoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X											X	X			X					X					11

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: LOW DOSE

ANIMAL NUMBER	0222	0334	0440	0001	0220	0226	0221	0337	0339	0119	0004	0449	0441	0550	0224	0425	0446	0111	0228	0442	0116	0118	0003	0321	0133
WEEKS ON STUDY	0006	0009	0009	0411	0419	0549	0556	0557	0561	0665	0665	0666	0671	0744	0747	0777	0822	0822	0844	0855	0858	0888	0901	0997	
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	−	+	−	+	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	−	+	−	−	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	−	+	−	−	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS														X						X		X		X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																				X					
Thyroid	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
C-cell adenoma																									X
Parathyroid	−	+	−	−	−	−	−	+	+	+	−	+	+	+	+	+	−	+	−	+	+	−	+	+	+
Adenoma, NOS																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	+	+	N	N	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+
Adenocarcinoma, NOS														X											
Fibroadenoma																X					X	X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp										X	X				X					X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																					X				X

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	00007	00002	00005	00006	00008	00009	00110	00112	00114	00115	00117	00123	00127	00129	00130	00131	00133	00135	00136	00138	00143	00144	00145	00147	00148	TOTAL:
WEEKS ON STUDY	101	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																				X						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS															X											1
Adenoma, NOS	X		X			X					X		X				X	X		X					X	13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma														X												1
Pheochromocytoma															X											2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
C-cell adenoma														X												2
Parathyroid	+	+	+	–	–	+	+	+	+	+	–	+	+	+	+	–	–	+	–	+	+	+	+	+	+	34
Adenoma, NOS		X																								1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	N	N	+	+	+	+	N	N	N	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma	X			X																X						6
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp									X	X				X	X		X						X	X		11
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell								X								X										4

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: HIGH DOSE

ANIMAL NUMBER	04445	04407	01724	02447	03737	01414	03636	01109	01154	00424	03939	03111	04121	03838	03309	03344	01616	02727	04242	04499	00101	00999	00033
WEEKS ON STUDY	00001	00004	00006	00008	00009	01012	01113	01116	01119	02220	02221	02224	02226	02227	03131	03355	03366	03377	03387	03388	03399	04141	04242
INTEGUMENTARY SYSTEM																							
Subcutaneous tissue	N	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Fibroma																							
RESPIRATORY SYSTEM																							
Lungs and bronchi	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																							
Bone marrow	+	+	+	+	+	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	A	+	+	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	+	+	+	A	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																							
Heart	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
Salivary gland	−	A	+	+	+	A	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Liver	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																							
Bile duct	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	−	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	A	+	+	+	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Small intestine	−	A	+	−	+	A	+	−	−	−	+	−	−	+	−	+	+	−	−	−	+	−	−	+
Large intestine	−	A	+	+	+	A	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+
URINARY SYSTEM																							
Kidney	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	A	A	+	+	A	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	−	+
ENDOCRINE SYSTEM																							
Pituitary	+	A	+	+	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							
Adrenal	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																							
Thyroid	−	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Parathyroid	−	A	+	−	+	A	−	+	+	−	−	+	+	−	+	+	+	+	−	+	+	+	−	A
REPRODUCTIVE SYSTEM																							
Mammary gland	N	N	N	+	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	N	N	+	N
Uterus	−	A	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																							
Ovary	−	A	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																							
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																							
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																							

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	023	029	028	043	013	026	011	046	012	032	006	021	022	050	008	025	002	019	018	005	007	020	033	035	048	TOTAL:
WEEKS ON STUDY	042	042	045	045	046	050	052	052	053	059	060	060	063	068	067	077	091	093	095	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																X										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+	41
Thymus	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																							X			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	−	+	+	+	+	+	−	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	42
Small intestine	+	−	+	−	−	+	+	+	+	−	+	−	+	+	A	+	+	+	+	+	+	+	+	+	+	28
Large intestine	+	+	+	−	−	+	+	+	+	−	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	40
URINARY SYSTEM																										
Kidney	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Urinary bladder	+	+	+	−	+	+	+	+	+	−	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	40
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS																	X	X	X			X	X	X		6
Adrenal	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cortical adenoma																								X		1
Thyroid	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	45
Parathyroid	+	−	+	+	−	−	+	+	+	−	+	−	+	+	+	+	+	+	+	−	+	+	+	−	+	32
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	+	N	+	N	N	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Endometrial stromal polyp									X																	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell																	X					X				2

* Animals necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(49)	(50)
Sarcoma, NOS	1 (2%)		1 (2%)
Fibroma	1 (2%)	1 (2%)	
Fibrosarcoma	3 (6%)	3 (6%)	6 (12%)
Neurofibrosarcoma		1 (2%)	1 (2%)
RESPIRATORY SYSTEM			
#Peritracheal tissue	(50)	(49)	(47)
Neurofibrosarcoma, invasive		1 (2%)	
#Lung	(50)	(49)	(48)
Hepatocellular carcinoma, metastatic	5 (10%)		2 (4%)
Alveolar/bronchiolar adenoma	12 (24%)	4 (8%)	2 (4%)
Alveolar/bronchiolar carcinoma	5 (10%)	1 (2%)	1 (2%)
Fibrosarcoma, metastatic	1 (2%)	2 (4%)	
Neurofibrosarcoma, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(50)
Malignant lymphoma, lymphocytic type	2 (4%)	3 (6%)	2 (4%)
Malignant lymphoma, histiocytic type	1 (2%)		
Malignant lymphoma, mixed type	5 (10%)	5 (10%)	2 (4%)
#Spleen	(49)	(49)	(48)
Malig. lymphoma, undiffer type	1 (2%)		
CIRCULATORY SYSTEM			
#Splenic red pulp	(49)	(49)	(48)
Hemangiosarcoma		1 (2%)	
#Liver	(50)	(49)	(49)
Hemangioma	1 (2%)		
Hemangiosarcoma			1 (2%)
*Mesentery	(50)	(49)	(50)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(49)
Hepatocellular adenoma	10 (20%)	12 (24%)	4 (8%)
Hepatocellular carcinoma	6 (12%)	7 (14%)	5 (10%)
Fibrosarcoma		1 (2%)	
#Forestomach	(50)	(49)	(43)
Squamous cell papilloma	1 (2%)		
Squamous cell carcinoma	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(49)	(49)
Tubular cell adenoma		1 (2%)	
Tubular cell adenocarcinoma			1 (2%)
Fibrosarcoma, metastatic			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Adrenal	(50)	(49)	(49)
Cortical adenoma			1 (2%)
#Adrenal/capsule	(50)	(49)	(49)
Adenoma, NOS	2 (4%)	7 (14%)	4 (8%)
#Adrenal medulla	(50)	(49)	(49)
Pheochromocytoma		1 (2%)	
#Thyroid	(50)	(49)	(47)
Follicular cell adenoma	2 (4%)	1 (2%)	
REPRODUCTIVE SYSTEM			
#Testis	(50)	(49)	(49)
Interstitial cell tumor	1 (2%)	2 (4%)	
*Epididymis	(50)	(49)	(50)
Adenoma, NOS		1 (2%)	
Lipoma		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(49)	(50)
Adenoma, NOS	6 (12%)	2 (4%)	2 (4%)
Adenocarcinoma, NOS	1 (2%)	2 (4%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	15	20
Moribund sacrifice	7	3	8
Terminal sacrifice	39	31	15
Dosing accident			7
Animal missing		1	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	39	36	21
Total primary tumors	62	57	34
Total animals with benign tumors	29	25	11
Total benign tumors	36	33	14
Total animals with malignant tumors	23	20	16
Total malignant tumors	26	24	20
Total animals with secondary tumors##	6	3	4
Total secondary tumors	6	3	4

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

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(49)	(50)
Sarcoma, NOS	1 (2%)		
Sarcoma, NOS, invasive	1 (2%)		
Fibrosarcoma	1 (2%)		
Myxosarcoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	5 (10%)	3 (6%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	1 (2%)
Sarcoma, NOS, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(50)
Malignant lymphoma, lymphocytic type	5 (10%)	5 (10%)	8 (16%)
Malignant lymphoma, histiocytic type	2 (4%)	5 (10%)	
Malignant lymphoma, mixed type	10 (20%)	7 (14%)	
Granulocytic leukemia	1 (2%)		
#Lumbar lymph node	(49)	(47)	(45)
Malignant lymphoma, mixed type		1 (2%)	
#Uterus	(50)	(49)	(48)
Malig. lymphoma, histiocytic type			1 (2%)
CIRCULATORY SYSTEM			
#Spleen	(50)	(49)	(47)
Hemangiosarcoma	1 (2%)		
#Liver	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(50)
Hepatocellular adenoma	4 (8%)	2 (4%)	2 (4%)
Hepatocellular carcinoma	2 (4%)	1 (2%)	3 (6%)
#Forestomach	(48)	(48)	(48)
Squamous cell papilloma		1 (2%)	
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary intermedia	(46)	(47)	(45)
Adenoma, NOS	2 (4%)		
#Anterior pituitary	(46)	(47)	(45)
Adenoma, NOS	5 (11%)	9 (19%)	5 (11%)
#Adrenal	(50)	(49)	(50)
Cortical adenoma	1 (2%)		
#Adrenal/capsule	(50)	(49)	(50)
Adenoma, NOS		1 (2%)	

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(50)	(49)	(50)
Pheochromocytoma			1 (2%)
#Thyroid	(48)	(49)	(47)
Follicular cell adenoma		4 (8%)	2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(49)	(50)
Adenocarcinoma, NOS	1 (2%)		
#Uterus	(50)	(49)	(48)
Leiomyoma		1 (2%)	
Endometrial stromal polyp	3 (6%)	1 (2%)	
#Ovary	(50)	(49)	(48)
Papillary cystadenoma, NOS		1 (2%)	
Luteoma	1 (2%)		
Ganglioneuroma			1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(49)	(50)
Adenoma, NOS	2 (4%)	3 (6%)	
MUSCULOSKELETAL SYSTEM			
*Sacrum	(50)	(49)	(50)
Osteosarcoma	1 (2%)		
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(50)
Osteosarcoma, metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	9	12
Moribund sacrifice	3	1	1
Terminal sacrifice	38	39	37
Accidentally killed, nda		1	

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	37	35	20
Total primary tumors	50	49	27
Total animals with benign tumors	20	23	9
Total benign tumors	23	28	14
Total animals with malignant tumors	26	21	12
Total malignant tumors	27	21	13
Total animals with secondary tumors##	2		
Total secondary tumors	3		

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

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: VEHICLE CONTROL

ANIMAL NUMBER	503	544	505	546	537	536	548	513	509	508	514	501	502	504	506	507	510	511	512	515	516	517	518	519	520
WEEKS ON STUDY	075	078	080	086	091	095	095	096	098	101	101	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS				X																					
Fibroma																									
Fibrosarcoma				X															X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic							X																		
Alveolar/bronchiolar adenoma				X		X										X		X	X						
Alveolar/bronchiolar carcinoma										X								X				X	X		
Fibrosarcoma, metastatic				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig lymphoma, undiffer type																	X								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	−	+	+	−	−	−	+	+	+	−	+	+	+	+	−	+	−	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma						X				X					X						X			X	
Hepatocellular carcinoma							X		X																
Hemangioma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma						X																			
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	−	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS							X						X												
Adenocarcinoma, NOS																		X							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig lymphoma, lymphocytic type														X											
Malig lymphoma, histiocytic type	X																								
Malignant lymphoma, mixed type								X			X		X												

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

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	52 1	52 2	52 3	52 4	52 5	52 6	52 7	52 8	52 9	53 0	53 1	53 2	53 3	53 4	53 5	53 8	53 9	54 0	54 1	54 2	54 3	54 5	54 7	54 9	55 0	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma																	X									1
Fibrosarcoma																		X								3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic		X							X	X		X														5
Alveolar/bronchiolar adenoma			X				X	X					X				X						X	X		12
Alveolar/bronchiolar carcinoma											X															5
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malig. lymphoma, undiffer type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	−	+	+	+	−	+	−	+	+	+	−	−	+	+	+	+	+	−	+	+	+	−	+	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma						X					X		X	X									X			10
Hepatocellular carcinoma		X							X	X		X														6
Hemangioma		X																								1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma													X													1
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	−	+	+	+	+	+	43
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS										X									X							2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma					X																			X		2
Parathyroid	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	43
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS							X				X									X					X	6
Adenocarcinoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig lymphoma, lymphocytic type									X																	2
Malig lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																				X			X			5

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: LOW DOSE

ANIMAL NUMBER	54 45	54 49	54 44	50 08	54 46	53 38	54 47	54 43	50 06	52 22	51 10	52 28	52 26	53 37	51 11	55 50	50 09	51 19	50 01	50 02	50 03	50 04	50 05	50 07	51 12
WEEKS ON STUDY	01 7	01 8	02 0	02 2	02 2	02 3	02 5	03 8	05 0	05 9	06 7	07 5	07 8	08 5	08 7	08 7	09 4	09 8	10 4	10 4	10 4	10 4	10 4	10 4	10 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma																		X							
Neurofibrosarcoma															X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X			X						X				
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic																		X							
Trachea	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma, invasive															X										
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Lymph nodes	−	−	+	+	+	+	M	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−
Thymus	+	−	+	+	−	+	M	+	+	+	−	−	+	+	−	+	−	+	−	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X				
Hepatocellular carcinoma												X				X						X		X	
Fibrosarcoma																									X
Bile duct	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	+	+	+	M	+	+	+	N	+	+	N	N	N	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	−	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	−	+	−	−	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	−	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	−	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	−	+	+	+	+	M	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																	X				X				
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	−	+	+	+	+	M	+	+	−	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Prostate	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Epididymis	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Lipoma										X															
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																			X						
Adenocarcinoma, NOS																					X		X		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig lymphoma, lymphocytic type														X											
Malignant lymphoma, mixed type												X					X					X			

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	51 13	51 14	51 15	51 16	51 17	51 18	52 20	52 21	52 23	52 24	52 25	52 27	52 29	53 30	53 31	53 32	53 33	53 34	53 35	53 36	53 39	54 40	54 41	54 42	54 48	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibroma						X																				1
Fibrosarcoma				X						X																3
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma				X																						4
Alveolar/bronchiolar carcinoma																			X							1
Fibrosarcoma, metastatic										X																2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neurofibrosarcoma, invasive																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma	X				X	X		X					X		X	X			X				X	X	X	12
Hepatocellular carcinoma																				X	X	X				7
Fibrosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma																							X			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X					X		X					X	X											7
Pheochromocytoma												X														1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																						X				1
Parathyroid	+	+	+	−	+	+	−	+	−	+	+	+	−	+	+	+	+	−	−	+	+	−	+	−	−	35
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X														X											2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Epididymis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenoma, NOS																								X		1
Lipoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenoma, NOS											X															2
Adenocarcinoma, NOS																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malig lymphoma, lymphocytic type												X										X				3
Malignant lymphoma, mixed type											X							X								5

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: HIGH DOSE

ANIMAL NUMBER	50 7	54 4	51 7	51 9	52 2	52 3	52 7	52 8	52 9	51 4	53 6	53 3	51 1	51 6	51 8	54 2	51 0	54 0	54 9	50 4	50 2	50 1	50 5	53 5	50 8
WEEKS ON STUDY	00 1	00 1	00 2	00 2	00 2	00 2	00 2	00 2	00 2	00 7	00 9	01 1	01 5	01 7	01 9	02 2	02 4	02 6	03 0	04 1	04 2	05 0	05 1	07 2	07 3
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibrosarcoma																								X	
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	−	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Neurofibrosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	−	+	−	A	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	−	+	−	A	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	−	+	+	A	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	−	−	−	−	+	A	−	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	−	+	−	A	−	+	+	+	+	+	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	−	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Hemangiosarcoma																								X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	N	+	+	+	+	+	+	N	N	+	N	N	+	N	N	N	N	+	+	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	~	−	+	+	A	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	−	+	+	−	+	+	+	+	−	+	+	A	+	−	+	+	−	A	+	+	+	+
Small intestine	+	+	+	−	+	+	+	+	+	+	+	−	−	−	A	−	−	+	−	−	A	+	+	+	+
Large intestine	+	+	+	−	+	+	+	+	+	+	+	−	+	−	A	−	−	+	−	−	A	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Fibrosarcoma, metastatic																									
Urinary bladder	+	+	+	−	+	+	−	+	+	+	+	−	+	+	A	+	+	+	−	−	A	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	−	+	−	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Cortical Adenoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	−	+	−	A	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	−	−	+	+	−	−	−	+	−	+	−	−	−	A	+	−	−	+	−	+	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	−	+	+	A	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	−	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	−	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangioma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type																									
Malignant lymphoma, mixed type																									

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	53 39	54 46	51 13	52 26	55 50	53 32	53 38	52 24	52 25	53 34	50 03	50 06	50 09	51 12	51 15	52 20	52 21	53 30	53 31	53 37	54 41	54 43	54 45	54 47	54 48	TOTAL:
WEEKS ON STUDY	07 7	08 8	09 1	09 3	09 8	10 1	10 1	10 2	10 2	10 2	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS								X																		1
Fibrosarcoma	X	X				X			X	X																6
Neurofibrosarcoma					X																					1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic				X			X																			2
Alveolar/bronchiolar adenoma																						X	X			2
Alveolar/bronchiolar carcinoma																								X		1
Neurofibrosarcoma, metastatic					X																					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	+	−	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma										X	X								X			X				4
Hepatocellular carcinoma	X			X	X		X						X													5
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	N	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenocarcinoma																									X	1
Fibrosarcoma, metastatic	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	+	−	−	+	+	−	+	+	+	+	41
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS												X				X						X	X			4
Cortical Adenoma								X																		1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	−	+	−	+	+	+	+	29
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS														X										X		2
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangioma																								X		1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, lymphocytic type												X				X										2
Malignant lymphoma, mixed type								X															X			2

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: VEHICLE CONTROL

ANIMAL NUMBER	00006	00029	00033	00039	00334	00338	00222	00044	00112	00226	00227	00449	00501	00025	00057	00078	00110	00111	00113	00114	00115	00116	00117	00118
WEEKS ON STUDY	069	069	070	071	094	095	096	098	099	099	099	102	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																								
Subcutaneous tissue	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS			X																					
Sarcoma, NOS, invasive			X																					
Fibrosarcoma																					X			
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X			X							X			X	
Alveolar/bronchiolar carcinoma				X																				
Sarcoma, NOS, metastatic			X																					
Trachea	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Thymus	+	+	−	−	−	−	−	−	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	−	+	+	+	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X				X							X								
Hepatocellular carcinoma																							X	
Hemangiosarcoma																								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	N	N	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+
Pancreas	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	−	→	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	−	+	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																	X							
Thyroid	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	−	−	−	−	−	+	−	+	−	−	−	−	+	−	−	+	−	+	+	−	−	+	−
REPRODUCTIVE SYSTEM																								
Mammary gland	N	+	N	N	N	N	N	N	N	N	N	N	+	+	+	+	N	+	+	N	+	+	N	N	+
Adenocarcinoma, NOS																		X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp										X						X								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Luteoma																								
NERVOUS SYSTEM																								
Brain	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																								
MUSCULOSKELETAL SYSTEM																								
Bone	N	N	N	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																								
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma, metastatic																								
Malig. lymphoma, lymphocytic type					X							X												
Malig. lymphoma, histiocytic type														X										
Malignant lymphoma, mixed type	X					X	X			X					X	X						X		X
Granulocytic leukemia								X																

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

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0119	0201	0211	0233	0244	0255	0288	0301	0312	0323	0333	0355	0366	0377	0399	0400	0411	0422	0433	0444	0455	0466	0477	0488	0500	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Sarcoma, NOS, invasive																										1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																						5
Alveolar/bronchiolar carcinoma																										1
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma														X												1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																		X								4
Hepatocellular carcinoma																							X			2
Hemangiosarcoma														X												1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS					X						X	X		X					X			X				7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	−	−	+	+	−	+	+	−	−	−	−	+	+	−	+	−	−	+	−	−	+	+	−	+	−	20
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	+	+	+	N	N	+	N	N	N	N	N	+	N	+	N	+	N	N	N	N	N	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp											X															3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Luteoma		X																								1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS			X				X																			2
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma							X																			1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma, metastatic							X																			1
Malig lymphoma, lymphocytic type									X									X			X					5
Malig lymphoma, histiocytic type					X																					2
Malignant lymphoma, mixed type						X										X										10
Granulocytic leukemia																										1

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: LOW DOSE

ANIMAL NUMBER	011	047	049	015	039	020	013	014	012	043	024	001	002	003	004	005	006	007	008	009	010	016	017	018	019
WEEKS ON STUDY	000	000	044	072	072	082	085	093	097	100	101	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Myxosarcoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X												X				
Alveolar/bronchiolar carcinoma																						X			
Trachea	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	A	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Thymus	+	−	A	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																X									
Hepatocellular carcinoma								X																	
Bile duct	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	A	N	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma														X											
Small intestine	−	−	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS														X						X					
Adrenal	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Thyroid	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																				X		X	X		
Parathyroid	−	−	A	−	−	+	+	−	−	+	−	+	+	−	−	+	+	+	+	−	−	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	A	N	N	N	N	N	N	+	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N
Uterus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma										X															
Endometrial stromal polyp																		X							
Ovary	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									X
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type						X						X								X					X
Malig. lymphoma, histiocytic type					X				X						X										
Malignant lymphoma, mixed type							X				X										X				

