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TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

(CAS NO. 147-24-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

(CAS NO. 147-24-0)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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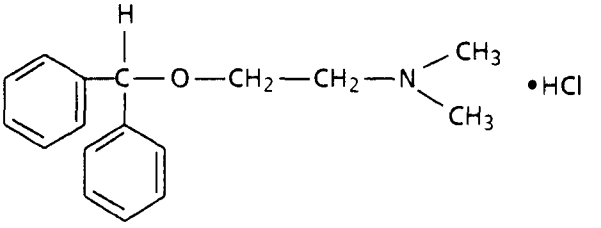

DIPHENHYDRAMINE HYDROCHLORIDE

CAS No. 147-24-0

$C_{17}H_{21}NO \cdot HCl$ Molecular weight 291.8

Synonyms: 2-diphenylmethoxy-*N*,*N*-dimethylethanamine hydrochloride; 2-(benzhydryloxy)-*N*,*N*-dimethylethylamine hydrochloride; β-dimethylaminoethyl benzhydryl ether hydrochloride; benzhydramine hydrochloride

Trade Names: Alleran; Benadryl

ABSTRACT

Diphenhydramine hydrochloride is a widely used antihistaminic drug in human and veterinary medicine. Toxicology and carcinogenesis studies were conducted by feeding diets containing USP-grade diphenhydramine hydrochloride (greater than 99% pure) to groups of F344/N rats and B6C3F$_1$ mice of each sex for 14 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse L5178Y cells, and Chinese hamster ovary (CHO) cells.

Fourteen-Day and Thirteen-Week Studies: In the 14-day studies, dietary concentrations ranged from 620 to 10,000 ppm for rats and from 310 to 5,000 ppm for mice. All rats that received diets containing 10,000 ppm and 9/10 rats that received diets containing 5,000 ppm died before the end of the studies. The final mean body weights of rats receiving 1,250 or 2,500 ppm were 12%-13% or 30%-34% lower than those of controls. Feed consumption by rats at the three highest concentrations was more than 30% less than that by controls. All mice receiving 5,000 ppm, 4/5 males and 4/5 females receiving 2,500 ppm, and 4/5 males receiving 1,250 ppm died before the end of the studies. The final mean body weights of mice that received 1,250 or 2,500 ppm were lower than the initial weights. All dosed rats and mice were hyperactive and sensitive to sound and/or touch.

In the 13-week studies, dietary concentrations of diphenhydramine hydrochloride ranged from 156 to 2,500 ppm for rats and from 78 to 1,250 ppm for mice. All rats lived to the end of the studies. The final mean body weights of rats receiving 1,250 or 2,500 ppm were about 15% or 35% lower than those of controls. The final mean body weight of female rats receiving 625 ppm was 9% lower than that of controls. Increased activity was observed for all male and female rats receiving 1,250 and 2,500 ppm. Cytoplasmic vacuolization of the liver, characteristic of fat accumulation, was observed in male and female rats receiving 313-2,500 ppm. The severity of this change increased with increased dose. For mice, 1/10 males receiving 313 ppm, 2/10 males receiving 625 ppm, and 8/10 males receiving 1,250 ppm died before the end of the studies. The final mean body weights of mice that received 625 or 1,250 ppm were about 9% or 16% lower than those of controls. No compound-related histopathologic effects were observed in mice.

Based on the mortality and body weight effects of diphenhydramine hydrochloride in the short-term studies, dietary concentrations selected for the 2-year studies were 0, 313, and 625 ppm diphenhydramine hydrochloride for male rats and 0, 156, and 313 ppm for female rats and male and female mice.

Body Weight and Survival in the Two-Year Studies: Mean body weights of dosed and control rats were similar throughout the studies, and mean body weights of dosed mice were 3%-13% lower than those of controls throughout most of the studies. No significant differences in survival were observed between any groups of rats or mice of either sex (male rats: control, 29/50; low dose, 32/50; high dose, 24/50; female rats: 35/50; 32/50; 36/50; male mice: 29/50; 30/50; 24/48; female mice: 37/50; 39/50; 32/50). The estimated average daily feed consumption by dosed rats and dosed mice was similar to that by controls. The average amount of diphenhydramine hydrochloride consumed per day was approximately 13 or 27 mg/kg for low dose or high dose male rats, 7 or 15 mg/kg for low dose or high dose female rats, and 21 or 46-47 mg/kg for low dose or high dose male and female mice.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: For three high dose male rats, astrocytomas were found in brain sections taken by routine sampling procedures. Gliomas, containing neoplastic astrocytes and oligodendrocytes, were found in one control and one additional high dose male rat. The incidence of glial cell tumors in high dose male rats (4/50) exceeded the highest incidence in historical controls in the Program (2/50). The historical incidence of glial cell tumors is less than 0.7% in approximately 2,000 untreated control male F344/N rats. Three additional sections of brain were prepared from the residual fixed tissues of each male and female rat. One additional astrocytoma in a high dose male rat and one astrocytoma in a high dose female rat were observed in these sections.

Adenomas of the anterior pituitary gland in female rats occurred with a significant positive trend; the incidences in low dose male and high dose female rats were marginally greater than those in controls (male: control, 11/49; low dose, 21/50; high dose, 14/49; female: 23/50; 26/50; 35/50).

The incidence of alveolar/bronchiolar adenomas in low dose male rats was slightly greater than that in controls (0/49; 5/50; 3/50). The incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in dosed male rats were not significantly different from that in controls (1/49; 6/50; 5/50) but exceeded the highest incidence in historical controls (4/49). The historical incidence of alveolar/bronchiolar neoplasms in untreated control male F344/N rats is approximately 2.2%. Adenomatous hyperplasia of the lung was not increased in incidence in dosed male rats compared with controls.

The incidences of granulomas of the liver were increased in dosed rats (male: 0/49; 3/50; 4/50; female: 8/50; 15/49; 18/50).

At no site were the incidences of neoplastic lesions in dosed mice considered to be compound related. Cytoplasmic vacuolization (fatty metamorphosis) of the liver was observed at an increased incidence in high dose female mice (0/49; 1/49; 8/49).

Genetic Toxicology: Diphenhydramine hydrochloride was not mutagenic in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested in either the presence or absence of exogenous metabolic activation. Exposure to this chemical did not induce trifluorothymidine (Tft) resistance in mouse L5178Y lymphoma cells with or without metabolic activation. In cytogenetic tests with cultured CHO cells, diphenhydramine hydrochloride induced chromosomal aberrations in the absence, but not the presence, of exogenous metabolic activation (S9); no induction of sister chromatid exchanges (SCEs) was observed in these cells with or without S9.

Conclusions: Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity** of diphenhydramine hydrochloride for male F344/N rats, based on marginally increased incidences of uncommon brain neoplasms (astrocytomas or gliomas) and of alveolar/bronchiolar neoplasms. There was *equivocal evidence of carcinogenic activity* for female F344/N rats, based on a marginal increase in the incidence of pituitary gland adenomas. There was *no evidence of carcinogenic activity* for male or female B6C3F$_1$ mice fed diets containing 156 or 313 ppm diphenhydramine hydrochloride.

SUMMARY OF THE TWO-YEAR FEED AND GENETIC TOXICOLOGY STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Dietary concentrations			
0, 313, or 625 ppm diphenhydramine hydrochloride	0, 156, or 313 ppm diphenhydramine hydrochloride	0, 156, or 313 ppm diphenhydramine hydrochloride	0, 156, or 313 ppm diphenhydramine hydrochloride
Body weights in the 2-year study			
Similar in all groups	Similar in all groups	Reduced in dosed groups	Reduced in high dose group
Survival rates in the 2-year study			
29/50; 32/50; 24/50	35/50; 32/50; 36/50	29/50; 30/50; 24/48	37/50; 39/50; 32/50
Nonneoplastic effects			
None	None	None	None
Neoplastic effects			
Astrocytomas or gliomas of the brain: 1/49; 0/49; 5/50; alveolar/bronchiolar adenomas or carcinomas (combined): 1/49; 6/50; 5/50	Pituitary gland adenomas: 23/50; 26/50; 35/50	None	None
Level of evidence of carcinogenic activity			
Equivocal evidence	Equivocal evidence	No evidence	No evidence
Genetic toxicology			
Salmonella (gene mutation)	Mouse L5178Y/TK$^{+/-}$ (Tft resistance)	CHO Cells in Vitro	
		SCE	Aberration
Negative with and without S9	Negative with and without S9	Negative with and without S9	Positive without S9; negative with S9

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

A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 9.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

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

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Diphenhydramine Hydrochloride is based on the 13-week studies that began in March 1980 and ended in June 1980 and on the 2-year studies that began in February 1981 and ended in April 1983 at SRI International (Menlo Park, CA).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on Diphenhydramine Hydrochloride on October 3, 1988, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

On October 3, 1988, the draft Technical Report on the toxicology and carcinogenesis studies of diphenhydramine hydrochloride received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

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

Dr. Garman, a principal reviewer, agreed with the conclusions. In view of the rather high incidence of glial cell tumors in male rats, he wondered if consideration had been given to evaluating spinal cords from these rats. Dr. S. Eustis, NIEHS, said that pieces of spinal cord were saved but not the entire organ. He doubted that any additional tumors could be located.

Dr. McKnight, the second principal reviewer, agreed with the conclusions. Both Dr. Garman and Dr. McKnight asked that more specific and detailed information be included about the Pathology Working Group (PWG) process. Dr. Melnick described the PWG processes used to evaluate the tissues from these studies and mentioned that additional sections of brain from control and exposed male and female rats were evaluated. Dr. Garman suggested that a listing of the target organs evaluated by the PWG be included in the Report.

Dr. Klaassen, the third principal reviewer, agreed with the conclusions, although he voiced some reservation about the conclusion for male rats, noting that the increased incidence of brain tumors in male rats was not statistically significant, was not observed in female rats, and did not show a dose response. Dr. Melnick said that the term "marginal," as used with equivocal evidence, meant a borderline effect with potential biologic significance. Factors to be considered in interpreting a marginal increase and the difficulty in assigning the correct level of evidence based on the incidences of brain tumors were then discussed.

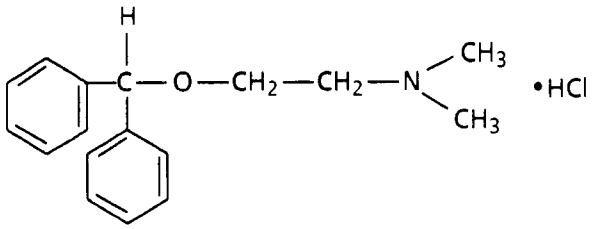
Dr. Adrianne Rogers, Boston University, representing Parke Davis, stated that the conclusions for both male and female rats should not include the lung or pituitary gland tumors as evidence of carcinogenic activity. In male rats, the increase in lung tumors represented primarily adenomas; there was no increase in hyperplasia, and the trend test was not significant at 5%. In female rats, the incidences of pituitary gland tumors in all dosed groups were within the historical control range, and there were no associated increases in the incidence of hyperplasia. In response to Dr. Ashby, Dr. Rogers concurred with the conclusion for male rats, based on the incidences of brain tumors.

Dr. Garman moved that the Technical Report on diphenhydramine hydrochloride be accepted with the revisions discussed and with the conclusions as written for male and female rats, equivocal evidence of carcinogenic activity, and for male and female mice, no evidence of carcinogenic activity. Dr. Gallo seconded the motion, which was approved by eight panelists, with one abstention (Dr. Newberne).

I. INTRODUCTION

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

I. INTRODUCTION



DIPHENHYDRAMINE HYDROCHLORIDE

CAS No. 147-24-0

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Synonyms: 2-diphenylmethoxy-*N*,*N*-dimethylethanamine hydrochloride; 2-(benzhydryloxy)-*N*,*N*-dimethylethylamine hydrochloride; β-dimethylaminoethyl benzhydryl ether hydrochloride; benzhydramine hydrochloride

Trade Names: Alleran; Benadryl

Diphenhydramine hydrochloride is a white, odorless, crystalline powder used primarily as an antihistamine in human and veterinary medicine (Merck, 1983; Douglas, 1985). Diphenhydramine hydrochloride also possesses anticholinergic, antitussive, antiemetic, and sedative properties. Preparations containing diphenhydramine are available as oral solids (capsule or tablet), oral liquids (syrup or elixir), injection, or cream formulations (PDR, 1988). The recommended therapeutic dosage of diphenhydramine hydrochloride for adults is 25-50 mg every 4-6 hours (not to exceed 300 mg in 24 hours); for children 6-12 years of age, the recommended therapeutic dosage is 12.5-25 mg every 4-6 hours (not to exceed 150 mg in 24 hours) (Fed. Regist., 1985).

Diphenhydramine hydrochloride has been approved by the Food and Drug Administration for use as an over-the-counter drug for the symptomatic treatment of allergic rhinitis and the common cold (Fed. Regist., 1985), as well as for nonprescription use as a nighttime sleep aid (Fed. Regist., 1982). In 1983, nearly 40,800 pounds of diphenhydramine hydrochloride were imported into the United States (USITC, 1984). Recent domestic production volume of diphenhydramine hydrochloride is not available (USITC, 1986; CEH, 1987). Approximately 20,000 workers, mostly in the health services, are potentially exposed to diphenhydramine hydrochloride, as estimated from data compiled from the National Occupational Exposure Survey (NIOSH, unpublished data).

Diphenhydramine is a member of the ethanolamine class of antihistamines that competitively antagonize the action of histamine by binding to H_1 receptor sites (Douglas, 1985). Diphenhydramine hydrochloride has been widely used in the symptomatic treatment of the common cold and allergic responses of the skin or mucous membranes. It is effective in blocking the constrictor action of histamine on respiratory smooth muscle and in antagonizing the vasodilation and the increase in capillary permeability and formation of edema caused by histamine (Loew et al., 1945; Sherrod et al., 1947; Douglas, 1985). Suppression of the cough reflex and sedation caused by diphenhydramine hydrochloride may be due to its binding to H_1 receptors in the brain. H_1-receptor antagonists may stimulate or depress the central nervous system, and undesirable side effects, such as drowsiness, nervousness, dizziness, and nausea as well as dryness of the mouth, nose, and throat, have been associated with the therapeutic use of diphenhydramine hydrochloride (Douglas, 1985; Garnett, 1986). The syndrome of acute poisoning from an overdose of diphenhydramine hydrochloride in humans includes impaired consciousness, hallucinations, excitement, mydriasis, tachycardia, ataxia, incoordination, and convulsions; coma

may develop, with the patient dying of cardiopulmonary arrest (Douglas, 1985; Garnett, 1986; Koppel et al., 1987).

Animal Toxicity Studies

LD_{50} values reported for diphenhydramine hydrochloride in rats, mice, guinea pigs, rabbits, dogs, and hamsters are presented in Table 1. Species differences in sensitivity to diphenhydramine hydrochloride appear to follow the order rat < mouse < dog < hamster < rabbit. Animal deaths after administration of lethal doses of diphenhydramine hydrochloride are due to neuromotor excitment and convulsions, followed by respiratory failure and myocardial depression (Gruhzit and Fisken, 1947). Beliles (1972) found no difference in the acute toxicity of diphenhydramine hydrochloride in pregnant and nonpregnant CD®-1 mice. Four-day-old Holtzman rats were more sensitive to diphenhydramine hydrochloride administered by subcutaneous injection than were 40-day-old rats (Goldenthal, 1971).

Gruhzit and Fisken (1947) studied the toxicologic effects resulting from diphenhydramine hydrochloride administration to rats, mice, and dogs. This compound at lethal doses caused congestion and edema of the lung and congestion of the liver, kidney, spleen, adrenal gland, and gastrointestinal tract mucosa. Albino mice were fed diets containing 500-10,000 ppm diphenhydramine hydrochloride for 14 days (daily doses were 100, 183, 469, 540, and 828 mg/kg); body weight gain was depressed in all groups, and mortality was 100% in the 540 and 828 mg/kg groups and 20% in the 469 mg/kg group. Histopathologic changes observed in the 183 mg/kg dose group included moderate-to-severe chronic inflammatory foci in the lungs, congestion of the spleen, and slight edema of the liver, with mild spotty fatty degenerative infiltration. In addition, the thyroid gland showed mild depletion of colloid substance and mild follicular cell hypertrophy. For rats fed diets containing 750-10,000 ppm diphenhydramine hydrochloride for 28 days (daily doses were 72, 101, 158, 249, and 719 mg/kg), weight gain was normal at doses up to 158

TABLE 1. LD_{50} VALUES OF DIPHENHYDRAMINE HYDROCHLORIDE IN RATS, MICE, GUINEA PIGS, RABBITS, DOGS, AND HAMSTERS (a)

Species	Route of Administration				Reference
	Oral	Subcutaneous	Intraperitoneal	Intravenous	
Rat			82		Loew et al., 1945
			61		Winder et al., 1946
	545			45.7	Rieveschl and Gruhzit, 1945
	500	474		42	Gruhzit and Fisken, 1947
(4-day-old)	725	200			Goldenthal, 1971
(40-day-old)	856	362			Goldenthal, 1971
Mouse			75		Sherrod et al., 1947
		126		31	Lands et al., 1949
				35.5	Beliles, 1972
	167	130	82		Rieveschl and Gruhzit, 1945
			89		Way and Herbert, 1952
	164	127	98		Gruhzit and Fisken, 1947
	200	144	80	35	Hoppe and Lands, 1949
			74.6		Reinhard and Scudi, 1947
Guinea pig			75		Loew et al., 1945
Rabbit				10.5	Rieveschl and Gruhzit, 1945
				10	Gruhzit and Fisken, 1947
Dog				30	Rieveschl and Gruhzit, 1945
				24	Gruhzit and Fisken, 1947
Hamster				18	Hoppe and Lands, 1949

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

mg/kg. All animals that were fed diets containing 10,000 ppm diphenhydramine hydrochloride refused their feed and were dead within 1 week. Mortality in the 719 and 249 mg/kg groups was 85% and 10%, respectively. Histopathologic changes in rats in the 249 mg/kg group were similar to those in mice in the 183 mg/kg group. Diphenhydramine hydrochloride caused no apparent adverse effects in dogs that received 10 mg/kg doses for 193 days; the compound given in two divided daily doses of 25-40 mg/kg caused occasional emesis. Mild congestion and scattered petechial hemorrhages of the intestinal mucosa were observed in dogs that received 40 mg/kg per day. When a single daily dose of 40 mg/kg was administered, the animals became irritable and developed slight incoordination. It was concluded that a single daily dose of 25-40 mg/kg diphenhydramine hydrochloride causes considerable neurogenic reaction.

Metabolism and Pharmacokinetics

Diphenhydramine hydrochloride is extensively metabolized in humans and in laboratory animals. Products of diphenhydramine metabolism which have been identified in urine include the unchanged drug, the primary and secondary amine analogs of diphenhydramine formed by *N*-demethylation, diphenhydramine-*N*-oxide, diphenylmethoxyacetic acid (DPMA) formed by oxidative deamination, benzhydrol, and conjugates of DPMA with glutamine in rhesus monkeys or with glycine in dogs (Drach and Howell, 1968; Drach et al., 1970; Chang et al., 1974). A postulated pathway for the biotransformation of diphenhydramine is shown in Figure 1. The relative amounts of these metabolites in 0- to 48-hour urine collections from male rhesus monkeys are 45%-50% glutamine conjugate of DPMA, 10%-20% DPMA, 7%-13% diphenhydramine-*N*-oxide, 2%-8% unchanged diphenhydramine, 5%-7% *N*-demethyldiphenhydramine, 3%-6% *N*,*N*-didemethyldiphenhydramine, and 1%-2% benzhydrol (Drach and Howell, 1968). A similar level of unchanged diphenhydramine (2%-4% of the administered oral dose) was excreted in the urine of human volunteers (Albert et al., 1975; Meredith et al., 1984).

N-Demethylation of diphenhydramine was initially demonstrated in in vitro studies where it was found that formaldehyde was formed by rat liver microsomes incubated with diphenhydramine (Roozemond et al., 1965). The rate of liver microsomal *N*-demethylation of diphenhydramine was greater in males than in females for six different strains of rats (Kato et al., 1970) and was stimulated in rats pretreated with methaqualone (Ali et al., 1980). Oxidative deamination of the side chain of diphenhydramine was suggested as the major route of metabolism of this drug in monkeys because DPMA and its glutamine conjugate accounted for nearly two-thirds of the urinary metabolites of diphenhydramine collected from monkeys dosed orally (Drach and Howell, 1968).

In rhesus monkeys given intravenous injections of [^{3}H]diphenhydramine hydrochloride, plasma levels of the parent compound declined rapidly (half-life of approximately 1 hour), whereas tritium concentrations rose over a period of 4 hours to levels fourfold greater than the 1-minute post-dose concentrations and then declined with a half-life of 10-12 hours (Drach et al., 1970). More than 90% of the radiolabeled material in the plasma 4 hours after dosing was identified as DPMA. It was suggested that diphenhydramine is rapidly removed from blood by various tissues and organs and then slowly returned to the plasma as DPMA. The accumulation and longer half-life of DPMA was attributed to extensive plasma protein binding by this metabolite. Similar plasma profiles were observed after oral administration of diphenhydramine hydrochloride, except that peak plasma levels of the parent compound occurred between 1 and 2 hours after dosing. Divergent plasma profiles (radioactivity versus parent compound) were also observed in the rabbit, mouse, dog, and guinea pig but not in the rat. In the latter species, plasma levels of radioactivity and parent compound declined simultaneously, and no free or conjugated DPMA was detected in the urine.

In metabolic disposition studies of diphenhydramine hydrochloride administered subcutaneously to rats or guinea pigs, the highest concentrations of parent compound were found in the lung, with progressively lower concentrations in the spleen, kidney, brain, liver, and muscle tissue (Glazko and Dill, 1949a). Concentrations of diphenhydramine in these organs and tissue were

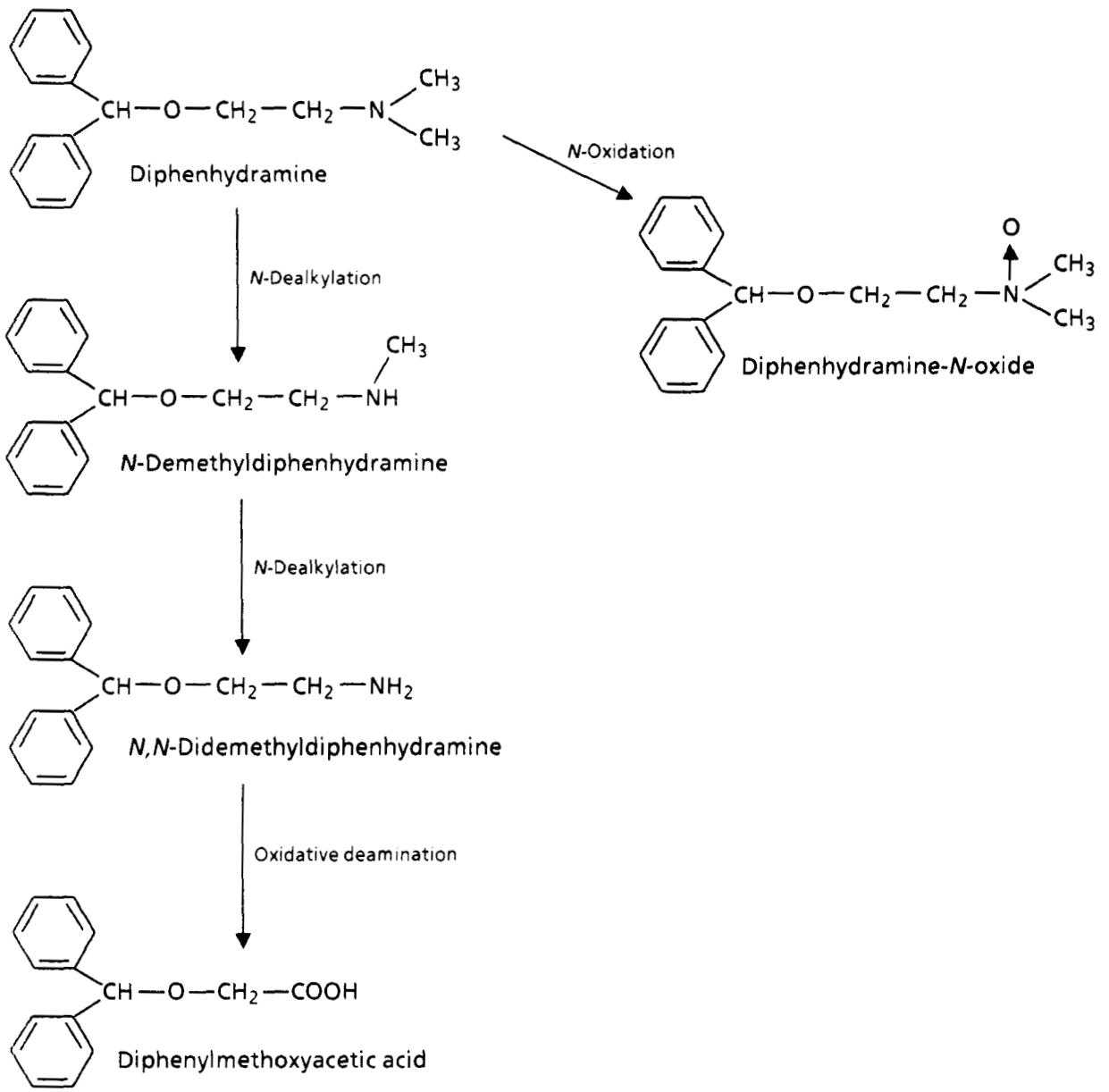

FIGURE 1. POSTULATED PATHWAY OF DIPHENHYDRAMINE METABOLISM

greater than that in the plasma. Peak tissue concentrations occurred about 1-2 hours after dosing. The liver was the site of greatest metabolic activity for diphenhydramine in rats, guinea pigs, and rabbits (Glazko and Dill, 1949b). A large first-pass effect (approximately 50% metabolism by the liver) was reported in volunteers given oral doses of diphenhydramine hydrochloride (Albert et al., 1975). In a case report of a person fatally intoxicated with diphenhydramine, concentrations of this drug were 4-10 times higher in the lung, kidney, liver, pancreas, spleen, and brain than in the plasma (5 µg/ml) (Hausmann et al., 1983). Diphenhydramine has been shown to be transported between the blood and central nervous system of New Zealand white rabbits and Sprague Dawley rats by carrier-mediated transport processes (Goldberg et al., 1987).

Pharmacokinetic parameters of diphenhydramine hydrochloride in volunteers are shown in Table 2. Peak levels of about 50-80 ng diphenhydramine/ml plasma are reached about 2-3 hours after a single 50-mg oral dose. Plasma levels of 25 ng/ml produce an antihistaminic effect, whereas sedative effects have been observed at plasma levels of 50 ng/ml and above (Carruthers et al., 1978). In cases of diphenhydramine poisoning in humans, plasma levels of the unchanged drug ranged from 0.1 to 4.7 µg/ml; this wide range probably reflects differences in ingested dose and time between ingestion and blood sampling (Koppel et al., 1987).

The systemic availability of orally administered diphenhydramine was reported to be only about 40%-70%, presumably due to first-pass hepatic metabolism (Albert et al., 1975) or incomplete absorption of the drug (Carruthers et al., 1978). Plasma half-life values for diphenhydramine in humans were reported to vary from about 3 to 9 hours (Table 2). The plasma half-life of diphenhydramine was increased by about 60% in patients with impaired liver function (e.g., cirrhotic patients) compared with that in healthy subjects (Meredith et al., 1984). Alcohol ingestion did not appear to directly affect the disposition of diphenhydramine in humans (Calvert and Parry, 1986). The plasma half-life of diphenhydramine is longer in humans than in most laboratory animal species. In monkeys, dogs, guinea pigs, and rats, the plasma half-life was 1 hour; in rabbits, it was 0.3 hours; and in mice, it was 0.1 hours (Drach et al., 1970). Parry and Calvert (1982) reported a plasma half-life of

TABLE 2. PHARMACOKINETIC PARAMETERS (MEAN VALUES) FOR DIPHENHYDRAMINE HYDROCHLORIDE IN HUMANS

Reference	t_{max} (hours)	Peak Plasma Concentration (ng/ml)	Systemic Availability (percent)	Plasma $t_{1/2}$ (hours)	Clearance (ml/min/kg)	Volume of Distribution (liters/kg)
Glazko et al., 1974	2-4	(a) 121		6.8		
Albert et al., 1975	2	(b) 67	50	5.6		
Carruthers et al., 1978	2.5	(b) 58	43	3.3	11.2	3.3
Spector et al., 1980						
Orientals	2	(c) 53	58	4.3	18.8	6.9
Caucasians	2-3	(c) 83	61	4.1	12.1	4.2
Meredith et al., 1984						
Healthy subjects				9.3	9.8	6.5
Cirrhotic patients				15.2	7.8	8.5
Blyden et al., 1986	2.3	(b) 66	72	8.4	6.2	4.5
Calvert and Parry, 1986			60	8.5	8.6	6.0

(a) Peak plasma concentration of unchanged drug is given for a single 100-mg oral dose.
(b) Peak plasma concentrations of unchanged drug are given for a single 50-mg oral dose.
(c) Peak plasma concentrations of unchanged drug are given for a single oral dose of 50 mg/70 kg body weight.

1.6 hours for diphenhydramine in rabbits. Spector et al. (1980) noted increased plasma clearance and volume of distribution of diphenhydramine in Orientals compared with those in Caucasians and suggested that the difference was a result of lower plasma protein binding of diphenhydramine in Orientals and possibly also of increased tissue *N*-demethylase activity.

Plasma concentrations of diphenhydramine were determined in F344 rats fed diets containing 313 or 625 ppm diphenhydramine hydrochloride for up to 30 days (Appendix H). A plasma concentration of 3.3 ng/ml was determined in blood samples taken at 2:00 a.m. from rats that received 625 ppm diphenhydramine hydrochloride for 30 days. Diphenhydramine was not detected in blood samples taken at 9:00 a.m. from animals receiving 625 ppm or at any time in plasma of rats that received 313 ppm diphenhydramine hydrochloride. The concentrations of diphenhydramine in rat plasma were more than an order of magnitude lower than the peak plasma concentrations measured in volunteers who received a single oral dose of 50 mg diphenhydramine hydrochloride (Table 2).

Developmental Toxicity

Yoo et al. (1986) demonstrated that maternal-fetal transfer of diphenhydramine in pregnant sheep is rapid and extensive. Peak fetal plasma concentrations of diphenhydramine were observed within 5 minutes after intravenous injections to pregnant sheep, and the fetal to maternal ratio of the areas under the plasma concentration versus time curves averaged 0.85.

Saxen (1974) reported that the percentage of mothers whose children had a cleft palate was significantly increased in women who had taken diphenhydramine hydrochloride more frequently during the first trimester of pregnancy.

Diphenhydramine hydrochloride was given in drinking water to Swiss-Webster mice throughout pregnancy and lactation at doses of about 20, 100, and 200 mg/kg per day (Naranjo and de Naranjo, 1968). The dose solutions were also made available to the offspring through 40 days of age. These doses of diphenhydramine hydrochloride did not cause maternal toxicity or teratogenicity; however, there was evidence of embryo- and fetotoxicity, as shown by the increased incidence of premature parturitions, reduced litter size and fetal weight, altered fetal sex ratios, and increased prenatal mortality in the dosed groups. Dose-related depression of weight gain, increased mortality, and retarded physical development were observed in pups dosed through 40 days of age, indicating that diphenhydramine hydrochloride is more toxic to the embryo, fetus, and newborn than to the adult animal.

Fraile et al. (1977) administered single intraperitoneal injections of diphenhydramine (5, 12, 25, or 50 mg/kg) to pregnant rats on gestational days 5, 7, 10, or 13, as well as multiple intraperitoneal injections of 12 mg/kg on gestational days 4-7, 7-10, 10-13, or 13-16. The highest incidence of malformations occurred after administration of a single 12 mg/kg dose on gestational day 10; the malformations included cleft palate, cryptorchid testes, hydronephrosis, and deficient cranial ossification.

Teratologic evaluations of diphenhydramine hydrochloride in timed-pregnant CD® rats and CD®-1 mice were performed for the National Toxicology Program (NTP) (NTP, unpublished results). In the rat study, diphenhydramine hydrochloride was administered by gavage in distilled water at doses of 0, 25, 50, or 100 mg/kg per day on gestational days 6 through 15. Maternal body weight gain was lower in the high dose group than in the vehicle controls; however, there was no significant difference among dose groups for gravid uterine weight or for the number of implantation sites per dam, the number or percentage of resorptions, or the number of live fetuses per litter. The average fetal body weight per litter in the high dose groups was lower than that in the vehicle controls. There was no clear evidence of teratogenicity in CD® rats, even in the highest dose group in which signs of maternal and fetal toxicity were evident.

Two separate developmental toxicology studies were performed in CD®-1 mice (NTP, unpublished results). In the first study, diphenhydramine hydrochloride was administered by gavage in distilled water at doses of 0, 40, 80, or 160 mg/kg per day on days 6 through 15 of gestation.