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	021	022	023	025	026	027	028	029	030	031	032	033	034	035	036	037	038	040	041	042	044	045	046	048	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Myxosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma							X			X	X															5
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malignant lymphoma, mixed type																								X		1
Thymus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																		X								2
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS				X		X			X				X					X					X	X		9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS															X											1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma									X																	4
Parathyroid	–	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	–	29
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	+	N	N	N	N	N	N	+	+	+	N	N	N	+	N	N	N	N	+	N	*49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma																										1
Endometrial stromal polyp																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary cystadenoma, NOS			X																							1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenoma, NOS												X											X			3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malig. lymphoma, lymphocytic type																									X	5
Malig. lymphoma, histiocytic type		X									X															5
Malignant lymphoma, mixed type					X										X				X	X						7

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE: HIGH DOSE

ANIMAL NUMBER	0026	0003	0028	0021	0023	0118	0008	0048	0004	0027	0030	0116	0042	0001	0002	0005	0006	0007	0009	0010	0011	0012	0013	0014	0015
WEEKS ON STUDY	0002	0009	0115	0118	0449	0552	0666	0772	0800	0833	0833	0900	0966	1004	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	−	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	−	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	+	+	A	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	A	A	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																					X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	+	N	N	+	N	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	−	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Stomach	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+
Adenoma, NOS														X									X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma														X											
Parathyroid	+	−	−	−	+	A	−	−	−	−	−	+	+	−	+	−	−	+	-	+	+	+	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	+	+	N	N	N	N	+	N	N	N	N	N	N	N	+	N	+
Uterus	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig lymphoma, histiocytic type																									
Ovary	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ganglioneuroma				X																					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig lymphoma, lymphocytic type												X	X		X			X		X	X			X	X

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	01 17	01 19	02 20	02 22	02 24	02 25	02 29	03 31	03 32	03 33	03 34	03 35	03 36	03 37	03 38	03 39	04 40	04 41	04 43	04 44	04 45	04 46	04 47	04 49	05 50	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																		X		3
Alveolar/bronchiolar carcinoma																					X					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	47
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	45
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X		X															2
Hepatocellular carcinoma																			X				X			3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	45
Adenoma, NOS						X			X														X			5
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																							X			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																							X			2
Parathyroid	−	+	−	−	−	+	+	+	+	+	+	−	−	−	−	−	+	−	+	+	−	−	−	−	+	20
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	N	N	N	N	N	N	+	N	+	N	N	+	N	N	N	N	N	N	N	N	N	N	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malig. lymphoma, histiocytic type															X											1
Ovary	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Ganglioneuroma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, lymphocytic type																										8

* Animals necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Fibrosis, focal	1 (2%)		
Atrophy, focal			1 (2%)
Hyperplasia, focal	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Abscess, chronic	1 (2%)		
RESPIRATORY SYSTEM			
#Trachea	(50)	(49)	(49)
Inflammation, acute/chronic		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
Metaplasia, squamous	1 (2%)		
#Peritracheal tissue	(50)	(49)	(49)
Inflammation, suppurative		1 (2%)	
#Lung/bronchus	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
#Lung/bronchiole	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
Hyperplasia, epithelial		2 (4%)	1 (2%)
#Lung	(50)	(50)	(50)
Aspiration, foreign body			2 (4%)
Edema, NOS	2 (4%)	3 (6%)	2 (4%)
Inflammation, interstitial			3 (6%)
Pneumonia, interstitial chronic	4 (8%)	2 (4%)	
Inflammation, granulomatous focal	4 (8%)	3 (6%)	1 (2%)
Hyperplasia, alveolar epithelium	1 (2%)	1 (2%)	
#Lung/alveoli	(50)	(50)	(50)
Hemorrhage	2 (4%)	2 (4%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(49)
Hyperplasia, granulocytic	1 (2%)	1 (2%)	4 (8%)
Hyperplasia, reticulum cell	1 (2%)		
#Splenic follicles	(49)	(50)	(50)
Inflammation, granulomatous focal		1 (2%)	
Depletion, lymphoid	1 (2%)	3 (6%)	2 (4%)
#Splenic red pulp	(49)	(50)	(50)
Congestion, NOS	1 (2%)		
Fibrosis, focal	3 (6%)	1 (2%)	1 (2%)
Fibrosis, multifocal	2 (4%)	2 (4%)	
Necrosis, focal		1 (2%)	
Infarct, healed	1 (2%)		
Hemosiderosis	1 (2%)	2 (4%)	1 (2%)
Hematopoiesis			1 (2%)
#Mandibular lymph node	(48)	(49)	(45)
Cyst, NOS	1 (2%)		
Inflammation, chronic focal	2 (4%)	1 (2%)	
Inflammation, granulomatous focal		2 (4%)	1 (2%)
Angiectasis	1 (2%)		1 (2%)
Hyperplasia, lymphoid	2 (4%)		
#Pancreatic lymph node	(48)	(49)	(45)
Inflammation, granulomatous focal			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(48)	(49)	(45)
Cyst, NOS	1 (2%)		
Multiple cysts	1 (2%)		
Inflammation, active chronic	2 (4%)		
Inflammation, chronic focal	2 (4%)		
Inflammation, granulomatous focal			1 (2%)
Angiectasis	2 (4%)	1 (2%)	
#Renal lymph node	(48)	(49)	(45)
Inflammation, granulomatous focal		1 (2%)	
#Thymic lymph node	(48)	(49)	(45)
Multiple cysts		1 (2%)	
Inflammation, chronic focal	1 (2%)		
Angiectasis			2 (4%)
Plasmacytosis			2 (4%)
#Liver	(50)	(50)	(50)
Hematopoiesis			1 (2%)
#Jejunum	(49)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)		
#Colon	(49)	(49)	(49)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	
#Adrenal cortex	(49)	(50)	(49)
Hematopoiesis		1 (2%)	
#Thymus	(44)	(43)	(44)
Congestion, acute		1 (2%)	
Hemorrhage		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#Mesenteric lymph node	(48)	(49)	(45)
Lymphangiectasis		1 (2%)	
#Right atrium	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
#Left atrium	(50)	(50)	(50)
Mineralization	2 (4%)		
Thrombus, organized	3 (6%)	1 (2%)	1 (2%)
Thrombus, mural		1 (2%)	
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	47 (94%)	43 (86%)	40 (80%)
#Endocardium of left atrium	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
*Aorta	(50)	(50)	(50)
Mineralization			1 (2%)
*Pulmonary artery	(50)	(50)	(50)
Mineralization			1 (2%)
Inflammation, acute/chronic		1 (2%)	
*Sup pancreaticoduodenal artery	(50)	(50)	(50)
Periarteritis		1 (2%)	3 (6%)
DIGESTIVE SYSTEM			
*Mucosa of tongue	(50)	(50)	(50)
Hyperplasia, epithelial			1 (2%)
#Salivary gland	(50)	(50)	(49)
Dilatation/ducts		2 (4%)	
Inflammation, acute focal		1 (2%)	
Atrophy, focal	2 (4%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Liver	(50)	(50)	(50)
Inflammation, granulomatous focal	3 (6%)	4 (8%)	2 (4%)
Basophilic cyto change	26 (52%)	32 (64%)	23 (46%)
Eosinophilic cyto change			1 (2%)
Clear cell change	10 (20%)	9 (18%)	10 (20%)
Hyperplasia, nodular		1 (2%)	
Angiectasis		2 (4%)	
#Liver/hepatocytes	(50)	(50)	(50)
Degeneration, cystic	17 (34%)	9 (18%)	4 (8%)
Necrosis, focal			1 (2%)
Cytoplasmic vacuolization	1 (2%)	3 (6%)	1 (2%)
#Bile duct	(50)	(50)	(50)
Hyperplasia, focal	46 (92%)	43 (86%)	40 (80%)
#Pancreas	(50)	(47)	(49)
Dilatation/ducts		4 (9%)	
Congestion, acute		1 (2%)	
Inflammation, active chronic			1 (2%)
#Pancreatic acinus	(50)	(47)	(49)
Necrosis, focal			1 (2%)
Atrophy, focal	23 (46%)	15 (32%)	16 (33%)
Atrophy, diffuse		1 (2%)	
#Esophagus	(50)	(49)	(50)
Dilatation, NOS		1 (2%)	
#Periesophageal tissue	(50)	(49)	(50)
Hemorrhage		1 (2%)	
Inflammation, suppurative		1 (2%)	
#Glandular stomach	(50)	(50)	(49)
Mineralization		1 (2%)	
Ulcer, acute		1 (2%)	
Inflammation, active chronic	2 (4%)	1 (2%)	
Inflammation, chronic focal	1 (2%)		
Necrosis, focal	1 (2%)	1 (2%)	
#Forestomach	(50)	(50)	(49)
Inflammation, active chronic	1 (2%)	1 (2%)	
Ulcer, chronic	1 (2%)		
Hyperplasia, epithelial		1 (2%)	
#Ileum	(49)	(50)	(49)
Ulcer, NOS		1 (2%)	
Inflammation, acute focal		1 (2%)	
#Colon	(49)	(49)	(49)
Parasitism	1 (2%)	2 (4%)	2 (4%)
#Colonic mucosa	(49)	(49)	(49)
Necrosis, focal		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Mineralization	1 (2%)		
Hydronephrosis		1 (2%)	
Inflammation, interstitial			1 (2%)
Nephropathy	48 (96%)	48 (96%)	42 (84%)
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Multiple cysts	1 (2%)	1 (2%)	
#Kidney/tubule	(50)	(50)	(50)
Necrosis, focal		2 (4%)	
Pigmentation, NOS	3 (6%)		
#Renal pelvis/mucosa	(50)	(50)	(50)
Hyperplasia, epithelial			1 (2%)
Hyperplasia, papillary	6 (12%)	2 (4%)	1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#Urinary bladder	(49)	(48)	(49)
Calculus, microscopic examination	1 (2%)		
Hemorrhage	1 (2%)		1 (2%)
Inflammation, necrotizing			1 (2%)
Inflammation, acute focal			2 (4%)
Inflammation, acute/chronic		1 (2%)	2 (4%)
Hyperplasia, epithelial	3 (6%)	3 (6%)	1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(47)
Cyst, NOS		4 (8%)	3 (6%)
Multiple cysts	1 (2%)	4 (8%)	
Hemorrhagic cyst	2 (4%)	1 (2%)	
Hyperplasia, NOS		1 (2%)	
Hyperplasia, focal	8 (16%)	14 (28%)	5 (11%)
#Adrenal cortex	(49)	(50)	(49)
Accessory structure	1 (2%)		
Ectopia		1 (2%)	
Degeneration, NOS	1 (2%)		
Metamorphosis, fatty	9 (18%)	11 (22%)	8 (16%)
Hypertrophy, focal		2 (4%)	2 (4%)
Hyperplasia, focal	6 (12%)	13 (26%)	9 (18%)
#Adrenal medulla	(49)	(50)	(49)
Hyperplasia, focal	4 (8%)	8 (16%)	5 (10%)
#Thyroid	(50)	(49)	(47)
Embryonal duct cyst	2 (4%)		2 (4%)
Follicular cyst, NOS	1 (2%)	1 (2%)	
Hemorrhage			1 (2%)
Hyperplasia, C-cell	30 (60%)	24 (49%)	28 (60%)
Hyperplasia, follicular cell			2 (4%)
#Thyroid follicle	(50)	(49)	(47)
Cyst, NOS		1 (2%)	
Hyperplasia, cystic	2 (4%)		
#Parathyroid	(42)	(44)	(45)
Hyperplasia, focal			1 (2%)
Hyperplasia, diffuse	1 (2%)		
#Pancreatic islets	(50)	(47)	(49)
Hyperplasia, focal	2 (4%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, cystic	14 (28%)	10 (20%)	13 (26%)
*Preputial gland	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)	1 (2%)	1 (2%)
#Prostate	(49)	(50)	(50)
Inflammation, acute focal			1 (2%)
Abscess, NOS	2 (4%)	2 (4%)	3 (6%)
Inflammation, active chronic	8 (16%)	10 (20%)	12 (24%)
Inflammation, granulomatous focal			1 (2%)
Hyperplasia, epithelial		1 (2%)	
*Seminal vesicle	(50)	(50)	(50)
Retention fluid			1 (2%)
Hyperplasia, epithelial			1 (2%)
#Testis	(49)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, chronic focal			1 (2%)
Hyperplasia, interstitial cell	8 (16%)	11 (22%)	7 (14%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Testis/tubule	(49)	(50)	(50)
Mineralization	5 (10%)	2 (4%)	
Atrophy, focal	4 (8%)	1 (2%)	1 (2%)
Atrophy, pressure	40 (82%)	37 (74%)	35 (70%)
Atrophy, diffuse		2 (4%)	
*Epididymis	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, acute	1 (2%)		
Inflammation, active chronic		1 (2%)	
Inflammation, chronic			1 (2%)
Granuloma, spermatic		1 (2%)	
NERVOUS SYSTEM			
#Cerebrum	(50)	(50)	(50)
Mineralization	1 (2%)		
Hydrocephalus, NOS			1 (2%)
Hemorrhage	2 (4%)		
Atrophy, pressure	1 (2%)	3 (6%)	
#Cerebellum	(50)	(50)	(50)
Hemorrhage	1 (2%)		1 (2%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, active chronic		2 (4%)	
Inflammation, chronic focal			1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, focal	1 (2%)	3 (6%)	5 (10%)
*Eye/crystalline lens	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
Cataract	1 (2%)	2 (4%)	5 (10%)
MUSCULOSKELETAL SYSTEM			
*Femur	(50)	(50)	(50)
Osteosclerosis		2 (4%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Inflammation, active chronic	1 (2%)	1 (2%)	
*Mesentery	(50)	(50)	(50)
Inflammation, active chronic	2 (4%)		1 (2%)
Inflammation, granulomatous focal	1 (2%)	3 (6%)	2 (4%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mineralization	1 (2%)	1 (2%)	
Hyperplasia, focal	1 (2%)		
SPECIAL MORPHOLOGY SUMMARY			
Auto/necropsy/histo perf			1

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

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Fibrosis, diffuse			1 (2%)
RESPIRATORY SYSTEM			
#Lung/bronchiole	(50)	(50)	(48)
Inflammation, acute/chronic		1 (2%)	
#Lung	(50)	(50)	(48)
Aspiration, foreign body	2 (4%)	2 (4%)	
Edema, NOS		2 (4%)	2 (4%)
Inflammation, interstitial	1 (2%)	2 (4%)	1 (2%)
Inflammation, granulomatous focal			1 (2%)
Hyperplasia, alveolar epithelium	1 (2%)	1 (2%)	
#Lung/alveoli	(50)	(50)	(48)
Hemorrhage		2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(48)
Inflammation, granulomatous focal			1 (2%)
Myelofibrosis		1 (2%)	
Hyperplasia, granulocytic	1 (2%)	1 (2%)	
Hyperplasia, reticulum cell	3 (6%)	4 (8%)	3 (6%)
Hypoplasia, hematopoietic	1 (2%)		
#Splenic follicles	(50)	(50)	(47)
Depletion, lymphoid	1 (2%)	1 (2%)	1 (2%)
#Splenic red pulp	(50)	(50)	(47)
Fibrosis, focal	1 (2%)		
Hemosiderosis	3 (6%)	2 (4%)	
Hematopoiesis	4 (8%)	6 (12%)	
#Mandibular lymph node	(44)	(47)	(41)
Hemorrhage		2 (4%)	
Inflammation, granulomatous focal			1 (2%)
Angiectasis	1 (2%)		
Histiocytosis		2 (4%)	1 (2%)
#Pancreatic lymph node	(44)	(47)	(41)
Hematopoiesis	1 (2%)		
#Mesenteric lymph node	(44)	(47)	(41)
Inflammation, chronic focal	1 (2%)		
Inflammation, granulomatous focal		2 (4%)	
Depletion, lymphoid	1 (2%)		1 (2%)
#Renal lymph node	(44)	(47)	(41)
Histiocytosis		1 (2%)	
#Thymic lymph node	(44)	(47)	(41)
Inflammation, active chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)		
Inflammation, granulomatous focal		1 (2%)	
Hemosiderosis		1 (2%)	
Angiectasis	1 (2%)		
#Liver	(50)	(50)	(49)
Leukemoid reaction	1 (2%)		
Hematopoiesis	3 (6%)		1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Thymus	(46)	(48)	(45)
Dilatation/ducts		1 (2%)	
Multiple cysts	1 (2%)		
Pigmentation, NOS			1 (2%)
Hyperplasia, epithelial	1 (2%)		
#Thymic medulla	(46)	(48)	(45)
Hemorrhage			1 (2%)
CIRCULATORY SYSTEM			
#Mandibular lymph node	(44)	(47)	(41)
Lymphangiectasis		1 (2%)	
#Thymic lymph node	(44)	(47)	(41)
Lymphangiectasis		2 (4%)	
#Lung	(50)	(50)	(48)
Perivasculitis			1 (2%)
#Heart	(50)	(50)	(48)
Periarteritis			1 (2%)
#Left atrium	(50)	(50)	(48)
Thrombus, organized			1 (2%)
Thrombus, mural		2 (4%)	
#Myocardium	(50)	(50)	(48)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal			1 (2%)
Degeneration, NOS	42 (84%)	38 (76%)	19 (40%)
*Aorta	(50)	(50)	(50)
Periarteritis		1 (2%)	
*Coronary artery	(50)	(50)	(50)
Atherosclerosis	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(49)	(46)
Atrophy, focal	1 (2%)	1 (2%)	
#Liver	(50)	(50)	(49)
Congestion, acute passive		1 (2%)	1 (2%)
Inflammation, acute necrotizing	2 (4%)		
Inflammation, acute/chronic		1 (2%)	
Inflammation, granulomatous		1 (2%)	
Inflammation, granulomatous focal	18 (36%)	26 (52%)	9 (18%)
Basophilic cyto change	34 (68%)	29 (58%)	7 (14%)
Focal cellular change	1 (2%)	3 (6%)	
Clear cell change	3 (6%)	3 (6%)	2 (4%)
#Liver/hepatocytes	(50)	(50)	(49)
Degeneration, NOS	2 (4%)		
Necrosis, focal	1 (2%)		3 (6%)
Cytoplasmic vacuolization	4 (8%)	1 (2%)	
#Bile duct	(50)	(50)	(49)
Hyperplasia, focal	29 (58%)	10 (20%)	9 (18%)
#Pancreatic acinus	(50)	(50)	(46)
Atrophy, focal	22 (44%)	8 (16%)	2 (4%)
#Esophagus	(50)	(50)	(49)
Lacerated wound		1 (2%)	
Dilatation, NOS		1 (2%)	3 (6%)
#Glandular stomach	(50)	(45)	(42)
Inflammation, active chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(50)	(45)	(42)
Inflammation, active chronic	1 (2%)		
Hyperkeratosis	1 (2%)		
Acanthosis	1 (2%)		
#Jejunum	(49)	(44)	(28)
Ulcer, NOS		1 (2%)	
Inflammation, active chronic		2 (5%)	
#Colon	(49)	(44)	(40)
Diverticulosis			1 (3%)
Parasitism		3 (7%)	
#Cecum	(49)	(44)	(40)
Ulcer, NOS			1 (3%)
Inflammation, active chronic			1 (3%)
URINARY SYSTEM			
#Kidney	(50)	(48)	(46)
Hydronephrosis	1 (2%)		
Nephropathy	35 (70%)	27 (56%)	9 (20%)
#Kidney/cortex	(50)	(48)	(46)
Mineralization			1 (2%)
#Kidney/tubule	(50)	(48)	(46)
Necrosis, focal	1 (2%)	1 (2%)	
Necrosis, diffuse	1 (2%)		
Cytologic degeneration		1 (2%)	
#Renal pelvis/mucosa	(50)	(48)	(46)
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder	(49)	(46)	(40)
Inflammation, active chronic		1 (2%)	
Hyperplasia, epithelial	5 (10%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(48)	(45)
Cyst, NOS		5 (10%)	1 (2%)
Multiple cysts	7 (15%)	7 (15%)	1 (2%)
Hemorrhagic cyst	6 (13%)		
Hemosiderosis		1 (2%)	
Hyperplasia, focal	11 (23%)	10 (21%)	2 (4%)
#Adrenal cortex	(50)	(49)	(47)
Hemorrhage		1 (2%)	
Metamorphosis, fatty	14 (28%)	9 (18%)	4 (9%)
Hemosiderosis		1 (2%)	
Focal cellular change	5 (10%)	5 (10%)	
Hyperplasia, NOS	3 (6%)	2 (4%)	1 (2%)
Hyperplasia, focal	5 (10%)	10 (20%)	1 (2%)
#Adrenal medulla	(50)	(49)	(47)
Mineralization			1 (2%)
Hyperplasia, focal	4 (8%)	1 (2%)	
#Thyroid	(47)	(46)	(45)
Follicular cyst, NOS		1 (2%)	
Hyperplasia, C-cell	25 (53%)	25 (54%)	11 (24%)
#Parathyroid	(33)	(34)	(32)
Hyperplasia, focal		1 (3%)	
#Pancreatic islets	(50)	(50)	(46)
Hyperplasia, focal	1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, cystic	29 (58%)	16 (32%)	11 (22%)
*Clitoral gland	(50)	(50)	(50)
Inflammation, active chronic		1 (2%)	
Inflammation, chronic focal			1 (2%)
#Uterus	(49)	(50)	(46)
Dilatation, NOS	4 (8%)	6 (12%)	8 (17%)
Hemorrhage, chronic		1 (2%)	
Inflammation, acute/chronic			1 (2%)
#Cervix uteri	(49)	(50)	(46)
Diverticulum	1 (2%)	2 (4%)	
#Uterus/endometrium	(49)	(50)	(46)
Cyst, NOS	1 (2%)		
Multiple cysts	1 (2%)		
Hyperplasia, cystic	9 (18%)	8 (16%)	16 (35%)
#Endometrial stroma	(49)	(50)	(46)
Inflammation, acute diffuse			1 (2%)
Hyperplasia, focal			1 (2%)
#Ovary	(49)	(50)	(46)
Follicular cyst, NOS	3 (6%)	6 (12%)	1 (2%)
Parovarian cyst	2 (4%)	4 (8%)	2 (4%)
Congestion, NOS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
#Cerebral ventricle	(50)	(49)	(49)
Hydrocephalus, NOS	2 (4%)	2 (4%)	1 (2%)
Hemorrhage	1 (2%)		
#Cerebrum	(50)	(49)	(49)
Hemorrhage	1 (2%)	1 (2%)	
Necrosis, focal			1 (2%)
Atrophy, pressure	3 (6%)	4 (8%)	1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Collapse		1 (2%)	1 (2%)
Inflammation, acute/chronic			1 (2%)
Synechia, anterior		1 (2%)	
Atrophy, focal			1 (2%)
*Eye/cornea	(50)	(50)	(50)
Inflammation, active chronic		1 (2%)	
*Eye/iris	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
Atrophy, focal	3 (6%)	2 (4%)	4 (8%)
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	3 (6%)	2 (4%)	5 (10%)
MUSCULOSKELETAL SYSTEM			
*Carpal bone	(50)	(50)	(50)
Osteoarthropathy, hypertrophic		1 (2%)	
*Femur	(50)	(50)	(50)
Osteosclerosis	6 (12%)	3 (6%)	4 (8%)
*Tarsal joint	(50)	(50)	(50)
Osteoarthropathy, hypertrophic		1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Inflammation, granulomatous focal		3 (6%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, acute focal		1 (2%)	
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			6
Auto/necropsy/histo perf	1		5