Absolute maternal weight gain during gestation and average fetal body weight per litter were decreased in the high dose group compared with those in vehicle controls. The incidences of resorptions and of dead and malformed fetuses were not increased in dosed groups; however, a dose-related trend toward an increased incidence of cleft palate was observed (vehicle control, 0/273; low dose, 0/285; mid dose, 4/281; high dose, 4/204). In a subsequent study, diphenhydramine hydrochloride was administered by gavage at doses of 0, 80, 160, or 200 mg/kg per day on gestational days 11 through 14 (the period of palate formation). The absolute maternal body weight gain during gestation was reduced only for dams dosed with 160 mg/kg per day, and the average fetal body weight per litter in all dose groups was lower than that in vehicle controls. A dose-related trend toward an increased incidence of cleft palate was again observed; however, the incidence in any of the dose groups was not significantly greater than that in the vehicle control group. Thus, diphenhydramine hydrochloride appears to be teratogenic for CD®-1 mice when administered at doses that produce overt signs of fetal and maternal toxicity.

Carcinogenicity

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). Hepatocellular carcinomas and cholangiocarcinomas developed in nearly all male and female F344 rats administered 1,000 ppm methapyrilene in feed with or without 2,000 ppm sodium nitrite for 64 weeks (Lijinsky et al., 1980). In a subsequent study, administration of diets containing 250 ppm methapyrilene hydrochloride resulted in increased incidences of hepatocellular carcinomas or neoplastic nodules of the liver in male and female F344 rats (Lijinsky, 1984a). Incorporation of 2,000 ppm pyrilamine maleate (another antihistaminic drug) into the diet produced an increase in the incidence of liver neoplasms in F344 female rats but not in male rats.

Administration of 2,000 ppm diphenhydramine hydrochloride or 1,000 ppm chlorpheniramine maleate to groups of 24 male or 24 female F344 rats for 106 weeks did not produce any significant increase in tumor incidence in comparison with untreated control groups (Lijinsky, 1984b); however, simultaneous feeding of either of these antihistaminic drugs with 2,000 ppm sodium nitrite resulted in a significant increase in the incidence of liver neoplasms in male rats in comparison with nitrite-dosed control animals. Thus, in vivo nitrosation of diphenhydramine or chlorpheniramine may produce carcinogenic compounds.

There was no evidence of carcinogenicity for chlorpheniramine maleate administered by gavage in deionized water to F344/N rats or $B6C3F_1$ mice 5 days per week for 2 years (NTP, 1986). The doses of chlorpheniramine maleate used in those studies were 15 or 30 mg/kg for male rats, 30 or 60 mg/kg for female rats, 25 or 50 mg/kg for male mice, and 100 or 200 mg/kg for female mice. Other antihistaminic drugs under study by the NTP for carcinogenicity include doxylamine, pyrilamine, tripelennamine, and triprolidine.

Genetic Toxicology

Diphenhydramine hydrochloride has been tested for mutagenicity in a variety of bacterial and animal systems, and with one exception the results have been uniformally negative. Diphenhydramine hydrochloride was not mutagenic to *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1536, TA1537, or TA1538 when tested with or without exogenous metabolic activation (Minnich et al., 1976; Andrews et al., 1984). Negative results were also obtained by the NTP in reverse mutation assays in *S. typhimurium* strains TA98, TA100, TA1535, or TA1537 preincubated in the presence or absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Zeiger et al., 1987; Table 22). Nitrosation of diphenhydramine (reaction with nitrite in acetic acid) yielded products that were mutagenic to strain TA98 with or without liver S9 (Andrews et al., 1984).

Sex-linked recessive lethal mutations were not observed in adult male *Drosophila melanogaster* exposed for 7 days to nutrient media supplemented with two drops of a pharmaceutical

preparation (purity unspecified) of diphenhydramine hydrochloride (Rapoport et al., 1971). Unscheduled DNA synthesis was not induced in primary cultures of Fischer rat hepatocytes treated with diphenhydramine hydrochloride at concentrations up to 1,000 nmol/ml (Probst et al., 1981).

When tested by the NTP in an in vitro cytogenetic assay with Chinese hamster ovary cells, diphenhydramine hydrochloride did not induce sister chromatid exchanges (SCEs) in either the presence or absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Loveday et al., 1989; Table 24). Diphenhydramine (free base) was also tested for mutagenicity in *Escherichia coli* and *S. typhimurium* (Cline and McMahon, 1977) and for induction of SCEs in cultured human lymphocytes (Debova, 1981); results of these three tests were negative.

Two laboratories reported that diphenhydramine hydrochloride did not induce chromosomal aberrations in cultured human lymphocytes or fibroblasts exposed at maximum concentrations of 50 or 100 µg/ml for 24 hours (one-cell cycle) in the absence of exogenous metabolic activation (Meisner and Inhorn, 1972; Zhurkov, 1975). However, when tested by the NTP in the absence of S9, diphenhydramine hydrochloride produced increases in the frequency of chromosomal aberrations at doses of 100 µg/ml and above when culture times were extended 6-10 hours to compensate for chemical-induced cell-cycle delay; no increases in the frequency of chromosomal aberrations were observed in the presence of S9 (Loveday et al., 1989; Table 25).

Human Effects

In the preliminary screening for carcinogenicity of commonly used medicinal drugs, no positive associations were found for diphenhydramine hydrochloride and cancers at any of 56 primary cancer sites in 10,131 users, and in the 2-year followup, no positive associations were found in 425 users (Friedman and Ury, 1980, 1983). In these studies, drug dispensing records at the San Francisco offices of the Kaiser-Permanente Medical Care Program were used to identify outpatients who had at least one recorded prescription between 1969 and 1978. Cancer occurrence was detected primarily from hospital records that usually included a histologic examination of tissue. The authors recognized shortcomings in these studies, including inadequate duration of followup for cancer with long latency periods and confounding variables that may have concealed associations.

Study Rationale

Diphenhydramine hydrochloride was selected for toxicology and carcinogenicity studies because of its widespread human use as an antihistamine and because there were insufficient carcinogenicity data on this drug. The feed route of administration was selected because human exposure is usually via the oral route.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF DIPHENHYDRAMINE HYDROCHLORIDE

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

GENETIC TOXICOLOGY

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF DIPHENHYDRAMINE HYDROCHLORIDE

Diphenhydramine hydrochloride was obtained in one lot (lot no. 258-YY-151), labeled USP grade XIX with a manufacturer's certificate of analysis indicating 99.47% purity, from Ganes Chemicals, Inc. (New York, NY). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on analyses performed in support of the studies on diphenhydramine hydrochloride are on file at the National Institute of Environmental Health Sciences.

The study chemical was received in two fiberboard drums. The contents of the two drums were combined, blended, and sampled. The study chemical was identified as diphenhydramine hydrochloride by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra (Figures 2 and 3) were consistent with those expected for the structure and with the literature spectra (Sadtler Standard Spectra).

The purity of lot no. 258-YY-151 was determined by elemental analysis, weight loss on drying to determine water content, potentiometric titration of the amine group in glacial acetic acid: 0.2 M mercuric acetate TS (25:3) with 0.1 N perchloric acid, thin-layer chromatography, and high-performance liquid chromatography. Thin-layer chromatography was performed on silica gel plates with cyclohexane:ethyl acetate:methanol:*p*-dioxane:ammonium hydroxide (50:30:10:10:1) (system 1) or with *n*-butanol:toluene:*p*-dioxane:ammonium hydroxide (70:20:10:1) (system 2). Visualization was with visible light and ultraviolet light (254 and 366 nm) and with an iodoplatinate spray reagent. High-performance liquid chromatography was performed with an isocratic program on a Varian MCH10 C_{18} column with a solvent system of 19% aqueous and 81% methanolic 9 mM trimethylamine (containing 0.03%, v/v, phosphoric acid).

Cumulative data indicated a purity of greater than 99% for the study material. The results of elemental analysis for hydrogen, nitrogen, and chlorine were in agreement with the theoretical values, whereas results for carbon were slightly high. Weight loss on drying indicated 0.031% water (USP specification: not more than 0.5%). Nonaqueous titration of the amine group with perchloric acid indicated a purity of 100.0% (USP specification: not less than 98% or more than 100.5%). Thin-layer chromatography indicated a trace impurity by system 1 and two trace impurities by system 2. High-performance liquid chromatography resolved two impurities before the major peak with a combined area of 0.38% relative to that of the major peak. This lot of diphenhydramine hydrochloride met the specifications of all analyses required in the twentieth revision of the United States Pharmacopeia (USP, 1979).

Stability studies performed by high-performance liquid chromatography with the same program as described previously, but with a solvent ratio of 10:90, indicated that diphenhydramine hydrochloride was stable in the dark for 2 weeks at temperatures up to 60° C. The bulk chemical was stored at room temperature at the study laboratory. The stability of the bulk study material during the studies was monitored four times per year at the study laboratory by comparing the analyses of the bulk chemical with those of a frozen reference standard. Analysis by infrared spectroscopy, ultraviolet spectroscopy, and nonaqueous titrations indicated that no notable degradation occurred during the studies. Therefore, it is concluded that the diphenhydramine hydrochloride study material remained stable during the studies.

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

Formulated diets were prepared by adding a dry premix of feed and diphenhydramine hydrochloride to the appropriate amount of feed and blending for 15 minutes (Table 3). A study to determine the homogeneity of a formulated diet mixture indicated an approximately 1.5% deviation from the target concentration of samples taken from three locations in the blender. The stability of diphenhydramine hydrochloride in

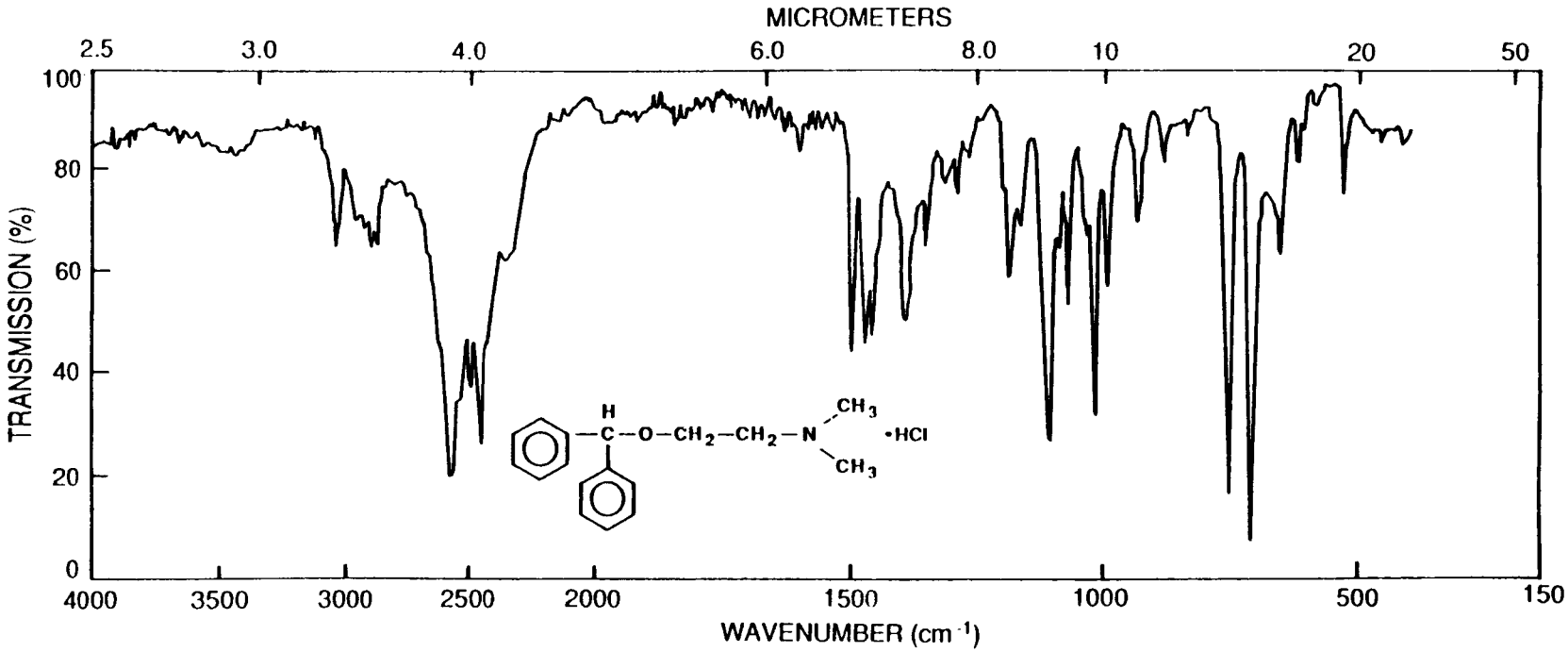

FIGURE 2. INFRARED ABSORPTION SPECTRUM OF DIPHENHYDRAMINE HYDROCHLORIDE (LOT NO. 285-YY-151)

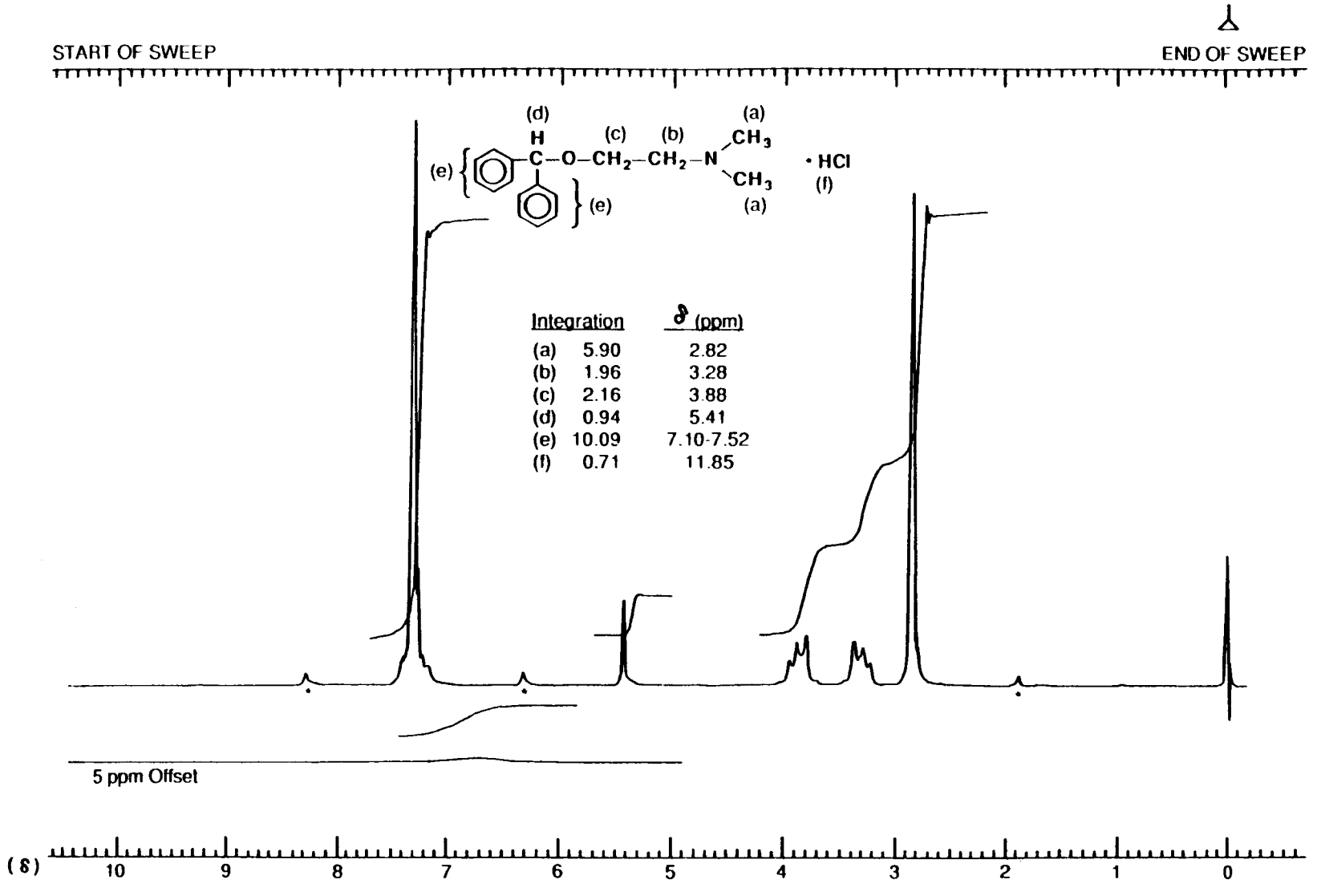

FIGURE 3. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DIPHENHYDRAMINE HYDROCHLORIDE (LOT NO. 285-YY-151)

TABLE 3. PREPARATION AND STORAGE OF FORMULATED DIETS IN THE FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
A premix, consisting of total amount of chemical and one-third of the feed, was mixed with remaining feed in an 8-qt twin-shell V-blender for 15 min	Same as 14-d studies except 8- or 16-qt blender used	Same as 13-wk studies
Maximum Storage Time		
1 wk	2 wk	24 d
Storage Conditions		
4° C in the dark	5° C in the dark	5° C in the dark

feed (concentration of 1,000 ppm) was determined by gas chromatography with flame ionization detection and a 3% SP2100 DB column with docosane in chloroform (0.27 mg/ml) as an internal standard after extraction of the formulated diet sample with acetonitrile:acetic acid (99:1). Diphenhydramine hydrochloride in feed was found to be stable at concentrations of 1,000 ppm when stored in the dark for 2 weeks at temperatures up to 25° C. A second stability study was conducted on feed blends containing 150 ppm diphenhydramine hydrochloride. Analysis was performed by gas chromatography with flame ionization detection on a 10% SP2100 column, with anthracene in acetone (40 µg/ml) as an internal standard (after extraction of the formulated diet samples with methanol:deionized water:concentrated hydrochloric acid [85:14:1]). Diphenhydramine hydrochloride in feed was found to be stable at concentrations of 150 ppm when stored in the dark for 24 days at 5° C. In the 13-week studies, the formulated diets were stored at 5° C no longer than 2 weeks. In the 2-year studies, the formulated diets were stored at 5° C no longer than 24 days.

Periodic analysis for diphenhydramine hydrochloride in formulated diets was conducted at the study laboratory and the analytical chemistry laboratory by extraction of the formulated diet mixture by the same methods as described above and with the same gas chromatographic system but with anthracene in acetonitrile as the internal standard. Formulated diets were analyzed, and the homogeneity of the highest and lowest dose formulated diet mixtures was determined once before the start of the 13-week studies (Table 4). There was an apparent problem with achieving a homogeneous blend of the lowest concentration mixture (78 ppm) during the 13-week studies. This problem was not observed with the other concentrations used during the 13-week or 2-year studies.

During the 2-year studies, the formulated diets were analyzed at approximately 8-week intervals. Beginning on December 16, 1982, every eighth blend was analyzed. For the diphenhydramine hydrochloride studies, the mixtures were formulated within ±10% of the target concentrations approximately 98% (43/44) of the time throughout the 2-year studies (Table 5). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results from the study laboratory (Table 6).

TABLE 4. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE THIRTEEN-WEEK FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Date Mixed	Concentration of Diphenhydramine Hydrochloride in Feed (ppm) Target	Determined	Determined as a Percent of Target
02/25/80	(a) 78	81.1	104
	(b) 78	72.9	94
	(c) 78	67.6	(d) 86
	(a) 2,500	2,459	99
	(b) 2,500	2,582	103
	(c) 2,500	2,579	103
03/05/80	78	76	94
	156	142	91
	313	317	101
	625	670	107
	1,250	1,340	107
	2,500	2,724	109

(a) Sampled from top left of blender
(b) Sampled from top right of blender
(c) Sampled from bottom of blender
(d) Out of specifications

TABLE 5. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Date Mixed	Concentration of Diphenhydramine Hydrochloride in Feed for Target Concentration (ppm) (a) 156	313	625
02/10/81	154	317	622
04/15/81	147	(b) 312	679
06/09/81	147	297	651
08/18/81	(c) 133	291	576
08/21/81	(d) 152		
10/13/81	162	345	661
12/08/81	154	290	650
01/13/82		325	606
			592
02/02/82	146	284	587
04/13/82	152	312	633
06/22/82	147	319	618
08/17/82	166	334	642
10/11/82	156	313	651
12/06/82	158	313	614
01/17/83	147	307	660
02/28/83	(e) 154	304	
Mean (ppm)	152	311	629
Standard deviation	8.1	16.5	30.4
Coefficient of variation (percent)	5.3	5.3	4.8
Range (ppm)	133-166	284-345	576-679
Number of samples	14	15	15

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

TABLE 6. RESULTS OF REFEREE ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory (a)	Referee Laboratory (b)
02/10/81	156	154	156.7
08/18/81	625	576	617
02/02/82	313	284	309
08/17/82	156	166	161
02/28/83	313	304	320

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

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 12 days before the studies began. The animals were 6-8 weeks old when placed on study. Groups of five rats of each sex were fed diets containing 0, 620, 1,250, 2,500, 5,000, or 10,000 ppm diphenhydramine hydrochloride for 14 consecutive days. Groups of five mice of each sex were fed diets containing 0, 310, 620, 1,250, 2,500, or 5,000 ppm according to the same schedule. The rats and mice were observed twice per day and weighed on days 0, 7, and 14. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 7.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to diphenhydramine hydrochloride and to determine the concentrations to be used in the 2-year studies.

Four- to five-week-old male and female F344/N rats and 5- to 6-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 2 weeks, distributed to weight classes, and then assigned to cages according to a table of random numbers. Cages were assigned to dosed and control groups according to another table of random numbers.

Groups of 10 rats of each sex were given diets containing 0, 156, 313, 625, 1,250, or 2,500 ppm diphenhydramine hydrochloride for 13 weeks. Groups of 10 mice of each sex were given diets containing 0, 78, 156, 313, 625, or 1,250 ppm according to the same schedule. Control diets consisted of NIH 07 Rat and Mouse Ration. Formulated or control diets and water were available ad libitum.

Animals were observed two times per day; moribund animals were killed. Feed consumption was measured once per week by cage. Individual animal weights were recorded once per week. Further experimental details are summarized in Table 7.

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 7.

TWO-YEAR STUDIES

Study Design

Diets containing 0, 313, or 625 ppm diphenhydramine hydrochloride were fed to groups of 50 male rats for 103 weeks. Diets containing 0, 156, or 313 ppm were fed to groups of 50 female rats and 48 or 50 male and 50 female mice for 103 (female rats and female mice) or 105 (male mice) weeks.

TABLE 7. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	48 or 50 males and 50 females of each species
Doses		
Rats--0, 620, 1,250, 2,500, 5,000, or 10,000 ppm diphenhydramine hydrochloride in feed; mice--0, 310, 620, 1,250, 2,500, or 5,000 ppm	Rats--0, 156, 313, 625, 1,250, or 2,500 ppm diphenhydramine hydrochloride in feed; mice--0, 78, 156, 313, 625, or 1,250 ppm	Rats--male: 0, 313, or 625 ppm diphenhydramine hydrochloride in feed; female: 0, 156, or 313 ppm; mice--0, 156, or 313 ppm
Date of First Dose		
9/26/79	Rats--3/12/80; mice--3/11/80	Rats--2/19/81; mice--male: 2/23/81; female: 4/20/81
Date of Last Dose		
10/9/79	Rats--6/11/80; mice--6/10/80	Rats--2/15/83; mice--male: 2/28/83; female: 4/14/83
Duration of Dosing		
14 consecutive d	13 wk	Rats and female mice: 103 wk; male mice: 105 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially and 1 × wk thereafter; feed consumption measured 1 × wk	Same as 14-d studies	Observed 2 × d; weighed 1 × wk for 12 wk and then 1 × mo; feed consumption measured 1 wk per mo
Necropsy and Histologic Examinations		
Necropsy performed on all animals; histologic exams performed on mice in the control and 1,250-ppm groups; tissues examined include adrenal glands, kidneys, liver, lungs, and pancreas	Necropsy performed on all animals; histologic exams performed on male mice in the 625-ppm group, mice dying before the end of the studies, all controls, and all high dose animals; tissues examined include: adrenal glands, bone marrow, brain, colon, duodenum, esophagus, gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, heart, ileum, jejunum, kidneys, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, pancreas, parathyroids, pituitary gland, prostate/seminal vesicles/testes or ovaries/uterus, rectum, salivary glands, skin, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Liver examined from all other dosed groups	Necropsy and histologic exams performed on all animals; the following tissues were examined: adrenal glands, brain, cecum, colon, duodenum, epididymis/prostate/testes or ovaries/uterus, esophagus, eyes (if grossly abnormal), femur or sternebrae or vertebrae including marrow, gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, heart, ileum, jejunum, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular or mesenteric lymph nodes, nasal cavity and turbinates, pancreas, parathyroids, pituitary gland, preputial or clitoral gland, rectum, salivary glands, skin, spinal cord (if neurologic signs present), spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder; cecum, epididymis, nasal cavity, rectum, and small intestine examined for all animals only after mo 15
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source		
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory		
SRI International	SRI International	SRI International

TABLE 7. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Method of Animal Identification		
Ear clip	Ear clip	Ear punch
Time Held Before Study		
12 d	14 d	2 wk
Age When Placed on Study		
Rats--6-7 wk; mice--6-8 wk	Rats--6-7 wk; mice--7-8 wk	Rats--6-7 wk; mice--7-8 wk
Age When Killed		
Rats--8-9 wk; mice--8-10 wk	Rats--19-20 wk; mice--20-21 wk	Rats--110-113; mice--male: 113-114 wk; female: 111-113 wk
Necropsy Dates		
10/11/79	Rats--6/12/80-6/13/80; mice--6/11/80-6/12/80	Rats--2/18/83-3/3/83; mice--male: 3/4/83-3/10/83; female: 4/19/83-4/25/83
Method of Animal Distribution		
Animals distributed to weight classes and then assigned to cages and groups by a table of random numbers	Same as 14-d studies	Same as 14-d studies
Feed		
Purina Rodent Lab Chow® #5001 (Ralston Purina, St. Louis, MO)	NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding		
Hardwood chips (Pressed Wood, Inc.)	AbSorb Dri® (Lab Products, Inc., Maywood, NY)	Same as 13-wk studies
Water		
Automatic watering system (SRI); deionized, filtered, ultraviolet-sterilized water; available ad libitum	Same as 14-d studies	Same as 14-d studies
Cages		
Drawer-type polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as 14-d studies	Same as 14-d studies
Cage Filters		
Nonwoven polyester fiber (Lab Products, Inc., Maywood, NY, or Research Equipment Co., Bryan, TX)	Nonwoven polyester fiber (Lab Products, Inc., Maywood, NY)	Same as 13-wk studies
Animals per Cage		
5	5	5
Other Chemicals on Study in the Same Room		
None	None	None
Animal Room Environment		
Temp--72°-76° F; hum--50%-65%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--71°-76° F; hum--46%-73%; fluorescent light 12 h/d; 13 room air changes/h	Temp--64°-81° F; hum--17%-87%; fluorescent light 12 h/d; 13.5 room air changes/h

II. MATERIALS AND METHODS

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice at 5-6 weeks of age. The animals were quarantined at the study facility for 2 weeks. 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 6-7 weeks of age and the mice at 7-8 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix E).

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

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

Male mice from the C3H colony and female mice from the C57BL/6N colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but the interpretation of the results of the studies is not affected because all potential effects in the dosed groups were compared with those in the concurrent controls.

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 7.

Clinical Examinations and Pathology

All animals were observed two times per day. Body weights were recorded once per week for the first 12 weeks 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 missexed. Some tissues were excessively autolyzed or cannibalized, and 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 7.

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

organs, the randomly selected 10% of animals, and in tissues with unusual incidence patterns or trends. Tissues are generally not evaluated in a "blinded" fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle.

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

Statistical Methods

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

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin 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: The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was an incidental tumor analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, the proportions of tumor-bearing animals in dosed and control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined to obtain a single overall result.

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

Tests of significance include pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are

one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

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

GENETIC TOXICOLOGY

Salmonella Protocol: Testing was performed as reported by Haworth et al. (1983) with modifications listed below and described in greater detail by Zeiger et al. (1987) and Mortelmans et al. (1986). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

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

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate. All negative assays were repeated, and all positive assays were repeated under the conditions that elicited the positive response.

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

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 5 mg/ml. Mouse lymphoma L5178Y cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

All doses within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 ml of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with the study chemical continued for 4 hours, after which time the medium plus chemical was removed and the cells were resuspended in 20 ml of fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with Tft for selection of Tft-resistant

cells ($TK^{+/+}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C under 5% carbon dioxide for 10-12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P < 0.05$) for a chemical to be considered capable of inducing Tft resistance; a single significant response led to an "equivocal" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

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

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985, 1987) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

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

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; colcemid was added, and incubation was continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the chromosomal aberration test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

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

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

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference

occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.003$) trend test or a significantly increased dose point ($P<0.05$) was sufficient to indicate a chemical effect.

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

III. RESULTS: RATS

FOURTEEN-DAY STUDIES

All 10 rats that received 10,000 ppm and 9/10 rats that received 5,000 ppm died before the end of the studies (Table 8). The final mean body weights of rats that received 1,250 or 2,500 ppm were 12% or 34% lower than that of controls for males and 13% or 30% lower for females. Female rats that received 2,500 or 5,000 ppm lost weight. Feed consumption at the three highest doses was more than 30% less than that by the controls. All dosed animals were hyperactive and sensitive to sound and/or touch starting after 5-7 days. The rats were not examined histopathologically.

TABLE 8. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 1	Week 2
MALE							
0	5/5	128 ± 2	192 ± 2	+64 ± 3		14	16
620	5/5	121 ± 2	191 ± 5	+70 ± 3	99	14	15
1,250	5/5	121 ± 2	168 ± 2	+47 ± 2	88	12	16
2,500	5/5	121 ± 2	126 ± 2	+5 ± 1	66	7	11
5,000	(e) 0/5	116 ± 2	(f)	(f)	(f)	4	6
10,000	(g) 0/5	120 ± 2	(f)	(f)	(f)	2	3
FEMALE							
0	5/5	104 ± 2	138 ± 3	+34 ± 2		10	11
620	5/5	112 ± 4	137 ± 2	+25 ± 3	99	11	11
1,250	5/5	107 ± 1	120 ± 1	+13 ± 2	87	8	9
2,500	5/5	136 ± 2	96 ± 2	−40 ± 1	70	5	7
5,000	(h) 1/5	88 ± 3	67	−20	49	3	7
10,000	(i) 0/5	112 ± 4	(f)	(f)	(f)	1	(f)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.
(e) Day of death: 5,6,6,12,13
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: 4,5,5,6,8
(h) Day of death: 4,5,6,6
(i) Day of death: 5,5,6,7,8

THIRTEEN-WEEK STUDIES

All rats lived to the end of the studies (Table 9). The final mean body weights of rats that received 1,250 or 2,500 ppm were 12% or 37% lower than that of controls for males and 17% or 32% lower for females. The final mean body weight of female rats that received 625 ppm was 9% lower than that of controls. Increased activity was observed for all male and female rats that received 1,250 and 2,500 ppm. Moderate aggression, rough coats, and humped backs were observed for all rats that received 2,500 ppm. Cytoplasmic vacuolization of the liver, characteristic of fat accumulation, was observed in 10/10 males and 5/10 females that received 2,500 ppm and in all rats that received 1,250, 625, and 313 ppm. The severity of this change increased with increased dose.

Dose Selection Rationale: Because of lower weight gain for males at 1,250 ppm or higher and for females at 625 ppm or higher, dietary concentrations of diphenhydramine hydrochloride selected for rats for the 2-year studies were 313 and 625 ppm for males and 156 and 313 ppm for females.

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of dosed and control male rats were comparable throughout the study (Table 10 and Figure 4). Mean body weights of high dose female rats were generally 3%-5% lower than those of the controls throughout the study. The average daily feed consumption per rat was 2%-4% lower for each dosed group than for their controls (Tables F1 and F2). The average amount of diphenhydramine hydrochloride consumed per day was approximately 13 or 27 mg/kg for low dose or high dose male rats and 7 or 15 mg/kg for low dose or high dose female rats. No compound-related clinical signs were observed.