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(49)	(50)
Ulcer, NOS		2 (4%)	1 (2%)
Hyperkeratosis		1 (2%)	3 (6%)
Acanthosis		1 (2%)	3 (6%)
*Subcutaneous tissue	(50)	(49)	(50)
Abscess, NOS			1 (2%)
Inflammation, acute/chronic	1 (2%)	†3 (6%)	3 (6%)
Inflammation, chronic focal	1 (2%)	1 (2%)	1 (2%)
Fibrosis, focal	1 (2%)		1 (2%)
Fibrosis, multifocal	1 (2%)		
RESPIRATORY SYSTEM			
#Peritracheal tissue	(50)	(49)	(47)
Hemorrhage			1 (2%)
Inflammation, chronic focal			1 (2%)
#Lung	(50)	(49)	(48)
Inflammation, interstitial	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute focal			1 (2%)
Inflammation, chronic focal		1 (2%)	
Hyperplasia, epithelial	2 (4%)	5 (10%)	3 (6%)
#Lung/alveoli	(50)	(49)	(48)
Foreign material, NOS	1 (2%)		
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(47)
Necrosis, focal		1 (2%)	
Histiocytosis			1 (2%)
Myelofibrosis			1 (2%)
Hyperplasia, granulocytic	5 (10%)	2 (4%)	7 (15%)
#Splenic follicles	(49)	(49)	(48)
Necrosis, focal			1 (2%)
Depletion, lymphoid		9 (18%)	14 (29%)
Hyperplasia, lymphoid		1 (2%)	
#Splenic red pulp	(49)	(49)	(48)
Fibrosis, multifocal			1 (2%)
Hemosiderosis		1 (2%)	
Angiectasis			1 (2%)
Hematopoiesis	6 (12%)	4 (8%)	11 (23%)
#Mandibular lymph node	(50)	(45)	(44)
Hemorrhage			1 (2%)
Depletion, lymphoid		1 (2%)	
Hematopoiesis	1 (2%)	1 (2%)	
#Mediastinal lymph node	(50)	(45)	(44)
Hematopoiesis		1 (2%)	
#Lumbar lymph node	(50)	(45)	(44)
Histiocytosis			1 (2%)
#Mesenteric lymph node	(50)	(45)	(44)
Plasmacytosis		1 (2%)	
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Hematopoiesis	15 (30%)	7 (16%)	5 (11%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Inguinal lymph node	(50)	(45)	(44)
Cyst, NOS	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Angiectasis		1 (2%)	
Plasmacytosis	1 (2%)		
#Lung	(50)	(49)	(48)
Leukocytosis, NOS		1 (2%)	
#Liver	(50)	(49)	(49)
Hematopoiesis	1 (2%)		1 (2%)
#Peyer's patch	(50)	(45)	(40)
Hyperplasia, lymphoid	1 (2%)		
#Thymus	(35)	(38)	(39)
Ectopia		1 (3%)	
Depletion, lymphoid	1 (3%)	4 (11%)	9 (23%)
#Thymic lymphocytes	(35)	(38)	(39)
Necrosis, focal	1 (3%)	2 (5%)	1 (3%)
Necrosis, diffuse		4 (11%)	9 (23%)
CIRCULATORY SYSTEM			
#Myocardium	(50)	(49)	(49)
Inflammation, acute focal		2 (4%)	
Inflammation, acute/chronic			1 (2%)
Degeneration, NOS	2 (4%)		2 (4%)
*Artery	(50)	(49)	(50)
Inflammation, acute/chronic			1 (2%)
*Pulmonary artery	(50)	(49)	(50)
Thrombus, organized		1 (2%)	
#Periprostatic tissue	(50)	(49)	(48)
Periarteritis	1 (2%)		
DIGESTIVE SYSTEM			
*Tooth	(50)	(49)	(50)
Necrosis, focal	1 (2%)		
*Root of tooth	(50)	(49)	(50)
Dysplasia, NOS	3 (6%)	1 (2%)	
*Periodontal tissues	(50)	(49)	(50)
Inflammation, acute/chronic		1 (2%)	
#Salivary gland	(50)	(49)	(48)
Inflammation, chronic focal		1 (2%)	
Cytoplasmic vacuolization		1 (2%)	
Atrophy, focal			1 (2%)
#Liver	(50)	(49)	(49)
Torsion			1 (2%)
Inflammation, acute focal	3 (6%)		
Inflammation, acute/chronic	3 (6%)	1 (2%)	
Inflammation, chronic focal		1 (2%)	
Necrosis, focal	3 (6%)	3 (6%)	5 (10%)
Basophilic cyto change	1 (2%)		
Focal cellular change	3 (6%)	3 (6%)	
Angiectasis	1 (2%)		
#Liver/hepatocytes	(50)	(49)	(49)
Degeneration, cystic		2 (4%)	
Cytoplasmic vacuolization	6 (12%)	1 (2%)	4 (8%)
*Gallbladder	(50)	(49)	(50)
Dilatation, NOS		1 (2%)	
Inflammation, acute/chronic			1 (2%)
#Bile duct	(50)	(49)	(49)
Cyst, NOS	3 (6%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Pancreatic acinus	(50)	(48)	(47)
Cytoplasmic vacuolization	1 (2%)		
Focal cellular change			1 (2%)
Atrophy, focal	4 (8%)	3 (6%)	5 (11%)
#Esophagus	(50)	(49)	(49)
Lacerated wound			4 (8%)
#Periesophageal tissue	(50)	(49)	(49)
Inflammation, acute focal			2 (4%)
#Glandular stomach	(50)	(49)	(43)
Inflammation, acute/chronic	1 (2%)		
Dysplasia, NOS	1 (2%)		1 (2%)
#Jejunum	(50)	(45)	(40)
Necrosis, coagulative	1 (2%)		
#Colon	(50)	(47)	(41)
Parasitism	3 (6%)	2 (4%)	
*Rectum	(50)	(49)	(50)
Parasitism			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(49)	(49)
Hydronephrosis	2 (4%)	2 (4%)	2 (4%)
Pyelonephritis, acute	1 (2%)	5 (10%)	2 (4%)
Glomerulonephritis, subacute	1 (2%)		1 (2%)
Nephropathy	8 (16%)	11 (22%)	3 (6%)
#Kidney/cortex	(50)	(49)	(49)
Cyst, NOS		1 (2%)	
#Kidney/medulla	(50)	(49)	(49)
Necrosis, focal		1 (2%)	
#Kidney/tubule	(50)	(49)	(49)
Mineralization		1 (2%)	
Necrosis, focal		1 (2%)	
Regeneration, NOS	31 (62%)	21 (43%)	11 (22%)
#Kidney/pelvis	(50)	(49)	(49)
Hemorrhage		1 (2%)	
Hyperplasia, epithelial	1 (2%)		
*Ureter	(50)	(49)	(50)
Ectopia		1 (2%)	
#Urinary bladder	(50)	(47)	(43)
Dilatation, NOS	3 (6%)	11 (23%)	6 (14%)
Hemorrhage		1 (2%)	
Inflammation, acute necrotizing		3 (6%)	
Inflammation, acute/chronic			3 (7%)
Hyperplasia, epithelial	1 (2%)		1 (2%)
*Prostatic urethra	(50)	(49)	(50)
Obstruction, NOS		1 (2%)	
*Periurethral tissue	(50)	(49)	(50)
Inflammation, acute focal		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(43)	(44)	(41)
Cyst, NOS	1 (2%)	1 (2%)	
Multiple cysts		1 (2%)	
Hyperplasia, focal	1 (2%)	2 (5%)	
#Adrenal/capsule	(50)	(49)	(49)
Ectopia		1 (2%)	
Hyperplasia, focal	46 (92%)	33 (67%)	22 (45%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal cortex	(50)	(49)	(49)
Cyst, NOS		1 (2%)	1 (2%)
Degeneration, lipoid	8 (16%)	5 (10%)	3 (6%)
Hypertrophy, focal	12 (24%)	7 (14%)	3 (6%)
Hyperplasia, focal	3 (6%)	2 (4%)	
#Adrenal medulla	(50)	(49)	(49)
Hyperplasia, focal	4 (8%)	7 (14%)	4 (8%)
#Thyroid	(50)	(49)	(47)
Follicular cyst, NOS	2 (4%)	2 (4%)	
Hyperplasia, follicular cell	4 (8%)	3 (6%)	3 (6%)
#Parathyroid	(43)	(35)	(29)
Embryonal duct cyst	1 (2%)	2 (6%)	
Focal cellular change	1 (2%)		
REPRODUCTIVE SYSTEM			
*Penis	(50)	(49)	(50)
Inflammation, acute necrotizing			1 (2%)
*Prepuce	(50)	(49)	(50)
Inflammation, chronic focal			1 (2%)
Hyperkeratosis	1 (2%)		
Acanthosis	1 (2%)		
*Preputial gland	(50)	(49)	(50)
Dilatation/ducts		1 (2%)	
Inflammation, acute/chronic	6 (12%)	7 (14%)	4 (8%)
Atrophy, focal	2 (4%)	3 (6%)	2 (4%)
Hyperplasia, focal		1 (2%)	
#Prostate	(50)	(49)	(48)
Inflammation, suppurative	1 (2%)		
Inflammation, acute focal	1 (2%)	2 (4%)	1 (2%)
Inflammation, acute diffuse		2 (4%)	
Inflammation, acute/chronic		3 (6%)	7 (15%)
*Seminal vesicle	(50)	(49)	(50)
Retention fluid	2 (4%)	7 (14%)	4 (8%)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal		1 (2%)	1 (2%)
#Testis	(50)	(49)	(49)
Spermatocele		1 (2%)	
Degeneration, NOS	1 (2%)	1 (2%)	1 (2%)
*Epididymis	(50)	(49)	(50)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic focal	1 (2%)	1 (2%)	1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(49)	(47)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
Inflammation, acute focal			1 (2%)
#Cerebrum	(50)	(49)	(47)
Mineralization	1 (2%)		
Inflammation, focal	1 (2%)		
Necrosis, focal	1 (2%)		
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(49)	(50)
Hyperplasia, epithelial	1 (2%)	1 (2%)	1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*Tarsal joint	(50)	(49)	(50)
Inflammation, acute/chronic			1 (2%)
Hyperostosis	29 (58%)	24 (49%)	10 (20%)
Metaplasia, osseous	29 (58%)	24 (49%)	8 (16%)
*Abdominal muscle	(50)	(49)	(50)
Mineralization			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(49)	(50)
Foreign body, NOS			4 (8%)
Hemorrhage			1 (2%)
Inflammation, acute focal			4 (8%)
*Peritoneum	(50)	(49)	(50)
Inflammation, acute/chronic		1 (2%)	
*Subpleural tissue	(50)	(49)	(50)
Inflammation, acute focal			1 (2%)
*Pericardial cavity	(50)	(49)	(50)
Foreign body, NOS			1 (2%)
*Mesentery	(50)	(49)	(50)
Inflammation, chronic focal		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(50)
Inflammation, acute/chronic	1 (2%)		1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1
Animal missing/no necropsy		1	
Auto/necropsy/histo perf			2

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site
† Multiple occurrence of morphology in the same organ; tissue is counted once only.

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
None			
RESPIRATORY SYSTEM			
*Nasal turbinate	(50)	(49)	(50)
Hematocele	1 (2%)		
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute focal		1 (2%)	
Degeneration, NOS	11 (22%)	11 (22%)	5 (10%)
#Lung	(50)	(49)	(50)
Foreign body, NOS		1 (2%)	
Congestion, acute			2 (4%)
Edema, NOS			1 (2%)
Hemorrhage		1 (2%)	1 (2%)
Inflammation, interstitial	1 (2%)		1 (2%)
Inflammation, necrotizing		1 (2%)	
Inflammation, granulomatous focal	1 (2%)		
Hyperplasia, epithelial	1 (2%)	2 (4%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(50)
Leukocytosis, NOS	1 (2%)		
*Subcutaneous tissue	(50)	(49)	(50)
Plasmacytosis	1 (2%)		
#Bone marrow	(50)	(48)	(47)
Angiectasis			1 (2%)
Myelofibrosis	3 (6%)	15 (31%)	6 (13%)
Hyperplasia, granulocytic	2 (4%)	4 (8%)	1 (2%)
#Spleen	(50)	(49)	(47)
Hemorrhagic cyst	1 (2%)		
Inflammation, granulomatous focal		1 (2%)	
#Splenic follicles	(50)	(49)	(47)
Depletion, lymphoid		1 (2%)	1 (2%)
Hyperplasia, lymphoid	3 (6%)	1 (2%)	
#Splenic red pulp	(50)	(49)	(47)
Angiectasis		1 (2%)	
Hematopoiesis	8 (16%)	5 (10%)	
#Pancreatic lymph node	(49)	(47)	(45)
Inflammation, granulomatous focal		1 (2%)	
#Mesenteric lymph node	(49)	(47)	(45)
Inflammation, acute/chronic	1 (2%)		
Hematopoiesis	4 (8%)		
#Lung	(50)	(49)	(50)
Leukocytosis, NOS		1 (2%)	
Hyperplasia, lymphoid	1 (2%)		
#Liver	(50)	(49)	(50)
Hematopoiesis		3 (6%)	1 (2%)
#Thymus	(37)	(44)	(45)
Depletion, lymphoid	1 (3%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	1 (3%)	1 (2%)	
#Thymic medulla	(37)	(44)	(45)
Hemorrhage			1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#Lung	(50)	(49)	(50)
Thrombus, organized		1 (2%)	
#Myocardium	(50)	(49)	(50)
Mineralization		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Degeneration, NOS	1 (2%)	1 (2%)	
Focal cellular change		1 (2%)	
*Aortic tunica adventitia	(50)	(49)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
*Hepatic vein	(50)	(49)	(50)
Thrombus, mural	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(46)	(49)	(49)
Atrophy, focal			2 (4%)
#Liver	(50)	(49)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, acute diffuse	1 (2%)		
Inflammation, acute/chronic	3 (6%)	3 (6%)	
Necrosis, focal	4 (8%)	1 (2%)	
Basophilic cyto change			1 (2%)
Focal cellular change		1 (2%)	
Eosinophilic cyto change	1 (2%)		
Angiectasis	1 (2%)		
#Liver/hepatocytes	(50)	(49)	(50)
Nuclear shape alteration	1 (2%)		
Cytoplasmic vacuolization	3 (6%)	1 (2%)	
#Bile duct	(50)	(49)	(50)
Multiple cysts	2 (4%)		
#Pancreas	(48)	(47)	(47)
Dilatation/ducts	1 (2%)		
#Pancreatic acinus	(48)	(47)	(47)
Cytoplasmic vacuolization	1 (2%)		
Focal cellular change	1 (2%)	1 (2%)	
Atrophy, focal	2 (4%)		
#Glandular stomach	(48)	(48)	(48)
Cyst, NOS		1 (2%)	
Ulcer, acute	1 (2%)		
#Forestomach	(48)	(48)	(48)
Acanthosis			1 (2%)
#Ileum	(47)	(46)	(48)
Amyloidosis			1 (2%)
#Colon	(48)	(48)	(48)
Parasitism	1 (2%)		1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(49)	(48)
Hydronephrosis	1 (2%)		
Inflammation, interstitial	2 (4%)		
Nephropathy	8 (16%)	1 (2%)	
#Kidney/cortex	(50)	(49)	(48)
Cyst, NOS		1 (2%)	
Multiple cysts	2 (4%)		
Necrosis, focal	2 (4%)		
#Urinary bladder	(48)	(48)	(48)
Dilatation, NOS	1 (2%)		
Inflammation, acute/chronic		1 (2%)	1 (2%)
Hyperplasia, epithelial	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#Urinary bladder/submucosa	(48)	(48)	(48)
Edema, NOS	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(47)	(45)
Cyst, NOS		3 (6%)	1 (2%)
Multiple cysts	1 (2%)	2 (4%)	
Hyperplasia, focal	6 (13%)	4 (9%)	5 (11%)
#Adrenal/capsule	(50)	(49)	(50)
Hyperplasia, focal	47 (94%)	44 (90%)	41 (82%)
#Adrenal cortex	(50)	(49)	(50)
Accessory structure		1 (2%)	
Ectopia	1 (2%)	1 (2%)	
Cyst, NOS	2 (4%)	1 (2%)	
Degeneration, lipoid	1 (2%)	3 (6%)	
Focal cellular change	1 (2%)		
Hypertrophy, focal		2 (4%)	1 (2%)
Hyperplasia, focal	2 (4%)	1 (2%)	3 (6%)
#Adrenal medulla	(50)	(49)	(50)
Hyperplasia, focal		1 (2%)	
#Thyroid	(48)	(49)	(47)
Embryonal duct cyst	1 (2%)		
Follicular cyst, NOS	2 (4%)	10 (20%)	13 (28%)
Inflammation, acute focal	1 (2%)		
Inflammation, chronic focal		4 (8%)	5 (11%)
Hyperplasia, follicular cell	3 (6%)	29 (59%)	36 (77%)
#Thyroid follicle	(48)	(49)	(47)
Crystals, NOS		1 (2%)	
#Pancreatic islets	(48)	(47)	(47)
Hyperplasia, focal	1 (2%)		
REPRODUCTIVE SYSTEM			
#Uterus	(50)	(49)	(48)
Prolapse		1 (2%)	
Dilatation, NOS		1 (2%)	
Hemorrhage	1 (2%)	1 (2%)	
Pyometra		1 (2%)	
Inflammation, acute focal	1 (2%)	1 (2%)	
Inflammation, chronic focal		2 (4%)	
Angiectasis	1 (2%)		
#Endometrial gland	(50)	(49)	(48)
Hyperplasia, cystic	48 (96%)	45 (92%)	44 (92%)
Metaplasia, squamous	1 (2%)		
#Ovary	(50)	(49)	(48)
Follicular cyst, NOS	16 (32%)	18 (37%)	17 (35%)
Parovarian cyst	3 (6%)	7 (14%)	5 (10%)
Abscess, NOS	1 (2%)		
Atrophy, senile	14 (28%)	3 (6%)	5 (10%)
Angiectasis			1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(48)	(49)	(50)
Lymphocytic inflammatory infiltrate	2 (4%)	9 (18%)	14 (28%)
#Cerebrum	(48)	(49)	(50)
Atrophy, pressure	2 (4%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*Eye	(50)	(49)	(50)
Collapse		1 (2%)	
*Harderian gland	(50)	(49)	(50)
Inflammation, chronic focal	1 (2%)		
Hyperplasia, epithelial	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Maxilla	(50)	(49)	(50)
Hyperostosis	1 (2%)		
*Femur	(50)	(49)	(50)
Hyperostosis	2 (4%)	9 (18%)	7 (14%)
*Tarsal joint	(50)	(49)	(50)
Hyperostosis		1 (2%)	
Metaplasia, osseous		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(49)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
*Mesentery	(50)	(49)	(50)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(50)
Amyloidosis	1 (2%)		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1
Auto/necropsy/histo perf			2
Autolysis/no necropsy		1	

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

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	Vehicle Control	15 mg/kg	30 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	9.7%	6.9%	4.2%
Terminal Rates (c)	3/31 (10%)	2/29 (7%)	1/24 (4%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.300N	P=0.531N	P=0.399N
Incidental Tumor Tests (d)	P=0.300N	P=0.531N	P=0.399N
Cochran-Armitage Trend Test (d)	P=0.222N		
Fisher Exact Test (d)		P=0.500N	P=0.309N
Integumentary System: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	11.5%	6.9%	4.2%
Terminal Rates (c)	3/31 (10%)	2/29 (7%)	1/24 (4%)
Week of First Observation	38	104	104
Life Table Tests (d)	P=0.169N	P=0.363N	P=0.249N
Incidental Tumor Tests (d)	P=0.099N	P=0.310N	P=0.136N
Cochran-Armitage Trend Test (d)	P=0.118N		
Fisher Exact Test (d)		P=0.339N	P=0.181N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	8.9%	6.9%	0.0%
Terminal Rates (c)	2/31 (6%)	2/29 (7%)	0/24 (0%)
Week of First Observation	97	104	
Life Table Tests (d)	P=0.122N	P=0.539N	P=0.174N
Incidental Tumor Tests (d)	P=0.131N	P=0.550N	P=0.190N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N
Subcutaneous Tissue: Fibroma, Neurofibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	8.9%	9.7%	3.4%
Terminal Rates (c)	2/31 (6%)	2/29 (7%)	0/24 (0%)
Week of First Observation	97	97	97
Life Table Tests (d)	P=0.340N	P=0.615	P=0.409N
Incidental Tumor Tests (d)	P=0.380N	P=0.597	P=0.455N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.661	P=0.309N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	25/50 (50%)	14/50 (28%)	11/50 (22%)
Adjusted Rates (b)	58.1%	37.3%	32.7%
Terminal Rates (c)	14/31 (45%)	7/29 (24%)	2/24 (8%)
Week of First Observation	71	76	84
Life Table Tests (d)	P=0.049N	P=0.075N	P=0.078N
Incidental Tumor Tests (d)	P=0.011N	P=0.031N	P=0.018N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.020N	P=0.003N
Liver: Neoplastic Nodule			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	12.9%	6.0%	19.5%
Terminal Rates (c)	4/31 (13%)	1/29 (3%)	4/24 (17%)
Week of First Observation	104	93	97
Life Table Tests (d)	P=0.285	P=0.373N	P=0.339
Incidental Tumor Tests (d)	P=0.264	P=0.386N	P=0.323
Cochran-Armitage Trend Test (d)	P=0.424		
Fisher Exact Test (d)		P=0.339N	P=0.500

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	16.1%	9.3%	23.6%
Terminal Rates (c)	5/31 (16%)	2/29 (7%)	5/24 (21%)
Week of First Observation	104	93	97
Life Table Tests (d)	P=0.274	P=0.397N	P=0.320
Incidental Tumor Tests (d)	P=0.256	P=0.408N	P=0.306
Cochran-Armitage Trend Test (d)	P=0.432		
Fisher Exact Test (d)		P=0.357N	P=0.500
Pituitary Gland: Adenoma			
Overall Rates (a)	12/50 (24%)	16/50 (32%)	8/47 (17%)
Adjusted Rates (b)	32.8%	44.7%	32.5%
Terminal Rates (c)	8/31 (26%)	10/29 (34%)	7/23 (30%)
Week of First Observation	85	79	89
Life Table Tests (d)	P=0.500N	P=0.188	P=0.499N
Incidental Tumor Tests (d)	P=0.445N	P=0.164	P=0.446N
Cochran-Armitage Trend Test (d)	P=0.257N		
Fisher Exact Test (d)		P=0.252	P=0.276N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	21/49 (43%)	8/50 (16%)	5/49 (10%)
Adjusted Rates (b)	56.0%	26.7%	21.7%
Terminal Rates (c)	15/31 (48%)	7/29 (24%)	5/23 (22%)
Week of First Observation	87	101	104
Life Table Tests (d)	P=0.001N	P=0.010N	P=0.005N
Incidental Tumor Tests (d)	P=0.001N	P=0.009N	P=0.004N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.003N	P<0.001N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	21/49 (43%)	9/50 (18%)	5/49 (10%)
Adjusted Rates (b)	56.0%	30.0%	21.7%
Terminal Rates (c)	15/31 (48%)	8/29 (28%)	5/23 (22%)
Week of First Observation	87	101	104
Life Table Tests (d)	P=0.002N	P=0.018N	P=0.005N
Incidental Tumor Tests (d)	P=0.001N	P=0.017N	P=0.004N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.007N	P<0.001N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	7/50 (14%)	6/49 (12%)	3/47 (6%)
Adjusted Rates (b)	20.9%	19.7%	12.2%
Terminal Rates (c)	5/31 (16%)	5/29 (17%)	2/23 (9%)
Week of First Observation	101	97	100
Life Table Tests (d)	P=0.264N	P=0.567N	P=0.311N
Incidental Tumor Tests (d)	P=0.293N	P=0.590N	P=0.344N
Cochran-Armitage Trend Test (d)	P=0.151N		
Fisher Exact Test (d)		P=0.516N	P=0.185N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	7/49 (14%)	3/47 (6%)
Adjusted Rates (b)	25.1%	23.1%	12.2%
Terminal Rates (c)	5/31 (16%)	6/29 (21%)	2/23 (9%)
Week of First Observation	93	97	100
Life Table Tests (d)	P=0.138N	P=0.472N	P=0.168N
Incidental Tumor Tests (d)	P=0.161N	P=0.509N	P=0.198N
Cochran-Armitage Trend Test (d)	P=0.061N		
Fisher Exact Test (d)		P=0.410N	P=0.075N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	Vehicle Control	15 mg/kg	30 mg/kg
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	3/50 (6%)	1/47 (2%)	1/49 (2%)
Adjusted Rates (b)	9.2%	3.6%	2.6%
Terminal Rates (c)	2/31 (6%)	1/28 (4%)	0/24 (0%)
Week of First Observation	102	104	82
Life Table Tests (d)	P=0.275N	P=0.348N	P=0.403N
Incidental Tumor Tests (d)	P=0.256N	P=0.360N	P=0.370N
Cochran-Armitage Trend Test (d)	P=0.209N		
Fisher Exact Test (d)		P=0.332N	P=0.316N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	1/47 (2%)	1/49 (2%)
Adjusted Rates (b)	15.5%	3.6%	2.6%
Terminal Rates (c)	4/31 (13%)	1/28 (4%)	0/24 (0%)
Week of First Observation	102	104	82
Life Table Tests (d)	P=0.084N	P=0.131N	P=0.174N
Incidental Tumor Tests (d)	P=0.077N	P=0.136N	P=0.156N
Cochran-Armitage Trend Test (d)	P=0.052N		
Fisher Exact Test (d)		P=0.117N	P=0.107N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	9.7%	0.0%	0.0%
Terminal Rates (c)	3/31 (10%)	0/29 (0%)	0/24 (0%)
Week of First Observation	104		
Life Table Tests (d)	P=0.051N	P=0.132N	P=0.169N
Incidental Tumor Tests (d)	P=0.051N	P=0.132N	P=0.169N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	9.7%	3.4%	0.0%
Terminal Rates (c)	3/31 (10%)	1/29 (3%)	0/24 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.085N	P=0.328N	P=0.169N
Incidental Tumor Tests (d)	P=0.085N	P=0.328N	P=0.169N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	44/49 (90%)	43/50 (86%)	38/50 (76%)
Adjusted Rates (b)	100.0%	97.7%	100.0%
Terminal Rates (c)	31/31 (100%)	28/29 (97%)	24/24 (100%)
Week of First Observation	79	65	59
Life Table Tests (d)	P=0.200	P=0.371	P=0.222
Incidental Tumor Tests (d)	P=0.354	P=0.537	P=0.273
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.394N	P=0.060N

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

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	Vehicle Control	30 mg/kg	60 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	11/50 (22%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	31.0%	14.8%	25.9%
Terminal Rates (c)	6/29 (21%)	2/24 (8%)	1/6 (17%)
Week of First Observation	67	85	91
Life Table Tests (d)	P=0.277N	P=0.135N	P=0.605N
Incidental Tumor Tests (d)	P=0.261N	P=0.225N	P=0.459N
Cochran-Armitage Trend Test (d)	P=0.004N		
Fisher Exact Test (d)		P=0.045N	P=0.008N
Pituitary Gland: Adenoma			
Overall Rates (a)	24/48 (50%)	13/48 (27%)	6/45 (13%)
Adjusted Rates (b)	58.1%	43.9%	66.7%
Terminal Rates (c)	12/28 (43%)	8/24 (33%)	3/6 (50%)
Week of First Observation	67	71	91
Life Table Tests (d)	P=0.464N	P=0.145N	P=0.409
Incidental Tumor Tests (d)	P=0.254N	P=0.058N	P=0.478N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.018N	P<0.001N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	25/48 (52%)	14/48 (29%)	6/45 (13%)
Adjusted Rates (b)	60.7%	47.4%	66.7%
Terminal Rates (c)	13/28 (46%)	9/24 (38%)	3/6 (50%)
Week of First Observation	67	71	91
Life Table Tests (d)	P=0.440N	P=0.154N	P=0.448
Incidental Tumor Tests (d)	P=0.233N	P=0.064N	P=0.433N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.019N	P<0.001N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	3/50 (6%)	2/49 (4%)	0/47 (0%)
Adjusted Rates (b)	9.3%	7.3%	0.0%
Terminal Rates (c)	2/29 (7%)	1/24 (4%)	0/6 (0%)
Week of First Observation	99	84	
Life Table Tests (d)	P=0.378N	P=0.617N	P=0.513N
Incidental Tumor Tests (d)	P=0.371N	P=0.633N	P=0.502N
Cochran-Armitage Trend Test (d)	P=0.090N		
Fisher Exact Test (d)		P=0.510N	P=0.133N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	4/47 (9%)	2/46 (4%)	0/45 (0%)
Adjusted Rates (b)	12.8%	7.9%	0.0%
Terminal Rates (c)	3/29 (10%)	1/24 (4%)	0/6 (0%)
Week of First Observation	99	97	
Life Table Tests (d)	P=0.260N	P=0.462N	P=0.416N
Incidental Tumor Tests (d)	P=0.299N	P=0.617N	P=0.396N
Cochran-Armitage Trend Test (d)	P=0.040N		
Fisher Exact Test (d)		P=0.349N	P=0.064N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	(e) 14/50 (28%)	6/50 (12%)	0/50 (0%)
Adjusted Rates (b)	41.2%	20.1%	0.0%
Terminal Rates (c)	10/29 (34%)	2/24 (8%)	0/6 (0%)
Week of First Observation	85	74	
Life Table Tests (d)	P=0.026N	P=0.136N	P=0.073N
Incidental Tumor Tests (d)	P=0.016N	P=0.126N	P=0.065N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.039N	P<0.001N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	Vehicle Control	30 mg/kg	60 mg/kg
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	8.1%	2.7%	0.0%
Terminal Rates (c)	1/29 (3%)	0/24 (0%)	0/6 (0%)
Week of First Observation	70	71	
Life Table Tests (d)	P=0.254N	P=0.401N	P=0.506N
Incidental Tumor Tests (d)	P=0.104N	P=0.293N	P=0.268N
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	15/50 (30%)	7/50 (14%)	0/50 (0%)
Adjusted Rates (b)	42.5%	22.3%	0.0%
Terminal Rates (c)	10/29 (34%)	2/24 (8%)	0/6 (0%)
Week of First Observation	70	71	
Life Table Tests (d)	P=0.028N	P=0.162N	P=0.063N
Incidental Tumor Tests (d)	P=0.007N	P=0.099N	P=0.030N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.045N	P<0.001N
Clitoral Gland: Adenoma			
Overall Rates (a)	5/50 (10%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	14.7%	0.0%	0.0%
Terminal Rates (c)	3/29 (10%)	0/24 (0%)	0/6 (0%)
Week of First Observation	67		
Life Table Tests (d)	P=0.045N	P=0.060N	P=0.338N
Incidental Tumor Tests (d)	P=0.030N	P=0.049N	P=0.186N
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Test (d)		P=0.028N	P=0.028N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	11/49 (22%)	11/50 (22%)	1/46 (2%)
Adjusted Rates (b)	30.9%	36.6%	5.9%
Terminal Rates (c)	6/28 (21%)	7/24 (29%)	0/6 (0%)
Week of First Observation	74	61	53
Life Table Tests (d)	P=0.410N	P=0.385	P=0.307N
Incidental Tumor Tests (d)	P=0.147N	P=0.593	P=0.133N
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Test (d)		P=0.574N	P=0.003N

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

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	Vehicle Control	25 mg/kg	50 mg/kg
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	3/49 (6%)	6/50 (12%)
Adjusted Rates (b)	7.1%	9.1%	25.2%
Terminal Rates (c)	2/39 (5%)	2/32 (6%)	0/15 (0%)
Week of First Observation	86	98	72
Life Table Tests (d)	P=0.021	P=0.558	P=0.030
Incidental Tumor Tests (d)	P=0.098	P=0.518	P=0.156
Cochran-Armitage Trend Test (d)	P=0.179		
Fisher Exact Test (d)		P=0.651	P=0.243
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	3/50 (6%)	4/49 (8%)	8/50 (16%)
Adjusted Rates (b)	7.1%	11.6%	33.2%
Terminal Rates (c)	2/39 (5%)	2/32 (6%)	0/15 (0%)
Week of First Observation	86	87	72
Life Table Tests (d)	P=0.003	P=0.384	P=0.005
Incidental Tumor Tests (d)	P=0.027	P=0.359	P=0.053
Cochran-Armitage Trend Test (d)	P=0.067		
Fisher Exact Test (d)		P=0.489	P=0.100
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	4/50 (8%)	5/49 (10%)	8/50 (16%)
Adjusted Rates (b)	9.7%	14.6%	33.2%
Terminal Rates (c)	3/39 (8%)	3/32 (9%)	0/15 (0%)
Week of First Observation	86	87	72
Life Table Tests (d)	P=0.007	P=0.370	P=0.010
Incidental Tumor Tests (d)	P=0.047	P=0.349	P=0.088
Cochran-Armitage Trend Test (d)	P=0.135		
Fisher Exact Test (d)		P=0.487	P=0.178
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	12/50 (24%)	4/49 (8%)	2/48 (4%)
Adjusted Rates (b)	28.8%	11.2%	13.3%
Terminal Rates (c)	10/39 (26%)	2/32 (6%)	2/15 (13%)
Week of First Observation	86	75	104
Life Table Tests (d)	P=0.058N	P=0.078N	P=0.166N
Incidental Tumor Tests (d)	P=0.033N	P=0.060N	P=0.126N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.030N	P=0.005N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	5/50 (10%)	1/49 (2%)	1/48 (2%)
Adjusted Rates (b)	12.4%	3.1%	6.7%
Terminal Rates (c)	4/39 (10%)	1/32 (3%)	1/15 (7%)
Week of First Observation	101	104	104
Life Table Tests (d)	P=0.203N	P=0.158N	P=0.420N
Incidental Tumor Tests (d)	P=0.171N	P=0.194N	P=0.347N
Cochran-Armitage Trend Test (d)	P=0.053N		
Fisher Exact Test (d)		P=0.107N	P=0.112N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	16/50 (32%)	5/49 (10%)	3/48 (6%)
Adjusted Rates (b)	37.8%	14.2%	20.0%
Terminal Rates (c)	13/39 (33%)	3/32 (9%)	3/15 (20%)
Week of First Observation	86	75	104
Life Table Tests (d)	P=0.035N	P=0.031N	P=0.131N
Incidental Tumor Tests (d)	P=0.017N	P=0.027N	P=0.081N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.007N	P=0.001N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	2/50 (4%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	5.1%	8.8%	13.3%
Terminal Rates (c)	2/39 (5%)	2/32 (6%)	2/15 (13%)
Week of First Observation	104	85	104
Life Table Tests (d)	P=0.236	P=0.407	P=0.327
Incidental Tumor Tests (d)	P=0.250	P=0.429	P=0.327
Cochran-Armitage Trend Test (d)	P=0.593		
Fisher Exact Test (d)		P=0.490	P=0.691N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	5/50 (10%)	5/49 (10%)	2/50 (4%)
Adjusted Rates (b)	12.0%	14.3%	11.9%
Terminal Rates (c)	3/39 (8%)	3/32 (9%)	1/15 (7%)
Week of First Observation	96	75	102
Life Table Tests (d)	P=0.562	P=0.486	P=0.637N
Incidental Tumor Tests (d)	P=0.362N	P=0.394	P=0.424N
Cochran-Armitage Trend Test (d)	P=0.179N		
Fisher Exact Test (d)		P=0.616	P=0.218N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	9/50 (18%)	8/49 (16%)	4/50 (8%)
Adjusted Rates (b)	21.0%	22.4%	24.4%
Terminal Rates (c)	6/39 (15%)	5/32 (16%)	3/15 (20%)
Week of First Observation	75	75	102
Life Table Tests (d)	P=0.502	P=0.516	P=0.578
Incidental Tumor Tests (d)	P=0.385N	P=0.509	P=0.445N
Cochran-Armitage Trend Test (d)	P=0.098N		
Fisher Exact Test (d)		P=0.519N	P=0.117N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	10/50 (20%)	12/49 (24%)	4/49 (8%)
Adjusted Rates (b)	24.2%	37.5%	24.4%
Terminal Rates (c)	8/39 (21%)	12/32 (38%)	3/15 (20%)
Week of First Observation	95	104	102
Life Table Tests (d)	P=0.426	P=0.211	P=0.621N
Incidental Tumor Tests (d)	P=0.533	P=0.158	P=0.456N
Cochran-Armitage Trend Test (d)	P=0.080N		
Fisher Exact Test (d)		P=0.384	P=0.080N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	6/50 (12%)	7/49 (14%)	5/49 (10%)
Adjusted Rates (b)	14.3%	20.1%	22.6%
Terminal Rates (c)	4/39 (10%)	5/32 (16%)	1/15 (7%)
Week of First Observation	95	75	77
Life Table Tests (d)	P=0.164	P=0.341	P=0.225
Incidental Tumor Tests (d)	P=0.390	P=0.320	P=0.551
Cochran-Armitage Trend Test (d)	P=0.454N		
Fisher Exact Test (d)		P=0.484	P=0.514N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	16/50 (32%)	19/49 (39%)	9/49 (18%)
Adjusted Rates (b)	37.0%	55.6%	42.6%
Terminal Rates (c)	12/39 (31%)	17/32 (53%)	4/15 (27%)
Week of First Observation	95	75	77
Life Table Tests (d)	P=0.162	P=0.120	P=0.295
Incidental Tumor Tests (d)	P=0.395	P=0.076	P=0.532N
Cochran-Armitage Trend Test (d)	P=0.086N		
Fisher Exact Test (d)		P=0.310	P=0.091N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	Vehicle Control	25 mg/kg	50 mg/kg
Adrenal Capsule: Adenoma			
Overall Rates (a)	2/50 (4%)	7/49 (14%)	4/49 (8%)
Adjusted Rates (b)	5.1%	21.1%	26.7%
Terminal Rates (c)	2/39 (5%)	6/32 (19%)	4/15 (27%)
Week of First Observation	104	94	104
Life Table Tests (d)	P=0.022	P=0.042	P=0.040
Incidental Tumor Tests (d)	P=0.031	P=0.030	P=0.040
Cochran-Armitage Trend Test (d)	P=0.286		
Fisher Exact Test (d)		P=0.075	P=0.329
Harderian Gland: Adenoma			
Overall Rates (a)	6/50 (12%)	2/49 (4%)	2/50 (4%)
Adjusted Rates (b)	14.8%	6.3%	13.3%
Terminal Rates (c)	5/39 (13%)	2/32 (6%)	2/15 (13%)
Week of First Observation	95	104	104
Life Table Tests (d)	P=0.370N	P=0.213N	P=0.578N
Incidental Tumor Tests (d)	P=0.324N	P=0.248N	P=0.506N
Cochran-Armitage Trend Test (d)	P=0.081N		
Fisher Exact Test (d)		P=0.141N	P=0.134N
Harderian Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	7/50 (14%)	4/49 (8%)	2/50 (4%)
Adjusted Rates (b)	17.3%	12.5%	13.3%
Terminal Rates (c)	6/39 (15%)	4/32 (13%)	2/15 (13%)
Week of First Observation	95	104	104
Life Table Tests (d)	P=0.359N	P=0.391N	P=0.487N
Incidental Tumor Tests (d)	P=0.318N	P=0.433N	P=0.419N
Cochran-Armitage Trend Test (d)	P=0.055N		
Fisher Exact Test (d)		P=0.274N	P=0.080N