TABLE 9. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 7	Week 13
MALE							
0	10/10	131 ± 1	329 ± 4	+198 ± 4		18	16
156	10/10	128 ± 3	333 ± 4	+205 ± 3	101	19	16
313	10/10	135 ± 2	330 ± 3	+195 ± 2	100	18	16
625	10/10	132 ± 2	323 ± 2	+191 ± 2	98	19	16
1,250	10/10	130 ± 2	291 ± 3	+161 ± 2	88	17	15
2,500	10/10	132 ± 2	208 ± 5	+76 ± 4	63	13	22
FEMALE							
0	10/10	102 ± 1	193 ± 3	+91 ± 2		13	10
156	10/10	105 ± 2	193 ± 3	+88 ± 2	100	12	12
313	10/10	99 ± 2	182 ± 3	+83 ± 1	94	12	11
625	10/10	103 ± 1	175 ± 1	+72 ± 1	91	12	11
1,250	10/10	102 ± 1	161 ± 1	+59 ± 2	83	13	10
2,500	10/10	98 ± 3	131 ± 3	+33 ± 2	68	9	14

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Weeks on Study	Control Av. Wt. (grams)	Control No. of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of controls)	Low Dose No. of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of controls)	High Dose No. of Survivors
MALE				**313 ppm**			**625 ppm**	
0	130	50	126	97	50	126	97	50
1	162	50	161	99	50	159	98	50
2	200	50	199	100	50	196	98	50
3	226	50	231	102	50	225	100	50
4	248	50	249	100	50	241	97	50
5	279	50	274	98	50	272	97	50
6	294	50	290	99	50	287	98	50
7	309	50	305	99	50	301	97	50
8	322	50	318	99	50	314	98	50
9	330	50	328	99	50	323	98	50
10	340	50	336	99	50	330	97	50
11	351	50	347	99	50	341	97	50
12	359	50	354	99	50	347	97	50
17	389	50	385	99	50	379	97	50
21	410	50	408	100	50	402	98	50
25	429	50	423	99	50	418	97	50
31	439	50	439	100	50	434	99	50
35	456	50	454	100	50	449	98	50
39	465	49	462	99	50	459	99	50
43	474	49	472	100	50	469	99	50
48	481	49	478	99	50	472	98	50
51	486	49	485	100	50	481	99	50
55	486	49	487	100	50	479	99	50
59	490	49	493	101	50	486	99	50
63	496	49	490	99	50	487	98	50
69	491	48	493	100	48	485	99	49
74	484	48	491	101	47	485	100	46
79	478	47	483	101	47	478	100	44
83	477	46	483	101	47	476	100	42
86	475	45	485	102	44	479	101	41
90	471	40	480	102	43	469	100	38
94	468	39	479	102	40	460	98	37
99	458	36	462	101	34	469	102	27
103	440	31	454	103	32	446	101	24
FEMALE				**156 ppm**			**313 ppm**	
0	103	50	103	100	50	102	99	50
1	124	50	125	101	50	123	99	50
2	141	50	144	102	50	141	100	50
3	152	50	154	101	50	151	99	50
4	163	50	166	102	50	161	99	50
5	171	50	174	102	50	169	99	50
6	180	50	181	101	50	175	97	50
7	185	50	188	102	50	182	98	50
8	191	50	193	101	50	186	97	50
9	195	50	197	101	50	191	98	50
10	198	50	200	101	50	192	97	50
11	203	50	205	101	50	197	97	50
12	205	50	208	101	50	200	98	50
17	216	50	219	101	50	213	99	50
21	227	50	228	100	50	221	97	50
25	232	50	234	101	50	225	97	50
31	235	50	239	102	50	230	98	50
35	244	50	248	102	50	239	98	50
39	252	50	255	101	50	246	98	50
43	260	50	263	101	50	252	97	50
48	265	50	267	101	50	258	97	50
51	273	50	276	101	50	264	97	50
55	274	50	278	101	50	265	97	50
59	285	50	290	102	49	274	96	50
63	297	50	300	101	49	284	96	49
69	313	50	315	101	49	302	96	49
74	323	49	328	102	48	312	97	49
79	332	44	334	101	48	318	96	49
83	338	43	337	100	48	324	96	49
86	345	40	341	99	46	329	95	46
90	344	40	338	98	43	334	97	44
94	348	37	340	98	40	333	96	43
99	346	36	344	99	34	332	96	41
103	353	35	344	97	32	334	95	37

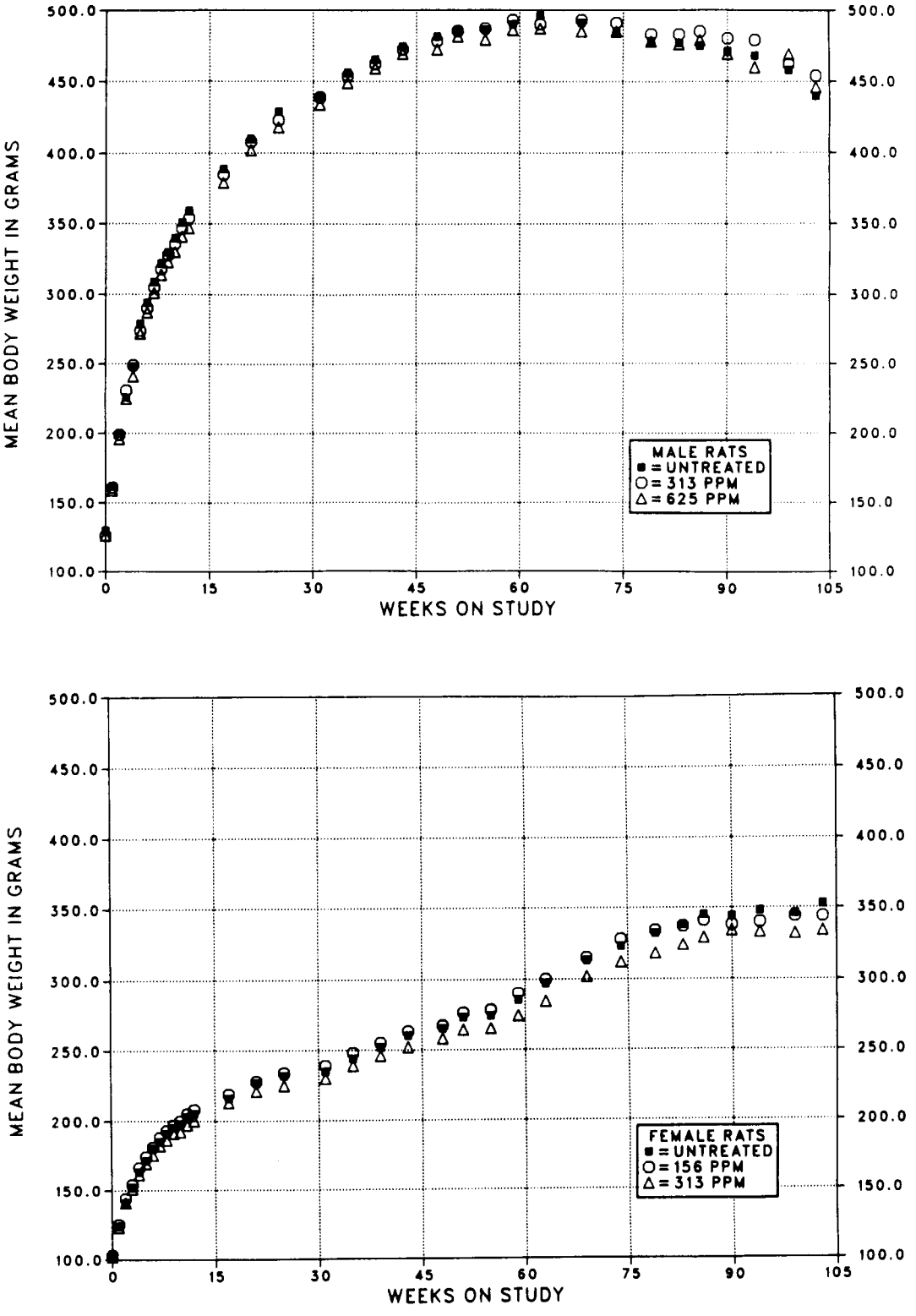

FIGURE 4. GROWTH CURVES FOR RATS FED DIETS CONTAINING DIPHENHYDRAMINE HYDROCHLORIDE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing diphenhydramine hydrochloride at the concentrations used in these studies and for controls are shown in Table 11 and in the Kaplan and Meier curves in Figure 5. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the brain, anterior pituitary gland, lung, and liver.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

TABLE 11. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

	Control	156 ppm	313 ppm	625 ppm
MALE (a)				
Animals initially in study	50		50	50
Natural deaths	7		0	4
Moribund kills	18		20	23
Animals surviving until study termination	(b) 29		(c) 32	(d) 24
Survival P values (e)	0.249		0.775	0.282
FEMALE (a)				
Animals initially in study	50	50	50	
Nnatural deaths	2	5	3	
Moribund kills	15	17	12	
Animals surviving until study termination	(c) 35	(b) 32	(d) 36	
Survival P values (e)	0.720	0.821	0.808	

(a) Termination period: weeks 104-106
(b) Four animals died or were killed in a moribund condition during the termination period and were combined, for statistical purposes, with those killed at termination.
(c) Two animals died or were killed in a moribund condition during the termination period and were combined, for statistical purposes, with those killed at termination.
(d) One animal died or was killed in a moribund condition during the termination period and was combined, for statistical purposes, with those killed at termination.
(e) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.

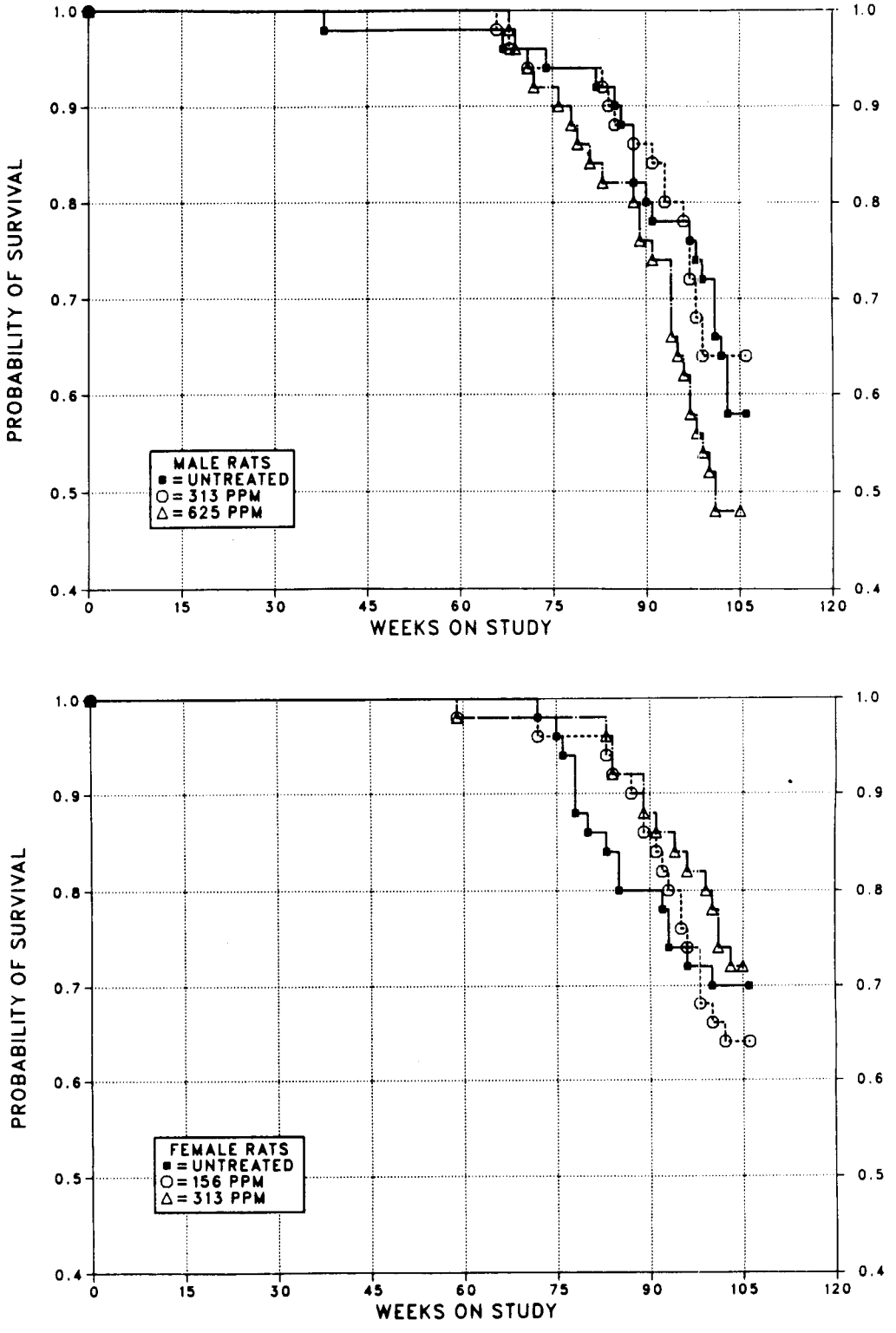

FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING DIPHENHYDRAMINE HYDROCHLORIDE FOR TWO YEARS

Brain: Astrocytomas were observed in three high dose male rats and none was observed in control male rats in the three brain sections prepared by routine sampling procedures (Table 12). These sections were taken at the levels of the frontal cortex and basal ganglia, parietal cortex and thalamus, and cerebellum and pons. Gliomas, consisting of both neoplastic astrocytes and oligodendrocytes, occurred in one control male and one high dose male rat. Although the incidence of astrocytomas or gliomas (combined) in high dose male rats was not significantly greater than that in controls, it exceeded the highest incidence observed in historical untreated controls (2/50). No glial cell tumors were observed in female rats.

TABLE 12. BRAIN TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (a)

	Control	313 ppm (b)	625 ppm (b)
Glioma (three sections)			
Overall Rates	1/49 (2%)	0/49 (0%)	1/50 (2%)
Astrocytoma (three sections)			
Overall Rates	0/49 (0%)	0/49 (0%)	3/50 (6%)
Adjusted Rates	0.0%	0.0%	10.2%
Terminal Rates	0/29 (0%)	0/31 (0%)	2/24 (8%)
Week of First Observation			68
Life Table Tests	P=0.030	(c)	P=0.103
Incidental Tumor Tests	P=0.048	(c)	P=0.152
Astrocytoma or Glioma (three sections) (d)			
Overall Rates	1/49 (2%)	0/49 (0%)	4/50 (8%)
Adjusted Rates	3.4%	0.0%	12.0%
Terminal Rates	1/29 (3%)	0/31 (0%)	2/24 (8%)
Week of First Observation	104		68
Life Table Tests	P=0.067	P=0.487N	P=0.152
Incidental Tumor Tests	P=0.127	P=0.487N	P=0.264
Glioma (six sections) (e)			
Overall Rates	1/49 (2%)	0/49 (0%)	1/50 (2%)
Astrocytoma (six sections) (e)			
Overall Rates	0/49 (0%)	0/49 (0%)	4/50 (8%)
Adjusted Rates	0.0%	0.0%	14.2%
Terminal Rates	0/29 (0%)	0/31 (0%)	3/24 (13%)
Week of First Observation			68
Life Table Tests	P=0.010	(c)	P=0.048
Incidental Tumor Tests	P=0.017	(c)	P=0.071
Astrocytoma or Glioma (six sections) (e)			
Overall Rates	1/49 (2%)	0/49 (0%)	5/50 (10%)
Adjusted Rates	3.4%	0.0%	16.0%
Terminal Rates	1/29 (3%)	0/31 (0%)	3/24 (13%)
Week of First Observation	104		68
Life Table Tests	P=0.027	P=0.487N	P=0.080
Incidental Tumor Tests	P=0.054	P=0.487N	P=0.144

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table A3 (footnotes).
(b) The estimated dose in milligrams per kilograms per day is given in Section III (Body Weights, Feed Consumption, and Clinical Signs) and in Appendix F.
(c) No tumors were observed in the control and 313-ppm groups.
(d) Historical incidence of glial cell tumors in NTP studies (mean ± SD): 13/1,928 (0.7% ± 1%)
(e) Six sections include original three sections and three additional sections; diagnoses from the three additional sections are not included in Tables A1 and A2.

There are three types of glial cells in the brain (astrocytes, oligodendrocytes, and microglial cells), but brain tumors in rats are usually derived from astrocytes or oligodendrocytes. Those glial tumors consisting of a relatively pure population of neoplastic cells are classified according to the predominant cell type as astrocytoma or oligodendroglioma. Frequently, however, glial tumors in the rat contain neoplastic cells with histologic features characteristic of both astrocytes and oligodendrocytes and are simply called gliomas.

Three of the glial tumors in the high dose males and the one in the control male were found during the gross examinations at necropsy. The fourth glial tumor in the high dose group was identified after routine sectioning of the brain. The glioma in the control male rat was an approximately 1-cm diameter mass in the cerebral cortex and thalamus and had invaded the ventricles. The glioma in the high dose male was an irregular, oval-shaped mass about 0.8 × 1.8 cm in the cerebrum and thalamus and effaced the hippocampus. The three astrocytomas included: one 1 × 0.4 cm mass in the medulla oblongata with extension to the meninges; one 0.3 × 0.4 cm mass in the cerebral cortex lateral to the hippocampus; and one 0.3 × 0.3 cm mass located near the dorsal surface of the anterior cerebral cortex.

Because the incidence of brain tumors in the high dose male rats exceeded that in historical controls, additional sections of brain from all control and dosed male and female rats were cut and examined microscopically. After the trimming and sectioning of each brain for the original histopathologic evaluations, the three remaining coronal samples of brain were saved with the other residual formalin-fixed tissues of each rat. These samples were embedded in paraffin and a single section was cut from the middle of each, avoiding the exposed surface from which the original section was taken. One additional astrocytoma in a high dose male rat and one astrocytoma in a high dose female rat were observed by microscopic examination of these additional sections.

Anterior Pituitary Gland: Adenomas in female rats occurred with a significant positive trend; the incidences in low dose male and high dose female rats were significantly greater than that in controls (Table 13). Carcinomas were not seen in male or female rats. The incidences of hyperplasia were similar in all groups of female rats.

Lung: The incidence of alveolar/bronchiolar adenomas in low dose male rats was significantly greater than that in controls (Table 14). The incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in dosed male rats were not significantly different from that in the controls but were greater than the highest incidence observed in untreated historical controls (4/49). Adenomatous hyperplasia, adenomas, and carcinomas are part of a morphologic continuum. Hyperplasia is characterized by alveoli that are lined with uniform cuboidal or low columnar cells. When the extent of proliferation of the epithelial cells results in distortion and effacement of normal architectural features, the lesion is classified as an adenoma. Typically, adenomas consist of papillary and interlacing cords of cuboidal or columnar cells with a scant fibrovascular stroma. Tumors with cellular atypia and pleomorphism are considered malignant and are classified as carcinomas. The incidences of adenomatous hyperplasia were similar in all groups of male rats.

Liver: Granulomas were observed at increased incidences in dosed rats (male: control, 0/49; low dose, 3/50; high dose, 4/50; female: 8/50; 15/49; 18/50).

TABLE 13. ANTERIOR PITUITARY GLAND LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

	Control	156 ppm	313 ppm	625 ppm
MALE				
Hyperplasia				
Overall Rates	6/49 (12%)		6/50 (12%)	9/49 (18%)
Adenoma (a)				
Overall Rates	11/49 (22%)		21/50 (42%)	14/49 (29%)
Adjusted Rates	31.4%		57.9%	44.4%
Terminal Rates	7/29 (24%)		17/32 (53%)	8/24 (33%)
Week of First Observation	88		84	72
Life Table Tests	P=0.133		P=0.049	P=0.181
Incidental Tumor Tests	P=0.198		P=0.028	P=0.256
FEMALE				
Hyperplasia				
Overall Rates	10/50 (20%)	9/50 (18%)	9/50 (18%)	
Adenoma (b)				
Overall Rates	23/50 (46%)	26/50 (52%)	35/50 (70%)	
Adjusted Rates	55.7%	61.2%	74.1%	
Terminal Rates	17/35 (49%)	16/32 (50%)	24/36 (67%)	
Week of First Observation	78	83	59	
Life Table Tests	P=0.047	P=0.292	P=0.052	
Incidental Tumor Tests	P=0.021	P=0.485	P=0.022	

(a) Historical incidence of adenomas or carcinomas (combined) in NTP studies (mean ± SD): 459/1,830 (25% ± 10%)
(b) Historical incidence of adenomas or carcinomas (combined) in NTP studies (mean ± SD): 939/1,922 (49% ± 11%)

TABLE 14. ALVEOLAR/BRONCHIOLAR LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Control	313 ppm	625 ppm
Adenomatous Hyperplasia			
Overall Rates	4/49 (8%)	5/50 (10%)	3/50 (6%)
Adenoma			
Overall Rates	0/49 (0%)	5/50 (10%)	3/50 (6%)
Adjusted Rates	0.0%	15.6%	10.3%
Terminal Rates	0/29 (0%)	5/32 (16%)	2/24 (8%)
Week of First Observation		104	76
Life Table Tests	P=0.089	P=0.041	P=0.100
Incidental Tumor Tests	P=0.118	P=0.041	P=0.152
Carcinoma			
Overall Rates	1/49 (2%)	1/50 (2%)	2/50 (4%)
Adenoma or Carcinoma (a)			
Overall Rates	1/49 (2%)	6/50 (12%)	5/50 (10%)
Adjusted Rates	3.4%	18.8%	16.1%
Terminal Rates	1/29 (3%)	6/32 (19%)	3/24 (13%)
Week of First Observation	104	104	68
Life Table Tests	P=0.060	P=0.072	P=0.080
Incidental Tumor Tests	P=0.095	P=0.072	P=0.144

(a) Historical incidence in NTP studies (mean ± SD): 43/1,933 (2% ± 2%)

FOURTEEN-DAY STUDIES

All 10 mice that received 5,000 ppm, 8/10 mice that received 2,500 ppm, and 4/5 males that received 1,250 ppm died before the end of the studies (Table 15). The final mean body weights of mice that received 1,250 or 2,500 ppm were lower than the initial mean body weights. Dosed animals were hyperactive and hypersensitive to sound and/or touch after 5 days. No compound-related lesions were observed at necropsy or by microscopic examination of the lung, pancreas, adrenal glands, liver, or kidneys of mice that received 1,250 ppm.

TABLE 15. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 1	Week 2
MALE							
0	5/5	23.8 ± 0.7	26.2 ± 0.5	+2.4 ± 0.2		4.8	4.5
310	5/5	25.4 ± 0.5	29.0 ± 0.7	+3.6 ± 0.6	110.7	4.7	4.1
620	5/5	26.6 ± 0.5	27.0 ± 0.8	+0.4 ± 0.4	103.1	4.2	4.4
1,250	(e) 1/5	26.8 ± 0.7	28.0	−1.0	106.9	3.3	8.0
2,500	(f) 1/5	26.8 ± 0.6	23.0	−4.0	87.8	5.0	8.6
5,000	(g) 0/5	27.2 ± 0.4	(h)	(h)	(h)	7.4	(h)
FEMALE							
0	5/5	20.0 ± 0.5	21.6 ± 0.5	+1.6 ± 0.2		3.8	4.0
310	5/5	19.8 ± 0.4	21.2 ± 0.4	+1.4 ± 0.4	98.1	3.3	4.0
620	5/5	18.8 ± 0.6	20.4 ± 0.4	+1.6 ± 0.2	94.4	4.1	3.6
1,250	5/5	19.8 ± 0.4	19.4 ± 0.2	−0.4 ± 0.2	89.8	3.7	4.3
2,500	(i) 1/5	20.2 ± 0.4	20.0	−1.0	92.6	5.0	9.1
5,000	(j) 0/5	17.0 ± 0.3	(h)	(h)	(h)	7.8	(h)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.
(e) Day of death: 4,5,6,6
(f) Day of death: 4,4,5,5
(g) Day of death: 2,3,3,3,5
(h) No data are reported due to the 100% mortality in this group.
(i) Day of death: 4,5,6,7
(j) Day of death: 2,2,3,3,4

THIRTEEN-WEEK STUDIES

Eight of 10 male mice that received 1,250 ppm, 2/10 males that received 625 ppm, and 1/10 males that received 313 ppm died before the end of the study (Table 16). The final mean body weights of mice that received 625 or 1,250 ppm were 8% or 17% lower than that of the controls for males and 10% or 15% lower for females. The unusually high feed consumption data for the high dose male group was probably due to scattering of feed. Compound-related clinical signs included humped backs and rough coats. No compound-related histopathologic effects were observed.

Dose Selection Rationale: Because of deaths and lower weight gain at higher concentrations, dietary concentrations of diphenhydramine hydrochloride selected for mice for the 2-year studies were 156 and 313 ppm.

TWO-YEAR STUDIES

Body Weights, Feed Consumption, and Clinical Signs

Mean body weights of high dose male mice were 5%-12% lower than those of controls after week 12 (Table 17 and Figure 6). Mean body weights of low dose male mice were 4%-7% lower than those of controls after week 58. Mean body weights of high dose female mice were 5%-13% lower than those of controls after week 16. Mean body weights of low dose female mice were 3%-11% lower than those of controls between weeks 30 and 81. The average daily feed consumption by dosed mice was similar to that by controls (Tables F3 and F4). The average amount of diphenhydramine hydrochloride consumed per day was approximately 21 or 46-47 mg/kg for low dose or high dose male and female mice. No compound-related clinical signs were observed.

TABLE 16. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 7	Week 13
MALE							
0	10/10	26.7 ± 0.5	32.7 ± 0.8	+6.0 ± 0.6		4.3	4.8
78	10/10	27.1 ± 0.6	33.1 ± 0.9	+6.0 ± 0.5	101.2	4.9	4.6
156	10/10	23.7 ± 0.6	32.7 ± 0.5	+9.0 ± 0.4	100.0	4.5	4.8
313	(e) 9/10	24.8 ± 0.8	30.7 ± 0.6	+6.1 ± 0.5	93.9	7.3	5.3
625	(f) 8/10	24.0 ± 0.9	30.2 ± 0.5	+6.1 ± 0.8	92.4	4.9	6.3
1,250	(g) 2/10	24.7 ± 0.4	27.0 ± 0.1	+1.1 ± 0.2	82.6	11.3	12.2
FEMALE							
0	(h) 9/10	21.3 ± 0.5	26.6 ± 0.8	+5.3 ± 0.3		4.4	4.4
78	10/10	21.6 ± 0.6	27.0 ± 0.9	+5.4 ± 0.4	101.5	4.6	4.6
156	10/10	21.8 ± 0.5	25.9 ± 0.5	+4.1 ± 0.3	97.4	4.5	4.8
313	10/10	21.6 ± 0.4	26.5 ± 0.4	+4.9 ± 0.4	99.6	4.8	4.8
625	10/10	20.8 ± 0.5	23.9 ± 0.5	+3.1 ± 0.2	89.8	4.9	5.2
1,250	(i) 9/10	20.8 ± 0.6	22.6 ± 0.7	+1.7 ± 0.3	85.0	5.5	5.8

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for scatter.
(e) Week of death: 2
(f) Week of death: 1,8
(g) Week of death: 1,1,1,1,2,2,2,3
(h) Death accidental
(i) Animal reported missing during week 4

TABLE 17. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

Weeks on Study	Control Av. Wt. (grams)	Control No. of Survivors	156 ppm Av. Wt. (grams)	156 ppm Wt. (percent of controls)	156 ppm No. of Survivors	313 ppm Av. Wt. (grams)	313 ppm Wt. (percent of controls)	313 ppm No. of Survivors
MALE								
0	24.8	50	23.6	95	50	24.5	99	48
1	22.7	50	23.0	101	50	22.5	99	47
2	24.0	50	23.1	96	50	22.7	95	47
3	23.9	50	23.2	97	50	22.0	92	46
4	26.4	50	25.3	96	50	22.8	86	46
5	29.2	50	28.2	97	50	26.9	92	46
6	28.4	50	28.2	99	50	27.6	97	46
7	27.8	50	29.7	107	50	28.8	104	46
8	29.9	50	29.9	100	50	29.3	98	46
9	30.0	50	29.1	97	50	28.2	94	46
10	29.6	50	29.3	99	50	28.9	98	46
11	28.5	50	27.8	98	50	27.5	96	46
12	30.4	50	29.7	98	50	28.3	93	46
16	31.7	49	30.3	96	49	29.9	94	46
20	33.8	48	31.6	93	47	31.5	93	43
24	34.6	47	33.6	97	46	33.0	95	42
30	35.8	45	34.1	95	43	33.7	94	41
34	36.6	44	35.1	96	42	34.5	94	39
38	37.8	44	36.3	96	41	34.8	92	36
42	39.1	44	37.3	95	41	34.4	88	34
47	37.8	44	36.6	97	41	35.2	93	32
50	39.3	44	38.0	97	41	35.9	91	32
54	39.4	44	38.7	98	41	36.4	92	32
58	39.8	44	38.3	96	41	36.5	92	32
62	39.7	42	38.1	96	40	36.7	92	32
68	39.7	41	38.3	96	39	36.6	92	32
73	39.4	41	38.0	96	39	36.3	92	32
78	39.4	41	37.3	95	39	36.3	92	31
82	39.3	41	37.8	96	39	36.4	93	31
85	39.2	40	37.1	95	39	36.2	92	30
89	39.3	37	37.0	94	38	36.5	93	29
93	39.8	36	37.2	93	36	35.9	90	28
98	39.2	33	37.1	95	35	35.3	90	26
102	39.2	31	36.5	93	32	35.0	89	26
FEMALE								
0	19.4	50	19.6	101	50	19.0	98	50
1	19.2	50	19.1	99	50	18.6	97	50
2	19.9	50	19.9	100	50	19.8	99	50
3	20.5	50	20.5	100	50	20.0	98	50
4	21.3	50	21.2	100	50	20.7	97	49
5	22.3	50	22.3	100	50	21.9	98	49
6	23.1	50	22.5	97	50	22.2	96	49
7	23.0	50	22.9	100	50	22.8	99	49
8	22.7	50	22.6	100	50	22.5	99	49
9	24.1	50	22.9	95	50	23.5	98	48
10	23.3	50	23.0	99	50	22.8	98	48
11	24.7	49	23.1	94	50	23.5	95	48
12	24.2	49	23.8	98	50	23.5	97	48
13	25.2	48	24.5	97	50	24.1	96	48
16	26.1	48	25.2	97	50	24.7	95	48
22	27.6	48	26.6	96	50	26.3	95	48
26	28.6	48	27.9	98	49	27.1	95	48
30	30.1	48	29.1	97	49	28.0	93	48
34	32.1	48	30.6	95	49	29.0	90	48
39	32.9	48	30.9	94	49	29.2	89	48
42	34.6	48	32.3	93	49	30.2	87	48
46	36.1	48	32.0	89	49	31.9	88	48
50	36.7	47	34.0	93	49	32.4	88	48
54	36.9	47	34.2	93	49	32.8	89	48
60	38.1	47	35.9	94	48	33.8	89	48
65	37.9	47	35.8	94	48	33.5	88	48
70	38.7	47	36.1	93	47	34.0	88	47
74	38.8	47	37.2	96	46	34.7	89	47
77	38.9	47	37.3	96	46	34.7	89	46
81	39.7	46	38.6	97	46	35.4	89	44
85	39.8	45	39.1	98	45	36.0	90	42
90	39.9	42	39.6	99	44	36.8	92	39
94	40.2	41	40.2	100	42	36.1	90	36
98	40.6	39	41.0	101	41	37.1	91	35
102	40.4	38	40.7	101	39	37.6	93	33

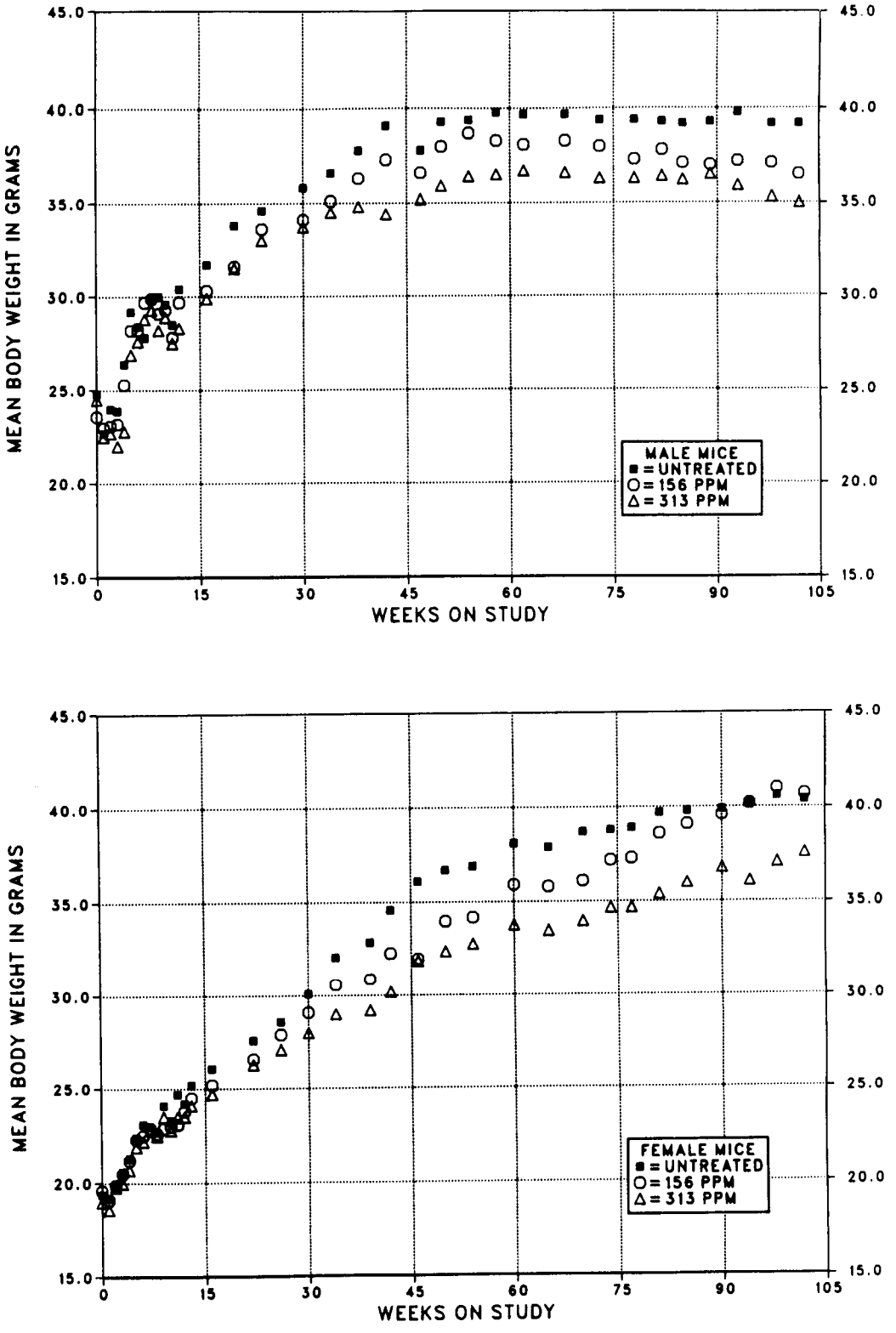

FIGURE 6. GROWTH CURVES FOR MICE FED DIETS CONTAINING DIPHENHYDRAMINE HYDROCHLORIDE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing diphenhydramine hydrochloride at the concentrations used in these studies and for controls are shown in Table 18 and in the Kaplan and Meier curves in Figure 7. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, lung, hematopoietic system, ovary, and spleen.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice, respectively.