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

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	5/50 (10%)	5/49 (10%)	3/50 (6%)
Adjusted Rates (b)	12.7%	12.4%	8.1%
Terminal Rates (c)	4/38 (11%)	4/39 (10%)	3/37 (8%)
Week of First Observation	99	97	104
Life Table Tests (d)	P=0.320N	P=0.619N	P=0.378N
Incidental Tumor Tests (d)	P=0.452N	P=0.558	P=0.480N
Cochran-Armitage Trend Test (d)	P=0.298N		
Fisher Exact Test (d)		P=0.617	P=0.357N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	6/49 (12%)	4/50 (8%)
Adjusted Rates (b)	14.5%	14.9%	10.8%
Terminal Rates (c)	4/38 (11%)	5/39 (13%)	4/37 (11%)
Week of First Observation	71	97	104
Life Table Tests (d)	P=0.342N	P=0.608N	P=0.398N
Incidental Tumor Tests (d)	P=0.492N	P=0.514	P=0.530N
Cochran-Armitage Trend Test (d)	P=0.314N		
Fisher Exact Test (d)		P=0.606	P=0.370N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	5/50 (10%)	5/49 (10%)	8/50 (16%)
Adjusted Rates (b)	12.2%	12.3%	20.5%
Terminal Rates (c)	3/38 (8%)	4/39 (10%)	6/37 (16%)
Week of First Observation	94	82	90
Life Table Tests (d)	P=0.196	P=0.623N	P=0.245
Incidental Tumor Tests (d)	P=0.167	P=0.580N	P=0.124
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test (d)		P=0.616	P=0.277
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	2/50 (4%)	5/49 (10%)	1/50 (2%)
Adjusted Rates (b)	5.3%	11.8%	2.7%
Terminal Rates (c)	2/38 (5%)	3/39 (8%)	1/37 (3%)
Week of First Observation	104	72	104
Life Table Tests (d)	P=0.434N	P=0.228	P=0.509N
Incidental Tumor Tests (d)	P=0.561N	P=0.154	P=0.509N
Cochran-Armitage Trend Test (d)	P=0.412N		
Fisher Exact Test (d)		P=0.210	P=0.500N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	10/50 (20%)	8/49 (16%)	0/50 (0%)
Adjusted Rates (b)	23.0%	19.4%	0.0%
Terminal Rates (c)	6/38 (16%)	6/39 (15%)	0/37 (0%)
Week of First Observation	69	85	
Life Table Tests (d)	P=0.003N	P=0.398N	P=0.003N
Incidental Tumor Tests (d)	P=0.006N	P=0.447N	P=0.011N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.416N	P<0.001N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	17/50 (34%)	18/49 (37%)	9/50 (18%)
Adjusted Rates (b)	38.1%	40.7%	23.1%
Terminal Rates (c)	11/38 (29%)	13/39 (33%)	7/37 (19%)
Week of First Observation	69	72	90
Life Table Tests (d)	P=0.085N	P=0.511	P=0.093N
Incidental Tumor Tests (d)	P=0.148N	P=0.440	P=0.243N
Cochran-Armitage Trend Test (d)	P=0.050N		
Fisher Exact Test (d)		P=0.470	P=0.055N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	18/50 (36%)	18/49 (37%)	9/50 (18%)
Adjusted Rates (b)	39.5%	40.7%	23.1%
Terminal Rates (c)	11/38 (29%)	13/39 (33%)	7/37 (19%)
Week of First Observation	69	72	90
Life Table Tests (d)	P=0.061N	P=0.565N	P=0.068N
Incidental Tumor Tests (d)	P=0.123N	P=0.498	P=0.224N
Cochran-Armitage Trend Test (d)	P=0.032N		
Fisher Exact Test (d)		P=0.553	P=0.035N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/50 (8%)	2/49 (4%)	2/50 (4%)
Adjusted Rates (b)	9.5%	5.1%	5.4%
Terminal Rates (c)	2/38 (5%)	2/39 (5%)	2/37 (5%)
Week of First Observation	94	104	104
Life Table Tests (d)	P=0.276N	P=0.340N	P=0.372N
Incidental Tumor Tests (d)	P=0.431N	P=0.435N	P=0.613N
Cochran-Armitage Trend Test (d)	P=0.253N		
Fisher Exact Test (d)		P=0.349N	P=0.339N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	2/50 (4%)	1/49 (2%)	3/50 (6%)
Adjusted Rates (b)	5.3%	2.3%	8.1%
Terminal Rates (c)	2/38 (5%)	0/39 (0%)	3/37 (8%)
Week of First Observation	104	93	104
Life Table Tests (d)	P=0.378	P=0.502N	P=0.488
Incidental Tumor Tests (d)	P=0.284	P=0.572N	P=0.488
Cochran-Armitage Trend Test (d)	P=0.400		
Fisher Exact Test (d)		P=0.508N	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	3/49 (6%)	5/50 (10%)
Adjusted Rates (b)	14.6%	7.3%	13.5%
Terminal Rates (c)	4/38 (11%)	2/39 (5%)	5/37 (14%)
Week of First Observation	94	93	104
Life Table Tests (d)	P=0.468N	P=0.249N	P=0.535N
Incidental Tumor Tests (d)	P=0.469	P=0.350N	P=0.544
Cochran-Armitage Trend Test (d)	P=0.432N		
Fisher Exact Test (d)		P=0.254N	P=0.500N
Pituitary Gland: Adenoma			
Overall Rates (a)	5/46 (11%)	9/47 (19%)	5/45 (11%)
Adjusted Rates (b)	13.2%	23.1%	14.7%
Terminal Rates (c)	5/38 (13%)	9/39 (23%)	5/34 (15%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.477	P=0.204	P=0.560
Incidental Tumor Tests (d)	P=0.477	P=0.204	P=0.560
Cochran-Armitage Trend Test (d)	P=0.544		
Fisher Exact Test (d)		P=0.205	P=0.616
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	0/48 (0%)	4/49 (8%)	2/47 (4%)
Adjusted Rates (b)	0.0%	10.3%	5.4%
Terminal Rates (c)	0/37 (0%)	4/39 (10%)	2/37 (5%)
Week of First Observation		104	104
Life Table Tests (d)	P=0.219	P=0.070	P=0.238
Incidental Tumor Tests (d)	P=0.219	P=0.070	P=0.238
Cochran-Armitage Trend Test (d)	P=0.214		
Fisher Exact Test (d)		P=0.061	P=0.242

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORPHENIRAMINE MALEATE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	3/50 (6%)	1/49 (2%)	0/48 (0%)
Adjusted Rates (b)	7.5%	2.6%	0.0%
Terminal Rates (c)	2/38 (5%)	1/39 (3%)	0/37 (0%)
Week of First Observation	99	104	
Life Table Tests (d)	P=0.066N	P=0.302N	P=0.134N
Incidental Tumor Tests (d)	P=0.103N	P=0.359N	P=0.219N
Cochran-Armitage Trend Test (d)	P=0.064N		
Fisher Exact Test (d)		P=0.316N	P=0.129N
Harderian Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	3/49 (6%)	0/50 (0%)
Adjusted Rates (b)	5.3%	7.7%	0.0%
Terminal Rates (c)	2/38 (5%)	3/39 (8%)	0/37 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.207N	P=0.512	P=0.244N
Incidental Tumor Tests (d)	P=0.207N	P=0.512	P=0.244N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.490	P=0.247N

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

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN CONTROL F344/N RATS AND B6C3F$_1$ MICE

TABLE F1. HISTORICAL INCIDENCE OF LEUKEMIA IN MALE F344/N RATS

Study	Incidence in Controls
Historical Incidence in All Water Gavage Controls	
Chlorpheniramine maleate (a)	25/50
THPS (a)	30/50
THPC (a)	19/50
TOTAL	74/150 (49.3%)
SD (b)	11.02%
Range (c)	
High	30/50
Low	19/50
Overall Historical Incidence in Untreated Controls (d)	
TOTAL	458/1,727 (26.5%)
SD (b)	8.83%
Range (c)	
High	23/50
Low	5/50

(a) All studies performed at Battelle Columbus Laboratories; no other water gavage studies have been performed in F344/N rats by NTP.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Data as of August 3, 1984, for studies of at least 104 weeks

TABLE F2. HISTORICAL INCIDENCE OF PHEOCHROMOCYTOMAS IN MALE F344/N RATS

Study	Incidence in Controls	
	Pheochromocytoma	Pheochromocytoma or Malignant Pheocytoma
Historical Incidence in All Water Gavage Controls		
Chlorpheniramine maleate (a)	21/49	21/49
THPS (a)	22/50	23/50
THPC (a)	19/50	19/50
TOTAL	62/149 (41.6%)	63/149 (42.3%)
SD (b)	3.19%	4.03%
Range (c)		
High	22/50	23/50
Low	19/50	19/50
Overall Historical Incidence in Untreated Controls (d)		
TOTAL	338/1,702 (19.9%)	358/1,702 (21.0%)
SD (b)	9.87%	9.63%
Range (c)		
High	20/49	21/49
Low	2/50	3/50

(a) All studies performed at Battelle Columbus Laboratories; no other water gavage studies have been performed in F344/N rats by NTP.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Data as of August 3, 1984, for studies of at least 104 weeks

TABLE F3. HISTORICAL INCIDENCE OF CLITORAL GLAND TUMORS IN FEMALE F344/N RATS

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in All Water Gavage Controls			
Chlorpheniramine maleate (a)	5/50	0/50	5/50
THPS (a)	4/49	4/49	8/49
THPC (a)	0/50	(b) 3/50	(b) 3/50
TOTAL	9/149 (6.0%)	7/149 (4.7%)	16/149 (10.7%)
SD (c)	5.32%	4.23%	5.21%
Overall Historical Incidence in Untreated Controls (d)			
TOTAL	(e) 27/1,772 (1.5%)	(f) 44/1,772 (2.5%)	(e,f) 71/1,772 (4.0%)
SD (c)	1.88%	2.84%	3.27%
Range (g)			
High	3/50	6/49	6/49
Low	0/88	0/50	0/50

(a) Battelle Columbus Laboratories
(b) Adenocarcinoma
(c) Standard deviation
(d) Data as of August 3, 1984, for studies of at least 104 weeks
(e) Includes one cystadenoma, NOS
(f) Includes six squamous cell carcinomas and five adenocarcinomas, NOS
(g) Range and SD are presented for groups of 35 or more animals.

TABLE F4. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE

Study	Incidence in Controls		
	Fibroma	Sarcoma or Fibrosarcoma	Fibroma, Sarcoma, or Fibrosarcoma
Historical Incidence in All Water Gavage Controls			
Chlorpheniramine maleate (a)	1/50	3/50	4/50
THPC (a)	0/50	7/50	7/50
THPS (a)	2/50	11/50	13/50
Chlorinated trisodium phosphate (b)	2/50	6/50	7/50
TOTAL	5/200 (2.5%)	27/200 (13.5%)	31/200 (15.5%)
SD (c)	1.91%	6.61%	7.55%
Range (d)			
High	2/50	11/50	13/50
Low	0/50	3/50	4/50
Overall Historical Incidence in Untreated Controls (e)			
TOTAL	(f) 29/1,791 (1.6%)	(g) 99/1,791 (5.5%)	(f,g) 123/1,791 (6.9%)
SD (c)	2.90%	6.04%	7.32%
Range (d)			
High	6/50	(h) 15/50	(i) 19/50
Low	0/50	0/50	0/50

(a) Battelle Columbus Laboratories
(b) EG&G Mason Research Institute
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Data as of August 3, 1984, for studies of at least 104 weeks
(f) Includes two neurofibromas
(g) Includes four neurofibrosarcomas
(h) Second highest: 7/50
(i) Second highest: 9/50

TABLE F5. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in All Water Gavage Controls			
Chlorpheniramine maleate (a)	12/50	5/50	16/50
THPC (a)	1/50	3/50	4/50
THPS (a)	5/50	2/50	7/50
Chlorinated trisodium phosphate (b)	2/50	6/50	8/50
TOTAL	20/200 (10.0%)	16/200 (8.0%)	35/200 (17.5%)
SD (c)	9.93%	3.65%	10.25%
Range (d)			
High	12/50	6/50	16/50
Low	1/50	2/50	4/50
Overall Historical Incidence in Untreated Controls (e)			
TOTAL	215/1,780 (12.1%)	87/1,780 (4.9%)	296/1,780 (16.6%)
SD (c)	6.80%	4.06%	8.22%
Range (d)			
High	14/50	8/48	17/50
Low	1/50	0/50	1/49

(a) Battelle Columbus Laboratories
(b) EG&G Mason Research Institute
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Data as of August 3, 1984, for studies of at least 104 weeks

TABLE F6. HISTORICAL INCIDENCE OF ADRENAL GLAND CAPSULE OR CORTICAL TUMORS IN MALE B6C3F$_1$ MICE

Study	Incidence in Controls	
	Adenoma	Adenoma or Carcinoma
Historical Incidence in All Water Gavage Controls		
Chlorpheniramine maleate (a)	2/50	2/50
THPC (a)	2/50	2/50
THPS (a)	2/49	2/49
Chlorinated trisodium phosphate (b)	2/49	2/49
TOTAL	8/198 (4.0%)	8/198 (4.0%)
SD (c)	0.05%	0.05%
Range (d)		
High	2/50	2/50
Low	2/49	2/49
Overall Historical Incidence in Untreated Controls (e)		
TOTAL	(f) 41/1,716 (2.4%)	(f) 43/1,716 (2.5%)
SD (c)	2.6%	2.7%
Range (d)		
High	4/46	4/46
Low	0/50	0/50

(a) Battelle Columbus Laboratories
(b) EG&G Mason Research Institute
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Data as of August 3, 1984, for studies of at least 104 weeks
(f) Includes eight adenomas, NOS, of the adrenal gland capsule. All other tumors were diagnosed in the adrenal gland cortex.

TABLE F7. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN FEMALE $B6C3F_1$ MICE

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in All Water Gavage Controls			
Chlorpheniramine maleate (a)	0/48	0/48	0/48
THPC (a)	1/48	0/48	1/48
THPS (a)	1/49	0/49	1/48
Chlorinated trisodium phosphate (b)	1/48	0/48	1/48
TOTAL	3/193 (1.6%)	0/193 (0.0%)	3/193 (1.6%)
SD (c)	1.03%	0.00%	1.03%
Range (d)			
High	1/48	0/49	1/48
Low	0/48	0/49	0/48
Overall Historical Incidence in Untreated Controls (e)			
TOTAL	(f) 36/1,661 (2.2%)	7/1,661 (0.4%)	(f) 43/1,661 (2.6%)
SD (c)	2.40%	1.21%	3.15%
Range (d)			
High	4/48	3/48	7/48
Low	0/50	0/50	0/50

(a) Battelle Columbus Laboratories
(b) EG&G Mason Research Institute
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Data as of August 3, 1984, for studies of at least 104 weeks
(f) Includes one papillary cystadenoma, NOS, and two cystadenomas, NOS, one of which was in an animal with a follicular cell adenoma

APPENDIX G

GENETIC TOXICOLOGY OF

CHLORPHENIRAMINE MALEATE

TABLE G1. MUTAGENICITY OF CHLORPHENIRAMINE MALEATE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	115 ± 5.0	143 ± 6.3	129 ± 3.8
	333	138 ± 20.4	120 ± 12.1	119 ± 13.9
	666	121 ± 2.7	127 ± 13.5	121 ± 12.4
	1,000	106 ± 3.0	127 ± 4.0	114 ± 12.9
	1,666	96 ± 4.5	120 ± 10.0	110 ± 13.1
	3,333	(c) 0 ± 0.0	(c) 98 ± 8.4	(c) 75 ± 2.8
TA1535	0	34 ± 6.4	7 ± 0.6	7 ± 0.7
	100	29 ± 1.7		
	333	22 ± 1.0	9 ± 4.4	5 ± 1.5
	666		9 ± 2.9	6 ± 1.7
	1,000	38 ± 5.8	3 ± 0.7	7 ± 2.3
	1,666		6 ± 0.3	5 ± 0.6
	3,333	46 ± 2.9	(c) 2 ± 0.3	4 ± 0.3
	10,000	(c) 0 ± 0.0		
TA1537	0	6 ± 0.6	6 ± 0.9	9 ± 1.7
	100			8 ± 0.7
	333	3 ± 0.7	8 ± 1.0	6 ± 0.9
	666	3 ± 0.9	7 ± 0.9	
	1,000	4 ± 0.6	6 ± 1.5	10 ± 2.1
	1,666	5 ± 1.2	7 ± 1.5	
	3,333	(c) 1 ± 0.0	(c) 2 ± 0.9	6 ± 0.9
	10,000			(c) 3 ± 1.5
TA98	0	14 ± 0.7	28 ± 1.8	18 ± 1.2
	333	13 ± 0.6	29 ± 4.6	25 ± 4.2
	666	13 ± 1.8	27 ± 1.2	24 ± 3.2
	1,000	19 ± 2.6	26 ± 3.5	26 ± 4.3
	1,666	15 ± 0.9	24 ± 1.5	26 ± 1.9
	3,333	(c) 0 ± 0.0	(c) 14 ± 1.2	24 ± 3.5

(a) The S9 fractions were prepared from the liver of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and study compound or solvent (DMSO) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Mean ± standard error
(c) Slightly toxic

TABLE G2. MUTAGENICITY OF CHLORPHENIRAMINE MALEATE IN MOUSE L5178Y/TK$^{+/-}$ LYMPHOMA CELLS (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutant Count	Mutant Fraction (c)
-S9					
Trial 1					
Dimethyl sulfoxide		91.8 ± 3.8	100.0 ± 1.5	122.5 ± 7.5	45.0 ± 3.7
Chlorpheniramine maleate	10	84.0 ± 12.0	83.5 ± 4.5	98.5 ± 2.5	40.0 ± 7.0
	50	63.5 ± 2.5	42.0 ± 9.0	112.0 ± 18.0	59.5 ± 12.5
	90	72	37	122	56
	130	90.0 ± 5.0	19.0 ± 1.0	167.5 ± 1.5	62.0 ± 4.0
	170	66.5 ± 8.5	8.5 ± 0.5	127.0 ± 18.0	63.0 ± 1.0
	210	Lethal	--	--	--
Methyl methanesulfonate	15	39.0 ± 4.0	20.5 ± 9.5	422.5 ± 39.5 (d)	360.5 ± 0.5
Trial 2					
Dimethyl sulfoxide		92.3 ± 2.9	100.0 ± 7.1	99.0 ± 10.4	35.5 ± 3.0
Chlorpheniramine maleate	75	64.5 ± 3.5	27.5 ± 3.5	106.5 ± 13.5	55.0 ± 4.0
	150	87.5 ± 11.5	25.5 ± 3.5	106.5 ± 3.5	41.0 ± 4.0
	175	74.5 ± 9.5	15.5 ± 6.5	94.5 ± 8.5	42.5 ± 1.5
	200	65.5 ± 18.5	10.0 ± 4.0	52.0 ± 9.0	27.5 ± 3.5
	225	64.5 ± 19.5	9.5 ± 0.5	50.5 ± 10.5	27.0 ± 3.0
	250	Lethal	--	--	--
Ethyl methanesulfonate	250	67.0 ± 0.0	82.5 ± 2.5	374.0 ± 24.0 (d)	186.0 ± 13.0
Methyl methanesulfonate	15	80.0 ± 3.0	76.5 ± 2.5	81.0 ± 6.0	34.0 ± 4.0
+S9 (e)					
Trial 1					
Dimethyl sulfoxide		68.8 ± 3.5	100.3 ± 2.8	113.3 ± 2.8	55.5 ± 3.0
Chlorpheniramine maleate	90	100.0 ± 1.0	114.0 ± 9.0	144.5 ± 13.5	48.0 ± 5.0
	120	86.0 ± 4.0	81.0 ± 22.0	125.5 ± 7.5	49.0 ± 1.0
	150	89.5 ± 6.5	68.5 ± 17.5	157.0 ± 9.0	58.5 ± 1.5
	180	78.0 ± 2.0	83.0 ± 2.0	103.5 ± 21.5	44.0 ± 8.0
	210	68.5 ± 8.5	26.5 ± 1.5	146.0 ± 12.0	71.5 ± 3.5
Methylcholanthrene	2.5	64.0 ± 5.0	33.0 ± 4.0	669.5 ± 53.5 (d)	347.0 ± 1.0
Trial 2					
Dimethyl sulfoxide		80.3 ± 2.3	100.0 ± 8.5	141.0 ± 11.8	58.3 ± 3.5
Chlorpheniramine maleate	110	83.5 ± 1.5	82.0 ± 10.0	122.0 ± 10.0	48.5 ± 4.5
	140	76.5 ± 0.5	73.5 ± 4.5	113.5 ± 11.5	49.5 ± 5.5
	170	86.5 ± 7.5	53.0 ± 5.0	162.0 ± 0.0	63.0 ± 5.0
	200	82.0 ± 20.0	45.0 ± 0.0	116.0 ± 3.0	50.0 ± 11.0
	230	84.5 ± 9.5	32.0 ± 3.0	122.0 ± 8.0	48.5 ± 2.5
Methylcholanthrene	2.5	47.5 ± 4.5	15.0 ± 1.0	712.0 ± 10.0 (d)	503.5 ± 40.5

TABLE G2. MUTAGENICITY OF CHLORPHENIRAMINE MALEATE IN MOUSE L5178Y/TK$^{+/-}$ LYMPHOMA CELLS (Continued)

(a) Study performed at Inveresk Research International. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). Indepth explanations and mathematical derivations of assay characteristics are presented by Myhr et al. (1985). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in duplicate; the average for both tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
(b) Mean ± standard error from replicate tests with approximately 3×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered mutagenic. If only one of these responses is significant, the call is "questionable"; the absence of both trend and peak response results in a "negative" call.
(c) Mutant fraction (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.
(d) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.
(e) Tests conducted with metabolic activation were performed as described in (a) except that S9, prepared from the liver of Aroclor 1254-induced F344 rats, was added at the same time as the study chemical and/or solvent.