TABLE 18. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

	Control	156 ppm	313 ppm
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	15	11	13
Moribund kills	6	9	11
Animals missexed	0	0	2
Animals surviving until study termination	29	30	24
Survival P values (b)	0.319	0.916	0.347
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	7	6	11
Moribund kills	7	5	7
Animals surviving until study termination	(c) 37	39	32
Survival P values (b)	0.292	0.796	0.350

(a) Termination period: male--week 106; female--weeks 104-105.
(b) The result of the life table trend test is in the control column, and the results of the life table pairwise comparisons with the controls are in the dosed columns.
(c) One animal died or was killed in a moribund condition during the termination period and was combined, for statistical purposes, with those killed at termination.

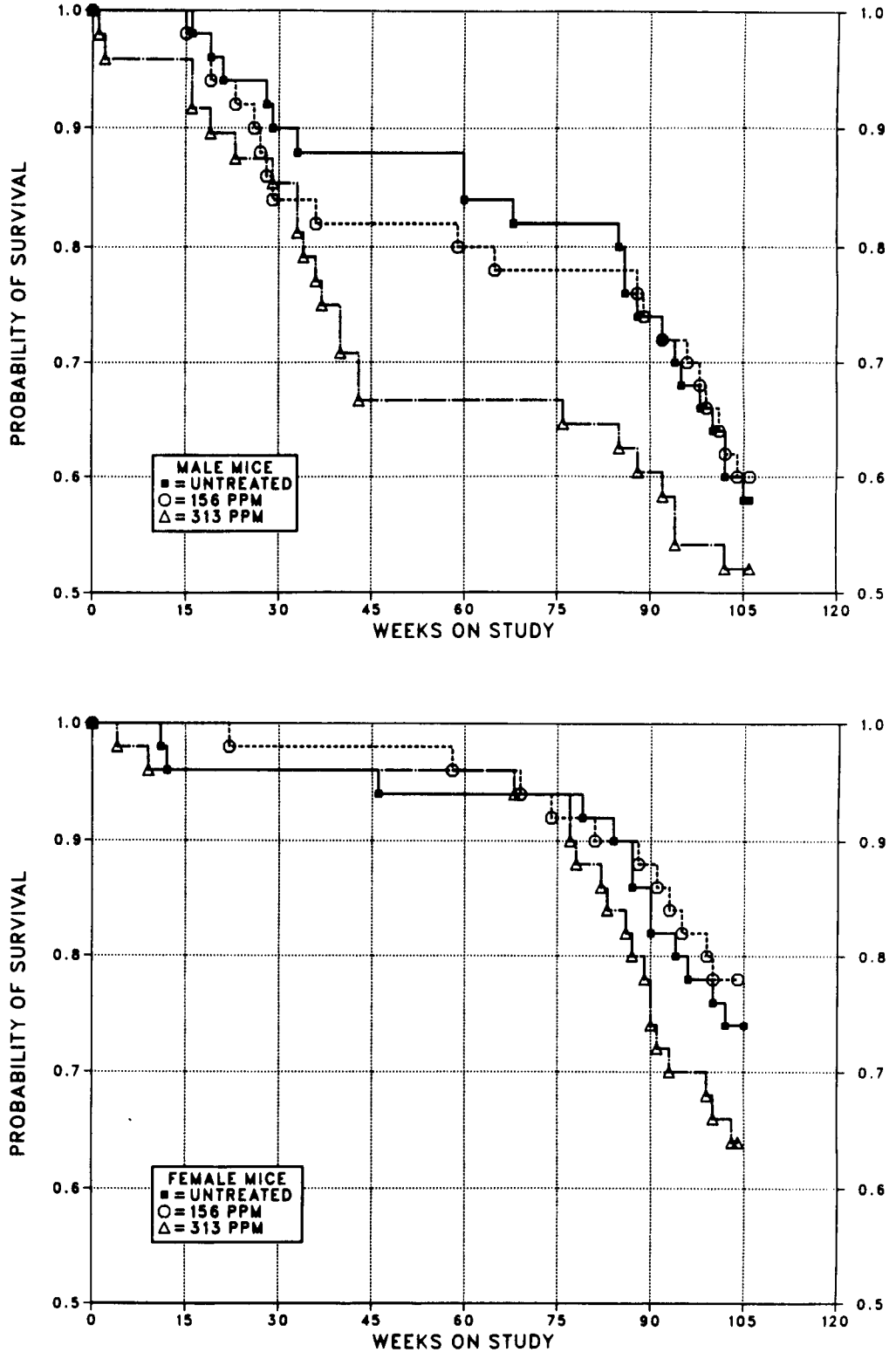

FIGURE 7. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING DIPHENHYDRAMINE HYDROCHLORIDE FOR TWO YEARS

Liver: Cytoplasmic vacuolization, referred to as fatty metamorphosis in Table D5, was observed at an increased incidence in high dose female mice (male: none observed; female: control, 0/49; low dose, 1/49; high dose, 8/49). The incidence of hepatocellular carcinomas in low dose male mice was significantly greater than that in controls; the incidences of hepatocellular adenomas or carcinomas (combined) in dosed male mice were not significantly different from that in controls (Table 19).

Lung: The incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in high dose male mice was significantly lower than that in controls (Table 20).

Hematopoietic System: The incidence of lymphomas in high dose female mice was marginally lower than that in controls by the incidental tumor test (Table 21). Because these tumors are generally considered to be fatal, the more appropriate analysis is provided by the life table test.

Ovary: Ten abscesses were observed in high dose female mice, but none was seen in low dose or control females. The utero-ovarian abscesses observed in high dose female mice were similar to those described for a Klebsiella sp. infection (Rao et al., 1987).

Spleen: Myeloid metaplasia occurred at an increased incidence in high dose female mice (control, 9/49; low dose, 7/49; high dose, 19/49). This increase was primarily associated with the higher incidence of utero-ovarian abscesses in high dose females. Inflammatory processes stimulate the proliferation of immature cells of the granulocytic series, which are normally present in low numbers in the spleen.

TABLE 19. HEPATOCELLULAR TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (a)

	Control	156 ppm (b)	313 ppm (b)
Adenoma			
Overall Rates	9/46 (20%)	7/49 (14%)	7/47 (15%)
Carcinoma			
Overall Rates	4/46 (9%)	14/49 (29%)	5/47 (11%)
Adjusted Rates	11.6%	41.9%	18.1%
Terminal Rates	1/29 (3%)	11/30 (37%)	3/24 (13%)
Week of First Observation	86	89	76
Life Table Tests	P=0.289	P=0.014	P=0.371
Incidental Tumor Tests	P=0.243	P=0.006	P=0.305
Adenoma or Carcinoma (c)			
Overall Rates	12/46 (26%)	18/49 (37%)	12/47 (26%)
Adjusted Rates	36.8%	52.4%	45.4%
Terminal Rates	9/29 (31%)	14/30 (47%)	10/24 (42%)
Week of First Observation	86	89	76
Life Table Tests	P=0.306	P=0.162	P=0.369
Incidental Tumor Tests	P=0.258	P=0.108	P=0.325

(a) The statistical analyses used are discussed in Section II (Statistical Methods) and Table C3 (footnotes).
(b) The estimated dose in milligrams per kilograms per day is given in Section III (Body Weights, Feed Consumption, and Clinical Signs) and in Appendix F.
(c) Historical incidence in NTP studies (mean ± SD): 609/2,032 (30% ± 8%)

TABLE 20. ALVEOLAR/BRONCHIOLAR LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Control	156 ppm	313 ppm
Epithelial Hyperplasia			
Overall Rates	3/48 (6%)	1/50 (2%)	1/48 (2%)
Adenoma			
Overall Rates	4/48 (8%)	5/50 (10%)	0/48 (0%)
Carcinoma			
Overall Rates	2/48 (4%)	2/50 (4%)	0/48 (0%)
Adenoma or Carcinoma (a)			
Overall Rates	6/48 (13%)	7/50 (14%)	0/48 (0%)
Adjusted Rates	19.5%	23.3%	0.0%
Terminal Rates	5/29 (17%)	7/30 (23%)	0/24 (0%)
Week of First Observation	92	106	
Life Table Tests	P=0.040N	P=0.525	P=0.031N
Incidental Tumor Tests	P=0.038N	P=0.525	P=0.028N

(a) Historical incidence in NTP studies (mean ± SD): 348/2,034 (17% ± 7%)

TABLE 21. MALIGNANT LYMPHOMAS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (a)

	Control	156 ppm	313 ppm
Overall Rates	21/49 (43%)	23/49 (47%)	11/50 (22%)
Adjusted Rates	45.1%	51.9%	30.7%
Terminal Rates	12/37 (32%)	18/39 (46%)	8/32 (25%)
Week of First Observation	12	69	82
Life Table Tests	P=0.080N	P=0.493	P=0.086N
Incidental Tumor Tests	P=0.021N	P=0.387	P=0.035N

(a) Historical incidence of lymphomas or leukemia (combined) in NTP studies (mean ± SD): 636/2,041 (31% ± 13%)

Diphenhydramine hydrochloride did not induce reverse mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 when tested at doses up to 3,333 μg per plate with a preincubation protocol in either the presence or absence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Table 22; Zeiger et al., 1987). No induction of trifluorothymidine resistance was observed in mouse L5178Y lymphoma cells after exposure to diphenhydramine hydrochloride in the presence or absence of Aroclor 1254-induced male F344 rat liver S9 (Table 23). When tested in an in vitro cytogenetics assay with Chinese hamster ovary cells, diphenhydramine hydrochloride did not induce sister chromatid exchanges in either the presence or absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Table 24; Loveday et al., 1989). However, in the absence of S9, exposure to diphenhydramine hydrochloride produced an increase in chromosomal aberrations in two of three trials at doses of 100 μg/ml and higher when harvest times were extended 6-10 hours to compensate for chemical-induced cell cycle delay (Table 25; Loveday et al., 1989). The increase noted in trial 2 was not reproduced in trial 3, but in a fourth trial, in which a modified treatment regimen was used (16-hour exposure and 6-hour recovery), increases in aberrations were seen at all three doses tested. No increase in aberrations was observed in the presence of S9.

TABLE 22. MUTAGENICITY OF DIPHENHYDRAMINE HYDROCHLORIDE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
TA100	0	111 ± 3.6	90 ± 11.2	159 ± 9.2	115 ± 14.0	152 ± 15.6	112 ± 10.7
	10	--	78 ± 9.3	--	92 ± 4.7	--	103 ± 3.2
	33	88 ± 2.9	83 ± 6.3	191 ± 2.6	95 ± 4.2	171 ± 3.0	84 ± 4.3
	100	108 ± 0.3	86 ± 4.5	187 ± 7.2	91 ± 3.8	173 ± 7.8	91 ± 1.5
	333	110 ± 5.2	86 ± 3.3	188 ± 2.3	92 ± 4.1	203 ± 3.8	87 ± 11.7
	1,000	92 ± 0.3	78 ± 1.8	176 ± 5.6	83 ± 9.8	180 ± 4.0	86 ± 6.6
	3,333	0 ± 0.0	--	Toxic	--	Toxic	--
Trial summary		Negative	Negative	Negative	Negative	Equivocal	Negative
Positive control (c)		777 ± 10	511 ± 14.7	2,144 ± 105.9	1,212 ± 23.5	2,197 ± 32.5	1,439 ± 31.5
TA1535	0	10 ± 3.2	9 ± 0.6	12 ± 3.6	12 ± 1.5	12 ± 2.7	8 ± 2.0
	10	--	8 ± 0.6	--	13 ± 0.3	--	6 ± 1.5
	33	10 ± 1.2	7 ± 1.2	13 ± 1.2	11 ± 2.5	11 ± 1.3	8 ± 0.3
	100	15 ± 1.8	6 ± 3.8	13 ± 1.9	9 ± 2.0	12 ± 1.9	6 ± 1.2
	333	6 ± 0.7	4 ± 0.6	13 ± 1.2	8 ± 2.7	14 ± 1.2	6 ± 2.2
	1,000	6 ± 0.6	5 ± 0.5	11 ± 0.9	5 ± 3.1	14 ± 2.0	5 ± 2.3
	3,333	0 ± 0.0	--	Toxic	--	Toxic	--
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		986 ± 22.7	408 ± 6.9	124 ± 23.7	57 ± 3.5	115 ± 17.1	103 ± 7.5
TA1537	0	7 ± 0.5	4 ± 1.5	12 ± 3.2	9 ± 2.4	8 ± 0.9	6 ± 1.2
	10	--	2 ± 0.6	--	8 ± 1.9	--	7 ± 2.6
	33	3 ± 0.3	3 ± 0.3	15 ± 1.2	8 ± 1.8	10 ± 2.9	7 ± 0.9
	100	5 ± 0.6	3 ± 0.3	14 ± 1.0	7 ± 1.7	14 ± 0.6	7 ± 1.8
	333	4 ± 0.6	2 ± 0.6	11 ± 0.6	5 ± 2.1	13 ± 2.3	6 ± 1.7
	1,000	Toxic	Toxic	12 ± 1.7	7 ± 1.2	14 ± 2.6	6 ± 2.0
	3,333	0 ± 0.0	--	Toxic	--	Toxic	--
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		982 ± 21.7	769 ± 48.3	176 ± 4.9	135 ± 7.7	88 ± 16.4	89 ± 7.4
TA98	0	21 ± 6.4	12 ± 4.5	32 ± 4.4	23 ± 4.6	34 ± 6.1	26 ± 4.4
	10	--	12 ± 1.5	--	24 ± 1.3	--	24 ± 2.7
	33	22 ± 3.3	12 ± 1.9	38 ± 1.9	26 ± 2.4	38 ± 1.9	29 ± 2.0
	100	22 ± 3.0	15 ± 3.1	27 ± 1.5	19 ± 0.3	39 ± 2.6	29 ± 3.2
	333	24 ± 2.3	14 ± 0.9	42 ± 3.7	21 ± 4.4	36 ± 1.8	23 ± 4.0
	1,000	18 ± 3.0	7 ± 1.5	35 ± 1.9	24 ± 0.3	40 ± 2.3	26 ± 2.3
	3,333	Toxic	--	Toxic	--	Toxic	--
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		243 ± 8.5	206 ± 7.9	1,602 ± 78.8	926 ± 34.4	1,599 ± 27.7	900 ± 36.6

(a) Study performed at Case Western Reserve University. The detailed protocol is presented by Haworth et al. (1983). Data are presented in Zeiger et al. (1987). Cells and study compound or solvent (distilled water) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE 23. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY DIPHENHYDRAMINE HYDROCHLORIDE IN MOUSE L5178Y LYMPHOMA CELLS (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
-S9					
Trial 1					
Distilled water (d)		101.8 ± 4.0	100.0 ± 3.6	90.8 ± 6.2	29.5 ± 1.0
Diphenhydramine hydrochloride	20	93.0 ± 3.6	73.0 ± 2.1	96.0 ± 4.0	34.7 ± 0.3
	30	92.7 ± 1.8	58.7 ± 6.2	84.3 ± 3.9	30.3 ± 0.9
	40	93.3 ± 3.9	51.3 ± 1.5	88.3 ± 8.7	31.7 ± 2.4
	50	94.3 ± 3.2	41.7 ± 4.6	93.0 ± 13.1	33.0 ± 3.8
	60	86.7 ± 7.2	36.3 ± 2.3	91.0 ± 11.2	35.3 ± 3.3
	80	69.0 ± 5.9	9.3 ± 0.3	121.7 ± 8.4	(e) 59.0 ± 1.5
Methyl methanesulfonate	5	82.0 ± 7.9	44.0 ± 6.1	411.7 ± 36.4	(e) 167.3 ± 4.4
Trial 2					
Distilled water (d)		108.0 ± 1.7	100.0 ± 7.5	127.5 ± 5.7	39.3 ± 1.3
Diphenhydramine hydrochloride	20	80.3 ± 5.6	49.3 ± 0.3	69.3 ± 4.9	29.0 ± 1.7
	30	98.0 ± 7.5	55.3 ± 6.3	93.7 ± 5.8	32.3 ± 2.3
	40	101.7 ± 4.3	49.7 ± 3.3	69.7 ± 8.1	22.7 ± 2.3
	50	(f) 98.0 ± 3.0	36.5 ± 4.5	97.0 ± 21.0	33.0 ± 6.0
	60	(g) 109	37	122	37
	80	105.3 ± 2.4	12.0 ± 1.7	78.3 ± 15.6	25.0 ± 5.3
	100	Lethal	--	--	--
Methyl methanesulfonate	5	55.7 ± 7.8	27.7 ± 3.4	523.7 ± 39.0	(e) 328.3 ± 57.0
Trial 3					
Distilled water (d)		109.3 ± 3.0	100.0 ± 10.4	95.8 ± 5.2	29.3 ± 2.1
Diphenhydramine hydrochloride	40	114.0 ± 3.2	56.3 ± 5.8	71.7 ± 10.7	21.0 ± 3.6
	50	101.0 ± 6.0	39.7 ± 0.9	61.0 ± 1.7	20.3 ± 0.7
	60	108.3 ± 5.0	39.7 ± 0.9	65.3 ± 5.6	20.0 ± 1.5
	70	96.0 ± 4.9	19.0 ± 0.0	71.7 ± 8.0	25.0 ± 1.5
	80	(h) 111.0 ± 3.0	21.0 ± 2.0	56.0 ± 1.0	17.0 ± 0.0
	100	(h) 108.0 ± 3.0	6.5 ± 0.5	68.5 ± 7.5	21.0 ± 3.0
	120	Lethal	--	--	--
Methyl methanesulfonate	5	70.0 ± 10.0	29.7 ± 4.7	445.0 ± 19.3	(e) 219.3 ± 24.3
+S9 (i)					
Trial 1					
Distilled water (d)		92.0 ± 2.3	100.0 ± 7.0	94.0 ± 10.4	34.3 ± 4.6
Diphenhydramine hydrochloride	10	102.3 ± 8.3	129.3 ± 16.2	84.0 ± 2.6	27.7 ± 2.8
	20	87.0 ± 7.6	105.3 ± 6.2	127.0 ± 16.1	48.0 ± 3.0
	30	93.0 ± 3.2	101.0 ± 1.2	91.3 ± 6.6	32.7 ± 1.2
	40	88.3 ± 1.5	105.0 ± 2.5	75.0 ± 9.1	28.3 ± 3.2
	60	98.3 ± 3.5	92.3 ± 0.9	93.7 ± 9.4	31.7 ± 2.4
	80	99.3 ± 4.3	92.0 ± 6.7	96.7 ± 17.3	32.3 ± 4.9
Methylcholanthrene	2.5	74.0 ± 6.9	43.7 ± 1.2	837.0 ± 7.0	(e) 384.3 ± 32.7

TABLE 23. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE BY DIPHENHYDRAMINE HYDROCHLORIDE IN MOUSE L5178Y LYMPHOMA CELLS (Continued)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
+S9 (Continued)					
Trial 2					
Distilled water (d)		112.3 ± 3.7	99.8 ± 14.4	112.0 ± 10.8	33.3 ± 3.0
Diphenhydramine hydrochloride	25	114.3 ± 2.7	92.3 ± 5.8	139.0 ± 6.0	40.7 ± 2.7
	50	113.0 ± 6.7	75.3 ± 1.5	102.7 ± 4.4	30.7 ± 3.2
	75	128.7 ± 5.0	53.0 ± 4.0	92.0 ± 11.4	24.0 ± 3.8
	100	109.3 ± 10.1	28.7 ± 8.1	86.0 ± 16.7	25.7 ± 2.9
	150	Lethal	--	--	--
Methylcholanthrene	2.5	105.7 ± 5.8	59.7 ± 5.2	972.0 ± 12.1 (e)	308.3 ± 13.7
Trial 3					
Distilled water (d)		86.3 ± 10.0	99.8 ± 12.5	91.0 ± 7.6	38.3 ± 8.4
Diphenhydramine hydrochloride	30	103.7 ± 5.6	101.3 ± 2.2	117.0 ± 10.5	37.7 ± 1.5
	40	93.7 ± 8.7	86.7 ± 14.3	106.7 ± 3.7	38.7 ± 3.9
	60	111.7 ± 6.4	76.0 ± 3.8	113.3 ± 12.9	33.7 ± 2.2
	80	108.0 ± 8.0	57.3 ± 3.7	120.7 ± 7.7	37.3 ± 0.3
	100	101.0 ± 5.6	18.0 ± 2.9	98.7 ± 13.0	32.3 ± 3.0
	120	Lethal	--	--	--
Methylcholanthrene	2.5	96.0 ± 0.6	68.7 ± 7.2	821.7 ± 55.1 (e)	285.7 ± 20.5

(a) Study performed at Litton Bionetics, Inc. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in triplicate; the average for the three tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.
(b) Mean ± standard error from replicate trials of 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 capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.
(c) Mutant fraction (frequency) is a ratio of the Tft-resistant cells to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.
(d) Data presented are the results of four tests.
(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.
(f) Data presented are the results of two tests.
(g) Data presented are the results of one test.
(h) Data presented are for two tests; the dose in one test was lethal.
(i) 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 (distilled water).

TABLE 24. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY DIPHENHYDRAMINE HYDROCHLORIDE (a)

Compound	Dose (μg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)--Summary: Negative								
Medium		50	1,043	368	0.35	7.4	27.0	--
Diphenhydramine hydrochloride	5	50	1,034	398	0.38	8.0	27.0	108.1
	15	50	1,040	396	0.38	7.9	27.0	106.8
	50	50	1,039	372	0.36	7.4	27.0	100.0
Mitomycin C	0.002	50	1,037	583	0.56	11.7	27.0	158.1
	0.01	10	210	343	1.63	34.3	27.0	463.5
+S9 (d)--Summary: Negative								
Medium		50	1,045	460	0.44	9.2	25.5	--
Diphenhydramine hydrochloride	15	50	1,047	433	0.41	8.7	25.5	94.6
	50	50	1,046	415	0.40	8.3	25.5	90.2
	150	50	1,043	436	0.42	8.7	25.5	94.6
Cyclophosphamide	0.5	50	1,041	749	0.72	15.0	25.5	163.0
	2.5	10	211	396	1.88	39.6	25.5	430.4

(a) Study performed at Bioassay Systems Corp. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985, 1987). Data are presented in Loveday et al. (1989). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (medium) as described in (c) or (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air-dried, and stained.

(b) SCEs/cell in treated culture expressed as a percent of the SCEs/cell in the control culture

(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.

(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE 25. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY DIPHENHYDRAMINE HYDROCHLORIDE (a)

Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
−S9 (b) Trial 1--Harvest time 10.5 h				
Medium	100	16	0.16	4.0
Diphenhydramine hydrochloride				
15.2	100	1	0.01	1.0
50.5	100	2	0.02	2.0
150	100	1	0.01	1.0
300	39	1	0.03	3.0
Summary: Negative				
Mitomycin C				
5	100	52	0.52	38.0
−S9 Trial 3--Harvest time 18.5 h (c)				
Medium	100	2	0.02	1.0
Diphenhydramine hydrochloride				
100	100	0	0.00	0.0
161	100	3	0.03	3.0
181	27	0	0.00	0.0
201	67	0	0.00	0.0
Summary: Negative				
Mitomycin C				
5	100	580	5.80	92.0
+S9 (d) Trial 1--Harvest time 12 h				
Medium	100	0	0	0.0
Diphenhydramine hydrochloride				
30.3	100	2	0.02	2.0
101	100	3	0.03	3.0
300	100	3	0.03	2.0
Summary: Negative				
Cyclophosphamide				
50	100	60	0.60	32.0
−S9 Trial 2--Harvest time 18.5 h (c)				
Medium	100	0	0.00	0.0
Diphenhydramine hydrochloride				
10	100	0	0.00	0.0
50	100	1	0.01	1.0
100	100	1	0.01	1.0
150	100	9	0.09	8.0
200	100	29	0.29	17.0
Summary: Positive				
Mitomycin C				
5	100	540	5.40	81.0
−S9 Trial 4--Harvest time 22.0 h (c)				
Medium	100	2	0.02	2.0
Diphenhydramine hydrochloride				
100	100	22	0.22	13.0
125	100	14	0.14	12.0
150	41	18	0.44	44.0
Summary: Positive				
Mitomycin C				
5	15	128	8.53	93.0

(a) Study performed at Bioassay Systems Corp. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is presented by Galloway et al. (1985, 1987). Data are presented in Loveday et al. (1989). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (medium) as indicated in (b) or (d). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.

(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (medium) for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.

(c) Because of significant chemically induced cell cycle delay, incubation time before addition of colcemid was lengthened to provide sufficient metaphases at harvest.

(d) In the presence of S9, cells were incubated with study compound or solvent (medium) for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

IV. DISCUSSION AND CONCLUSIONS

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Toxicology and carcinogenesis studies of diphenhydramine hydrochloride (greater than 99% pure), an antihistaminic drug widely used in human and veterinary medicine, were conducted by administration of this compound in the diet to male and female F344/N rats and $B6C3F_1$ mice. The selection of dietary concentrations of diphenhydramine hydrochloride for the 2-year studies, 313 or 625 ppm for male rats and 156 or 313 ppm for female rats and male and female mice, was based on results of the 14-day and 13-week feed studies.

In the 14-day studies, compound-related deaths occurred at the two highest dietary concentrations (5,000 and 10,000 ppm) in rats and at 1,250-5,000 ppm in mice. The average amount of diphenhydramine hydrochloride consumed per day by rats in the 2,500-ppm group (130-180 mg/kg) was equivalent to about one-third the oral LD_{50} of this compound in rats (see Table 1; Rieveschl and Gruhzit, 1945; Gruhzit and Fisken, 1947; Goldenthal, 1971), whereas, for mice given 1,250 ppm, the amount of diphenhydramine hydrochloride consumed per day (180-250 mg/kg) was nearly equivalent to the oral LD_{50} of this drug in this species (see Table 1; Rieveschl and Gruhzit, 1945; Gruhzit and Fisken, 1947; Hoppe and Lands, 1949). The oral LD_{50} of diphenhydramine hydrochloride is about three times greater in rats than in mice.

In the 13-week studies, no deaths occurred in rats that received up to 2,500 ppm diphenhydramine hydrochloride in the diet; however, a dose-related decrease in body weight was observed in each sex. The decreases in body weight gain at higher concentrations of diphenhydramine hydrochloride formed the basis for the selection of dietary concentrations (313 and 625 ppm for males and 156 and 313 ppm for females) for the 2-year studies in rats. Cytoplasmic vacuolization of the liver was observed in rats of each sex at 313 ppm and higher; however, this lesion is not considered to be life threatening and did not influence the selection of dietary concentrations for the 2-year studies. Eight of 10 male mice that received 1,250 ppm diphenhydramine hydrochloride died before the end of the 13-week study. At 625 ppm, 2/10 male mice died, and a 10% decrease in mean body weight was observed in female mice. No compound-related histopathologic effects were observed in mice that received up to 1,250 ppm diphenhydramine hydrochloride for 13 weeks. The dose-related mortality and the decreases in body weight gain at higher concentrations formed the basis for the selection of dietary concentrations (156 and 313 ppm) for the 2-year studies in mice.

In the 2-year studies, there were no significant differences in survival between any groups of rats or mice of either sex. A large number of early deaths in all groups of male mice was considered to be largely due to lesions received from fighting. Mean body weights of control and dosed rats were similar throughout the studies; in mice, dose-related decreases in mean body weights were observed. Based on measurements of feed consumption and body weight, the estimated average daily consumption of diphenhydramine hydrochloride was approximately 13 or 27 mg/kg for male rats, 7 or 15 mg/kg for female rats, and 21 or 46-47 mg/kg for male and female mice.

The recommended therapeutic dosage of diphenhydramine hydrochloride for human adults is 25-50 mg every 4-6 hours, not to exceed 300 mg in 24 hours (Douglas, 1985; Fed. Regist., 1985). Thus, for a 70-kg person, the maximum recommended daily dose is about 4.3 mg/kg body weight. In the 2-year studies, rats received approximately 1.5 to 6 times the maximum recommended human dose and mice received approximately 5 to 10 times that level.

In a separate study to measure blood levels of diphenhydramine, male rats were fed diets containing 625 ppm diphenhydramine hydrochloride for up to 30 days. A mean plasma concentration of diphenhydramine of 3.3 ng/ml was measured in blood samples taken at 2:00 a.m. on day 30. This concentration is about 20 times lower than the peak plasma concentrations of diphenhydramine in humans 2-3 hours after a single oral dose of 50 mg diphenhydramine hydrochloride (60-80 ng/ml; see Table 2; Albert et al., 1975; Carruthers et al., 1978; Spector et al., 1980; Meredith et al., 1984; Blyden et al., 1986). Diphenhydramine was not detected in blood samples taken at 9:00 a.m. from rats fed diets containing 625 ppm diphenhydramine hydrochloride or in blood samples taken at 2:00 a.m. or 9:00 a.m. from rats that received 313 ppm

diphenhydramine hydrochloride. The difference in plasma levels of diphenhydramine between blood samples taken at 2:00 a.m. and those taken at 9:00 a.m. probably reflects the nocturnal eating patterns of rats and the short half-life of diphenhydramine in plasma (Drach et al., 1970). The plasma level of diphenhydramine was lower in rats that received 625 ppm diphenhydramine hydrochloride in feed for 30 days (42 mg/kg body weight per day) than in humans who received a single dose of 50 mg (0.7 mg/kg body weight per day), perhaps because the intake of diphenhydramine hydrochloride occurred over a much greater time interval in rats than in the single dose studies in humans. Nevertheless, diphenhydramine hydrochloride at the highest dose used in the 2-year studies does not appear to result in higher plasma levels than have been measured in humans receiving a single therapeutic dose of this drug.

In the routine histopathologic examination of brain, three sections were taken (at the levels of the frontal cortex and basal ganglia, the parietal cortex and thalamus, and the cerebellum and pons). By this sampling procedure, four glial cell tumors were observed in male rats that received 625 ppm diphenhydramine hydrochloride compared with one in control male rats. Four of these five neoplasms were detected at necropsy (the one lesion detected microscopically was in a dosed rat). Although not statistically significant, the increased incidence may be related to ingestion of diphenhydramine hydrochloride because glial cell tumors are uncommon in untreated control male F344/N rats (0.5%-1%; see Table A4a; Ward and Rice, 1982; Solleveld et al., 1984), and the incidence range in controls observed in NTP studies is small, from 0/50 to 2/50 (0%-4%). The incidence of four brain tumors in 50 male rats is significantly greater than the incidence in untreated historical controls. In addition, the incidences of glial cell tumors in male F344/N rats in three other 2-year studies that were in progress at the study laboratory (SRI International) during the dosing phase of the diphenhydramine hydrochloride study were not different from the mean historical incidence of this tumor. Six glial cell tumors were observed in 500 control or dosed male F344/N rats (1.2%) in these other studies (furosemide, hydrochlorothiazide, and 8-methoxypsoralen), and the incidences in the untreated control groups ranged from 0/50 to 1/50 (0%-2%). Koestner (1986) indicated that brain tumors induced by neurocarcinogenic agents generally appear at an earlier age than do spontaneous brain tumors; in the diphenhydramine hydrochloride study, glial cell tumors were found in two high dose male rats that died after about 70 weeks of dosing, whereas all other brain tumors were observed at the end of the study. Because diphenhydramine readily passes from the blood into the central nervous system (Glazko and Dill, 1949a; Douglas, 1985; Goldberg et al., 1987), the brain is considered to be a potential target organ for toxic effects of this drug.

Because the incidence of brain tumors in high dose male rats was greater than the incidence in concurrent and historical controls, three additional sections of brain from all male and female rats were examined to provide a more definitive comparison of the incidence of brain tumors in dosed and control rats. An additional astrocytoma was observed in a high dose male rat, and one astrocytoma was found in a high dose female rat. Thus, the total incidence of brain tumors in high dose male rats is 5/50, and the incidence in controls is 1/49. However, because additional sections were examined in this evaluation, it is not appropriate to compare the incidence of 5/50 with the historical control incidence, which is based on three brain sections per animal. Nonetheless, the incidence in the control group in this study was not different from the mean historical control incidence of 0.5%-1%.

Astrocytes and oligodendrocytes are distinct neuroglial cells of ectodermal origin. These cells are renewed at a slow rate by differentiation of a reserve population of pluripotential stem cells in the subependymal zone (Solleveld et al., 1986). The type of tumor that may develop in the brain depends on the stage of neuroepithelial cell differentiation when the neoplastic transformation process occurs. Astrocytomas are the most common glial cell tumor in F344 rats (Ward and Rice, 1982).