TABLE G3. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY CHLORPHENIRAMINE MALEATE (a)

−S9 (b)		+S9 (c)	
Dose (μg/ml)	SCE/Cell (d)	Dose (μg/ml)	SCE/Cell (d)
		Negative control	8.98
DMSO (10 μl)	8.4	DMSO (10 μl)	8.86
Chlorpheniramine maleate		Chlorpheniramine maleate	
75	9.9	200	8.14
125	10.9	300	8.88
150	10.4	400	9.30
		500	9.82
Mitomycin C		Cyclophosphamide	
0.001	11.2	0.3	10.54
0.005	25.0	2.0	25.60

(a) SCE, sister-chromatid exchange; CHO, Chinese hamster ovary
(b) In the absence of S9, CHO cells were incubated with study compound or solvent at 37° C; 2 hours after initiation of treatment, 10 μM BrdU was added, and incubation was continued for an additional 22-24 hours. Due to chemically induced cell cycle delay, cells treated with study compound were allowed to incubate an additional 5 hours to accumulate sufficient metaphases for analysis. Cells were washed, fresh medium containing BrdU (10 μM) and colcemid (0.1 μg/ml) was added, and incubation was continued for 2-3 hours (Galloway et al., 1985).
(c) In the presence of S9, CHO cells were incubated with study compound or solvent for 2 hours at 37° C. Cells then were washed, and medium containing 10 μM BrdU was added. Cells were incubated for an additional 26 hours, with colcemid (0.1 μg/ml) present for the final 2-3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).
(d) Cells were collected by mitotic shake-off, treated for 3 minutes with potassium chloride (75 mM), washed twice with fixative, and dropped onto slides and air-dried (Galloway et al., 1985).

TABLE G4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY CHLORPHENIRAMINE MALEATE (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)	Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)
Negative control	1 (1)	Negative control	4 (3)
DMSO (10 µl)	3 (3)	DMSO (10 µl)	3 (3)
Chlorpheniramine maleate		Chlorpheniramine maleate	
100	0 (0)	16	3 (3)
200	1 (1)	50	3 (3)
300	3 (3)	160	1 (1)
400	2 (2)	500	19 (18)
Mitomycin C		Cyclophosphamide	
0.25	25 (23)	15	15 (13)
1.0	54 (36)	50	76 (54)

(a) Abs, aberrations; CHO, Chinese hamster ovary
(b) In the absence of S9, CHO cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 µg/ml) was added. After an additional 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa (Galloway et al., 1985).
(c) In the presence of S9, CHO cells were incubated with study compound or solvent for 2 hours at 37° C. Cells then were washed, fresh medium was added, and incubation was continued for 8-10 hours. Colcemid (0.1 µg/ml) was added for the last 2-3 hours of incubation. Cells then were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).

APPENDIX H

CHEMICAL CHARACTERIZATION OF CHLORPHENIRAMINE MALEATE

APPENDIX H. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Lot No. 2189ME Performed by the Analytical Chemistry Laboratory

	Determined	Literature Values
A. Appearance:	Fine white powder	White crystalline powder (U.S. Pharmacopeia, 1975)
Melting Point:	131°-134° C (Büchi 510 mp/bp instrument)	130°-135° C (U.S. Pharmacopeia, 1975)
B. Spectral data		
1. Infrared		
Instrument:	Beckman IR-12	
Phase:	1.5% in potassium bromide	
Results:	See Figure 7	Consistent with literature spectrum (Sadtler Standard Spectra)
2. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	Methanol	
Results:	No absorbance was detected between 350-800 nm using 1% solution in methanol	

λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$
268.9	3.724 ± 0.005	269.5	3.99
261.8	5.28 ± 0.02	262.5	5.46
258.4	5.01 ± 0.02	257.5	5.17
		(Sadtler Standard Spectra)	

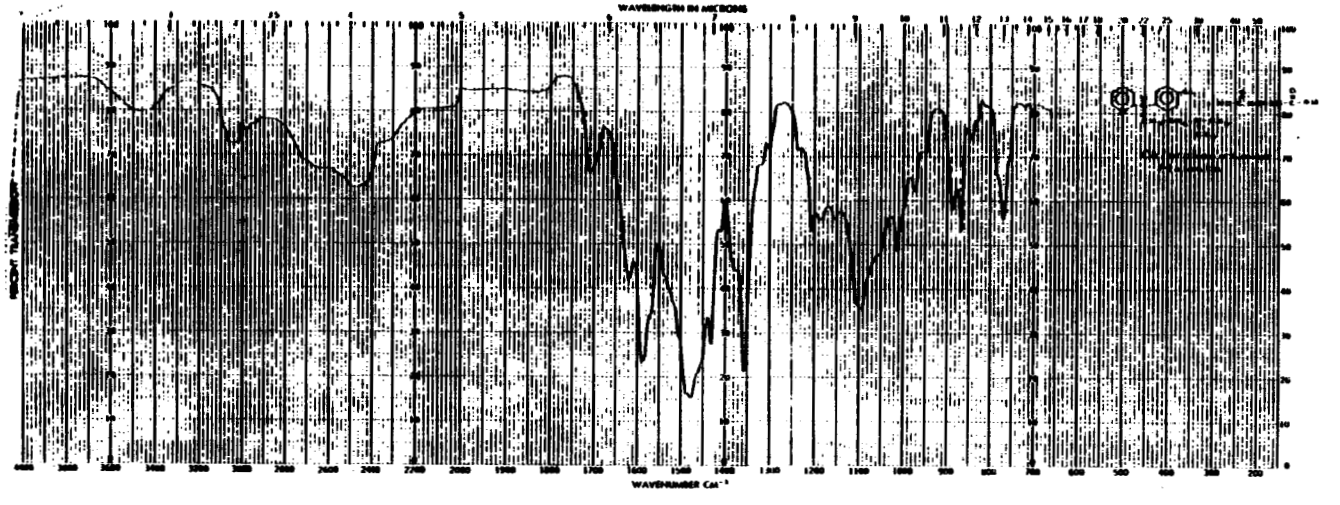

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF CHLORPHENIRAMINE MALEATE (LOT NO. 2189ME)

3. Nuclear magnetic resonance

	Determined	Literature Values
Instrument:	Varian EM-360-A	
Solvent:	Deuterated methanol with internal tetramethylsilane	
Assignments:	See Figure 8	Consistent with literature spectrum (Sadtler Standard Spectra)

Chemical shift (δ):

a	s	2.85 ppm
b	m	2.40-3.20 ppm, J_{b-c} = 7 Hz
c	t	4.20 ppm
d	s	6.25 ppm
e	m	7.10-7.45 ppm
f	s	7.30 ppm
g	m	7.70 pm
h	m	8.53 ppm
i	s	5.45 ppm (HDO)

Integration ratios:

a, b	10.36
c	0.81
d	1.98
e, f, g	6.94
h	0.90
i	1.71

C. **Water analysis (Karl Fischer):** 0.32% ± 0.02(δ)%

D. **Elemental analysis**

Element	C	H	N	Cl
Theory (T)	61.46	5.93	7.17	9.07
Determined (D)	61.94	6.10	7.19	9.02
	61.96	6.02	7.16	9.16
Percent D/T	100.8	102.2	100.1	100.2

E. **Amine titration:** Nonaqueous titration of two basic groups with perchloric acid in glacial acetic acid solvent

100.05% ± 0.24%

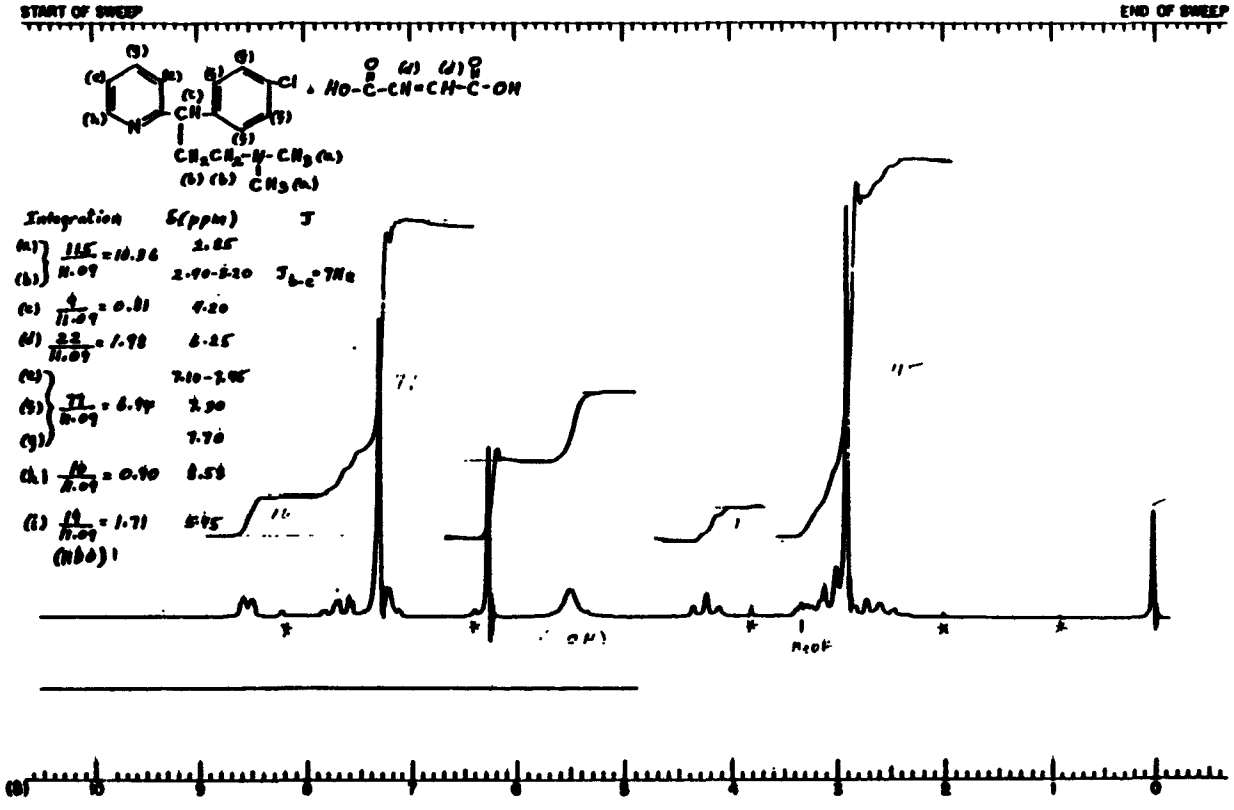

FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORPHENIRAMINE MALEATE (LOT NO. 2189ME)

F. Acid titration: Titration of two acid groups with sodium hydroxide

101.81% ± 0.09%

G. Chromatography

1. Thin-layer chromatography

Plates: Silica Gel 60 F-254 (0.25 mm layer)
Amount spotted: 100 and 300 µg in methanol
Reference standard: N,N-Dimethyl-*p*-phenylenedianiline hydrochloride (2 µl of 10 mg/ml in methanol)
Visualization: Ultraviolet light (254 nm) and 0.5% ninhydrin

System 1

Solvent: Methanol:butanol:ammonium hydroxide (60:40:1)

Results: R_f: 0.29
R_{st}: 0.45

System 2

Solvent: Toluene:dioxane:ammonium hydroxide (60:35:5)

Results: R_f: 0.32
R_{st}: 0.60

2. High-performance liquid chromatography

Instrumental System
Pump: Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Detection: 254 nm
Column: µBondapak C_{18}; 300 × 4 mm
Carrier flow rate: 1 ml/min
Sample injected: Chlorpheniramine maleate in water (5.06 mg/ml)

System 1

Solvent system
A: 5 mM heptanesulfonic acid in 1% aqueous acetic acid
B: 5 mM heptanesulfonic acid in acetonitrile:water containing 1% acetic acid (80:20)

Program A: A:B (65:35)

Results: Two peaks in front of major peak; the first large peak was identified by retention time as maleic acid.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	2.5	0.17	*
2	9.3	0.62	0.07
3	15.0	1.00	100

*Identified as maleic acid; quantitated in System 2 program B below

Program B: A:B (30:70)

Results: One impurity peak (maleic acid) in front of major peak and one following the major peak (unlikely to be the same impurity as that observed in program A above).

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	2.4	0.58	*
2	4.1	1.00	100
3	5.3	1.29	0.03

*Identified as maleic acid; quantitated in System 2 below.

Program C: 1% to 100% B

Results: No additional impurity peaks were seen.

System 2

Solvent system

A: 0.5 mM tetrabutyl ammonium hydroxide in water, pH adjusted to 7.4 with 1% phosphoric acid

B: 0.5 mM tetrabutyl ammonium hydroxide in methanol plus same volume of 1% phosphoric acid that was added to A

Program A: 0 to 100% B

Results: This system was used to search for additional impurities. No additional peaks were seen.

Program B: 100% A

Results: This system elutes only maleic acid and was used to quantitate the maleic acid content of chlorpheniramine maleate. By this method, a maleic acid content of 103.6% ± 1.7% of the theoretical was found.

H. Conclusions: The results of elemental analysis were in agreement with theoretical values. Analysis indicated 0.32% water. Results of amine titration and acid titration indicated 100.05% purity and 101.81% purity, respectively. Thin-layer chromatography indicated one homogeneous spot. High-performance liquid chromatography (HPLC) indicated two small impurities, one before the major peak (0.07%) and one after (0.03%). Maleic acid was quantitated by HPLC as 103.6% of theoretical. Infrared, ultraviolet/visible, and nuclear magnetic resonance spectra conformed to the structure.

II. Identity and Purity Determinations of Lot no. 21-110-1 Performed by the Analytical Chemistry Laboratory

	Determined	Literature Values
A. Appearance:	White, microcrystalline solid	
B. Spectral data		
1. Infrared		
Instrument:	Perkin-Elmer 283	
Phase:	1% in potassium bromide pellet	
Results:	See Figure 9	Consistent with literature spectrum (Sadtler Standard Spectra)
2. Ultraviolet/visible		
Instrument:	Cary 219	
Results:	No absorbance was observed from 800 to 350 nm with a 1% solution in methanol.	

λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$
277 (shoulder)[a]	1.03 ± 0.02(δ)	278 (shoulder)	1.26[b]
268 (shoulder)	3.84 ± 0.01(δ)	269.5	3.99
261	5.19 ± 0.01(δ)	262.5	5.46
256	4.95 ± 0.01(δ)	257.5	5.17
249 (shoulder)[a]	4.12 ± 0.01(δ)	250 (shoulder)	4.35[b]
221 (shoulder)[c]	36.3 ± 0.1(δ)	223 (shoulder)	20.3[b]

[a] The shoulder was observed but not calculated in the spectrum of lot no. 2189ME.
[b] The ε value was calculated from the literature spectrum.
[c] This shoulder was not observed in the spectrum of lot no. 2189ME because the solvent cutoff occurred at 224 nm.

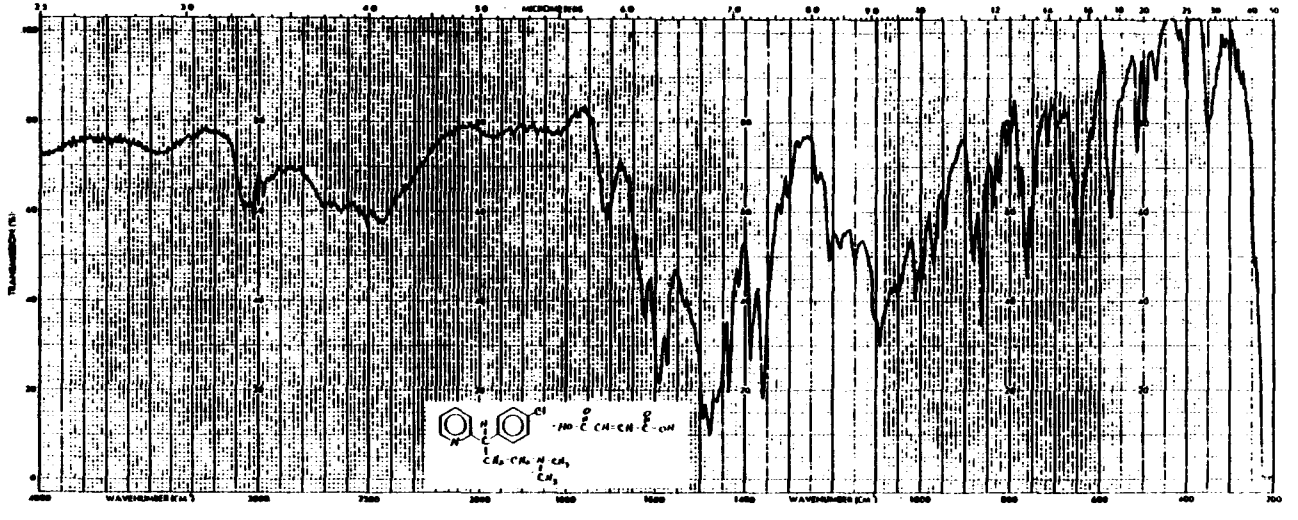

FIGURE 9. INFRARED ABSORPTION SPECTRUM OF CHLORPHENIRAMINE MALEATE (LOT NO. 21-110-1)

3. Nuclear magnetic resonance	Determined	Literature Values
Instrument:	Varian EM-360-A 60 MHz NMR Spectrometer	
Solvent:	Deuterated methanol with tetramethylsilane internal standard	
Assignments:	See Figure 10	Consistent with literature spectrum (Sadtler Standard Spectra)

Chemical shift (δ):

a	s	2.87 ppm
b	m	2.40-3.17 ppm, J_{b-c} = 7 Hz
c	t	4.23 ppm
d	s	6.26 ppm
e	m	7.08-7.47 ppm
f	s	7.32 ppm
g	m	7.71 ppm
h	m	8.54 ppm
i	broad s	5.40 ppm (HDO)

Integration ratios:

a, b		10.10
c		0.97
d		2.17
e, f, g		6.79
h		0.96
i	HDO	2.18

C. Water analysis (Karl Fischer): 0.05% ± 0.01(δ)%

D. Titration

Nonaqueous amine: Titration of two amine groups with 0.1N perchloric acid in glacial acetic acid medium, monitored potentiometrically with a combination pH/mV electrode (Note: USP [United States Pharmacopeia, 1975] specifies not less than 98.0% and not more than 100.5% of $C_{16}H_{19}ClN_2 \cdot C_4H_4O_4$, calculated on the dried weight basis.)

Results: 99.8% ± 0.4(δ)%

Acidimetric: Titration of two acid groups with 0.1N sodium hydroxide in aqueous medium, monitored potentiometrically with a combination pH/mV electrode

Results: 100.5% ± 0.6(δ)%

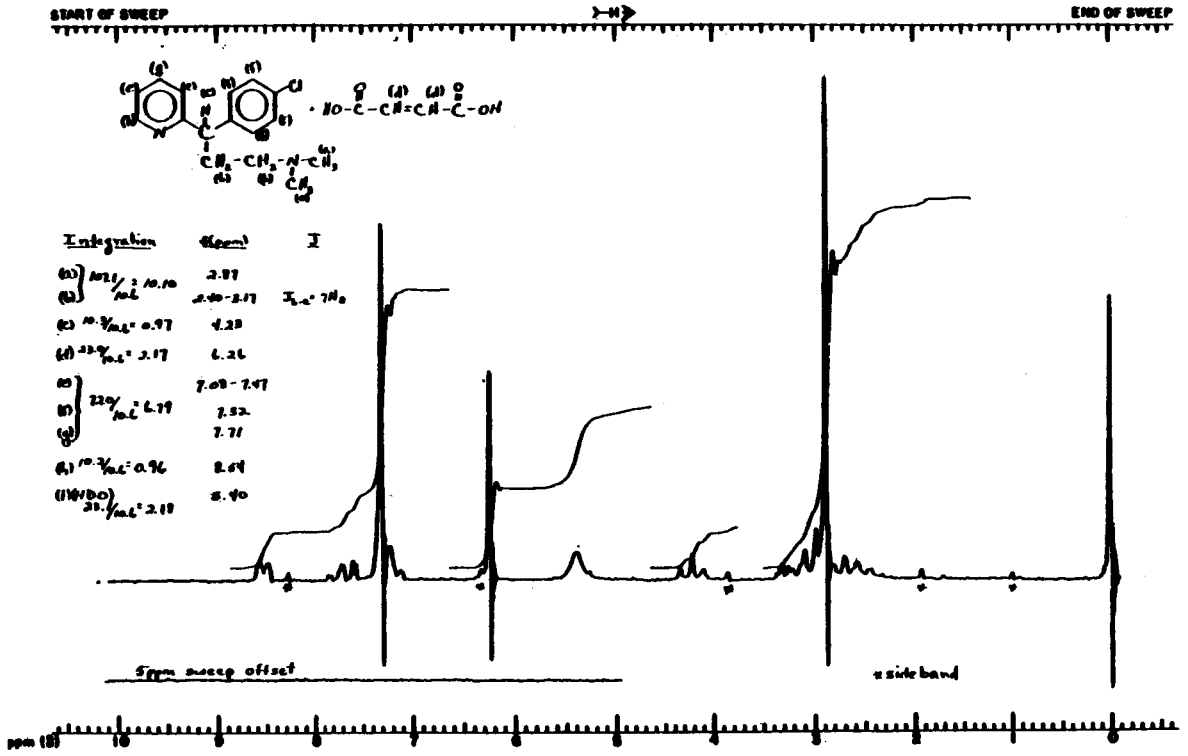

FIGURE 10. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORPHENIRAMINE MALEATE (LOT NO. 21-110-1)

E. Elemental analysis

Element	C	H	N	Cl
Theory (T)	61.46	5.93	7.17	9.07
Determined (D)	61.79	6.04	7.23	9.20
	61.71	6.13	7.20	9.17
Percent D/T	100.5	102.5	100.7	101.2

F. Chromatography

1. Thin-layer chromatography

Plates: Silica Gel 60 F-254, 0.25-mm layer
Amount spotted: 10, 100, 300 µg of a 10 µg/µl solution in methanol)
Reference standard: N,N-Dimethyl-*p*-phenylenedianiline hydrochloride, 10 µg (1 µl of a 10 µg/µl solution in methanol)
Visualization: Ultraviolet light (254 and 366 nm) and spray of 0.5% ninhydrin in butanol. Plates were heated in 100° C oven for several minutes after being sprayed.