A variety of classes of compounds has been shown to induce brain tumors (usually of glial cell origin) in rodents, including polycyclic

hydrocarbons (e.g., methylcholanthrene, benzo[*a*]pyrene), *N*-nitroso chemicals (e.g., methylnitrosourea, ethylnitrosourea), hydrazines (e.g., 1-methyl-2-benzylhydrazine, diethylhydrazine), aryl dialkyltriazenes (e.g., 1-phenyl-3,3-dimethyltriazene), and alkylating agents (e.g., acrylonitrile, propane sultone, propylene imine) (Swenberg, 1982; Ward and Rice, 1982; Solleveld et al., 1986). Inhalation exposure of F344 rats to ethylene oxide (6 hours per day, 5 days per week for 2 years at 0, 10, 33, or 100 ppm) caused an increase in the incidence of glial cell tumors (0 ppm, 1/196; 10 ppm, 0/99; 33 ppm, 3/98; 100 ppm, 6/99) that were morphologically similar to those observed in control rats (Garman et al., 1985). The incidence of glial cell tumors in rats exposed to ethylene oxide at 100 ppm was similar to that in male rats fed diets containing 625 ppm diphenhydramine hydrochloride. Neither diphenhydramine nor its metabolic intermediates appear to be structurally similar to those chemicals that have been found to induce brain tumors in rodents. Furthermore, the generally negative genotoxicity data for diphenhydramine hydrochloride, with and without S9 metabolic activation, indicate that this compound probably does not act as a mutagenic alkylating agent.

The major basis for considering that the marginally increased incidence of uncommon glial cell tumors in the high dose group of male rats may be related to the administration of diphenhydramine hydrochloride is that this incidence was two times greater than the highest incidence ever observed in groups of untreated control male F344/N rats in previous NTP studies and that diphenhydramine crosses the blood-brain barrier and distributes in brain tissue. However, a variety of characteristic effects associated with exposure to neurocarcinogenic agents (Koestner, 1986), including increased glial cell proliferation, increased degree of anaplasia, and a clear dose-response relationship, were not observed in male rats that received diphenhydramine hydrochloride. The absence of glial cell tumors in the low dose group of male rats fed diphenhydramine hydrochloride does not support a dose-effect relationship. Nonetheless, the difference in dietary concentrations (313 ppm vs. 625 ppm) could account for the absence of an effect in the low dose group. The incidences of brain tumors or glial cell were not increased in female rats or male or female mice that were fed diets containing diphenhydramine hydrochloride; however, the highest dietary concentration of diphenhydramine hydrochloride received by female rats and male and female mice was 313 ppm. Lijinsky (1984b) did not observe an increase in the incidence of glial cell tumors in groups of 24 male or 24 female rats fed diets containing 2,000 ppm diphenhydramine hydrochloride for 2 years. These factors, taken as a whole, contributed to the conclusion that the marginal increase in the incidence of brain tumors in the high dose group of male rats could not be related with certainty to the administration of diphenhydramine hydrochloride.

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 rats and F344 rats fed diets containing 1,000 ppm methapyrilene hydrochloride (Lijinsky and Taylor, 1977; Lijinsky et al., 1980). In the present studies, the incidences of liver neoplasms were not significantly increased in rats or mice given diphenhydramine hydrochloride; granulomas of the liver were observed at increased incidences in dosed rats. Results of a feed study of diphenhydramine hydrochloride with sodium nitrite indicated that in vivo nitrosation of diphenhydramine may produce compounds that are carcinogenic for the liver (Lijinsky, 1984b).

In low dose male rats and high dose female rats, increases in the incidences of anterior pituitary gland adenomas were observed. However, because the increased incidences of this lesion were not supported by increased incidences of hyperplasia in the dosed groups, because progression to carcinoma was not observed, and because this is a common tumor that occurs with a variable incidence, the marginally increased incidences in male and female rats cannot be related with certainty to administration of diphenhydramine hydrochloride. Furthermore, a dose-response relationship was not observed in male rats.

The incidences of alveolar/bronchiolar adenomas or carcinomas were marginally increased in dosed male rats. These increases may have been chemically related because the incidences in the

low and high dose groups were greater than the highest incidence in the historical controls. Furthermore, metabolic disposition studies in rats showed that diphenhydramine is sequestered in the lung (Glazko and Dill, 1949a). However, the incidences in the dosed groups were not significantly greater than that in the controls, there was not a concomitant increase in the incidence of adenomatous hyperplasia, a dose response for these lung neoplasms was not clearly demonstrated, and a similar increase was not observed in female rats.

There were no increased incidences of neoplastic lesions in dosed male or female mice which were considered to be compound related. In male mice, the incidence of hepatocellular carcinomas was increased in the low dose group. This increase was not considered to be chemically related, since the incidence in the high dose group was not increased, hepatocellular neoplasms are common in male $B6C3F_1$ mice, and the combined incidences of hepatocellular adenomas and carcinomas in dosed male mice were not different from that in controls.

A marginal decrease in the incidence of alveolar/bronchiolar neoplasms was observed in high dose male mice. This decrease was probably not due to diphenhydramine hydrochloride, since a marginally increased incidence of alveolar/bronchiolar neoplasms was observed in dosed male rats.

The experimental and tabulated data for the NTP Technical Report on diphenhydramine hydrochloride were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix I, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Under the conditions of these 2-year feed studies, there was *equivocal evidence of carcinogenic activity** of diphenhydramine hydrochloride for male F344/N rats, based on marginally increased incidences of uncommon brain neoplasms (astrocytomas or gliomas) and of alveolar/bronchiolar neoplasms. There was *equivocal evidence of carcinogenic activity* for female F344/N rats, based on a marginal increase in the incidence of pituitary gland adenomas. There was *no evidence of carcinogenic activity* for male or female $B6C3F_1$ mice fed diets containing 156 or 313 ppm diphenhydramine hydrochloride.

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

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	49	50	50
Animals examined histopathologically	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Squamous cell papilloma	2 (4%)	1 (2%)	
Basal cell tumor			1 (2%)
Sebaceous adenoma	1 (2%)	2 (4%)	1 (2%)
Keratoacanthoma	3 (6%)	1 (2%)	1 (2%)
*Subcutaneous tissue	(49)	(50)	(50)
Neoplasm, NOS		1 (2%)	
Sarcoma, NOS		2 (4%)	1 (2%)
Fibroma	2 (4%)	3 (6%)	
Fibrous histiocytoma, malignant		1 (2%)	
Lipoma			2 (4%)
RESPIRATORY SYSTEM			
#Trachea	(49)	(50)	(50)
Sarcoma, NOS, metastatic			1 (2%)
#Lung	(49)	(50)	(50)
Carcinoma, NOS, metastatic			1 (2%)
Alveolar/bronchiolar adenoma		5 (10%)	3 (6%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (2%)	2 (4%)
Tubular cell adenocarcinoma, metastatic			1 (2%)
Sarcoma, NOS, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Leukemia, NOS	1 (2%)		
Leukemia, mononuclear cell	27 (55%)	29 (58%)	27 (54%)
#Spleen	(49)	(49)	(50)
Tubular cell adenocarcinoma, metastatic			1 (2%)
Sarcoma, NOS	1 (2%)		
#Mediastinal lymph node	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
CIRCULATORY SYSTEM			
#Heart	(48)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
Neurilemoma	1 (2%)	2 (4%)	1 (2%)
DIGESTIVE SYSTEM			
*Oral mucosa	(49)	(50)	(50)
Squamous cell carcinoma	1 (2%)		
*Palate	(49)	(50)	(50)
Squamous cell papilloma	1 (2%)	2 (4%)	
*Tongue	(49)	(50)	(50)
Squamous cell papilloma			1 (2%)
#Salivary gland	(48)	(45)	(48)
Cystadenoma, NOS			1 (2%)
#Liver	(49)	(50)	(50)
Hepatocellular adenoma		1 (2%)	
Neoplastic nodule			1 (2%)
Tubular cell adenocarcinoma, metastatic			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(49)	(50)	(50)
Tubular cell adenocarcinoma, metastatic			1 (2%)
Acinar cell adenoma		1 (2%)	
#Forestomach	(49)	(50)	(50)
Squamous cell papilloma	2 (4%)		1 (2%)
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Tubular cell adenocarcinoma			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(50)	(49)
Adenoma, NOS	11 (22%)	21 (42%)	14 (29%)
#Adrenal medulla	(49)	(50)	(50)
Pheochromocytoma	17 (35%)	12 (24%)	14 (28%)
#Thyroid	(48)	(50)	(50)
Follicular cell carcinoma		1 (2%)	
C-cell adenoma	8 (17%)	4 (8%)	9 (18%)
C-cell carcinoma		1 (2%)	2 (4%)
Sarcoma, NOS, metastatic			1 (2%)
#Pancreatic islets	(49)	(50)	(50)
Islet cell adenoma	2 (4%)	1 (2%)	3 (6%)
Islet cell carcinoma	2 (4%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Fibroadenoma	1 (2%)	2 (4%)	2 (4%)
*Preputial gland	(49)	(50)	(50)
Carcinoma, NOS	1 (2%)		4 (8%)
Adenoma, NOS	4 (8%)	3 (6%)	5 (10%)
#Prostate	(49)	(48)	(50)
Adenoma, NOS	3 (6%)	5 (10%)	1 (2%)
#Testis	(49)	(50)	(50)
Tubular cell adenocarcinoma, metastatic			1 (2%)
Interstitial cell tumor	49 (100%)	46 (92%)	48 (96%)
NERVOUS SYSTEM			
#Brain	(49)	(49)	(50)
Glioma, NOS	1 (2%)		1 (2%)
Astrocytoma			3 (6%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(49)	(50)	(50)
Carcinoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Peritoneum	(49)	(50)	(50)
Tubular cell adenocarcinoma, metastatic			1 (2%)
*Pleura	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
BODY CAVITIES (Continued)			
*Epicardium	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic	1 (2%)		
*Mesentery	(49)	(50)	(50)
Tubular cell adenocarcinoma, metastatic			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Mesothelioma, NOS	2 (4%)		2 (4%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7		4
Moribund sacrifice	18	20	23
Terminal sacrifice	25	30	23
TUMOR SUMMARY			
Total animals with primary tumors**	49	49	50
Total primary tumors	145	150	152
Total animals with benign tumors	49	48	49
Total benign tumors	107	112	108
Total animals with malignant tumors	33	35	36
Total malignant tumors	36	37	41
Total animals with secondary tumors##	1		4
Total secondary tumors	2		13
Total animals with tumors--uncertain benign or malignant	2	1	3
Total uncertain tumors	2	1	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 A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: UNTREATED CONTROL

ANIMAL NUMBER	0 3 2	0 4 8	0 2 7	0 3 1	0 2 9	0 3 7	0 1 6	0 2 5	0 3 6	0 3 0	0 2 6	0 1 8	0 4 9	0 3 3	0 3 8	0 4 3	0 5 0	0 0 2	0 0 1	0 1 7	0 1 9	0 1 3	0 2 4	0 3 4	0 4 4
WEEKS ON STUDY	0 3 8	0 6 7	0 7 4	0 8 2	0 8 5	0 8 6	0 8 8	0 8 8	0 8 8	0 9 0	0 9 1	0 9 7	0 9 8	0 9 9	1 0 1	1 0 1	1 0 1	1 0 2	1 0 3	1 0 3	1 0 3	1 0 5	1 0 5	1 0 5	1 0 5
INTEGUMENTARY SYSTEM																									
Skin	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Squamous cell papilloma							X															X			
Sebaceous adenoma																									X
Keratoacanthoma															X										
Subcutaneous tissue	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Fibroma																						X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Lymph nodes	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	A	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	—	+	+	+	+	+	+	+
Neurilemoma																							X		
DIGESTIVE SYSTEM																									
Oral cavity	A	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
Squamous cell carcinoma																	X								
Salivary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	X					X									
Adrenal	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma														X		X				X		X			X
Thyroid	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
C-cell adenoma															X						X		X	X	
Parathyroid	A	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	–	+	+
Pancreatic islets	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																			X						
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Fibroadenoma																									
Testis	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																						X			
Preputial/clitoral gland	A	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											
Adenoma, NOS															X										
NERVOUS SYSTEM																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS																						X			
SPECIAL SENSE ORGANS																									
Zymbal gland	A	+	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																									
Pleura	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, metastatic																									
Pericardium	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, metastatic																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS		X											X												
Leukemia, NOS						X																			
Leukemia, mononuclear cell			X	X	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
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
S: Animal missexed
B: No necropsy performed
* Animals necropsied

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

ANIMAL NUMBER	00003	00004	00005	00006	00007	00008	00009	01010	01011	01012	01014	01015	02020	02021	02022	02023	02028	03035	03039	04040	04041	04042	04045	04046	04047	TOTAL:
WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Squamous cell papilloma																										2
Sebaceous adenoma																										1
Keratoacanthoma				X														X								3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibroma						X																				2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma																			X							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS														X												1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neurilemoma																										1
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	*49
Squamous cell papilloma																										1
Squamous cell carcinoma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																							X			2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X				X			X	X	X							X						X		11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma		X	X	X		X	X	X			X	X		X		X						X	X			17
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma					X											X	X				X					8
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	–	43
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma											X															2
Islet cell carcinoma						X																X				2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	*49
Fibroadenoma													X													1
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	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS							X						X													3
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	*49
Carcinoma, NOS																										1
Adenoma, NOS												X								X			X			4
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Glioma, NOS																										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	*49
Carcinoma, NOS																										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Alveolar/bronchiolar carcinoma, meta																				X						1
Pericardium	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
Alveolar/bronchiolar carcinoma, meta																				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	*49
Mesothelioma, NOS																										2
Leukemia, NOS																										1
Leukemia, mononuclear cell	X	X	X		X	X	X		X								X	X		X	X	X				27

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: LOW DOSE

ANIMAL NUMBER	0019	0005	0033	0118	0445	0006	0227	0337	0331	0443	0442	0338	0339	0441	0111	0222	0335	0449	0117	0221	0001	0002	0003	0004	0007
WEEKS ON STUDY	0666	0668	0711	0883	0884	0885	0888	0891	0993	0993	0996	0997	0997	0997	0998	0998	0999	0999	1044	1044	1055	1055	1055	1055	1055
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Squamous cell papilloma																									
Sebaceous adenoma					X																				
Keratoacanthoma																	X								
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Neoplasm, NOS																X									
Sarcoma, NOS					X																				
Fibroma		X									X														
Fibrous histiocytoma, malignant																									X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																						X			
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	–	–	+	+	+	+	+	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X							X					X	X	X				X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma												X					X		X	X					
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C cell adenoma																									
C cell carcinoma																			X						
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma												X													
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																X									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X		X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							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																
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	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X	

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

ANIMAL NUMBER	0008	0009	0110	0112	0113	0114	0115	0116	0120	0123	0124	0125	0126	0128	0129	0130	0132	0134	0136	0140	0144	0146	0147	0148	0150	
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	106	106	106	106	106	106	106	108	106	TOTAL: TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma					X																					1
Sebaceous adenoma															X											2
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Neoplasm, NOS																										1
Sarcoma, NOS																		X								2
Fibroma																X										3
Fibrous histiocytoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X		X								X		X								5
Alveolar/bronchiolar carcinoma																	X									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma																						X		X		2
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										X																2
Salivary gland	+	−	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																							X			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma								X																		1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X		X		X	X	X				X		X		X			X	X		X	X	X	X	X	21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma							X	X			X		X	X	X					X			X			12
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																								X		1
C-cell adenoma				X	X												X				X					4
C-cell carcinoma																										1
Parathyroid	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	45
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																	X									1
Islet cell carcinoma					X																					2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	*50
Fibroadenoma																								X		2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	46
Prostate	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	48
Adenoma, NOS	X																	X				X				5
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																	3
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				X	X	X	X	X					X	X	X			X	29

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: HIGH DOSE

ANIMAL NUMBER	0041	0003	0255	0244	0119	0336	0446	0443	0155	0055	0066	0388	0330	0117	0227	0422	0550	0007	0440	0022	0116	0088	0221	0299	0188
WEEKS ON STUDY	0668	0669	0771	0772	0776	0778	0779	0881	0883	0888	0889	0889	0891	0944	0944	0944	0944	0955	0996	0997	0997	0998	0999	1001	1001
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+
Basal cell tumor																									
Sebaceous adenoma																									
Keratoacanthoma																	X								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+
Sarcoma, NOS																									
Lipoma																								X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic															X										
Alveolar/bronchiolar adenoma					X																				
Alveolar/bronchiolar carcinoma	X																								
Tubular cell adenocarcinoma, metastatic																									
Sarcoma, NOS, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																									
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma, metastatic																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic	X																								
Thymus	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic	X																								
Neurilemoma																									
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																									
Salivary gland	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Tubular cell adenocarcinoma, metastatic																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma, metastatic																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

ANIMAL NUMBER	0045	0001	0004	0009	0110	0111	0112	0113	0114	0120	0132	0122	0123	0126	0128	0131	0133	0134	0135	0137	0139	0144	0147	0148	0149	TOTAL:
WEEKS ON STUDY	101	104	104	104	104	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Basal cell tumor										X																1
Sebaceous adenoma										X																1
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Sarcoma, NOS																							X			1
Lipoma																	X									2
RESPIRATORY SYSTEM																										
Lungs and bronchi	●	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma							X						X													3
Alveolar/bronchiolar carcinoma																X										2
Tubular cell adenocarcinoma, metastatic						X																				1
Sarcoma, NOS, metastatic																							X			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic																							X			1
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma, metastatic						X																				1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, meta																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	−	+	+	+	+	+	+	+	+	44
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, meta																										1
Neurilemoma																									X	1
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																							X			1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	48
Cystadenoma, NOS									X																	1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																								X		1
Tubular cell adenocarcinoma, metastatic						X																				1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma, metastatic						X																				1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

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

ANIMAL NUMBER	041	003	025	024	019	036	046	043	015	005	006	038	030	017	027	042	050	007	040	002	016	008	021	029	018
WEEKS ON STUDY	068	069	071	072	076	078	079	081	083	088	089	089	091	094	094	094	094	095	096	097	097	098	099	100	101
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X							X							X	X			X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma								X					X	X					X						X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma								X		X				X						X					
C-cell carcinoma																									
Sarcoma, NOS, metastatic																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma						X																			
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma, metastatic																									
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
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																				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
Carcinoma, NOS										X		X		X	X										
Adenoma, NOS																					X				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS			X																						
Astrocytoma	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
Tubular cell adenocarcinoma, metastatic																									
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
Tubular cell adenocarcinoma, metastatic																									
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
Mesothelioma, NOS					X																				
Leukemia, mononuclear cell		X					X	X	X	X	X		X	X		X	X	X	X	X		X	X		X

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

ANIMAL NUMBER	0045	0001	0004	0009	0110	0111	0112	0113	0114	0120	0132	0222	0223	0226	0228	0231	0233	0234	0235	0237	0239	0244	0247	0248	0249	TOTAL:
WEEKS ON STUDY	1001	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	TISSUES TUMORS
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma						X																				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X			X				X	X		X		X	X		X									14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X						X	X	X							X	X		X						X	14
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma					X					X					X				X						X	9
C-cell carcinoma		X							X																	2
Sarcoma, NOS, metastatic																							X			1
Parathyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	−	+	+	−	44
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma											X			X								X				3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma							X																			2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma, metastatic						X																				1
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	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										4
Adenoma, NOS					X							X							X	X						5
NERVOUS SYSTEM																										
Brain	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS																										1
Astrocytoma												X		X												3
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Tubular cell adenocarcinoma, metastatic						X																				1
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
Tubular cell adenocarcinoma, metastatic						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
Mesothelioma, NOS							X																			2
Leukemia, mononuclear cell				X				X			X		X	X	X	X	X		X			X		X		27

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Control	315 ppm	625 ppm
Skin: Keratoacanthoma			
Overall Rates (a)	3/49 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	9.5%	2.9%	2.7%
Terminal Rates (c)	2/29 (7%)	0/32 (0%)	0/24 (0%)
Week of First Observation	101	99	94
Life Table Tests (d)	P=0.256N	P=0.308N	P=0.376N
Incidental Tumor Tests (d)	P=0.176N	P=0.288N	P=0.292N
Cochran-Armitage Trend Test (d)	P=0.196N		
Fisher Exact Test (d)		P=0.301N	P=0.301N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	2/49 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	6.9%	7.5%	0.0%
Terminal Rates (c)	2/29 (7%)	1/32 (3%)	0/24 (0%)
Week of First Observation	104	68	
Life Table Tests (d)	P=0.236N	P=0.531	P=0.280N
Incidental Tumor Tests (d)	P=0.157N	P=0.563	P=0.280N
Cochran-Armitage Trend Test (d)	P=0.196N		
Fisher Exact Test (d)		P=0.510	P=0.242N
Subcutaneous Tissue: Fibroma or Sarcoma			
Overall Rates (a)	2/49 (4%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	6.9%	12.4%	4.2%
Terminal Rates (c)	2/29 (7%)	2/32 (6%)	1/24 (4%)
Week of First Observation	104	68	104
Life Table Tests (d)	P=0.479N	P=0.247	P=0.566N
Incidental Tumor Tests (d)	P=0.393N	P=0.239	P=0.566N
Cochran-Armitage Trend Test (d)	P=0.403N		
Fisher Exact Test (d)		P=0.226	P=0.492N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	0/49 (0%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	0.0%	15.6%	10.3%
Terminal Rates (c)	0/29 (0%)	5/32 (16%)	2/24 (8%)
Week of First Observation		104	76
Life Table Tests (d)	P=0.089	P=0.041	P=0.100
Incidental Tumor Tests (d)	P=0.118	P=0.041	P=0.152
Cochran-Armitage Trend Test (d)	P=0.137		
Fisher Exact Test (d)		P=0.030	P=0.125
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	1/49 (2%)	6/50 (12%)	5/50 (10%)
Adjusted Rates (b)	3.4%	18.8%	16.1%
Terminal Rates (c)	1/29 (3%)	6/32 (19%)	3/24 (13%)
Week of First Observation	104	104	68
Life Table Tests (d)	P=0.060	P=0.072	P=0.080
Incidental Tumor Tests (d)	P=0.095	P=0.072	P=0.144
Cochran-Armitage Trend Test (d)	P=0.103		
Fisher Exact Test (d)		P=0.059	P=0.107
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	27/49 (55%)	29/50 (58%)	27/50 (54%)
Adjusted Rates (b)	62.0%	64.1%	65.8%
Terminal Rates (c)	13/29 (45%)	16/32 (50%)	11/24 (46%)
Week of First Observation	74	66	69
Life Table Tests (d)	P=0.263	P=0.519	P=0.289
Incidental Tumor Tests (d)	P=0.509N	P=0.415	P=0.566N
Cochran-Armitage Trend Test (d)	P=0.496N		
Fisher Exact Test (d)		P=0.465	P=0.537N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Control	315 ppm	625 ppm
Hematopoietic System: Leukemia			
Overall Rates (a)	28/49 (57%)	29/50 (58%)	27/50 (54%)
Adjusted Rates (b)	62.9%	64.1%	65.8%
Terminal Rates (c)	13/29 (45%)	16/32 (50%)	11/24 (46%)
Week of First Observation	74	66	69
Life Table Tests (d)	P=0.316	P=0.543N	P=0.342
Incidental Tumor Tests (d)	P=0.428N	P=0.479	P=0.487N
Cochran-Armitage Trend Test (d)	P=0.415N		
Fisher Exact Test (d)		P=0.546	P=0.456N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	11/49 (22%)	21/50 (42%)	14/49 (29%)
Adjusted Rates (b)	31.4%	57.9%	44.4%
Terminal Rates (c)	7/29 (24%)	17/32 (53%)	8/24 (33%)
Week of First Observation	88	84	72
Life Table Tests (d)	P=0.133	P=0.049	P=0.181
Incidental Tumor Tests (d)	P=0.198	P=0.028	P=0.256
Cochran-Armitage Trend Test (d)	P=0.292		
Fisher Exact Test (d)		P=0.031	P=0.322
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	17/49 (35%)	12/50 (24%)	14/50 (28%)
Adjusted Rates (b)	52.6%	35.0%	42.9%
Terminal Rates (c)	14/29 (48%)	10/32 (31%)	7/24 (29%)
Week of First Observation	99	97	81
Life Table Tests (d)	P=0.511N	P=0.128N	P=0.580N
Incidental Tumor Tests (d)	P=0.365N	P=0.116N	P=0.418N
Cochran-Armitage Trend Test (d)	P=0.268N		
Fisher Exact Test (d)		P=0.172N	P=0.308N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	8/48 (17%)	4/50 (8%)	9/50 (18%)
Adjusted Rates (b)	25.3%	12.5%	29.0%
Terminal Rates (c)	6/29 (21%)	4/32 (13%)	5/24 (21%)
Week of First Observation	101	105	81
Life Table Tests (d)	P=0.307	P=0.144N	P=0.342
Incidental Tumor Tests (d)	P=0.387	P=0.132N	P=0.453
Cochran-Armitage Trend Test (d)	P=0.476		
Fisher Exact Test (d)		P=0.159N	P=0.537
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	8/48 (17%)	5/50 (10%)	11/50 (22%)
Adjusted Rates (b)	25.3%	15.6%	36.4%
Terminal Rates (c)	6/29 (21%)	5/32 (16%)	7/24 (29%)
Week of First Observation	101	104	81
Life Table Tests (d)	P=0.138	P=0.229N	P=0.173
Incidental Tumor Tests (d)	P=0.189	P=0.213N	P=0.249
Cochran-Armitage Trend Test (d)	P=0.276		
Fisher Exact Test (d)		P=0.251N	P=0.341
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	2/49 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	6.5%	3.1%	12.5%
Terminal Rates (c)	1/29 (3%)	1/32 (3%)	3/24 (13%)
Week of First Observation	103	104	104
Life Table Tests (d)	P=0.321	P=0.477N	P=0.405
Incidental Tumor Tests (d)	P=0.357	P=0.477N	P=0.455
Cochran-Armitage Trend Test (d)	P=0.408		
Fisher Exact Test (d)		P=0.492N	P=0.510

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Control	315 ppm	625 ppm
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	4/49 (8%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	13.1%	8.7%	12.5%
Terminal Rates (c)	3/29 (10%)	2/32 (6%)	3/24 (13%)
Week of First Observation	103	97	104
Life Table Tests (d)	P=0.522N	P=0.462N	P=0.611N
Incidental Tumor Tests (d)	P=0.465N	P=0.462N	P=0.569N
Cochran-Armitage Trend Test (d)	P=0.410N		
Fisher Exact Test (d)		P=0.489N	P=0.489N
Preputial Gland: Adenoma			
Overall Rates (a)	4/49 (8%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	12.8%	7.4%	19.4%
Terminal Rates (c)	3/29 (10%)	1/32 (3%)	4/24 (17%)
Week of First Observation	101	68	97
Life Table Tests (d)	P=0.333	P=0.472N	P=0.371
Incidental Tumor Tests (d)	P=0.450	P=0.439N	P=0.444
Cochran-Armitage Trend Test (d)	P=0.439		
Fisher Exact Test (d)		P=0.489N	P=0.513
Preputial Gland: Carcinoma			
Overall Rates (a)	1/49 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	2.7%	0.0%	10.0%
Terminal Rates (c)	0/29 (0%)	0/32 (0%)	0/24 (0%)
Week of First Observation	99		88
Life Table Tests (d)	P=0.071	P=0.517N	P=0.157
Incidental Tumor Tests (d)	P=0.102	P=0.500N	P=0.207
Cochran-Armitage Trend Test (d)	P=0.085		
Fisher Exact Test (d)		P=0.495N	P=0.187
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	3/50 (6%)	9/50 (18%)
Adjusted Rates (b)	15.2%	7.4%	27.4%
Terminal Rates (c)	3/29 (10%)	1/32 (3%)	4/24 (17%)
Week of First Observation	99	68	88
Life Table Tests (d)	P=0.091	P=0.341N	P=0.124
Incidental Tumor Tests (d)	P=0.160	P=0.304N	P=0.182
Cochran-Armitage Trend Test (d)	P=0.143		
Fisher Exact Test (d)		P=0.346N	P=0.205
Prostate: Adenoma			
Overall Rates (a)	3/49 (6%)	5/48 (10%)	1/50 (2%)
Adjusted Rates (b)	10.3%	16.7%	3.2%
Terminal Rates (c)	3/29 (10%)	5/30 (17%)	0/24 (0%)
Week of First Observation	104	104	97
Life Table Tests (d)	P=0.341N	P=0.372	P=0.379N
Incidental Tumor Tests (d)	P=0.316N	P=0.372	P=0.333N
Cochran-Armitage Trend Test (d)	P=0.257N		
Fisher Exact Test (d)		P=0.346	P=0.301N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	49/49 (100%)	46/50 (92%)	48/50 (96%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	29/29 (100%)	32/32 (100%)	24/24 (100%)
Week of First Observation	67	68	68
Life Table Tests (d)	P=0.152	P=0.203N	P=0.168
Incidental Tumor Tests (d)	P=0.531N	P=0.077N	P=0.500N
Cochran-Armitage Trend Test (d)	P=0.227N		
Fisher Exact Test (d)		P=0.061N	P=0.253N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Control	315 ppm	625 ppm
Brain: Astrocytoma (original three sections)			
Overall Rates (a)	0/49 (0%)	0/49 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	10.2%
Terminal Rates (c)	0/29 (0%)	0/31 (0%)	2/24 (8%)
Week of First Observation			68
Life Table Tests (d)	P=0.030	(e)	P=0.103
Incidental Tumor Tests (d)	P=0.048	(e)	P=0.152
Cochran-Armitage Trend Test (d)	P=0.039		
Fisher Exact Test (d)		(e)	P=0.125
Brain: Glioma or Astrocytoma (original three sections)			
Overall Rates (a)	1/49 (2%)	0/49 (0%)	4/50 (8%)
Adjusted Rates (b)	3.4%	0.0%	12.0%
Terminal Rates (c)	1/29 (3%)	0/31 (0%)	2/24 (8%)
Week of First Observation	104		68
Life Table Tests (d)	P=0.067	P=0.487N	P=0.152
Incidental Tumor Tests (d)	P=0.127	P=0.487N	P=0.264
Cochran-Armitage Trend Test (d)	P=0.085		
Fisher Exact Test (d)		P=0.500N	P=0.187
Brain: Astrocytoma (six sections) (f)			
Overall Rates (a)	0/49 (0%)	0/49 (0%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	14.2%
Terminal Rates (c)	0/29 (0%)	0/31 (0%)	3/24 (13%)
Week of First Observation			68
Life Table Tests (d)	P=0.010	(e)	P=0.048
Incidental Tumor Tests (d)	P=0.017	(e)	P=0.071
Cochran-Armitage Trend Test (d)	P=0.016		
Fisher Exact Test (d)		(e)	P=0.061
Brain: Glioma or Astrocytoma (six sections) (f)			
Overall Rates (a)	1/49 (2%)	0/49 (0%)	5/50 (10%)
Adjusted Rates (b)	3.4%	0.0%	16.0%
Terminal Rates (c)	1/29 (3%)	0/31 (0%)	3/24 (13%)
Week of First Observation	104		68
Life Table Tests (d)	P=0.027	P=0.487N	P=0.080
Incidental Tumor Tests (d)	P=0.054	P=0.487N	P=0.144
Cochran-Armitage Trend Test (d)	P=0.039		
Fisher Exact Test (d)		P=0.500N	P=0.107
All Sites: Benign Tumors			
Overall Rates (a)	49/49 (100%)	48/50 (96%)	49/50 (98%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	29/29 (100%)	32/32 (100%)	24/24 (100%)
Week of First Observation	67	68	68
Life Table Tests (d)	P=0.116	P=0.321N	P=0.135
Incidental Tumor Tests (d)	P=0.635	P=0.309N	P=0.718N
Cochran-Armitage Trend Test (d)	P=0.365N		
Fisher Exact Test (d)		P=0.253N	P=0.505N
All Sites: Malignant Tumors			
Overall Rates (a)	33/49 (67%)	35/50 (70%)	36/50 (72%)
Adjusted Rates (b)	71.4%	75.8%	80.9%
Terminal Rates (c)	16/29 (55%)	21/32 (66%)	16/24 (67%)
Week of First Observation	74	66	68
Life Table Tests (d)	P=0.116	P=0.538	P=0.137
Incidental Tumor Tests (d)	P=0.309	P=0.384	P=0.367
Cochran-Armitage Trend Test (d)	P=0.347		
Fisher Exact Test (d)		P=0.473	P=0.388

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Control	315 ppm	625 ppm
All Sites: All Tumors			
Overall Rates (a)	49/49 (100%)	49/50 (98%)	50/50 (100%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	29/29 (100%)	32/32 (100%)	24/24 (100%)
Week of First Observation	67	66	68
Life Table Tests (d)	P=0.092	P=0.384N	P=0.108
Incidental Tumor Tests (d)	P=0.571	P=0.581N	(g)
Cochran-Armitage Trend Test (d)	P=0.729		
Fisher Exact Test (d)		P=0.505N	P=1.000N

(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 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 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) No P value is reported because no tumors were observed in the control and 315-ppm groups.
(f) The diagnoses from the additional three sections are not included in Tables A1 and A2.
(g) No P value is reported because all animals in the control and 625-ppm groups had tumors.