System 1: Methanol:butanol:concentrated ammonium hydroxide (60:40:1)

Spot	R_f	R_{st}
Major	0.43	0.59
Reference	0.73	--

System 2: Toluene:dioxane:concentrated ammonium hydroxide (60:35:5). The aqueous layer was discarded when the solvent system was prepared.

Spot	R_f	R_{st}
Major	0.28	0.72
Reference	0.39	--

2. High-performance liquid chromatography

System 1

Instrument
Pump: Waters M6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Detection: Ultraviolet, 254 nm
Column: Waters μBondapak C_{18}, 300 × 3.9 mm ID
Guard column: Whatman CO:PELL ODS, 72 × 2.3 mm ID
Solvent system
A: Water with 5 mM heptanesulfonic acid sodium salt and the pH adjusted to 2.0 with concentrated phosphoric acid
B: Methanol with 5 mM heptanesulfonic acid sodium salt with volume of concentrated phosphoric acid equal to that used for the adjustment of solvent A.
Solvent ratio: A:B (47:53)
Flow rate: 1.0 ml/min
Samples injected: Solution of 5.000 mg/ml chlorpheniramine maleate in solvent B filtered into an amber septum vial
Volume injected: 15 μl

Results: Major peak and one impurity greater than 0.1% of the major peak area, which eluted before the major and had a 19.3-minute retention time. Maleic acid eluted on the solvent front and was not quantitated. A small impurity eluted before the major peak and had a retention volume of 14.2 ml, but its area was less than 0.1% of the major peak area.

No additional impurities were seen when injections of a solution of similar concentration were made at 100%, 80%, 65%, and 55% B. Methanol was used for the B solvent instead of acetonitrile, which was used originally. Heptanesulfonic acid is more soluble in methanol than in acetonitrile and gave the same chromatographic results. The pH was lowered to 2.0 this time to sharpen the major peak but did not otherwise alter the chromatography. An injection of a solution of lot no. 2189ME was made on the analytical system. The peak pattern was the same except the peak at 19.3 ml seen in lot no. 21-110-1 was not seen in lot no. 2189ME.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak) (a)
1	19.3	0.85	0.23
2	22.8	1.00	100.0

(a) Detector response is very dependent upon the absorbance of a substance at the detection wavelength used. The values reported are absolute areas expressed as percentages of the area of the major peak and do not take into account the different ε values of the compound and its impurities. Therefore, the areas reported do not necessarily reflect the actual weight percentages of the impurities in the sample.

System 2: Major peak comparison of lot no. 21-110-1 with USP standard and lot no. 2189ME

Samples: Lot no. 2189ME
Lot no. 21-110-1
USP standard--was dried according to USP procedures, at 105° C for 3 hours

Duplicate weighings of each sample of chlorpheniramine maleate were made, and samples were analyzed for chlorpheniramine maleate content by high-performance liquid chromatography. Internal standard peak heights were compared with chlorpheniramine maleate peak heights, and the chlorpheniramine maleate content was calculated relative to the USP standard. The following instrumental parameters were used.

Instrument
Pump: Waters M6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Detector: Ultraviolet, 254 nm
Column: Waters μBondapak C_{18}, 300 × 3.9 mm ID
Guard column: Whatman CO:PELL ODS, 72 × 2.3 mm ID
Solvent system
A: Water with 5 mM heptanesulfonic acid sodium salt and the pH adjusted to 2.0 with concentrated phosphoric acid
B: Methanol with 5 mM heptanesulfonic acid sodium salt with volume of concentrated phosphoric acid equal to that used for the adjustment of solvent A
Solvent ratio: A:B (35:65)
Flow rate: 1.5 ml/min
Sample injected: Accurately weighed solutions of approximately 1.8 mg/ml chlorpheniramine maleate and 0.4862 mg/ml valerophenone as internal standard, in solvent B filtered into an amber septum vial
Volume injected: 15 μl
Retention times
Chlorpheniramine maleate: 4.5 min
Valerophenone: 7.5 min

Results

Sample	Percent Chlorpheniramine Maleate Relative to the USP Standard
Lot no. 2189ME	98.9% ± 1.1%
Lot no. 21-110-1	99.1% ± 1.1%
USP	100.0% ± 1.1%

G. **Conclusions:** The results of elemental analysis for carbon, hydrogen, nitrogen, and chlorine were in agreement with the theoretical values. Karl Fischer titration indicated 0.05% ± 0.01(δ)% water. Results of titration of the amine group with perchloric acid indicated a purity of 99.8% ± 0.4(δ)%. Results of titration of the acid groups with sodium hydroxide indicated a purity of 100.5% ± 0.6(δ)%. Thin-layer chromatography by two systems indicated only a major spot for each system. High-performance liquid chromatography (HPLC) indicated one impurity, before the major peak, with a relative area of 0.23%. Comparison of the major peaks in the two lots by HPLC indicated purities of 98.9% ± 1.1% for lot no. 2189ME and 99.1% ± 1.1% for lot no. 21-100-1 relative to the USP reference standard. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of chlorpheniramine maleate.

III. Chemical Stability Study of Lot No. 2189ME Performed by the Analytical Chemistry Laboratory

A. Sample storage: Samples of chlorpheniramine maleate were stored 2 weeks in sealed bottles at −20° C, 5° C, 25° C, and 60° C.

B. Analytical method: Duplicate weighed samples (approximately 100 mg) from each temperature storage sample, were placed in volumetric flasks (100 ml) and diluted to volume with deionized water. An aliquot from each sample was filtered through a 0.5-μ Millipore filter and analyzed by high-performance liquid chromatography by the following system:

Instrument
Pump: Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Detection: 254 nm
Column: μBondapak C_{18}, 300 × 4 mm ID
Solvent system: 5 mM tetrabutyl ammonium hydroxide in methanol with 15.6 ml of 1% phosphoric acid in water added
Program: Isocratic
Carrier flow rate: 1 ml/min

C. Results

Storage Temperature	Percent Recovery
−20° C	100.0% ± 1.4(δ)%
5° C	99.0% ± 1.4(δ)%
25° C	100.2% ± 1.4(δ)%
60° C	99.0% ± 1.4(δ)%

D. Conclusion: Chlorpheniramine maleate showed no detectable change in composition during storage for 2 weeks at temperatures up to 60° C.

IV. Chemical Stability Study of Chlorpheniramine Maleate Performed by the Study Laboratory

A. Storage conditions

Bulk: Room temperature
Reference: −20° C in screw-cap glass vials

B. Analytical methods

1. **Infrared spectroscopy**

   Instrument: Digilab FTS-10 or FTS-14 (Fourier Transform IR System); samples run in potassium bromide pellet.

2. **Titration:** Two hundred-fifty milligrams of study and reference samples of chlorpheniramine maleate was dissolved in 20 ml of glacial acetic acid. Two drops of crystal violet (100 mg/10 ml acetic acid) were added. The mixtures were then titrated with 0.1 N perchloric acid to an emerald green end point. Determinations on blanks were performed and volumes adjusted. Each milliliter of 0.1 N perchloric acid is equivalent to 19.54 mg chlorpheniramine maleate.

C. Results

1. **Infrared spectroscopy:** Infrared spectra were similar to the spectrum submitted by the analytical chemistry laboratory and showed no significant differences between study and reference samples.

2. **Titration**

Date of Analysis	Lot No.	Percent Chlorpheniramine Maleate (a) Bulk	Reference
09/28/79	2189ME	100.56	100.56
01/23/80		100.44	(b) --
03/11/80		100.96	(b) --
08/15/80		100.59	(b) --
10/10/80		100.70	101.09
02/26/81		100.30	100.04
06/01/81	21-110-1	100.04	101.61
06/26/81 (c)		101.22	101.09
10/06/81		96.92	98.87
02/08/82		96.92	97.83
06/16/82		97.18	97.44
10/13/82		97.70	97.70
02/22/83		97.31	97.70
06/20/83		97.18	97.31
10/20/83		97.31	97.31

(a) The data presented are the results of triplicate analyses.
(b) Value not given; reported to be not significantly different from bulk.
(c) Bulk sample was from lot no. 21-110-1; reference sample was from lot no. 2189ME.

D. Conclusion: No notable degradation occurred throughout the studies.

APPENDIX I

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX I. PREPARATION AND CHARACTERIZATION

I. Room Temperature Stability Study of Chlorpheniramine Maleate in Water Conducted at the Analytical Chemistry Laboratory (Seven-day Study)

A. Stability study parameters

Concentration: 0.1%
Vehicle: Deionized water
Duration: 7 days
Temperature: Room temperature

B. Sample preparation and storage: Solutions of chlorpheniramine maleate in water were prepared in duplicate on five different days over a 7-day period. The days were chosen so that solutions, when analyzed on day 7, represented samples stored 0, 1, 5, 6, or 7 days at room temperature in the dark.

Solutions were prepared by weighing 100 mg of chemical to the nearest 0.01 mg and diluting with water to 100 ml in a volumetric flask. Each solution (approximately 3 ml) was filtered through a 0.5-µ Millipore filter into a 5-ml septum vial and sealed. The concentration of chlorpheniramine maleate in the solutions was approximately 1 mg/ml.

C. Analytical method: On day 7 of the stability study, the storage samples were analyzed for chlorpheniramine maleate content by injecting sample solutions directly into the high-performance liquid chromatographic system described below.

Instrument: Waters Associates Liquid Chromatograph
Column: µBondapak C_{18}, 300 mm × 4 mm ID
Detector: Ultraviolet at 254 nm
Solvent system: 45%: 5 mM 1-heptanesulfonic acid in water:acetic acid (99:1)
55%: 5 mM 1-heptanesulfonic acid in acetonitrile:water:acetic acid (89:10:1)
Flow rate: 1 ml/min
Injection volume: 10 µl
Retention time: 5 min

D. Quality control measures: Analysis was carried out by making duplicate injections of duplicate sample solutions. High-performance liquid chromatographic linearity was determined with standard solutions of chlorpheniramine maleate in water.

E. Results

Storage Time (days)	Determined Concentration (mg/ml)	Target Concentration (mg/ml)	Recovery (percent of target)
0	1.00	1.01	
0	1.00	1.00	(a) 99.5 ± 0.5
1	0.99	1.00	
1	1.01	1.00	100.0 ± 1
5	1.04	1.04	
5	1.00	1.00	100.0 ± 0
6	0.99	1.00	
6	1.00	1.00	99.5 ± 0.5
7	1.00	1.00	
7	1.00	1.00	100.0 ± 0

(a) Error values are deviations from the mean.

F. **Conclusion:** Chlorpheniramine maleate in water at a concentration of 1 mg/ml (0.1%) exhibited no measurable loss in stability, within the limits of study errors (± 1%), after storage for 7 days at room temperature in the dark.

II. Room Temperature Stability Study of Chlorpheniramine Maleate in Water Conducted at the Analytical Chemistry Laboratory (Fourteen-Day and Three-Hour Studies)

A. Stability study parameters

Concentration: 2.5 mg/ml
Vehicle: Deionized water
Storage conditions
5° C: 7 and 14 days; sealed, in the dark
Room temperature (20°-24° C): 1, 7, 12, and 14 days; sealed, in the dark
Room temperature (20°-24° C): 3 h; open to air and light

B. Sample preparation and storage: Samples were prepared in duplicate on four different days by dissolving approximately 250 mg (± 0.1 mg) of chlorpheniramine maleate in deionized water and diluting to 100 ml. Portions of the solutions (approximately 30 ml) were sealed in 30-ml septum vials and stored under the conditions described above. For analysis at zero-time, three solutions were prepared and analyzed twice.

Solutions for the 3-hour study were prepared twice as described above and stored in 125-ml Erlenmeyer flasks. The solutions were sampled three times and then left open to air and normal room lighting for 3 hours before being resampled for analysis.

C. Analysis procedure: Aliquots (5 ml) of the study solutions were mixed with 4 ml of internal-standard solution (1.01 mg/ml butyrophenone in acetonitrile) and diluted to 100 ml with acetonitrile. The diluted solutions were filtered through 0.45-µ filters and analyzed twice by the high-performance liquid chromatographic system described below.

Pump: Waters M6000A
Injector: Waters WISP 710B
Column: Waters µBondapak C_{18}, 300 mm × 4 mm ID
Detector: Ultraviolet at 254 nm
Mobile phase: 5 mM heptanesulfonic acid in acetonitrile:water:acetic acid (49.5:49.5:1 v/v)
Flow rate: 1 ml/min
Injection volume: 20 µl
Retention times: Chlorpheniramine maleate--5.4 min
Butyrophenone (internal standard)--8.2 min

The concentration of chlorpheniramine maleate in the samples was calculated by the internal-standard method, using a single matrix standard solution of chlorpheniramine maleate (approximately 0.1 mg/ml) injected after every third sample. The accuracy of this standard solution was verified with an independently prepared matrix standard.

The chromatographic system was evaluated for linearity of response with matrix standard solutions of chlorpheniramine maleate at concentrations ranging from approximately 0.07 to 0.14 mg/ml.

D. Results

1. Fourteen-day study

Storage Time (days)	Determined Concentration (mg/ml)	Target Concentration (mg/ml)	Recovery (percent of target)
0	2.49	2.51	
0	2.48	2.51	
0	2.42	2.42	
0	2.43	2.42	
0	2.50	2.51	
0	Lost	2.51	(a) 99.6 ± 0.6
1 (room temp)	2.49	2.49	
1	2.53	2.53	100.0 ± 0.0
7 (5° C)	2.54	2.54	
7	2.48	2.49	99.8 ± 0.3
7 (room temp)	2.56	2.55	
7	2.47	2.49	100.0 ± 1.1
12 (room temp)	2.48	2.51	
12	2.58	2.58	99.4 ± 0.8
14 (5° C)	2.54	2.57	
14	2.43	2.43	99.4 ± 0.8
14 (room temp)	2.51	2.57	
14	2.44	2.43	99.0 ± 1.9

(a) Error values are deviations from the mean.

2. Three-hour study

Storage Time (days)	Determined Concentration (mg/ml)	Target Concentration (mg/ml)	Recovery (percent of target)
0	2.50	2.51	
0	2.51	2.51	
0	2.50	2.51	
0	2.59	2.58	
0	2.60	2.58	
0	2.59	2.58	100.1 ± 0.5
3 (open to light and air)	2.51	2.51	
3	2.50	2.51	
3	2.50	2.51	
3	2.58	2.58	
3	2.58	2.58	
3	2.58	2.58	99.9 ± 0.2

E. **Conclusion:** Water solutions of chlorpheniramine maleate (2.5 mg/ml) are stable for 2 weeks under all study storage conditions. Solutions kept open to air and light for 3 hours are also stable.

APPENDIX J

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX J. METHODS OF ANALYSIS

I. Study Laboratory Analytical Method: Ultraviolet Spectrophotometry

Standards were prepared by serial dilution at 200 mg, 100 mg, 50 mg, and 25 mg chlorpheniramine maleate per 10 ml deionized water. Samples and standards were then diluted 100 µl to 10 ml and again 2 ml to 10 ml. Absorbance was read at 261 nm on a Gilford 2400S spectrophotometer. Concentrations were taken from the linear regression standard curve. Analysis was done in duplicate.

II. Analytical Chemistry Laboratory

A. Preparation of standard spiked water standard: Two standard solutions of chorpheniramine maleate were prepared independently in deionized water. These solutions were diluted with deionized water to make four additional standards. Aliquots of the six standard solutions were pipetted into individual volumetric flasks containing undosed water to make spiked water standards bracketing the specified concentration range of the referee sample. One volumetric flask containing undosed water was prepared for use as a blank. The spiked water standard and the water blank were diluted with deionized water and used in the analysis procedure described below.

B. Preparation of referee sample: Three portions of the referee water sample were pipetted into individual volumetric flasks and diluted to volume with deionized water. The samples were analyzed by the procedure described below.

C. Analysis procedure: Aliquots of each diluted referee water sample, spiked water standard, and blank, prepared as described above, were diluted with deionized water. After the solutions were mixed, the absorbance of the solutions was measured versus deionized water in 1-cm quartz cells on a Cary 219 or Cary 118 spectrophotometer at 260 or 262 nm.

The amount of chlorpheniramine maleate in the referee water samples was determined from the linear regression equation obtained from the standard data, relating the absorbance of each spiked water standard and blank to the amount of chemical in the respective spiked water standard.

D. Quality assurance measures: The referee water sample was analyzed in triplicate, and the undosed water sample was analyzed once. Individually spiked portions of undosed water (six concentrations bracketing the specified concentration range of the referee sample) were prepared from two independently weighed standards and were treated like the referee water samples for obtaining standard data.

APPENDIX K

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE K1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Date Mixed	Concentration of Chlorpheniramine Maleate in Deionized Water (mg/ml)		Determined as a Percent of Target
	Target	Determined (a)	
02/22/80	0.75	0.758	101.06
	1.25	1.261	100.88
	1.5	1.515	101.00
	2.5	2.545	101.80
	3.0	3.085	102.83
	5.0	5.130	102.60
	6.0	6.070	101.16
	10.0	9.530	95.30
	12.0	12.625	105.21
	20.0	20.170	100.85

(a) Results of duplicate analysis

TABLE K2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE (a)

Date Mixed	Concentration (a) of Chlorpheniramine Maleate in Deionized Water for Target Concentration						
	2.5 mg/ml	3 mg/ml	5 mg/ml	6 mg/ml	10 mg/ml	12 mg/ml	20 mg/ml
10/14/80		3.01		6.23		11.2	
10/21/80		3.02		6.17		12.8	
12/11/80		3.17		6.37		12.8	
01/27/81					10.20		20.2
02/17/81		3.14		6.14		12.6	
03/31/81		(b) 2.65		5.92	10.10	12.3	20.7
05/19/81		3.19		6.22	10.80	11.9	20.7
07/21/81		(b) 2.42		5.69	10.20	12.1	20.6
09/09/81		(b) 2.59		5.77	10.20	12.3	20.1
10/20/81	(c) 1.93	(c) 2.43	4.72	5.64	9.83	11.9	19.6
10/22/81	(d) 2.57	(d) 3.02					
11/10/81	2.27	2.76	4.61	5.63	9.52	11.4	19.2
01/19/82	2.70	3.30	5.37	6.06	9.77	12.2	19.2
03/17/82	(b) 2.79	3.23	5.36	6.29	10.70	12.4	21.2
05/19/82	2.34	2.81	4.57	5.89	9.71	11.9	19.7
06/10/82	2.31	2.81	4.84	5.85	9.90	12.3	21.1
08/24/82	2.30	3.00	4.90	5.55	9.70	11.8	19.5
10/19/82	2.26		4.74		9.76		19.7
12/14/82	2.60		4.88		9.86		19.3
01/16/83	2.46		4.98				
04/06/83	2.30		4.86				
06/01/83	2.62		4.92				
07/19/83	2.56		5.03				
09/20/83	2.58		5.04				
Mean (mg/ml)	2.43	2.90	4.92	5.96	10.02	12.13	20.06
Standard deviation	0.227	0.289	0.237	0.269	0.375	0.459	0.699
Coefficient of variation (percent)	9.3	10.0	4.8	4.5	3.7	3.8	3.5
Range (mg/ml)	1.93-2.79	2.42-3.30	4.57-5.37	5.55-6.37	9.52-10.80	11.20-12.80	19.20-21.20
Number of samples	14	15	14	15	14	15	14

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

TABLE K3. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF CHLORPHENIRAMINE MALEATE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
10/21/80	3.0	3.02	2.83
03/31/81	12.0	12.3	12.1
09/09/81	20.0	20.1	20.1
03/17/82	6.0	6.29	6.13
10/19/82	2.5	2.26	2.21
04/06/83	5.0	4.86	4.93
09/20/83	2.5	2.58	2.54

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

APPENDIX L

SENTINEL ANIMAL PROGRAM

APPENDIX L. SENTINEL ANIMAL PROGRAM

I. Methods

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

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia)	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai	MHV (mouse hepatitis virus)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6, 12, 18 mo)	RCV (rat coronavirus) Sendai (24 mo)	

II. Results

Positive serologic reactions were observed only for KRV in 5/10 rats examined at 24 months.

APPENDIX M

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

Pelleted Diet: September 1980 to September 1983

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

TABLE M1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

(a) NIH, 1978; NCI, 1976
(b) Ingredients should be ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE M2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE M3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.67 ± 0.80	22.2-25.3	36
Crude fat (percent by weight)	4.87 ± 0.49	3.3-5.1	36
Crude fiber (percent by weight)	3.35 ± 0.25	2.9-3.8	36
Ash (percent by weight)	6.62 ± 0.45	6.01-7.34	36
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,586 ± 3,820	4,100-24,000	36
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	17 ± 2.7	14.0-27.0	(b) 35
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.31 ± 0.15	0.08-1.69	36
Phosphorus (percent)	1.0 ± 0.06	0.88-1.11	36
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) was not analyzed for thiamine.