TABLE A4a. HISTORICAL INCIDENCE OF BRAIN TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence of Glial Cell Tumors in Controls
No 2-year studies by SRI International are included in the historical data base.	
Overall Historical Incidence	
TOTAL (b)	13/1,928 (0.7%)
SD (c)	1.24%
Range (d)	
High	2/50
Low	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Includes two gliomas, NOS, nine astrocytomas, and two oligodendrogliomas
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by SRI International are included in the historical data base.			
Overall Historical Incidence			
TOTAL	417/1,830 (22.8%)	42/1,830 (2.3%)	459/1,830 (25.1%)
SD (b)	10.75%	2.85%	10.32%
Range (c)			
High	24/46	5/45	25/46
Low	2/39	0/50	2/39

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4c. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by SRI International are included in the historical data base.			
Overall Historical Incidence			
TOTAL	25/1,933 (1.3%)	20/1,933 (1.0%)	43/1,933 (2.2%)
SD (b)	1.70%	1.77%	2.20%
Range (c)			
High	3/49	3/50	4/49
Low	0/50	0/50	0/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	49	50	50
Animals examined histopathologically	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Epidermal inclusion cyst	3 (6%)	1 (2%)	
Hyperkeratosis	2 (4%)	2 (4%)	
*Subcutaneous tissue	(49)	(50)	(50)
Abscess, NOS	2 (4%)		1 (2%)
Granuloma, NOS	2 (4%)		
RESPIRATORY SYSTEM			
#Nasal cavity	(49)	(50)	(50)
Hemorrhage	1 (2%)		1 (2%)
Inflammation, acute	2 (4%)		
Abscess, NOS			1 (2%)
Inflammation, chronic		1 (2%)	3 (6%)
Infection, fungal	1 (2%)		1 (2%)
#Lung	(49)	(50)	(50)
Atelectasis	1 (2%)	2 (4%)	1 (2%)
Congestion, NOS	3 (6%)		1 (2%)
Hemorrhage	2 (4%)	2 (4%)	1 (2%)
Pneumonia, interstitial chronic	1 (2%)		
Hyperplasia, adenomatous	4 (8%)	5 (10%)	3 (6%)
Histiocytosis	1 (2%)		
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(50)	(49)
Hypoplasia, NOS			1 (2%)
Hyperplasia, NOS	1 (2%)		
Myelofibrosis			1 (2%)
Hyperplasia, reticulum cell			1 (2%)
#Spleen	(49)	(49)	(50)
Congestion, NOS	6 (12%)	1 (2%)	1 (2%)
Fibrosis	1 (2%)		
Fibrosis, focal	1 (2%)	1 (2%)	1 (2%)
Infarct, NOS	1 (2%)	1 (2%)	2 (4%)
Metaplasia, myeloid	4 (8%)	5 (10%)	3 (6%)
#Lymph node	(49)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Hematoma, organized		1 (2%)	
Granuloma, NOS			3 (6%)
Hyperplasia, NOS	3 (6%)	1 (2%)	
Histiocytosis	1 (2%)	3 (6%)	3 (6%)
Plasmacytosis	6 (12%)	1 (2%)	4 (8%)
#Mandibular lymph node	(49)	(50)	(50)
Hyperplasia, NOS	1 (2%)		
#Thymus	(45)	(44)	(44)
Atrophy, NOS	1 (2%)		
Hyperplasia, NOS	1 (2%)		1 (2%)
Hyperplasia, epithelial		1 (2%)	
CIRCULATORY SYSTEM			
#Lymph node	(49)	(50)	(50)
Lymphangiectasis	1 (2%)	2 (4%)	
#Nasal cavity	(49)	(50)	(50)
Thrombosis, NOS			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
CIRCULATORY SYSTEM (Continued)			
#Lung	(49)	(50)	(50)
Embolism, NOS			1 (2%)
#Heart	(48)	(50)	(50)
Thrombus, mural	4 (8%)	3 (6%)	4 (8%)
Hemorrhage	1 (2%)		
Inflammation, chronic focal		1 (2%)	
Fibrosis, focal	20 (42%)	16 (32%)	19 (38%)
Necrosis, focal			1 (2%)
Infarct, NOS			1 (2%)
#Endocardium	(48)	(50)	(50)
Fibrosis, focal			1 (2%)
#Aortic valve	(48)	(50)	(50)
Thrombosis, NOS		1 (2%)	
*Artery	(49)	(50)	(50)
Medial calcification	1 (2%)		
*Superior pancreaticoduodenal artery	(49)	(50)	(50)
Periarteritis		1 (2%)	
*Jugular vein	(49)	(50)	(50)
Thrombosis, NOS	1 (2%)		
*Portal vein	(49)	(50)	(50)
Thrombosis, NOS			1 (2%)
Thrombus, organized	1 (2%)		
#Testis	(49)	(50)	(50)
Polyangiitis		1 (2%)	
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(50)
Congenital malformation, NOS	2 (4%)		
Congestion, NOS	1 (2%)	1 (2%)	
Congestion, chronic passive	1 (2%)		
Granuloma, NOS		3 (6%)	4 (8%)
Degeneration, cystic	2 (4%)		1 (2%)
Peliosis hepatis	11 (22%)	11 (22%)	7 (14%)
Degeneration, hydropic		1 (2%)	
Necrosis, NOS	2 (4%)		1 (2%)
Infarct, NOS	2 (4%)		1 (2%)
Metamorphosis, fatty	5 (10%)		3 (6%)
Basophilic cyto change	3 (6%)		1 (2%)
Eosinophilic cyto change	1 (2%)		
Clear cell change	3 (6%)		1 (2%)
Hyperplastic nodule		2 (4%)	
#Bile duct	(49)	(50)	(50)
Hyperplasia, NOS	33 (67%)	22 (44%)	25 (50%)
#Pancreas	(49)	(50)	(50)
Cyst, NOS			1 (2%)
Hematoma, NOS	1 (2%)		
Atrophy, focal		1 (2%)	
#Pancreatic acinus	(49)	(50)	(50)
Atrophy, NOS	9 (18%)	10 (20%)	5 (10%)
#Stomach	(49)	(50)	(50)
Edema, NOS			1 (2%)
Granuloma, foreign body	1 (2%)		
Erosion	1 (2%)	1 (2%)	1 (2%)
#Glandular stomach	(49)	(50)	(50)
Calcification, NOS	1 (2%)		
#Forestomach	(49)	(50)	(50)
Hyperplasia, epithelial			1 (2%)
#Colon	(48)	(50)	(50)
Edema, NOS		1 (2%)	
Parasitism	1 (2%)		1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM (Continued)			
#Cecum	(48)	(50)	(50)
Edema, NOS		1 (2%)	1 (2%)
Ulcer, NOS	1 (2%)		
Inflammation, acute		1 (2%)	
Erosion		2 (4%)	
Parasitism	1 (2%)		
*Rectum	(49)	(50)	(50)
Parasitism	1 (2%)		3 (6%)
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
Nephropathy	42 (86%)	44 (88%)	39 (78%)
Nephrosis, cholemic		1 (2%)	
Necrosis, focal		1 (2%)	
Infarct, NOS	1 (2%)		1 (2%)
#Kidney/pelvis	(49)	(50)	(50)
Dilatation, NOS			1 (2%)
#Urinary bladder	(48)	(48)	(48)
Edema, NOS			1 (2%)
Hemorrhage	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(50)	(49)
Cyst, NOS	1 (2%)	1 (2%)	
#Anterior pituitary	(49)	(50)	(49)
Cyst, NOS	1 (2%)	5 (10%)	2 (4%)
Hemorrhage	2 (4%)		1 (2%)
Infarct, NOS		1 (2%)	
Hyperplasia, NOS	6 (12%)	6 (12%)	9 (18%)
#Adrenal	(49)	(50)	(50)
Congestion, NOS	1 (2%)		
#Adrenal cortex	(49)	(50)	(50)
Degeneration, NOS	1 (2%)		
Infarct, focal	1 (2%)		
Metamorphosis, fatty	1 (2%)		
Hyperplasia, NOS	3 (6%)	2 (4%)	2 (4%)
#Adrenal medulla	(49)	(50)	(50)
Hyperplasia, NOS	4 (8%)		
#Thyroid	(48)	(50)	(50)
Cyst, NOS	1 (2%)		
Follicular cyst, NOS	1 (2%)		
Hyperplasia, C-cell	3 (6%)	3 (6%)	4 (8%)
Metaplasia, squamous		1 (2%)	
#Parathyroid	(43)	(45)	(44)
Hyperplasia, NOS			1 (2%)
Hyperplasia, secondary	7 (16%)	3 (7%)	
#Pancreatic islets	(49)	(50)	(50)
Hyperplasia, NOS	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Lactation	4 (8%)	1 (2%)	3 (6%)
*Preputial gland	(49)	(50)	(50)
Cyst, NOS	22 (45%)	27 (54%)	26 (52%)
Inflammation, acute		2 (4%)	1 (2%)
Abscess, NOS	3 (6%)	7 (14%)	2 (4%)
Inflammation, chronic	12 (24%)	6 (12%)	6 (12%)
Atrophy, NOS	25 (51%)	20 (40%)	34 (68%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
Preputial gland (Continued)	(49)	(50)	(50)
Hyperplasia, focal	1 (2%)		
Metaplasia, squamous			1 (2%)
#Prostate	(49)	(48)	(50)
Inflammation, acute	3 (6%)	2 (4%)	1 (2%)
Inflammation, chronic			2 (4%)
Atrophy, NOS		1 (2%)	
Hyperplasia, NOS	1 (2%)	1 (2%)	5 (10%)
*Seminal vesicle	(49)	(50)	(50)
Dilatation, NOS		1 (2%)	
Fibrosis			1 (2%)
Degeneration, NOS	1 (2%)		2 (4%)
Atrophy, NOS	15 (31%)	12 (24%)	13 (26%)
Hyperplasia, NOS			1 (2%)
#Testis	(49)	(50)	(50)
Atrophy, NOS	7 (14%)	7 (14%)	5 (10%)
Hyperplasia, interstitial cell	2 (4%)	4 (8%)	3 (6%)
*Epididymis	(49)	(50)	(50)
Edema, NOS			1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)
Granuloma, spermatic		1 (2%)	
Fibrosis	2 (4%)	1 (2%)	2 (4%)
Degeneration, NOS	22 (45%)	19 (38%)	11 (22%)
Cytoplasmic vacuolization	3 (6%)		1 (2%)
Atrophy, NOS		2 (4%)	2 (4%)
*Scrotum	(49)	(50)	(50)
Hydrocele		1 (2%)	
NERVOUS SYSTEM			
#Brain	(49)	(49)	(50)
Hydrocephalus, NOS	1 (2%)	1 (2%)	
Hemorrhage	3 (6%)	1 (2%)	1 (2%)
Degeneration, myelin	1 (2%)		
*Optic nerve	(49)	(50)	(50)
Hemorrhage	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye	(49)	(50)	(50)
Cataract	2 (4%)	2 (4%)	1 (2%)
Phthisis bulbi		1 (2%)	
*Eye/sclera	(49)	(50)	(50)
Metaplasia, osseous	1 (2%)		
*Eye/retina	(49)	(50)	(50)
Degeneration, NOS	2 (4%)	2 (4%)	1 (2%)
Atrophy, NOS	1 (2%)		
*Eyelid	(49)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Inflammation, chronic			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Bone	(49)	(50)	(50)
Fibrous osteodystrophy	5 (10%)		
*Skeletal muscle	(49)	(50)	(50)
Abscess, NOS	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
BODY CAVITIES			
*Abdominal wall	(49)	(50)	(50)
Hematoma, NOS	1 (2%)		
ALL OTHER SYSTEMS			
Adipose tissue			
Necrosis, fat	6	6	2
Atrophy, brown		1	
SPECIAL MORPHOLOGY SUMMARY			
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 B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)	1 (2%)	1 (2%)
Basal cell tumor	1 (2%)		
Keratoacanthoma	1 (2%)		1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS			2 (4%)
Neurilemoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma	3 (6%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma			1 (2%)
Sarcoma, NOS, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	11 (22%)	18 (36%)	9 (18%)
#Lymph node	(50)	(50)	(50)
Squamous cell carcinoma, metastatic	1 (2%)		
C-cell carcinoma, metastatic	1 (2%)		
#Thymus	(49)	(43)	(42)
Thymoma, benign		1 (2%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Neurilemoma	1 (2%)	1 (2%)	
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
*Tongue	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	1 (2%)
#Forestomach	(50)	(49)	(50)
Squamous cell papilloma	1 (2%)		
Squamous cell carcinoma		1 (2%)	
*Rectum	(50)	(50)	(50)
Leiomyosarcoma		1 (2%)	
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(50)
Adenoma, NOS	23 (46%)	26 (52%)	35 (70%)
#Adrenal medulla	(49)	(50)	(48)
Pheochromocytoma	1 (2%)	2 (4%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(49)	(49)
Follicular cell carcinoma		1 (2%)	1 (2%)
C-cell adenoma	5 (10%)	6 (12%)	6 (12%)
C-cell carcinoma	2 (4%)	1 (2%)	
#Parathyroid	(42)	(45)	(46)
Adenoma, NOS			1 (2%)
#Pancreatic islets	(50)	(50)	(50)
Islet cell adenoma		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)	2 (4%)	1 (2%)
Adenocarcinoma, NOS		3 (6%)	1 (2%)
Fibroadenoma	19 (38%)	18 (36%)	21 (42%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	4 (8%)		1 (2%)
Adenoma, NOS	2 (4%)	4 (8%)	3 (6%)
#Uterus	(50)	(50)	(50)
Endometrial stromal polyp	9 (18%)	11 (22%)	7 (14%)
Endometrial stromal sarcoma	2 (4%)		1 (2%)
#Uterus/endometrium	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
Adenocarcinoma, NOS	1 (2%)		
#Ovary	(50)	(50)	(49)
Granulosa cell tumor	1 (2%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteosarcoma			1 (2%)
*Mandible	(50)	(50)	(50)
Squamous cell carcinoma, invasive		1 (2%)	
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	5	3
Moribund sacrifice	15	17	12
Terminal sacrifice	33	28	35

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	47	46	46
Total primary tumors	90	100	99
Total animals with benign tumors	37	40	45
Total benign tumors	68	74	81
Total animals with malignant tumors	21	23	16
Total malignant tumors	21	26	18
Total animals with secondary tumors##	3	1	1
Total secondary tumors	3	1	1
Total animals with tumors--uncertain benign or malignant	1		
Total uncertain tumors	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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: UNTREATED CONTROL

ANIMAL NUMBER	02240	02405	02596	00228	01109	02606	00833	03707	11999	04808	00906	00505	00809	03909	11606	11202	10101	10404	00707	00909	01111	01313	01414	01505	01707
WEEKS ON STUDY	07202	07505	07606	07808	07708	07808	08000	08803	08805	08805	09202	09903	09903	09906	10000	10004	10006	10006	10006	10006	10006	10006	10006	10006	10006
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Squamous cell carcinoma		X																							
Basal cell tumor																									
Keratoacanthoma		X																							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
Alveolar/bronchiolar adenoma																					X				
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic		X																							
C cell carcinoma, metastatic																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma		X																							
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X	X				X			X	X	X					X		X		X	X
Adrenal	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell adenoma									X							X								X	
C cell carcinoma																									
Parathyroid	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS															X										
Fibroadenoma			X			X				X		X				X			X		X				
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS									X					X						X					
Adenoma, NOS															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adenocarcinoma, NOS																									
Endometrial stromal polyp					X			X					X		X	X									
Endometrial stromal sarcoma							X											X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																		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
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
*: Animals necropsied
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	0018	0021	0022	0023	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0038	0040	0041	0042	0043	0044	0045	0046	0047	0049	0050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Basal cell tumor	X																									1
Keratoacanthoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																							X			1
Alveolar/bronchiolar adenoma								X												X						3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic																										1
C-cell carcinoma, metastatic				X																						1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma																								X		1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	–	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS								X	X	X	X	X			X		X	X		X	X	X		X	X	23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																									X	1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell adenoma									X							X										5
C-cell carcinoma				X							X															2
Parathyroid	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	42
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										1
Fibroadenoma	X	X	X		X			X		X	X								X	X	X	X			X	19
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						4
Adenoma, NOS	X																									2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																									X	1
Adenocarcinoma, NOS																							X			1
Endometrial stromal polyp		X							X			X								X						9
Endometrial stromal sarcoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	48
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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: LOW DOSE

ANIMAL NUMBER	040	001	042	038	023	031	036	004	007	012	013	032	047	005	037	049	025	006	015	029	033	002	003	008	009
WEEKS ON STUDY	059	072	083	084	087	089	089	091	092	093	095	095	096	098	098	098	100	102	104	104	104	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma												X													
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma																							X		
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Small intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																							X		
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X		X			X	X	X		X	X	X		X		X	X		X				X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Follicular cell carcinoma																									
C cell adenoma	X													X					X			X			
C cell carcinoma																									
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma NOS																	X				X				
Adenocarcinoma, NOS			X																		X				
Fibroadenoma				X						X	X			X			X		X		X	X			
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma NOS														X							Y				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp	X			X	X				X		X				X	X						X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Squamous cell carcinoma, invasive												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						X	X		X	X	X			

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

ANIMAL NUMBER	0 1 0	0 1 1	0 1 4	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 4	0 2 6	0 2 7	0 2 8	0 3 0	0 4 5	0 3 4	0 3 5	0 3 9	0 4 1	0 4 3	0 4 4	0 4 6	0 4 8	0 5 0	TOTAL:
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	–	+	+	+	+	+	+	43
Thymoma, benign				X																						1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma																										1
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														X												1
Salivary gland	+	–	+	+	+	–	–	–	+	–	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma										X																1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Leiomyosarcoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X	X				X		X		X	X	X	X						X	X	X		X		X	26
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma										X									X							2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma												X														1
C cell adenoma																						X		X		6
C cell carcinoma					X																					1
Parathyroid	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	45
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																									X	1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										2
Adenocarcinoma, NOS																						X				3
Fibroadenoma	X								X	X			X		X	X				X	X	X	X			18
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X																					X			4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp				X										X									X			11
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	*50
Squamous cell carcinoma, invasive																										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							18

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: HIGH DOSE

ANIMAL NUMBER	00202	00244	01017	02121	02222	02299	04444	02323	04242	00707	01212	03303	05050	02828	00101	00303	00404	00505	00606	00808	00909	01100	04406	01101	01303
WEEKS ON STUDY	05909	08303	08404	08804	08909	08909	09091	09404	09606	09909	10100	10101	10101	10303	10404	10404	10404	10404	10404	10404	10404	10404	10404	10405	10505
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS															X	X									
Neurilemoma			X																						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Alveolar/bronchiolar carcinoma																					X				
Sarcoma, NOS, metastatic															X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X	X	X	X	X	X		X	X	X		X		X	X	X	X	X	X	X	X		X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Follicular cell carcinoma																									X
C cell adenoma	X			X										X								X			
Parathyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Adenoma, NOS					X																				
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X													
Adenocarcinoma, NOS																									
Fibroadenoma										X	X		X	X			X	X	X		X	X			X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS																									X
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
Endometrial stromal polyp																					X	X			
Endometrial stromal sarcoma																							X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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		

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

ANIMAL NUMBER	0114	0115	0116	0118	0119	0120	0125	0126	0127	0130	0131	0132	0134	0135	0136	0137	0138	0139	0140	0141	0143	0145	0147	0148	0149	TOTAL:
WEEKS ON STUDY	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma												X														1
Keratoacanthoma														X												1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										2
Neurilemoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X																	2
Alveolar/bronchiolar carcinoma																										1
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	–	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	42
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																									X	2
Salivary gland	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X		X	X	X					X	X	X	X			X		X		X		X	X	X		X	35
Adrenal	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																										1
C cell adenoma												X							X							6
Parathyroid	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	46
Adenoma, NOS																										1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																			X							1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS		X																								1
Fibroadenoma			X	X	X						X	X	X					X			X	X		X	X	21
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS										X																1
Adenoma, NOS								X												X						3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp	X							X									X				X		X			7
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
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							9

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Control	156 ppm	313 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	8.6%	3.1%	5.6%
Terminal Rates (c)	3/35 (9%)	1/32 (3%)	2/36 (6%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.390N	P=0.337N	P=0.487N
Incidental Tumor Tests (d)	P=0.390N	P=0.337N	P=0.487N
Cochran-Armitage Trend Test (d)	P=0.400N		
Fisher Exact Test (d)		P=0.309N	P=0.500N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	8.6%	3.1%	8.3%
Terminal Rates (c)	3/35 (9%)	1/32 (3%)	3/36 (8%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.581N	P=0.337N	P=0.651N
Incidental Tumor Tests (d)	P=0.581N	P=0.337N	P=0.651N
Cochran-Armitage Trend Test (d)	P=0.593		
Fisher Exact Test (d)		P=0.309N	P=0.661
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	11/50 (22%)	18/50 (36%)	9/50 (18%)
Adjusted Rates (b)	27.3%	40.9%	21.8%
Terminal Rates (c)	7/35 (20%)	8/32 (25%)	5/36 (14%)
Week of First Observation	72	59	84
Life Table Tests (d)	P=0.320N	P=0.102	P=0.361N
Incidental Tumor Tests (d)	P=0.413N	P=0.081	P=0.398N
Cochran-Armitage Trend Test (d)	P=0.364N		
Fisher Exact Test (d)		P=0.093	P=0.402N
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	23/50 (46%)	26/50 (52%)	35/50 (70%)
Adjusted Rates (b)	55.7%	61.2%	74.1%
Terminal Rates (c)	17/35 (49%)	16/32 (50%)	24/36 (67%)
Week of First Observation	78	83	59
Life Table Tests (d)	P=0.047	P=0.292	P=0.052
Incidental Tumor Tests (d)	P=0.021	P=0.485	P=0.022
Cochran-Armitage Trend Test (d)	P=0.010		
Fisher Exact Test (d)		P=0.345	P=0.013
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	5/50 (10%)	6/49 (12%)	6/49 (12%)
Adjusted Rates (b)	13.5%	17.0%	14.6%
Terminal Rates (c)	4/35 (11%)	4/31 (13%)	3/35 (9%)
Week of First Observation	85	59	59
Life Table Tests (d)	P=0.457	P=0.447	P=0.517
Incidental Tumor Tests (d)	P=0.351	P=0.445	P=0.467
Cochran-Armitage Trend Test (d)	P=0.424		
Fisher Exact Test (d)		P=0.486	P=0.486
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	7/49 (14%)	6/49 (12%)
Adjusted Rates (b)	19.1%	20.0%	14.6%
Terminal Rates (c)	6/35 (17%)	5/31 (16%)	3/35 (9%)
Week of First Observation	85	59	59
Life Table Tests (d)	P=0.428N	P=0.545	P=0.484N
Incidental Tumor Tests (d)	P=0.524N	P=0.544	P=0.531N
Cochran-Armitage Trend Test (d)	P=0.457N		
Fisher Exact Test (d)		P=0.597	P=0.516N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Control	156 ppm	313 ppm
Mammary Gland: Fibroadenoma			
Overall Rates (a)	19/50 (38%)	18/50 (36%)	21/50 (42%)
Adjusted Rates (b)	47.9%	47.8%	52.4%
Terminal Rates (c)	15/35 (43%)	13/32 (41%)	17/36 (47%)
Week of First Observation	76	84	99
Life Table Tests (d)	P=0.450	P=0.573	P=0.482
Incidental Tumor Tests (d)	P=0.440	P=0.500N	P=0.456
Cochran-Armitage Trend Test (d)	P=0.379		
Fisher Exact Test (d)		P=0.500N	P=0.419
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	20/50 (40%)	18/50 (36%)	22/50 (44%)
Adjusted Rates (b)	49.4%	47.8%	53.7%
Terminal Rates (c)	15/35 (43%)	13/32 (41%)	17/36 (47%)
Week of First Observation	76	84	99
Life Table Tests (d)	P=0.457	P=0.507N	P=0.491
Incidental Tumor Tests (d)	P=0.465	P=0.385N	P=0.502
Cochran-Armitage Trend Test (d)	P=0.379		
Fisher Exact Test (d)		P=0.418N	P=0.420
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	8.2%	2.8%
Terminal Rates (c)	0/35 (0%)	2/32 (6%)	1/36 (3%)
Week of First Observation		83	104
Life Table Tests (d)	P=0.399	P=0.119	P=0.506
Incidental Tumor Tests (d)	P=0.401	P=0.131	P=0.506
Cochran-Armitage Trend Test (d)	P=0.380		
Fisher Exact Test (d)		P=0.121	P=0.500
Mammary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	2.8%	10.9%	5.3%
Terminal Rates (c)	0/35 (0%)	2/32 (6%)	1/36 (3%)
Week of First Observation	100	83	101
Life Table Tests (d)	P=0.443	P=0.173	P=0.528
Incidental Tumor Tests (d)	P=0.508	P=0.293	P=0.634
Cochran-Armitage Trend Test (d)	P=0.408		
Fisher Exact Test (d)		P=0.181	P=0.500
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (a)	20/50 (40%)	19/50 (38%)	23/50 (46%)
Adjusted Rates (b)	49.4%	48.9%	56.1%
Terminal Rates (c)	15/35 (43%)	13/32 (41%)	18/36 (50%)
Week of First Observation	76	83	99
Life Table Tests (d)	P=0.388	P=0.573	P=0.417
Incidental Tumor Tests (d)	P=0.389	P=0.454N	P=0.419
Cochran-Armitage Trend Test (d)	P=0.306		
Fisher Exact Test (d)		P=0.500N	P=0.343
Clitoral Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	5.6%	11.8%	8.3%
Terminal Rates (c)	1/35 (3%)	3/32 (9%)	3/36 (8%)
Week of First Observation	100	98	104
Life Table Tests (d)	P=0.443	P=0.310	P=0.520
Incidental Tumor Tests (d)	P=0.478	P=0.430	P=0.560
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.339	P=0.500

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Control	156 ppm	313 ppm
Clitoral Gland: Carcinoma			
Overall Rates (a)	4/50 (8%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	10.4%	0.0%	2.8%
Terminal Rates (c)	2/35 (6%)	0/32 (0%)	1/36 (3%)
Week of First Observation	85		104
Life Table Tests (d)	P=0.078N	P=0.068N	P=0.166N
Incidental Tumor Tests (d)	P=0.063N	P=0.038N	P=0.137N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.059N	P=0.181N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	15.6%	11.8%	11.1%
Terminal Rates (c)	3/35 (9%)	3/32 (9%)	4/36 (11%)
Week of First Observation	85	98	104
Life Table Tests (d)	P=0.280N	P=0.401N	P=0.340N
Incidental Tumor Tests (d)	P=0.233N	P=0.243N	P=0.282N
Cochran-Armitage Trend Test (d)	P=0.303N		
Fisher Exact Test (d)		P=0.370N	P=0.370N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	9/50 (18%)	11/50 (22%)	7/50 (14%)
Adjusted Rates (b)	22.4%	26.1%	19.4%
Terminal Rates (c)	5/35 (14%)	4/32 (13%)	7/36 (19%)
Week of First Observation	78	59	104
Life Table Tests (d)	P=0.310N	P=0.398	P=0.359N
Incidental Tumor Tests (d)	P=0.344N	P=0.519	P=0.382N
Cochran-Armitage Trend Test (d)	P=0.348N		
Fisher Exact Test (d)		P=0.401	P=0.393N
All Sites: Benign Tumors			
Overall Rates (a)	37/50 (74%)	40/50 (80%)	45/50 (90%)
Adjusted Rates (b)	80.3%	85.0%	91.8%
Terminal Rates (c)	26/35 (74%)	25/32 (78%)	32/36 (89%)
Week of First Observation	75	59	59
Life Table Tests (d)	P=0.188	P=0.271	P=0.196
Incidental Tumor Tests (d)	P=0.049	P=0.456	P=0.053
Cochran-Armitage Trend Test (d)	P=0.027		
Fisher Exact Test (d)		P=0.317	P=0.033
All Sites: Malignant Tumors			
Overall Rates (a)	21/50 (42%)	23/50 (46%)	16/50 (32%)
Adjusted Rates (b)	48.0%	52.0%	38.2%
Terminal Rates (c)	13/35 (37%)	12/32 (38%)	11/36 (31%)
Week of First Observation	72	59	59
Life Table Tests (d)	P=0.164N	P=0.384	P=0.184N
Incidental Tumor Tests (d)	P=0.241N	P=0.420	P=0.250N
Cochran-Armitage Trend Test (d)	P=0.179N		
Fisher Exact Test (d)		P=0.420	P=0.204N
All Sites: All Tumors			
Overall Rates (a)	47/50 (94%)	46/50 (92%)	46/50 (92%)
Adjusted Rates (b)	94.0%	92.0%	93.9%
Terminal Rates (c)	32/35 (91%)	28/32 (88%)	33/36 (92%)
Week of First Observation	72	59	59
Life Table Tests (d)	P=0.318N	P=0.501	P=0.353N
Incidental Tumor Tests (d)	P=0.448N	P=0.451N	P=0.527N
Cochran-Armitage Trend Test (d)	P=0.424N		
Fisher Exact Test (d)		P=0.500N	P=0.500N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

(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 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 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 B4. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by SRI International are included in the historical data base.			
Overall Historical Incidence			
TOTAL	869/1,922 (45.2%)	72/1,922 (3.7%)	939/1,922 (48.9%)
SD (b)	11.77%	4.05%	11.34%
Range (c)			
High	33/47	8/49	33/47
Low	7/39	0/50	9/39

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst			1 (2%)
Abscess, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(48)	(50)
Hemorrhage	1 (2%)		
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)
Infection, fungal	1 (2%)		
Metaplasia, squamous	1 (2%)		
#Lung	(50)	(50)	(50)
Atelectasis	2 (4%)		2 (4%)
Congestion, NOS		1 (2%)	1 (2%)
Hemorrhage		1 (2%)	
Pneumonia, interstitial chronic	1 (2%)		
Granuloma, foreign body		1 (2%)	
Hyperplasia, adenomatous		1 (2%)	2 (4%)
#Lung/alveoli	(50)	(50)	(50)
Histiocytosis	2 (4%)	4 (8%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(50)
Granuloma, NOS	1 (2%)		
Hypoplasia, NOS			1 (2%)
Hyperplasia, reticulum cell	1 (2%)		
#Spleen	(50)	(50)	(50)
Hematoma, organized		1 (2%)	
Granuloma, NOS		1 (2%)	1 (2%)
Fibrosis, focal			1 (2%)
Infarct, NOS			1 (2%)
Hemosiderosis		3 (6%)	4 (8%)
Metaplasia, myeloid	5 (10%)	3 (6%)	6 (12%)
#Lymph node	(50)	(50)	(50)
Lymphedema			1 (2%)
Hemorrhage		1 (2%)	
Granuloma, NOS	2 (4%)	2 (4%)	2 (4%)
Hemosiderosis		1 (2%)	1 (2%)
Hyperplasia, NOS	2 (4%)		
Histiocytosis	2 (4%)		2 (4%)
Plasmacytosis	3 (6%)	5 (10%)	1 (2%)
#Liver	(50)	(49)	(50)
Metaplasia, myeloid			1 (2%)
#Thymus	(49)	(43)	(42)
Hemorrhage		1 (2%)	
Atrophy, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Thrombus, mural	1 (2%)	2 (4%)	
Inflammation, chronic focal	1 (2%)		
Fibrosis, focal	6 (12%)	2 (4%)	8 (16%)
Necrosis, focal	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
DIGESTIVE SYSTEM			
#Salivary gland	(44)	(43)	(48)
Inflammation, chronic focal		1 (2%)	
#Liver	(50)	(49)	(50)
Congenital malformation, NOS	1 (2%)		4 (8%)
Congestion, NOS		1 (2%)	
Inflammation, chronic focal		1 (2%)	1 (2%)
Granuloma, NOS	8 (16%)	15 (31%)	18 (36%)
Peliosis hepatis		2 (4%)	2 (4%)
Necrosis, NOS		1 (2%)	2 (4%)
Infarct, focal	1 (2%)		
Metamorphosis, fatty	8 (16%)	10 (20%)	6 (12%)
Basophilic cyto change	4 (8%)		6 (12%)
Clear cell change	2 (4%)		3 (6%)
Hyperplastic nodule	2 (4%)	3 (6%)	4 (8%)
#Bile duct	(50)	(49)	(50)
Hyperplasia, NOS	9 (18%)	3 (6%)	3 (6%)
#Pancreatic acinus	(50)	(50)	(50)
Atrophy, NOS	11 (22%)	5 (10%)	5 (10%)
#Stomach	(50)	(49)	(50)
Ulcer, NOS		1 (2%)	
Erosion	2 (4%)		
#Forestomach	(50)	(49)	(50)
Hyperplasia, epithelial	2 (4%)		
#Cecum	(50)	(48)	(48)
Necrosis, focal		1 (2%)	
*Rectum	(50)	(50)	(50)
Parasitism		2 (4%)	4 (8%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Pyelonephritis, chronic	1 (2%)		
Nephropathy	17 (34%)	15 (30%)	12 (24%)
Glomerulosclerosis, NOS		4 (8%)	2 (4%)
Infarct, NOS		1 (2%)	
Calcification, NOS	1 (2%)		2 (4%)
#Urinary bladder	(48)	(50)	(50)
Edema, NOS	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(50)
Cyst, NOS	21 (42%)	21 (42%)	13 (26%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, NOS	10 (20%)	9 (18%)	9 (18%)
Angiectasis	2 (4%)		3 (6%)
#Adrenal	(49)	(50)	(48)
Congestion, NOS	1 (2%)		
#Adrenal cortex	(49)	(50)	(48)
Congenital malformation, NOS			1 (2%)
Hemorrhage			1 (2%)
Degeneration, cystic	1 (2%)		
Metamorphosis, fatty		1 (2%)	2 (4%)
Hyperplasia, NOS	5 (10%)	4 (8%)	3 (6%)
#Adrenal medulla	(49)	(50)	(48)
Hyperplasia, NOS		1 (2%)	1 (2%)
#Thyroid	(50)	(49)	(49)
Hyperplasia, C-cell	8 (16%)	5 (10%)	7 (14%)
#Parathyroid	(42)	(45)	(46)
Hyperplasia, secondary	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cyst, NOS	1 (2%)		2 (4%)
Hyperplasia, NOS	1 (2%)	1 (2%)	3 (6%)
Lactation	13 (26%)	15 (30%)	15 (30%)
*Vulva	(50)	(50)	(50)
Colloid cyst			1 (2%)
*Clitoral gland	(50)	(50)	(50)
Cyst, NOS	17 (34%)	22 (44%)	24 (48%)
Inflammation, acute		1 (2%)	
Abscess, NOS	3 (6%)	3 (6%)	3 (6%)
Inflammation, chronic	2 (4%)		1 (2%)
Atrophy, NOS	6 (12%)	4 (8%)	5 (10%)
Hyperplasia, NOS	1 (2%)	1 (2%)	1 (2%)
Metaplasia, squamous			1 (2%)
*Vagina	(50)	(50)	(50)
Cyst, NOS			1 (2%)
#Uterus	(50)	(50)	(50)
Cyst, NOS	2 (4%)		1 (2%)
Abscess, NOS			1 (2%)
Infarct, NOS	1 (2%)		
Decidual alteration, NOS	1 (2%)		
#Cervix uteri	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Fibrosis			1 (2%)
#Uterus/endometrium	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)		2 (4%)
Hyperplasia, cystic			1 (2%)
#Fallopian tube	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
#Ovary	(50)	(50)	(49)
Cyst, NOS	3 (6%)	3 (6%)	2 (4%)
Corpus luteum cyst			1 (2%)
NERVOUS SYSTEM			
#Cerebral ventricle	(48)	(50)	(50)
Hemorrhage	1 (2%)		
#Brain	(48)	(50)	(50)
Hydrocephalus, NOS		2 (4%)	
Hemorrhage		1 (2%)	
Degeneration, myelin	1 (2%)		1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage		1 (2%)	1 (2%)
Sclerosis	1 (2%)		
Cataract	1 (2%)	7 (14%)	2 (4%)
Phthisis bulbi		1 (2%)	
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	1 (2%)
Atrophy, NOS	1 (2%)		
*Eye/conjunctiva	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
*Ear	(50)	(50)	(50)
Ulcer, NOS	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Hyperplasia, NOS	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Osteosclerosis	1 (2%)	1 (2%)	4 (8%)
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
Adipose tissue			
Necrosis, fat	9	8	5
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	49	50	48
Animals examined histopathologically	48	50	48
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(49)	(50)	(48)
Sarcoma, NOS	2 (4%)	3 (6%)	2 (4%)
Fibroma	2 (4%)	2 (4%)	2 (4%)
Fibrosarcoma	8 (16%)	5 (10%)	7 (15%)
Osteosarcoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(48)	(50)	(48)
Hepatocellular carcinoma, metastatic	2 (4%)	4 (8%)	2 (4%)
Alveolar/bronchiolar adenoma	4 (8%)	5 (10%)	
Alveolar/bronchiolar carcinoma	2 (4%)	2 (4%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(48)
Malignant lymphoma, histiocytic type	3 (6%)		
Malignant lymphoma, mixed type	2 (4%)	7 (14%)	1 (2%)
#Spleen	(48)	(49)	(47)
Malignant lymphoma, mixed type		1 (2%)	
#Lymph node	(45)	(48)	(44)
Hepatocellular carcinoma, metastatic		1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, metastatic		1 (2%)	
#Peyer's patch	(44)	(47)	(42)
Malignant lymphoma, mixed type			1 (2%)
CIRCULATORY SYSTEM			
#Heart	(48)	(50)	(48)
Alveolar/bronchiolar carcinoma, metastatic		1 (2%)	
#Liver	(46)	(49)	(47)
Hemangiosarcoma			2 (4%)
DIGESTIVE SYSTEM			
#Liver	(46)	(49)	(47)
Hepatocellular adenoma	9 (20%)	7 (14%)	7 (15%)
Hepatocellular carcinoma	4 (9%)	14 (29%)	5 (11%)
#Pancreas	(48)	(48)	(47)
Sarcoma, NOS, metastatic		1 (2%)	
#Stomach	(45)	(48)	(44)
Adenomatous polyp, NOS			1 (2%)
Sarcoma, NOS, metastatic		1 (2%)	
#Forestomach	(45)	(48)	(44)
Squamous cell papilloma		1 (2%)	
#Jejunum	(44)	(47)	(42)
Adenocarcinoma, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(48)	(50)	(48)
Alveolar/bronchiolar carcinoma, metastatic		1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(49)	(45)
Adenoma, NOS	1 (2%)		
#Adrenal/capsule	(48)	(49)	(48)
Adenoma, NOS			1 (2%)
#Adrenal medulla	(48)	(49)	(48)
Pheochromocytoma	1 (2%)	3 (6%)	1 (2%)
#Thyroid	(48)	(50)	(47)
Follicular cell adenoma	1 (2%)	1 (2%)	1 (2%)
#Pancreatic islets	(48)	(48)	(47)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Preputial gland	(49)	(50)	(48)
Carcinoma, NOS			1 (2%)
#Prostate	(46)	(49)	(46)
Sarcoma, NOS, metastatic		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(49)	(50)	(48)
Adenoma, NOS	1 (2%)	1 (2%)	
Adenocarcinoma, NOS	1 (2%)		1 (2%
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	15	11	13
Moribund sacrifice	6	9	11
Terminal sacrifice	29	30	24
Animal missexed			2

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	30	32	22
Total primary tumors	42	54	33
Total animals with benign tumors	18	15	9
Total benign tumors	19	21	13
Total animals with malignant tumors	19	25	17
Total malignant tumors	23	33	20
Total animals with secondary tumors##	2	5	2
Total secondary tumors	2	11	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 C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: UNTREATED CONTROL

ANIMAL NUMBER	05	04	03	03	02	01	01	03	04	04	01	02	04	01	01	04	02	00	00	00	04	03	00	00	00	00
	00	06	07	05	00	02	08	06	04	04	05	06	05	06	11	11	04	04	05	02	07	11	01	03	06	07
WEEKS ON STUDY	01	01	02	02	02	03	06	06	06	08	08	08	08	08	09	09	09	09	10	10	10	10	10	10	10	10
	06	09	01	08	09	03	00	00	08	05	06	06	08	02	04	05	08	00	02	02	05	06	06	06	06	06
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	N	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS												X														
Fibroma											X															
Fibrosarcoma								X	X					X				X				X	X			
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																				X						X
Alveolar/bronchiolar adenoma														X												
Alveolar/bronchiolar carcinoma																										X
Trachea	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	−	A	+	+	A	+	−	+	−	+	+	+	+	+	+	+	+	+
Thymus	+	−	−	+	+	+	+	+	−	A	+	−	A	−	−	·	−	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	−	−	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																		X					X			
Hepatocellular carcinoma												X						X		X						X
Bile duct	+	+	+	−	−	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	N	N	+	+	+	N	+	+	A	+	N	+	N	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	−	−	+	+	+	+	A	+	+	A	+	+	+	−	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	−	−	−	+	+	+	A	+	+	A	+	+	+	−	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																										
Large intestine	+	+	+	−	−	+	+	+	+	A	+	+	A	+	−	+	−	+	+	+	+	+	+	−	+	
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	−	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																										
Adrenal	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																			X							
Thyroid	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma															X											
Parathyroid	+	−	+	−	−	−	−	+	+	A	+	+	A	−	−	−	+	−	+	+	+	+	−	−	−	
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	+	
Testis	+	+	+	+	−	+	+	+	+	A	+	+	A	+	+	+	−	+	+	+	+	+	+	+	+	
Prostate	+	+	+	+	−	+	+	+	+	A	+	+	A	+	+	+	−	+	+	+	+	+	+	+	+	
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	
Adenoma, NOS																										
Adenocarcinoma, NOS																								X		
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	
Malignant lymphoma, histiocytic type															X		X									
Malignant lymphoma, mixed type												X														

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

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

ANIMAL NUMBER	0008	0009	0010	0013	0014	0017	0019	0021	0022	0023	0025	0027	0028	0029	0030	0032	0033	0034	0038	0039	0040	0042	0043	0048	0049	TOTAL:
WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Sarcoma, NOS													X													2
Fibroma				X																						2
Fibrosarcoma																				X			X			8
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic																										2
Alveolar/bronchiolar adenoma	X															X		X								4
Alveolar/bronchiolar carcinoma					X																					2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hepatocellular adenoma		X			X										X	X	X		X			X				9
Hepatocellular carcinoma																										4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma, NOS																									X	1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	46
Adenoma, NOS																				X						1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																										1
Parathyroid	+	−	+	+	−	−	+	−	+	−	−	−	−	−	−	+	+	+	+	+	+	+	−	+	−	24
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	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	46
Prostate	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	46
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	*49
Adenoma, NOS																										1
Adenocarcinoma, 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	*49
Malignant lymphoma, histiocytic type																								X		3
Malignant lymphoma, mixed type																					X					2

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: LOW DOSE

ANIMAL NUMBER	022	008	015	110	031	021	025	038	023	039	002	043	049	033	018	014	045	013	016	029	001	003	004	005	006
WEEKS ON STUDY	015	019	019	023	026	027	028	029	036	059	065	088	089	092	096	098	099	101	102	104	106	106	106	106	106
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																						X	X		X
Fibroma																						X			
Fibrosarcoma														X			X	X		X					
Osteosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																X									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar carcinoma, metastatic																									
Thymus	+	−	+	+	+	+	+	+	+	+	+	−	−	−	−	−	+	−	+	−	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma															X										X
Hepatocellular carcinoma													X			X	X					X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	N	+	+	+	+	+	+	N	N	+	+	N	+	+	+	+	+	N	+	+	+
Pancreas	+	+	+	+	+	+	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																									
Esophagus	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+
Squamous cell papilloma															X										
Sarcoma, NOS, metastatic																									
Small intestine	+	+	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
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	N	N	N	N	N	N	N	N	N	N
Testis	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																									
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																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, mixed type																			X						

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

ANIMAL NUMBER	0007	0009	0111	0112	0117	0119	0120	0224	0226	0227	0228	0230	0232	0234	0235	0236	0237	0240	0241	0242	0244	0246	0247	0248	0250	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS													X													3
Fibroma					X																					2
Fibrosarcoma																									X	5
Osteosarcoma	X																									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic								X			X		X													4
Alveolar/bronchiolar adenoma			X							X				X	X			X								5
Alveolar/bronchiolar carcinoma									X			X														2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type																			X							1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic													X													1
Alveolar/bronchiolar carcinoma, meta												X														1
Thymus	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	-	+	+	-	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, meta												X														1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	-	-	+	+	+	-	-	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma		X	X					X						X							X					7
Hepatocellular carcinoma	X	X						X			X	X	X						X	X	X				X	14
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	49
Gallbladder & common bile duct	+	N	+	N	+	+	+	N	+	+	N	+	+	+	+	N	+	+	N	+	N	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Sarcoma, NOS, metastatic													X													1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma																										1
Sarcoma, NOS, metastatic													X													1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, meta												X														1
Urinary bladder	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma									X											X	X					3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma										X																1
Parathyroid	+	-	-	-	+	+	+	-	-	+	+	+	+	-	+	-	+	+	+	+	-	-	-	+	+	34
Pancreatic islets	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
Islet cell adenoma																										1
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS, metastatic													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				1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, mixed type									X							X	X	X				X		X		7

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: HIGH DOSE

ANIMAL NUMBER	03381	03110	01018	03037	04141	03030	02028	02021	00404	04402	04242	03039	02207	02205	02025	00202	01616	01707	04705	00803	04049	02299	04043	03535
WEEKS ON STUDY	00101	00202	00404	00606	01116	01619	02203	02209	03303	03303	03404	03606	03707	04000	04400	04403	04303	07606	08505	08808	09002	09404	09904	10202
INTEGUMENTARY SYSTEM																								
Subcutaneous tissue	+	+	S	S	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																								
Fibroma																								
Fibrosarcoma																			X	X	X	X	X	X
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	S	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																								
Trachea	+	–	S	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	–	S	S	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	–	S	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	S	S	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	S	S	+	–	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																								
Thymus	+	–	S	S	+	+	+	+	+	+	+	+	+	–	+	+	–	+	–	–	+	+	–	–	+
CIRCULATORY SYSTEM																								
Heart	+	+	S	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	–	S	S	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	S	S	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								
Hepatocellular carcinoma																		X		X				
Hemangiosarcoma																								
Bile duct	+	+	S	S	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	S	S	+	N	+	+	+	N	+	N	+	N	N	N	+	+	+	+	+	+	+	+
Pancreas	+	+	S	S	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	–	S	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	S	S	+	–	+	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																								
Small intestine	+	+	S	S	+	–	+	+	+	–	+	–	–	–	+	+	+	–	+	+	+	+	+	+
Malignant lymphoma, mixed type																								
Large intestine	+	+	S	S	+	–	+	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	S	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	S	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	S	S	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	S	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																								
Pheochromocytoma																								
Thyroid	+	–	S	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																								
Parathyroid	–	–	S	S	–	+	–	–	–	+	–	+	+	+	–	+	–	+	+	–	–	+	+	+	–
REPRODUCTIVE SYSTEM																								
Mammary gland	N	N	S	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N
Testis	+	+	S	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	S	S	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	S	S	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	+	+	S	S	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
Harderian gland	N	N	S	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS																						X		
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	S	S	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, mixed type																								

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

ANIMAL NUMBER	0014	0001	0005	0006	0007	0008	0009	0011	0012	0013	0015	0019	0022	0023	0024	0026	0032	0033	0034	0036	0044	0045	0046	0048	0050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Sarcoma, NOS										X									X							2
Fibroma						X								X												2
Fibrosarcoma			X																							7
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic										X									X							2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Hepatocellular carcinoma, metastatic																			X							1
Thymus	−	−	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular adenoma			X			X		X											X		X	X			X	7
Hepatocellular carcinoma										X	X								X							5
Hemangiosarcoma						X															X					2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenomatous polyp, NOS			X																							1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Malignant lymphoma, mixed type																	X									1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS														X												1
Pheochromocytoma																								X		1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																						X				1
Parathyroid	−	+	+	+	−	−	+	+	+	−	+	−	+	+	−	−	−	+	−	−	−	+	+	+	−	24
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	*48
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	46
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	*48
Carcinoma, NOS																				X						1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
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	*48
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	*48
Malignant lymphoma, mixed type	X																									1

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Control	156 ppm	313 ppm
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	8/49 (16%)	5/50 (10%)	7/48 (15%)
Adjusted Rates (b)	22.0%	14.3%	22.7%
Terminal Rates (c)	3/29 (10%)	1/30 (3%)	1/24 (4%)
Week of First Observation	60	92	85
Life Table Tests (d)	P=0.506	P=0.285N	P=0.529
Incidental Tumor Tests (d)	P=0.318	P=0.377N	P=0.335
Cochran-Armitage Trend Test (d)	P=0.458N		
Fisher Exact Test (d)		P=0.264N	P=0.518N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	10/49 (20%)	7/50 (14%)	9/48 (19%)
Adjusted Rates (b)	26.9%	20.2%	29.4%
Terminal Rates (c)	4/29 (14%)	3/30 (10%)	3/24 (13%)
Week of First Observation	60	92	85
Life Table Tests (d)	P=0.466	P=0.304N	P=0.486
Incidental Tumor Tests (d)	P=0.296	P=0.401N	P=0.304
Cochran-Armitage Trend Test (d)	P=0.467N		
Fisher Exact Test (d)		P=0.282N	P=0.520N
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	10/49 (20%)	8/50 (16%)	9/48 (19%)
Adjusted Rates (b)	26.9%	23.2%	29.4%
Terminal Rates (c)	4/29 (14%)	4/30 (13%)	3/24 (13%)
Week of First Observation	60	92	85
Life Table Tests (d)	P=0.460	P=0.396N	P=0.486
Incidental Tumor Tests (d)	P=0.294	P=0.508N	P=0.304
Cochran-Armitage Trend Test (d)	P=0.468N		
Fisher Exact Test (d)		P=0.379N	P=0.520N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	12/49 (24%)	10/50 (20%)	11/48 (23%)
Adjusted Rates (b)	31.6%	29.1%	36.2%
Terminal Rates (c)	5/29 (17%)	6/30 (20%)	5/24 (21%)
Week of First Observation	60	92	85
Life Table Tests (d)	P=0.428	P=0.401N	P=0.450
Incidental Tumor Tests (d)	P=0.271	P=0.517N	P=0.274
Cochran-Armitage Trend Test (d)	P=0.474N		
Fisher Exact Test (d)		P=0.384N	P=0.523N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/48 (8%)	5/50 (10%)	0/48 (0%)
Adjusted Rates (b)	12.8%	16.7%	0.0%
Terminal Rates (c)	3/29 (10%)	5/30 (17%)	0/24 (0%)
Week of First Observation	92	106	
Life Table Tests (d)	P=0.100N	P=0.519	P=0.093N
Incidental Tumor Tests (d)	P=0.095N	P=0.519	P=0.083N
Cochran-Armitage Trend Test (d)	P=0.068N		
Fisher Exact Test (d)		P=0.526	P=0.059N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/48 (13%)	7/50 (14%)	0/48 (0%)
Adjusted Rates (b)	19.5%	23.3%	0.0%
Terminal Rates (c)	5/29 (17%)	7/30 (23%)	0/24 (0%)
Week of First Observation	92	106	
Life Table Tests (d)	P=0.040N	P=0.525	P=0.031N
Incidental Tumor Tests (d)	P=0.038N	P=0.525	P=0.028N
Cochran-Armitage Trend Test (d)	P=0.024N		
Fisher Exact Test (d)		P=0.532	P=0.013N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Control	156 ppm	313 ppm
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	3/49 (6%)	0/50 (0%)	0/48 (0%)
Adjusted Rates (b)	8.9%	0.0%	0.0%
Terminal Rates (c)	1/29 (3%)	0/30 (0%)	0/24 (0%)
Week of First Observation	94		
Life Table Tests (d)	P=0.049N	P=0.120N	P=0.169N
Incidental Tumor Tests (d)	P=0.060N	P=0.134N	P=0.202N
Cochran-Armitage Trend Test (d)	P=0.038N		
Fisher Exact Test (d)		P=0.118N	P=0.125N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	2/49 (4%)	8/50 (16%)	2/48 (4%)
Adjusted Rates (b)	5.9%	25.7%	8.0%
Terminal Rates (c)	1/29 (3%)	7/30 (23%)	1/24 (4%)
Week of First Observation	86	102	105
Life Table Tests (d)	P=0.463	P=0.052	P=0.615
Incidental Tumor Tests (d)	P=0.428	P=0.045	P=0.580
Cochran-Armitage Trend Test (d)	P=0.564		
Fisher Exact Test (d)		P=0.049	P=0.683
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	5/49 (10%)	8/50 (16%)	2/48 (4%)
Adjusted Rates (b)	14.3%	25.7%	8.0%
Terminal Rates (c)	2/29 (7%)	7/30 (23%)	1/24 (4%)
Week of First Observation	86	102	105
Life Table Tests (d)	P=0.304N	P=0.295	P=0.319N
Incidental Tumor Tests (d)	P=0.352N	P=0.254	P=0.379N
Cochran-Armitage Trend Test (d)	P=0.210N		
Fisher Exact Test (d)		P=0.290	P=0.227N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	9/46 (20%)	7/49 (14%)	7/47 (15%)
Adjusted Rates (b)	29.8%	22.2%	29.2%
Terminal Rates (c)	8/29 (28%)	6/30 (20%)	7/24 (29%)
Week of First Observation	100	96	106
Life Table Tests (d)	P=0.492N	P=0.362N	P=0.562N
Incidental Tumor Tests (d)	P=0.515N	P=0.380N	P=0.579N
Cochran-Armitage Trend Test (d)	P=0.320N		
Fisher Exact Test (d)		P=0.340N	P=0.374N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	4/46 (9%)	14/49 (29%)	5/47 (11%)
Adjusted Rates (b)	11.6%	41.9%	18.1%
Terminal Rates (c)	1/29 (3%)	11/30 (37%)	3/24 (13%)
Week of First Observation	86	89	76
Life Table Tests (d)	P=0.289	P=0.014	P=0.371
Incidental Tumor Tests (d)	P=0.243	P=0.006	P=0.305
Cochran-Armitage Trend Test (d)	P=0.464		
Fisher Exact Test (d)		P=0.012	P=0.514
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	12/46 (26%)	18/49 (37%)	12/47 (26%)
Adjusted Rates (b)	36.8%	52.4%	45.4%
Terminal Rates (c)	9/29 (31%)	14/30 (47%)	10/24 (42%)
Week of First Observation	86	89	76
Life Table Tests (d)	P=0.306	P=0.162	P=0.369
Incidental Tumor Tests (d)	P=0.258	P=0.108	P=0.325
Cochran-Armitage Trend Test (d)	P=0.518N		
Fisher Exact Test (d)		P=0.186	P=0.570N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Control	156 ppm	313 ppm
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	1/48 (2%)	3/49 (6%)	1/48 (2%)
Adjusted Rates (b)	3.1%	10.0%	4.2%
Terminal Rates (c)	0/29 (0%)	3/30 (10%)	1/24 (4%)
Week of First Observation	102	106	106
Life Table Tests (d)	P=0.545	P=0.315	P=0.716
Incidental Tumor Tests (d)	P=0.520	P=0.301	P=0.676
Cochran-Armitage Trend Test (d)	P=0.610N		
Fisher Exact Test (d)		P=0.316	P=0.753
All Sites: Benign Tumors			
Overall Rates (a)	18/49 (37%)	15/50 (30%)	9/48 (19%)
Adjusted Rates (b)	52.2%	48.1%	37.5%
Terminal Rates (c)	13/29 (45%)	14/30 (47%)	9/24 (38%)
Week of First Observation	86	96	106
Life Table Tests (d)	P=0.077N	P=0.294N	P=0.105N
Incidental Tumor Tests (d)	P=0.090N	P=0.336N	P=0.120N
Cochran-Armitage Trend Test (d)	P=0.032N		
Fisher Exact Test (d)		P=0.310N	P=0.040N
All Sites: Malignant Tumors			
Overall Rates (a)	19/49 (39%)	25/50 (50%)	17/48 (35%)
Adjusted Rates (b)	49.2%	67.5%	53.1%
Terminal Rates (c)	10/29 (34%)	18/30 (60%)	9/24 (38%)
Week of First Observation	60	89	76
Life Table Tests (d)	P=0.385	P=0.207	P=0.437
Incidental Tumor Tests (d)	P=0.176	P=0.085	P=0.196
Cochran-Armitage Trend Test (d)	P=0.411N		
Fisher Exact Test (d)		P=0.178	P=0.448N
All Sites: All Tumors			
Overall Rates (a)	30/49 (61%)	32/50 (64%)	22/48 (46%)
Adjusted Rates (b)	74.8%	84.2%	68.7%
Terminal Rates (c)	19/29 (66%)	24/30 (80%)	14/24 (58%)
Week of First Observation	60	89	76
Life Table Tests (d)	P=0.354N	P=0.481	P=0.388N
Incidental Tumor Tests (d)	P=0.548	P=0.281	P=0.581
Cochran-Armitage Trend Test (d)	P=0.077N		
Fisher Exact Test (d)		P=0.469	P=0.094N

(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 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 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 C4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by SRI International are included in the historical data base.			
Overall Historical Incidence			
TOTAL	259/2,032 (12.7%)	379/2,032 (18.7%)	609/2,032 (30.0%)
SD (b)	7.21%	6.50%	7.59%
Range (c)			
High	22/50	15/50	29/50
Low	0/49	4/50	8/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C4b. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by SRI International are included in the historical data base.			
Overall Historical Incidence			
TOTAL	255/2,034 (12.5%)	102/2,034 (5.0%)	348/2,034 (17.1%)
SD (b)	6.15%	3.42%	7.26%
Range (c)			
High	14/50	8/50	17/50
Low	1/50	0/50	3/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	49	50	48
Animals examined histopathologically	48	50	48
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(48)
Epidermal inclusion cyst	† 1 (2%)	2 (4%)	1 (2%)
Ulcer, NOS	3 (6%)	1 (2%)	3 (6%)
Inflammation, suppurative	1 (2%)		
Abscess, NOS	2 (4%)		3 (6%)
Inflammation, chronic			1 (2%)
Fibrosis	5 (10%)	2 (4%)	4 (8%)
Calcification, NOS	1 (2%)		
Alopecia	1 (2%)		
Hyperplasia, NOS		1 (2%)	
Hyperplasia, basal cell	1 (2%)		
Hyperkeratosis	1 (2%)		1 (2%)
Acanthosis			1 (2%)
*Subcutaneous tissue	(49)	(50)	(48)
Edema, NOS			1 (2%)
Abscess, NOS			1 (2%)
Inflammation, chronic	2 (4%)		
Fibrosis	1 (2%)		1 (2%)
Calcification, NOS	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal cavity	(48)	(47)	(46)
Inflammation, chronic	1 (2%)		
Amyloidosis	42 (88%)	39 (83%)	34 (74%)
#Lung	(48)	(50)	(48)
Atelectasis		1 (2%)	
Congestion, NOS	2 (4%)	3 (6%)	4 (8%)
Hemorrhage		1 (2%)	
Inflammation, NOS	1 (2%)		
Inflammation, interstitial	1 (2%)	2 (4%)	2 (4%)
Hyperplasia, alveolar epithelium	3 (6%)	1 (2%)	1 (2%)
#Lung/alveoli	(48)	(50)	(48)
Hemorrhage	1 (2%)		
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(49)	(47)
Hyperplasia, hematopoietic		2 (4%)	2 (4%)
#Spleen	(48)	(49)	(47)
Atrophy, NOS		1 (2%)	
Hyperplasia, lymphoid		5 (10%)	
Metaplasia, myeloid	6 (13%)	12 (24%)	6 (13%)
#Lymph node	(45)	(48)	(44)
Hemorrhage	4 (9%)	3 (6%)	6 (14%)
Inflammation, acute	1 (2%)	2 (4%)	1 (2%)
Hyperplasia, NOS	5 (11%)	7 (15%)	4 (9%)
Histiocytosis		2 (4%)	4 (9%)
Plasmacytosis	1 (2%)	3 (6%)	4 (9%)
Metaplasia, myeloid		2 (4%)	
#Mesenteric lymph node	(45)	(48)	(44)
Hyperplasia, atypical			1 (2%)
Hyperplasia, NOS		2 (4%)	
#Thymic lymph node	(45)	(48)	(44)
Hyperplasia, NOS		1 (2%)	
#Lung	(48)	(50)	(48)
Leukocytosis, NOS		3 (6%)	1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Kidney	(48)	(50)	(48)
Plasmacytosis	1 (2%)	1 (2%)	1 (2%)
#Thymus	(40)	(36)	(37)
Necrosis, NOS		2 (6%)	1 (3%)
Involution, NOS			1 (3%)
Hyperplasia, NOS		1 (3%)	
CIRCULATORY SYSTEM			
*Multiple organs	(49)	(50)	(48)
Periarteritis	1 (2%)		
#Lymph node	(45)	(48)	(44)
Lymphangiectasis	1 (2%)		1 (2%)
#Heart	(48)	(50)	(48)
Arteriosclerosis, NOS	1 (2%)		
*Mesenteric artery	(49)	(50)	(48)
Polyangiitis	1 (2%)		
*Jugular vein	(49)	(50)	(48)
Thrombosis, NOS	1 (2%)		
#Pancreas	(48)	(48)	(47)
Arteriosclerosis, NOS	1 (2%)		
#Kidney	(48)	(50)	(48)
Arteriosclerosis, NOS	1 (2%)		
#Urinary bladder	(47)	(50)	(48)
Arteriosclerosis, NOS	1 (2%)		
DIGESTIVE SYSTEM			
*Intestinal tract	(49)	(50)	(48)
Congenital malformation, NOS		1 (2%)	
#Liver	(46)	(49)	(47)
Inflammation, acute focal	1 (2%)		
Abscess, NOS	1 (2%)		
Inflammation, chronic			1 (2%)
Inflammation, chronic focal		1 (2%)	
Peliosis hepatis		1 (2%)	
Degeneration, hyaline			1 (2%)
Necrosis, focal		1 (2%)	1 (2%)
Infarct, focal		1 (2%)	
Atrophy, NOS		1 (2%)	
Angiectasis	1 (2%)		
#Pancreas	(48)	(48)	(47)
Inflammation, chronic		1 (2%)	
Cytoplasmic vacuolization		1 (2%)	
#Pancreatic acinus	(48)	(48)	(47)
Atrophy, NOS		1 (2%)	
Hyperplasia, NOS	1 (2%)		
#Stomach	(45)	(48)	(44)
Inflammation, acute/chronic		1 (2%)	
#Glandular stomach	(45)	(48)	(44)
Erosion	1 (2%)	1 (2%)	
#Small intestine	(44)	(47)	(42)
Amyloidosis			3 (7%)
#Cecum	(43)	(47)	(44)
Cyst, NOS			1 (2%)
Erosion			1 (2%)
*Anus	(49)	(50)	(48)
Ulcer, NOS			1 (2%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
URINARY SYSTEM			
#Kidney	(48)	(50)	(48)
Hydronephrosis	1 (2%)	2 (4%)	
Cyst, NOS	1 (2%)		
Pyelonephritis, acute	3 (6%)	2 (4%)	2 (4%)
Inflammation, chronic		1 (2%)	
Pyelonephritis, chronic	1 (2%)		
Inflammation, chronic focal	1 (2%)		
Degeneration, hydropic			1 (2%)
Glomerulosclerosis, NOS	38 (79%)	36 (72%)	31 (65%)
Calcification, focal	1 (2%)	6 (12%)	1 (2%)
Metaplasia, osseous		2 (4%)	
#Renal papilla	(48)	(50)	(48)
Inflammation, necrotizing	1 (2%)		
#Kidney/pelvis	(48)	(50)	(48)
Inflammation, acute		1 (2%)	2 (4%)
Inflammation, chronic			1 (2%)
#Urinary bladder	(47)	(50)	(48)
Dilatation, NOS			1 (2%)
Congestion, NOS	1 (2%)	1 (2%)	1 (2%)
Edema, NOS	2 (4%)		1 (2%)
Hemorrhage	1 (2%)		
Ulcer, NOS		1 (2%)	
Inflammation, acute	1 (2%)	2 (4%)	2 (4%)
Inflammation, chronic	1 (2%)		2 (4%)
Hypertrophy, NOS		1 (2%)	
#Urinary bladder/mucosa	(47)	(50)	(48)
Atypia, NOS	1 (2%)		1 (2%)
Cytomegaly	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(49)	(45)
Cyst, NOS		1 (2%)	
Hemorrhage	1 (2%)		
#Adrenal	(48)	(49)	(48)
Congestion, NOS	1 (2%)		
#Adrenal/capsule	(48)	(49)	(48)
Hyperplasia, NOS	6 (13%)		3 (6%)
#Adrenal cortex	(48)	(49)	(48)
Hyperplasia, NOS			1 (2%)
#Adrenal medulla	(48)	(49)	(48)
Hyperplasia, NOS	1 (2%)	2 (4%)	1 (2%)
#Thyroid	(48)	(50)	(47)
Cyst, NOS	1 (2%)		
Follicular cyst, NOS			1 (2%)
Hyperplasia, follicular cell	1 (2%)	3 (6%)	
#Parathyroid	(24)	(34)	(24)
Cyst, NOS	2 (8%)	1 (3%)	
#Pancreatic islets	(48)	(48)	(47)
Hyperplasia, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(48)
Abscess, NOS		1 (2%)	
*Penis	(49)	(50)	(48)
Inflammation, acute	1 (2%)	3 (6%)	3 (6%)
Ulcer, acute	1 (2%)		
Abscess, NOS			1 (2%)
Necrosis, NOS		1 (2%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
REPRODUCTIVE SYSTEM (Continued)			
*Prepuce	(49)	(50)	(48)
Ulcer, NOS			1 (2%)
Inflammation, acute	1 (2%)		1 (2%)
Abscess, NOS	1 (2%)	1 (2%)	2 (4%)
Inflammation, chronic		1 (2%)	
Fibrosis		4 (8%)	
*Preputial gland	(49)	(50)	(48)
Cyst, NOS		4 (8%)	1 (2%)
Abscess, NOS	2 (4%)	10 (20%)	3 (6%)
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)
Atrophy, NOS	1 (2%)		
Hyperplasia, NOS		1 (2%)	
#Prostate	(46)	(49)	(46)
Inflammation, acute	4 (9%)	5 (10%)	4 (9%)
Abscess, NOS			1 (2%)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic		2 (4%)	
*Seminal vesicle	(49)	(50)	(48)
Dilatation, NOS	4 (8%)	6 (12%)	12 (25%)
Distention	1 (2%)		
Inflammation, acute	1 (2%)	2 (4%)	
Atrophy, NOS		2 (4%)	
#Testis	(46)	(49)	(48)
Necrosis, fat			1 (2%)
Atrophy, NOS			1 (2%)
*Epididymis	(49)	(50)	(48)
Hemorrhage			1 (2%)
Granuloma, spermatic	1 (2%)		
*Scrotum	(49)	(50)	(48)
Abscess, NOS		1 (2%)	
NERVOUS SYSTEM			
#Brain	(48)	(48)	(46)
Calcification, focal	3 (6%)	4 (8%)	
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Bone	(49)	(50)	(48)
Exostosis		1 (2%)	
*Muscle of perineum	(49)	(50)	(48)
Inflammation, acute		1 (2%)	
BODY CAVITIES			
*Abdominal cavity	(49)	(50)	(48)
Abscess, NOS	1 (2%)		
ALL OTHER SYSTEMS			
Tail			
Fracture, NOS	3		
Adipose tissue			
Necrosis, fat	4	3	2

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1
Animal missexed/no necropsy			2
Autolysis/necropsy/no histopathology	1		
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
† Multiple occurrence of morphology in the same organ; tissue is counted once only.