TABLE M4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.49 ± 0.20	<0.05-1.06	36
Cadmium (ppm)	≤ 0.10	<0.01-0.10	36
Lead (ppm)	0.84 ± 0.65	0.33-3.57	36
Mercury (ppm) (a)	< 0.05		
Selenium (ppm)	0.29 ± 0.08	< 0.05-0.40	36
Aflatoxins (ppb) (a,b)	< 10	< 5.0-< 10.0	36
Nitrate nitrogen (ppm) (c)	8.76 ± 4.56	< 0.1-22.0	36
Nitrite nitrogen (ppm) (c)	2.16 ± 1.68	< 0.1-6.9	36
BHA (ppm) (d,e)	5.08 ± 4.63	0.4-16.0	36
BHT (ppm) (d)	2.75 ± 2.32	< 1.0-5.9	36
Aerobic plate count (CFU/g)	43,561 ± 33,572	6,600-130,000	36
Coliform (MPN/g) (f)	17.0 ± 25.0	<3-93	34
Coliform (MPN/g) (g)	33.0 ± 85.0	<3-460	36
E. coli (MPN/g) (h)	< 3.0		36
Total nitrosamines (ppb) (i,j,k)	4.90 ± 4.47		33
Total nitrosamines (ppb) (i,j,l)	15.97 ± 49.80		35
N-Nitrosodimethylamine (ppb) (i,j,k)	4.34 ± 4.53		33
N-Nitrosodimethylamine (ppb) (i,j,l)	15.32 ± 49.58		35
N-Nitrosopyrrolidine (ppb)	1.18 ± 0.51		31
Pesticides (ppm) (c)			
α-BHC (a,m)	<0.01		36
β-BHC (a)	<0.02		36
γ-BHC-Lindane (a)	<0.01		36
δ-BHC (a)	<0.01		36
Heptachlor (a)	<0.01		36
Aldrin (a)	<0.01		36
Heptachlor epoxide (a)	<0.01		36
DDE (a)	<0.01		36
DDD (a)	<0.01		36
DDT (a)	<0.01		36
HCB (a)	<0.01		36
Mirex (a)	<0.01		36
Methoxychlor (a, n)	<0.05	0.09 (8/26/81); 0.06 (7/26/83)	36
Dieldrin (a,o)	<0.01	0.01 (7/21/82)	36
Endrin (a)	<0.01		36
Telodrin (a)	<0.01		36
Chlordane (a)	<0.05		26
Toxaphene (a)	<0.1		36
Estimated PCB's (a)	<0.2		36
Ronnel (a)	<0.01		36
Ethion (a)	<0.02		36
Trithion (a)	<0.05		36
Diazinon (a,o)	<0.1	0.2 (4/27/81)	36
Methyl parathion (a)	<0.02		36
Ethyl parathion (a)	<0.02		36
Malathion (p)	0.10 ± 0.08		36
Endosulfan I (a,q)	<0.01		23
Endosulfan II (a,q)	<0.01		23
Endosulfan sulfate (a,q)	<0.03		23

TABLE M4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) Detection limit reduced from 10 ppb to 5 ppb after 7/81
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) One batch contained less than 0.5 ppm.
(f) Excludes one high value of 240 obtained for the batch produced on 11/25/80, and one high value of 460 obtained for the batch produced on 9/23/82.
(g) Includes the high values listed in footnote (f)
(h) All values were less than 3 MPN/g (MPN, most probable number).
(i) One batch (12/23/80) not analyzed for nitrosamines
(j) All values were corrected for percent recovery.
(k) Mean, standard deviation, and range exclude two very high values in the range of 117.6-279.5 ppb for batches produced on 1/26/81 and 4/27/81.
(l) Mean, standard deviation, and range include the very high values given in footnote (k).
(m) BHC, hexachlorocyclohexane or benzene hexachloride
(n) There were two observations above the detection limit; the values and the dates they were obtained are given under the range.
(o) There was one observation above the detection limit; the value and the date it was obtained are given under the range.
(p) Seventeen batches contained more than 0.05 ppm.
(q) Fourteen batches were not analyzed for Endosulfan I, Endosulfan II, or Endosulfan sulfate.

APPENDIX N

DISTRIBUTION AND EXCRETION OF CHLORPHENIRAMINE MALEATE IN RATS

APPENDIX N. DISTRIBUTION AND EXCRETION

A study of the distribution and excretion of chlorpheniramine maleate in rats was conducted at the University of Arizona under the sponsorship of the NTP (NIEHS contract number N01-ES-8-2130). The laboratory report is on file at NTP, NIEHS, Research Triangle Park, North Carolina.

I. Oral Administration Study

A. Methods: Two groups of three male F344 rats, each weighing 150-200 g, were administered 2 or 20 mg/kg body weight of chlorpheniramine maleate in water (0.5 ml) by oral intubation (gavage). Each dose contained about 50 μCi/kg of ^{14}C-labeled chlorpheniramine maleate. The maleate was not labeled. After they were dosed, the animals were housed individually in metabolism cages and given food and water *ad libitum*. Blood samples (duplicate 75-μl aliquots) were taken from the lateral tail veins at 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 24 hours, and every 24 hours thereafter until 9 days after dosing, at which time all animals were killed. Urine and feces samples were collected daily and analyzed for ^{14}C by counting in a Beckman LS-100 liquid scintillation counter. The animals were killed, and the brain, lung, liver, kidney, small intestine, large intestine, fat, skin, and muscle tissues were oxidized and analyzed for carbon-14 by liquid scintillation counting techniques.

B. Results: The urinary and fecal excretion of the labeled chlorpheniramine maleate are summarized in Table N1. No significant difference in excretion pattern was observed between the two dose groups. About 50% of the dose was excreted in the first 24 hours after dosing, 70% after 2 days, and 90% after 4 days. By day 9, 98%-99% of the label had been excreted from animals in both dose groups; the major route of excretion was via the urine (65%-70%).

Table N2 lists the tissue-to-blood ratios for the 1%-2% of the radioactive label that remained in the body 9 days after dosing. The liver and kidney had several-fold higher concentrations of label than did the blood.

II. Intravenous Administration Study

A. Methods: Male F344 rats were administered 2 mg/kg (50 μCi/kg) body weight of ^{14}C-chlorpheniramine maleate by injection into the lateral tail vein, with approximately 0.3 ml of solution injected per animal. The animals were housed in metabolism cages as in the oral administration study. Serial killing of three animals each was performed 15 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 1 day, 2 days, 3 days, 6 days, and 9 days after dosing. Brain, lung, liver, kidney, small intestine, large intestine, fat, skin, muscle, and the injection site were oxidized and then analyzed for carbon-14 by counting in a Beckman LS-100 liquid scintillation counter. The fraction of label remaining as parent compound or as metabolite was determined from the ratio of label in chlorpheniramine (extracted with hexane from the tissue digest, resuspended in isopropanol, and quantitatively analyzed by gas chromatography) to the total amount of label in each tissue sample. Assays were performed only for tissues containing 1% or more of the administered dose.

B. Results: Table N3 summarizes the percentage of total administered carbon-14 appearing in selected tissues over time. Muscle contained the largest percentage of dose and liver the second largest, compared with other tissues over the 9-day period after dosing. The data for percentage of dose in the blood versus time were best described by biexponential equations. Assays of the feces and urine indicated that virtually all of the administered dose was excreted as metabolites (Table N4). The excretion profile following intravenous administration of chlorpheniramine maleate was similar to the excretion profile following oral administration: 68% of the dose was excreted within 24 hours, and approximately 65% of the label excreted within 9 days appeared in the urine (Table N5).

TABLE N1. PERCENTAGE OF ORAL DOSE OF CHLORPHENIRAMINE MALEATE FOUND IN EXCRETA OF MALE RATS

Time (days)	2.0 mg/kg (a)		20 mg/kg (a)	
	Urine (percent) (b)	Feces (percent) (b)	Urine (percent) (b)	Feces (percent) (b)
1	49.35 ±12.9	11.54 ± 7.3	44.91 ± 9.0	0.35 ± 0.2
2	9.21 ± 3.6	7.64 ± 6.9	11.53 ± 3.4	9.19 ± 2.0
3	3.94 ± 1.2	6.89 ± 4.2	4.30 ± 1.9	6.47 ± 2.2
4	2.07 ± 0.8	2.92 ± 1.6	2.04 ± 0.8	7.61 ± 5.1
5	1.21 ± 0.3	3.06 ± 1.2	1.42 ± 0.5	1.81 ± 0.7
6	0.98 ± 0.4	2.02 ± 1.1	0.95 ± 0.2	1.16 ± 0.9
7	0.54 ± 0.1	1.08 ± 0.9	0.54 ± 0.1	0.95 ± 0.2
8	0.42 ± 0.1	1.06 ± 0.1	0.33 ± 0.1	0.44 ± 0.3
9	0.18 ± 0.05	0.27 ± 0.05	0.31 ± 0.05	0.44 ± 0.2
Cumulative	67.9 ± 13.5	36.48 ± 11.2	66.33 ± 9.9	28.42 ± 6.0
Total percentage dose excreted (c)	104.38 ± 17.5		94.75 ± 11.6	

(a) All doses include a ^{14}C tracer = 50 μCi/kg.
(b) Mean of three rats ± standard deviation
(c) Analysis of variance between the low dose and high dose groups shows no significant difference between the groups (P=0.817).

TABLE N2. TISSUE TO BLOOD RATIOS OF RADIOACTIVE LABEL IN INDIVIDUAL MALE F344 RATS NINE DAYS AFTER GAVAGE ADMINISTRATION OF CHLORPHENIRAMINE MALEATE

2 mg/kg	Rat No. 3 (a)	Rat No. 4	Rat No. 5	Mean
Brain	--	0.35	0.27	0.31
Liver	--	10.70	8.84	9.77
Lung	--	0.93	0.99	0.96
Kidney	--	4.61	5.52	5.07
Spleen	--	1.76	1.89	1.83
Fat	--	1.06	0.95	1.01
Small intestine	--	1.09	0.78	0.94
Large intestine	--	1.63	1.12	1.38
Muscle	--	0.69	0.66	0.68
Blood	--	1	1	1
20 mg/kg	**Rat No. 6**	**Rat No. 7**	**Rat No. 8**	**Mean ± Standard Deviation**
Brain	0.80	0.62	0.51	0.64± 0.15
Liver	10.60	7.91	7.99	8.83± 1.53
Lung	1.92	1.84	1.38	1.71± 0.29
Kidney	6.10	5.06	4.29	5.15± 0.91
Spleen	2.53	2.10	2.14	2.26± 0.24
Fat	2.09	1.53	2.26	1.96± 0.38
Small intestine	1.86	1.34	1.95	1.72± 0.33
Large intestine	2.21	2.16	2.58	2.32± 0.23
Muscle	0.97	1.15	1.06	1.06± 0.09
Blood	1	1	1	1

(a) No blood collected due to technical error

TABLE N3. SUMMARY OF PERCENTAGE DOSE RECOVERED IN TISSUES AND EXCRETA FROM MALE F344 RATS FOLLOWING INTRAVENOUS ADMINISTRATION OF CHLORPHENIRAMINE MALEATE (a)

Tissue	Minutes		Hours						Days			
	15	30	1	2	4	8	12	24	2	3	6	9
Brain	1.37 ± 0.69	1.07 ± 0.50	0.53 ± 0.08	0.49 ± 0.03	0.24 ± 0.17	0.21 ± 0.02	0.20 ± 0.03	0.04 ± 0.01	0.01 ± 0.01	<0.01 ± 0.003	<0.01 ± 0.001	<0.01 ± 0.001
Lung	4.50 ± 2.16	4.40 ± 1.07	4.89 ± 2.49	5.00 ± 1.71	4.02 ± 0.52	3.22 ± 1.33	3.11 ± 1.9	0.30 ± 0.08	0.13 ± 0.10	0.03 ± 0.02	0.01 ± 0.004	< 0.01 ± 0.001
Liver	12.46 ± 2.23	14.91 ± 1.17	13.41 ± 0.49	10.79 ± 1.36	7.44 ± 0.92	5.78 ± 0.16	5.16 ± 0.56	2.14 ± 0.35	1.23 ± 0.12	0.84 ± 0.06	0.43 ± 0.07	0.21 ± 0.04
Kidney	3.40 ± 0.53	3.42 ± 0.20	3.45 ± 0.22	3.61 ± 0.34	2.48 ± 0.21	1.59 ± 0.21	1.26 ± 0.21	0.31 ± 0.04	0.17 ± 0.10	0.06 ± 0.01	0.04 ± 0.01	0.02 ± 0.002
Small intestine	3.60 ± 0.33	6.66 ± 3.04	3.99 ± 0.72	5.32 ± 0.83	3.69 ± 0.77	3.21 ± 0.84	3.58 ± 1.2	1.22 ± 0.92	0.30 ± 0.05	0.09 ± 0.03	0.05 ± 0.01	0.02 ± 0.003
Large intestine	0.92 ± 0.35	0.95 ± 0.09	0.74 ± 0.12	0.76 ± 0.07	0.77 ± 0.25	0.86 ± 0.56	0.78 ± 0.18	0.81 ± 0.76	0.21 ± 0.18	0.05 ± 0.03	0.03 ± 0.004	0.01 ± 0.001
Fat	2.40 ± 1.03	3.05 ± 0.12	1.79 ± 0.11	1.80 ± 0.27	1.38 ± 0.55	0.72 ± 0.03	0.96 ± 0.38	0.42 ± 0.04	0.31 ± 0.14	0.19 ± 0.03	0.13 ± 0.03	0.22 ± 0.09
Muscle	35.33 ± 0.75	30.87 ± 1.5	29.68 ± 2.0	28.72 ± 2.90	16.39 ± 1.15	9.65 ± 1.90	8.80 ± 1.9	2.15 ± 0.34	1.10 ± 0.50	0.47 ± 0.14	0.31 ± 0.05	0.41 ± 0.24
Skin	6.64 ± 0.78	6.34 ± 0.15	6.38 ± 0.64	7.70 ± 0.69	4.27 ± 0.24	2.84 ± 0.38	2.69 ± 0.72	0.82 ± 0.02	0.53 ± 0.24	0.32 ± 0.08	0.25 ± 0.04	0.39 ± 0.33
Blood	1.91 ± 0.27	1.56 ± 0.06	1.53 ± 0.03	1.29 ± 0.09	0.80 ± 0.16	0.74 ± 0.11	0.91 ± 0.07	0.34 ± 0.05	0.19 ± 0.07	0.11 ± 0.02	0.09 ± 0.01	0.07 ± 0.003
Intestinal contents	3.50 ± 0.83	4.35 ± 1.31	8.20 ± 0.07	12.72 ± 3.67	18.01 ± 2.93	23.51 ± 0.80	24.64 ± 2.0	8.45 ± 3.9	3.75 ± 0.57	0.97 ± 0.59	0.39 ± 0.15	0.19 ± 0.03
Urinary bladder contents	0.24 ± 0.07	1.58 ± 1.76	(b) 1.38	--	9.66 ± 4.12	4.49 ± 1.3	3.37 ± 3.6	--	--	--	--	--
Injection site	3.67 ± 2.45	3.08 ± 2.2	3.49 ± 3.9	0.79 ± 0.07	0.87 ± 1.07	0.26 ± 0.08	0.71 ± 0.42	0.06 ± 0.04	0.14 ± 0.11	0.06 ± 0.04	0.05 ± 0.03	0.05 ± 0.01

(a) Dose = 2 mg/kg; data are the mean ± standard deviation for three determinations.
(b) Bladder contents from one animal only

TABLE N4. PERCENTAGE OF DOSE EXCRETED AS CHLORPHENIRAMINE IN URINE AND FECES OF MALE F344 RATS THREE DAYS AFTER GAVAGE ADMINISTRATION OF CHLORPHENIRAMINE MALEATE (a)

	Percentage of Dose			Mean ± Standard Deviation
	Rat No. 3 (a)	Rat No. 4	Rat No. 5	
Urine				
Day 1	0.0138	0.0711	0.172	0.0856 ± 0.0801
Day 2	(b)	0.0157	0.00903	0.0124 ± 0.00471
Day 3	0.000752	0.0034	0.0059	0.00335 ± 0.00257
Feces				
Day 1	0.00225	0.000288	0.00134	0.00129 ± 0.000982
Day 2	0.000164	0.000293	0.00064	0.000366 ± 0.000246
Day 3	0.000137	0.000129	0.00024	0.000169 ± 0.0000619

(a) Dose = 2 mg/kg
(b) Insufficient sample for analysis

TABLE N5. PERCENTAGE OF DOSE FOUND IN EXCRETA OF MALE F344 RATS AFTER INTRAVENOUS ADMINISTRATION OF CHLORPHENIRAMINE MALEATE (a)

Time (days)	Percentage of Dose ± Standard Deviation		
	Urine	Feces	Total
1	51.98 ± 0.81	16.45 ± 3.4	68.43 ± 3.49
2	5.14 ± 0.05	8.13 ± 0.60	13.27 ± 0.60
3	1.46 ± 0.22	3.03 ± 0.34	4.49 ± 0.40
4	0.60 ± 0.12	1.10 ± 0.08	1.70 ± 0.14
5	0.52 ± 0.14	0.54 ± 0.06	1.06 ± 0.15
6	0.35 ± 0.06	0.36 ± 0.06	0.71 ± 0.08
7	0.30 ± 0.08	0.25 ± 0.01	0.55 ± 0.08
8	0.46 ± 0.10	0.18 ± 0.04	0.64 ± 0.11
9	0.15 ± 0.05	0.19 ± 0.03	0.34 ± 0.06
Cumulative	60.96 ± 0.87	30.23 ± 3.5	91.19 ± 3.6

(a) n = 3; dose = 2 mg/kg

APPENDIX O

DATA AUDIT SUMMARY

APPENDIX O. DATA AUDIT SUMMARY

The archival data and pathology materials for the 2-year toxicology and carcinogenesis studies of chlorpheniramine maleate in F344/N rats and B6C3F$_1$ mice were audited for accuracy, completeness, and procedures consistent with Good Laboratory Practice regulations. The studies in rats were conducted from October 1980 to October 1982, and the studies in mice were conducted from February 1981 to October 1983, at Battelle Columbus Laboratories, Columbus, Ohio, under a subcontract with Tracor Jitco, Inc., from the National Cancer Institute. These studies began before the requirement of compliance with Good Laboratory Practices by the NTP in October 1981. The audit was conducted at the NTP Archives, Research Triangle Park, North Carolina, on August 13-18, 1985, by the Product Safety Assessment Division of Dynamac Corporation and involved the following personnel: J. Albert, M.S.; R. Bowman, B.S.; S. Brecher, Ph.D.; M. Blumenthal, B.S.; T. Cooper, B.A.; D. Hothi, D.V.M., Ph.D.; J. Kovach, B.A.; S. Taulbee; S. Shrivastava, Ph.D.; and K. Tripathi, D.V.M., Ph.D. The audit report was approved by NTP personnel and is on file at NTP, NIEHS, Research Triangle Park, North Carolina.

The audit consisted of a review of the data collected during the conduct of the studies, pathology materials, correspondence, the final laboratory report, and the draft NTP Technical Report. The in-life toxicology data review included examination of all records pertaining to animal receipt, husbandry, randomization, identification, dosing, mortality, environmental conditions, and diagnostic serology. Body weight data and clinical observations were reviewed for 10% of the animals. The analytical chemistry review included examination of records concerning receipt, purity, identity, stability, and use of chlorpheniramine maleate and analyses of the dose mixtures and of the feed. The audit of the pathology material included review of all Individual Animal Data Records (IADRs) for identity verification, correlation between gross and microscopic diagnoses, microscopic description versus diagnosis, and data entry errors. Wet tissues from a 10% random sample of animals from each group were examined for unidentified lesions and identity verification. Data from the same 10% random sample of animals were reviewed for correlation of diagnoses on Individual Animal Pathology Tables (IAPTs) and IADRs. Tissue bags were counted and labels checked for all animals. Slides and tissue blocks were matched for all high dose and vehicle control animals.

Review of the toxicologic data revealed no major discrepancies or problems that would affect the validity of the studies. On one occasion, 50% of the low dose male rats were administered the solution prepared for the high dose male mice; several fluctuations in body weight were noted which could not be attributed to environmental factors; a small number of masses (six in the rat studies and five in the mouse studies) were observed clinically but did not correlate with necropsy findings; and in a few instances the dates and modes of death indicated on the IADRs did not correlate with the data recorded in the clinical observation records. A review of the analytical chemistry data revealed no major discrepancies. Review of the pathology materials revealed no significant problems in wet tissue bag counts, in unidentified lesions, in correlation between gross and microscopic diagnoses, in microscopic description versus diagnosis, in correlation of diagnoses on IAPTs and IADRs, or in slide/block matches. Wet tissue examinations revealed that 12 of 38 rats and 11 of 43 mice lacked definitive identification, generally due to missing feet and/or ears. Poor tissue count was noted in various organs, particularly in the high dose male mouse group. Inappropriate disposition codes were used in a few instances in which deaths were possibly associated with gavage errors.

The minor discrepancies identified in this audit were adequately resolved or were considered not to affect the interpretation of these 2-year carcinogenesis studies of chlorpheniramine maleate. Thus, the data examined in this audit were considered adequate to meet the objectives of these studies.

 *U.S. GOVERNMENT PRINTING OFFICE:1986-491-292:41193