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	49	49	50
Animals examined histopathologically	49	49	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(49)	(49)	(50)
Sarcoma, NOS		1 (2%)	
Fibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(49)	(49)	(50)
Undifferentiated carcinoma, metastatic		1 (2%)	
Hepatocellular carcinoma, metastatic	1 (2%)		1 (2%)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	5 (10%)
Alveolar/bronchiolar carcinoma			2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(49)	(50)
Malignant lymphoma, NOS	1 (2%)	1 (2%)	
Malignant lymphoma, lymphocytic type		1 (2%)	
Malignant lymphoma, histiocytic type	1 (2%)	4 (8%)	
Malignant lymphoma, mixed type	18 (37%)	14 (29%)	11 (22%)
#Spleen	(49)	(49)	(49)
Malignant lymphoma, histiocytic type		1 (2%)	
Malignant lymphoma, mixed type		2 (4%)	
#Lymph node	(49)	(49)	(46)
Histiocytic sarcoma, metastatic			1 (2%)
Malignant lymphoma, mixed type	1 (2%)		
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Salivary gland	(47)	(47)	(45)
Undifferentiated carcinoma		1 (2%)	
#Liver	(49)	(49)	(49)
Hepatocellular adenoma	3 (6%)	3 (6%)	5 (10%)
Hepatocellular carcinoma	2 (4%)	2 (4%)	2 (4%)
Histiocytic sarcoma, metastatic			1 (2%)
#Glandular stomach	(47)	(49)	(47)
Adenomatous polyp, NOS			1 (2%)
#Forestomach	(47)	(49)	(47)
Squamous cell papilloma	1 (2%)		2 (4%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(48)	(44)
Adenoma, NOS	16 (33%)	14 (29%)	7 (16%)
#Adrenal medulla	(48)	(49)	(49)
Pheochromocytoma			1 (2%)
#Parathyroid	(34)	(30)	(39)
Adenoma, NOS	1 (3%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Pancreatic islets	(48)	(48)	(48)
Islet cell adenoma		1 (2%)	
Islet cell carcinoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(49)	(50)
Adenocarcinoma, NOS			1 (2%)
#Uterus	(49)	(49)	(49)
Histiocytic sarcoma			1 (2%)
Leiomyoma		1 (2%)	
Endometrial stromal polyp		2 (4%)	1 (2%)
Endometrial stromal sarcoma			1 (2%)
#Cervix uteri	(49)	(49)	(49)
Histiocytic sarcoma			1 (2%)
#Ovary	(49)	(49)	(48)
Cystadenoma, NOS			1 (2%)
Granulosa cell tumor			1 (2%)
Teratoma, NOS		1 (2%)	1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(49)	(49)	(50)
Adenoma, NOS	1 (2%)	1 (2%)	
Adenocarcinoma, NOS	1 (2%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Bone	(49)	(49)	(50)
Osteoma		1 (2%)	
Osteosarcoma		1 (2%)	
BODY CAVITIES			
*Mesentery	(49)	(49)	(50)
Hepatocellular carcinoma, metastatic	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(49)	(50)
Histiocytic sarcoma	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	6	11
Moribund sacrifice	7	5	7
Terminal sacrifice	36	39	32

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
TUMOR SUMMARY			
Total animals with primary tumors**	37	39	32
Total primary tumors	51	56	44
Total animals with benign tumors	23	20	17
Total benign tumors	25	25	23
Total animals with malignant tumors	25	27	18
Total malignant tumors	26	30	19
Total animals with secondary tumors##	1	1	2
Total secondary tumors	2	1	3
Total animals with tumors--uncertain benign or malignant		1	2
Total uncertain tumors		1	2

* 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 D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: UNTREATED CONTROL

ANIMAL NUMBER	05020	02029	02026	04041	02020	03033	04047	03031	03038	02025	04043	03035	02022	04040	00001	00002	00003	00004	00005	00006	00007	00008	00009	01010	01011
WEEKS ON STUDY	01112	01126	04679	07984	08787	08790	09004	09064	09605	10022	10044	10055	10055	10055	10055	10055	10055	10055	10055	10055	10055	10055	10055	10055	10055
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																		X							
Alveolar/bronchiolar adenoma			X							X															
Trachea	A	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type										X															
Thymus	A	–	+	+	+	+	+	–	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	A	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma														X		X				X					
Hepatocellular carcinoma										X								X							
Bile duct	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	A	+	+	+	N	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Pancreas	A	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	A	–	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	A	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X					X	X	X								X	
Adrenal	A	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	A	–	–	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	–	+	+	+	+
Adenoma, NOS																		X							
REPRODUCTIVE SYSTEM																									
Mammary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	A	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	A	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																									
Adenocarcinoma, NOS																									
BODY CAVITIES																									
Mesentery	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hepatocellular carcinoma, metastatic																		X							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Histiocytic sarcoma						X																			
Malignant lymphoma, NOS		X																							
Malignant lymphoma, histiocytic type																					X				
Malignant lymphoma, mixed type			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
* Animals necropsied

: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 1	0 2 3	0 2 4	0 2 7	0 2 8	0 3 0	0 3 2	0 3 4	0 3 6	0 3 7	0 3 9	0 4 2	0 4 4	0 4 5	0 4 6	0 4 8	0 4 9	TOTAL:
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibrosarcoma					X																					1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma								X																		3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																										3
Hepatocellular carcinoma																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma														X												1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X		X	X		X				X		X	X		X	X					X		X			16
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	+	+	+	+	–	+	+	+	–	+	–	–	+	–	+	–	+	–	–	–	+	+	+	+	+	34
Adenoma, NOS																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	*49
Adenoma, NOS													X													1
Adenocarcinoma, NOS	X																									1
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	*49
Hepatocellular carcinoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Histiocytic sarcoma																										1
Malignant lymphoma, NOS																										1
Malignant lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type			X	X				X	X							X				X					X	18

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: LOW DOSE

ANIMAL NUMBER	0161	0233	0306	0336	0110	0440	0043	0007	0222	0338	0501	0001	0002	0003	0004	0005	0006	0008	0009	0111	0112	0113	0114	0115	0117
WEEKS ON STUDY	0222	0558	0669	0774	0881	0888	0991	0993	0995	0999	1000	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044	1044
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Undifferentiated carcinoma, metastatic																									
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	+	+	+	A	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Undifferentiated carcinoma																									
Liver	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																			X		X				
Hepatocellular carcinoma									X																
Bile duct	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	−	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																X			X	X	X				X
Adrenal	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	+	+	−	−	A	+	+	−	+	+	−	−	+	−	+	+	−	−	−	−	+	+	−
Pancreatic islets	+	+	+	−	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma																							X		
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	N	+	N	+	A	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Leiomyoma																									
Endometrial stromal polyp																									
Ovary	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Teratoma, NOS	X																								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																								X	
Adenocarcinoma, NOS														X											
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteoma																									
Osteosarcoma					X																				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																									
Malignant lymphoma, lymphocytic type																									
Malignant lymphoma, histiocytic type			X	X							X						X								
Malignant lymphoma, mixed type						X		X				X	X			X				X	X		X		

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

ANIMAL NUMBER	0 1 8	0 1 9	0 2 0	0 2 1	0 2 4	0 2 5	0 2 6	0 2 7	0 2 8	0 2 9	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 7	0 3 9	0 4 1	0 4 2	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	0 4 9	TOTAL:
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Sarcoma, NOS		X																								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Undifferentiated carcinoma, metastatic																X										1
Alveolar/bronchiolar adenoma															X									X		2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, histiocytic type													X													1
Malignant lymphoma, mixed type	X					X																				2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Undifferentiated carcinoma																X										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																X										3
Hepatocellular carcinoma													X													2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	N	+	+	+	N	+	+	+	N	+	+	–	N	+	+	N	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS				X			X			X			X	X	X	X			X	X						14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	+	+	+	+	+	–	–	–	+	–	–	+	+	+	–	+	+	–	+	+	–	–	+	+	+	30
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																							X			1
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	*49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyoma														X												1
Endometrial stromal polyp																					X	X				2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Teratoma, NOS																										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																										1
Adenocarcinoma, NOS																										1
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	*49
Osteoma					X																					1
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	*49
Malignant lymphoma, NOS															X											1
Malignant lymphoma, lymphocytic type											X															1
Malignant lymphoma, histiocytic type																										4
Malignant lymphoma, mixed type		X			X		X		X									X					X			14

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE: HIGH DOSE

ANIMAL NUMBER	042	002	005	003	004	011	010	028	001	046	025	009	045	012	022	023	027	041	006	007	008	013	014	015	016
WEEKS ON STUDY	004	009	068	077	077	078	082	083	086	087	089	090	090	091	093	099	100	103	104	104	104	104	104	104	104
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic														X											
Alveolar/bronchiolar adenoma																X		X							
Alveolar/bronchiolar carcinoma																						X			
Trachea	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic												X													
Thymus	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+
Liver	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																			X						
Hepatocellular carcinoma														X											
Histiocytic sarcoma, metastatic												X													
Bile duct	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Pancreas	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma					X																				
Adenomatous polyp, NOS																									
Small intestine	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	–	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X								X					X
Adrenal	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	–	+	–	–	–	+	+	+	+	+	+	+	+	+	–	–	+	–	–	+	+	–	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	+	+	+	+	N	+	+	N	+	+	N	N	+	+	N	N	+	+	+	+	+
Adenocarcinoma, NOS						X																			
Uterus	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X		X													
Endometrial stromal polyp																									
Endometrial stromal sarcoma			X																						
Ovary	–	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS																									
Granulosa cell tumor																									
Teratoma, NOS		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
Malignant lymphoma, mixed type							X							X	X								X		

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

ANIMAL NUMBER	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 4	0 2 6	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 0	0 4 3	0 4 4	0 4 7	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	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma																			X	X						5
Alveolar/bronchiolar carcinoma													X													2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma, metastatic																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma			X				X		X											X						5
Hepatocellular carcinoma																						X				2
Histiocytic sarcoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma																									X	2
Adenomatous polyp, NOS																									X	1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma, NOS								X										X	X						X	7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma									X																	1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	39
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Endometrial stromal polyp					X																					1
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma, NOS																			X							1
Granulosa cell tumor														X												1
Teratoma, NOS																										1
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
Malignant lymphoma, mixed type							X		X		X			X	X						X			X		11

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Control	156 ppm	313 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/49 (6%)	2/49 (4%)	5/50 (10%)
Adjusted Rates (b)	7.1%	5.1%	14.6%
Terminal Rates (c)	1/37 (3%)	2/39 (5%)	3/32 (9%)
Week of First Observation	46	104	99
Life Table Tests (d)	P=0.223	P=0.482N	P=0.298
Incidental Tumor Tests (d)	P=0.235	P=0.546N	P=0.312
Cochran-Armitage Trend Test (d)	P=0.283		
Fisher Exact Test (d)		P=0.500N	P=0.369
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	2/49 (4%)	6/50 (12%)
Adjusted Rates (b)	7.1%	5.1%	17.6%
Terminal Rates (c)	1/37 (3%)	2/39 (5%)	4/32 (13%)
Week of First Observation	46	104	99
Life Table Tests (d)	P=0.129	P=0.482N	P=0.193
Incidental Tumor Tests (d)	P=0.136	P=0.546N	P=0.199
Cochran-Armitage Trend Test (d)	P=0.176		
Fisher Exact Test (d)		P=0.500N	P=0.254
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	1/49 (2%)	5/49 (10%)	0/50 (0%)
Adjusted Rates (b)	2.7%	11.4%	0.0%
Terminal Rates (c)	1/37 (3%)	2/39 (5%)	0/32 (0%)
Week of First Observation	104	69	
Life Table Tests (d)	P=0.434N	P=0.117	P=0.529N
Incidental Tumor Tests (d)	P=0.190N	P=0.321	P=0.529N
Cochran-Armitage Trend Test (d)	P=0.390N		
Fisher Exact Test (d)		P=0.102	P=0.495N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	19/49 (39%)	16/49 (33%)	11/50 (22%)
Adjusted Rates (b)	41.8%	38.8%	30.7%
Terminal Rates (c)	11/37 (30%)	14/39 (36%)	8/32 (25%)
Week of First Observation	46	88	82
Life Table Tests (d)	P=0.124N	P=0.299N	P=0.154N
Incidental Tumor Tests (d)	P=0.069N	P=0.515N	P=0.078N
Cochran-Armitage Trend Test (d)	P=0.045N		
Fisher Exact Test (d)		P=0.337N	P=0.055N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	21/49 (43%)	23/49 (47%)	11/50 (22%)
Adjusted Rates (b)	45.1%	51.9%	30.7%
Terminal Rates (c)	12/37 (32%)	18/39 (46%)	8/32 (25%)
Week of First Observation	12	69	82
Life Table Tests (d)	P=0.080N	P=0.493	P=0.086N
Incidental Tumor Tests (d)	P=0.021N	P=0.387	P=0.035N
Cochran-Armitage Trend Test (d)	P=0.020N		
Fisher Exact Test (d)		P=0.420	P=0.022N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/49 (6%)	3/49 (6%)	5/49 (10%)
Adjusted Rates (b)	8.1%	7.7%	15.6%
Terminal Rates (c)	3/37 (8%)	3/39 (8%)	5/32 (16%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.212	P=0.639N	P=0.277
Incidental Tumor Tests (d)	P=0.212	P=0.639N	P=0.277
Cochran-Armitage Trend Test (d)	P=0.282		
Fisher Exact Test (d)		P=0.661	P=0.357

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Control	156 ppm	313 ppm
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	5/49 (10%)	7/49 (14%)
Adjusted Rates (b)	13.0%	12.4%	20.9%
Terminal Rates (c)	4/37 (11%)	4/39 (10%)	6/32 (19%)
Week of First Observation	94	95	91
Life Table Tests (d)	P=0.233	P=0.598N	P=0.285
Incidental Tumor Tests (d)	P=0.260	P=0.604N	P=0.314
Cochran-Armitage Trend Test (d)	P=0.318		
Fisher Exact Test (d)		P=0.630	P=0.380
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	16/49 (33%)	14/48 (29%)	7/44 (16%)
Adjusted Rates (b)	40.9%	35.9%	22.1%
Terminal Rates (c)	14/37 (38%)	14/39 (36%)	6/30 (20%)
Week of First Observation	90	104	90
Life Table Tests (d)	P=0.066N	P=0.347N	P=0.082N
Incidental Tumor Tests (d)	P=0.064N	P=0.403N	P=0.075N
Cochran-Armitage Trend Test (d)	P=0.045N		
Fisher Exact Test (d)		P=0.440N	P=0.051N
All Sites: Benign Tumors			
Overall Rates (a)	23/49 (47%)	20/49 (41%)	17/50 (34%)
Adjusted Rates (b)	55.8%	51.3%	46.7%
Terminal Rates (c)	19/37 (51%)	20/39 (51%)	13/32 (41%)
Week of First Observation	46	104	77
Life Table Tests (d)	P=0.274N	P=0.262N	P=0.322N
Incidental Tumor Tests (d)	P=0.202N	P=0.322N	P=0.201N
Cochran-Armitage Trend Test (d)	P=0.113N		
Fisher Exact Test (d)		P=0.342N	P=0.134N
All Sites: Malignant Tumors			
Overall Rates (a)	25/49 (51%)	27/49 (55%)	18/50 (36%)
Adjusted Rates (b)	52.8%	58.5%	44.8%
Terminal Rates (c)	15/37 (41%)	20/39 (51%)	11/32 (34%)
Week of First Observation	12	69	68
Life Table Tests (d)	P=0.255N	P=0.504	P=0.276N
Incidental Tumor Tests (d)	P=0.050N	P=0.318	P=0.063N
Cochran-Armitage Trend Test (d)	P=0.080N		
Fisher Exact Test (d)		P=0.420	P=0.096N
All Sites: All Tumors			
Overall Rates (a)	37/49 (76%)	39/49 (80%)	32/50 (64%)
Adjusted Rates (b)	77.0%	82.9%	73.9%
Terminal Rates (c)	26/37 (70%)	31/39 (79%)	21/32 (66%)
Week of First Observation	12	22	9
Life Table Tests (d)	P=0.489N	P=0.546	P=0.518N
Incidental Tumor Tests (d)	P=0.117N	P=0.267	P=0.136N
Cochran-Armitage Trend Test (d)	P=0.118N		
Fisher Exact Test (d)		P=0.404	P=0.152N

(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 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 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 D4. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls	
	Lymphoma	Lymphoma or Leukemia
No 2-year studies by SRI International are included in the historical data base.		
Overall Historical Incidence		
TOTAL	617/2,040 (30.2%)	636/2,041 (31.2%)
SD (b)	13.32%	12.83%
Range (c)		
High	37/50	38/50
Low	5/50	6/50

(a) Data as of April 29, 1987, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Untreated Control	Low Dose	High Dose
Animals initially in study	50	50	50
Animals necropsied	49	49	50
Animals examined histopathologically	49	49	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(49)	(49)	(50)
Abscess, NOS			1 (2%)
RESPIRATORY SYSTEM			
#Nasal cavity	(49)	(49)	(49)
Inflammation, chronic		1 (2%)	
Amyloidosis	25 (51%)	32 (65%)	24 (49%)
#Lung/bronchus	(49)	(49)	(50)
Inflammation, chronic	1 (2%)		
#Lung	(49)	(49)	(50)
Atelectasis		2 (4%)	
Congestion, NOS	1 (2%)		
Inflammation, interstitial		1 (2%)	
Abscess, NOS			2 (4%)
Inflammation, chronic			1 (2%)
Hyperplasia, alveolar epithelium		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(49)	(50)
Hyperplasia, lymphoid	2 (4%)	6 (12%)	2 (4%)
#Bone marrow	(49)	(49)	(50)
Hyperplasia, hematopoietic			5 (10%)
#Spleen	(49)	(49)	(49)
Infarct, NOS	1 (2%)		
Hyperplasia, atypical			1 (2%)
Hyperplasia, lymphoid	10 (20%)	8 (16%)	4 (8%)
Metaplasia, myeloid	9 (18%)	7 (14%)	19 (39%)
#Lymph node	(49)	(49)	(46)
Hemorrhage			2 (4%)
Inflammation, acute			2 (4%)
Abscess, NOS			1 (2%)
Hyperplasia, NOS		4 (8%)	4 (9%)
Plasmacytosis	1 (2%)	1 (2%)	5 (11%)
Hyperplasia, lymphoid	6 (12%)		
#Mesenteric lymph node	(49)	(49)	(46)
Inflammation, acute			1 (2%)
#Thymic lymph node	(49)	(49)	(46)
Inflammation, acute			1 (2%)
*Soft tissue	(49)	(49)	(50)
Hyperplasia, lymphoid			1 (2%)
#Lung	(49)	(49)	(50)
Hyperplasia, lymphoid			1 (2%)
#Liver	(49)	(49)	(49)
Leukocytosis, NOS			2 (4%)
Hyperplasia, lymphoid	2 (4%)		
Metaplasia, myeloid			1 (2%)
#Stomach	(47)	(49)	(47)
Hyperplasia, lymphoid	1 (2%)		
#Small intestine	(46)	(49)	(47)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
#Kidney	(49)	(49)	(50)
Plasmacytosis			1 (2%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
#Urinary bladder	(48)	(49)	(48)
Hyperplasia, lymphoid	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
HEMATOPOIETIC SYSTEM (Continued)			
#Thymus	(45)	(43)	(45)
Hyperplasia, NOS	2 (4%)		1 (2%)
Plasmacytosis			1 (2%)
CIRCULATORY SYSTEM			
#Heart	(49)	(49)	(50)
Thrombus, mural		2 (4%)	
Inflammation, acute			1 (2%)
#Myocardium	(49)	(49)	(50)
Degeneration, NOS			1 (2%)
#Endocardium	(49)	(49)	(50)
Inflammation, acute focal			1 (2%)
DIGESTIVE SYSTEM			
*Palate	(49)	(49)	(50)
Hyperkeratosis			1 (2%)
#Liver	(49)	(49)	(49)
Inflammation, acute focal			1 (2%)
Inflammation, chronic		1 (2%)	
Necrosis, focal			2 (4%)
Infarct, NOS	3 (6%)	1 (2%)	1 (2%)
Metamorphosis, fatty		1 (2%)	8 (16%)
#Pancreas	(48)	(48)	(48)
Inflammation, chronic	1 (2%)	1 (2%)	
#Pancreatic acinus	(48)	(48)	(48)
Atrophy, NOS	1 (2%)		
Hyperplasia, NOS			2 (4%)
#Glandular stomach	(47)	(49)	(47)
Ulcer, NOS	1 (2%)		
#Forestomach	(47)	(49)	(47)
Perforation, inflammatory		1 (2%)	
#Small intestine	(46)	(49)	(47)
Amyloidosis		1 (2%)	1 (2%)
#Cecum	(47)	(49)	(47)
Inflammation, chronic	1 (2%)		
URINARY SYSTEM			
#Kidney	(49)	(49)	(50)
Hydronephrosis	2 (4%)		1 (2%)
Cyst, NOS			1 (2%)
Inflammation, chronic focal			1 (2%)
Nephropathy	1 (2%)		
Nephrosis, NOS	1 (2%)	1 (2%)	
Glomerulosclerosis, NOS	31 (63%)	36 (73%)	34 (68%)
Calcification, focal	2 (4%)	1 (2%)	
Metaplasia, osseous	1 (2%)		2 (4%)
#Urinary bladder/mucosa	(48)	(49)	(48)
Dysplasia, NOS			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(48)	(44)
Cyst, NOS	1 (2%)		1 (2%)
Congestion, NOS			1 (2%)
Hemorrhage	1 (2%)		
Hyperplasia, NOS	7 (14%)	7 (15%)	7 (16%)
Angiectasis	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
ENDOCRINE SYSTEM (Continued)			
#Adrenal	(48)	(49)	(49)
Inflammation, acute focal			1 (2%)
#Adrenal/capsule	(48)	(49)	(49)
Hyperplasia, NOS	13 (27%)	9 (18%)	12 (24%)
#Adrenal cortex	(48)	(49)	(49)
Necrosis, focal	1 (2%)		
Metamorphosis, fatty		1 (2%)	
Atrophy, NOS		1 (2%)	
Hyperplastic nodule		1 (2%)	
Hyperplasia, NOS	2 (4%)	5 (10%)	3 (6%)
#Adrenal medulla	(48)	(49)	(49)
Hyperplasia, NOS	2 (4%)	2 (4%)	
#Thyroid	(49)	(49)	(50)
Cyst, NOS		1 (2%)	
Inflammation, chronic focal		1 (2%)	
Hyperplasia, C-cell		1 (2%)	
Hyperplasia, follicular cell	2 (4%)	3 (6%)	2 (4%)
#Pancreatic islets	(48)	(48)	(48)
Hyperplasia, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(49)	(50)
Cyst, NOS			1 (2%)
Lactation	1 (2%)	2 (4%)	
*Clitoral gland	(49)	(49)	(50)
Cyst, NOS			1 (2%)
#Uterus	(49)	(49)	(49)
Dilatation, NOS			1 (2%)
Hydrometra			2 (4%)
Cyst, NOS	1 (2%)	6 (12%)	
Hematoma, NOS	1 (2%)	1 (2%)	
Pyometra			3 (6%)
Abscess, NOS			1 (2%)
#Uterus/endometrium	(49)	(49)	(49)
Cyst, NOS	6 (12%)	16 (33%)	15 (31%)
Inflammation, acute			3 (6%)
Hyperplasia, NOS		2 (4%)	2 (4%)
Hyperplasia, cystic	30 (61%)	16 (33%)	17 (35%)
Hyperplasia, adenomatous	1 (2%)		
Metaplasia, squamous			1 (2%)
#Ovary	(49)	(49)	(48)
Cyst, NOS	14 (29%)	14 (29%)	11 (23%)
Hemorrhage	1 (2%)		
Hematoma, NOS		2 (4%)	1 (2%)
Abscess, NOS			10 (21%)
Calcification, focal			1 (2%)
Hyperplasia, epithelial		2 (4%)	
NERVOUS SYSTEM			
#Brain	(48)	(49)	(49)
Deformity, NOS		1 (2%)	
Hydrocephalus, NOS			1 (2%)
Degeneration, myelin			1 (2%)
Calcification, focal	11 (23%)	3 (6%)	5 (10%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE (Continued)

	Untreated Control	Low Dose	High Dose
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Bone	(49)	(49)	(50)
Fibrous osteodystrophy	19 (39%)	25 (51%)	20 (40%)
BODY CAVITIES			
*Peritoneum	(49)	(49)	(50)
Inflammation, acute			1 (2%)
Adhesion, NOS	1 (2%)		
*Pleural cavity	(49)	(49)	(50)
Empyema			1 (2%)
*Pleura	(49)	(49)	(50)
Inflammation, chronic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(49)	(50)
Abscess, NOS			1 (2%)
Tail			
Fibrous dysplasia	1		
Adipose tissue			
Necrosis, fat	2	3	1
SPECIAL MORPHOLOGY SUMMARY			
Autolysis/no necropsy	1	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

SENTINEL ANIMAL PROGRAM

APPENDIX E. SENTINEL ANIMAL PROGRAM

Methods

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

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Data from animals surviving 24 months were collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

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

Results

Results are presented in Table E1.

TABLE E1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF DIPHENHYDRAMINE HYDROCHORIDE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	--	None positive
12	--	None positive
18	--	None positive
24	--	None positive
MICE		
6	--	None positive
12	--	None positive
18	--	None positive
24	2/10	MHV

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

APPENDIX F

FEED AND COMPOUND CONSUMPTION BY RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF DIPHENHYDRAMINE HYDROCHLORIDE

TABLE F1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Control		Low Dose			High Dose		
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
1	17	162	17	161	33	17	159	67
5	21	279	20	274	23	21	272	48
10	18	340	18	336	17	18	330	34
13	20	359	19	354	17	20	347	36
18	19	389	17	385	14	18	379	30
22	19	410	18	408	14	18	402	28
25	19	429	17	423	13	17	418	25
31	18	439	16	439	11	17	434	24
35	23	456	22	454	15	22	449	31
39	19	465	18	462	12	18	459	25
43	19	474	17	472	11	17	469	23
48	18	481	18	478	12	18	472	24
51	18	486	18	485	12	18	481	23
55	17	486	16	487	10	16	479	21
59	17	490	17	493	11	17	486	22
63	18	496	17	490	11	17	487	22
69	17	491	17	493	11	17	485	22
74	17	484	16	491	10	16	485	21
79	16	478	15	483	10	16	478	21
83	17	477	16	483	10	16	476	21
86	16	475	16	485	10	16	479	21
90	16	471	16	480	10	17	469	23
94	16	468	16	479	10	15	460	20
99	17	458	16	462	11	16	469	21
103	16	440	15	454	10	15	446	21
Mean	17.9	435	17.1	436	13	17.3	431	27
SD (c)	1.7		1.6		5.2	1.7		10.5
CV (d)	9.5		9.1		39.3	9.7		39.0

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Estimated milligrams of diphenhydramine hydrochloride consumed per day per kilogram of body weight; body weights used for weeks 13, 18, and 22 are those reported for weeks 12, 17, and 21.
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE F2. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

	Control		Low Dose			High Dose		
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
1	14	124	14	125	17	14	123	36
5	12	171	12	174	11	12	169	22
10	11	198	11	200	9	10	192	16
13	13	205	13	208	10	13	200	20
18	11	216	11	219	8	11	213	16
22	11	227	12	228	8	11	221	16
25	11	232	12	234	8	11	225	15
31	11	235	11	239	7	10	230	14
35	14	244	14	248	9	14	239	18
39	12	252	12	255	7	11	246	14
43	11	260	11	263	7	11	252	14
48	12	265	12	267	7	12	258	15
51	12	273	10	276	6	12	264	14
55	11	274	11	278	6	10	265	12
59	12	285	12	290	6	12	274	14
63	13	297	12	300	6	12	284	13
69	12	313	12	315	6	12	302	12
74	12	323	12	328	6	12	312	12
79	13	332	12	334	6	12	318	12
83	13	338	12	337	6	12	324	12
86	12	345	12	341	5	12	329	11
90	13	344	13	338	6	13	334	12
94	13	348	12	340	6	12	333	11
99	14	346	13	344	6	12	332	11
103	13	353	13	344	6	12	334	11
Mean	12.2	272	12.0	273	7	11.8	263	15
SD (c)	1.0		0.9		2.5	1.0		5.2
CV (d)	8.3		7.8		33.6	8.8		35.0

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Estimated milligrams of diphenhydramine hydrochloride consumed per day per kilogram of body weight; body weights used for weeks 13, 18, and 22 are those reported for weeks 12, 17, and 21.
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE F3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

Week	Control		Low Dose			High Dose		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
1	3.2	22.7	3.5	23.0	24	3.9	22.5	54
5	4.5	29.2	4.7	28.2	26	5.3	26.9	62
10	4.5	29.6	4.9	29.3	26	4.5	28.9	49
12	6.6	30.4	7.0	29.7	37	7.3	28.3	81
16	4.4	31.7	4.7	30.3	24	4.6	29.9	48
20	4.9	33.8	4.9	31.6	24	5.0	31.5	50
24	3.6	34.6	3.6	33.6	17	4.0	33.0	38
30	4.5	35.8	4.7	34.1	22	4.8	33.7	45
34	4.4	36.6	4.8	35.1	21	4.9	34.5	44
38	4.5	37.8	4.6	36.3	20	4.7	34.8	42
42	4.4	39.1	4.7	37.3	20	4.7	34.4	43
47	4.4	37.8	4.6	36.6	20	4.9	35.2	44
50	4.7	39.3	4.8	38.0	20	5.1	35.9	44
54	4.9	39.4	4.9	38.7	20	5.4	36.4	46
58	4.8	39.8	5.0	38.3	20	5.0	36.5	43
62	4.6	39.7	4.6	38.1	19	4.8	36.7	41
68	4.6	39.7	4.6	38.3	19	4.9	36.6	42
73	4.6	39.4	4.6	38.0	19	4.5	36.3	39
78	4.5	39.4	4.5	37.3	19	4.7	36.3	41
82	4.1	39.3	4.5	37.8	19	5.0	36.4	43
85	4.3	39.2	4.4	37.1	19	5.0	36.2	43
89	4.5	39.3	4.6	37.0	19	5.1	36.5	44
93	4.7	39.8	4.5	37.2	19	5.3	35.9	46
98	5.1	39.2	5.2	37.1	22	6.2	35.3	55
102	4.2	39.2	4.2	36.5	18	4.7	35.0	42
Mean	4.5	36.5	4.7	35.0	21	5.0	33.7	47
SD (c)	0.6		0.6		4	0.7		9
CV (d)	13.3		12.8		19.0	14.0		19.1

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Milligrams of diphenhydramine hydrochloride consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE F4. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF DIPHENHYDRAMINE HYDROCHLORIDE

Week	Control		Low Dose			High Dose		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
2	3.8	19.9	3.7	19.9	29	4.3	19.8	68
5	3.8	22.3	3.8	22.3	27	4.0	21.9	57
9	3.9	24.1	3.7	22.9	25	4.2	23.5	56
13	4.7	25.2	4.4	24.5	28	4.6	24.1	60
16	4.6	26.1	4.4	25.2	27	4.7	24.7	60
22	4.2	27.6	4.0	26.6	23	4.3	26.3	51
26	4.2	28.6	4.0	27.9	22	4.1	27.1	47
30	4.1	30.1	4.0	29.1	21	4.2	28.0	47
34	4.3	32.1	4.0	30.6	20	4.1	29.0	44
39	4.6	32.9	4.4	30.9	22	4.5	29.2	48
42	4.5	34.6	4.4	32.3	21	4.7	30.2	49
46	4.6	36.1	4.3	32.0	21	4.8	31.9	47
50	4.5	36.7	4.4	34.0	20	4.5	32.4	43
54	4.4	36.9	4.1	34.2	19	4.3	32.8	41
60	4.3	38.1	4.4	35.9	19	4.2	33.8	39
65	4.2	37.9	4.0	35.8	17	4.1	33.5	38
70	4.4	38.7	4.2	36.1	18	4.2	34.0	39
74	4.3	38.8	4.4	37.2	18	4.4	34.7	40
77	4.3	38.9	4.3	37.3	18	4.3	34.7	39
81	4.5	39.7	4.6	38.6	19	4.6	35.4	41
85	4.7	39.8	4.4	39.1	18	4.8	36.0	42
90	5.2	39.9	5.0	39.6	20	5.2	36.8	44
94	4.6	40.2	4.8	40.2	19	4.6	36.1	40
98	4.4	40.6	4.2	41.0	16	4.8	37.1	40
102	4.6	40.4	4.6	40.7	18	4.8	37.6	40
Mean	4.4	33.8	4.3	32.6	21	4.5	30.8	46
SD (c)	0.3		0.3		4	0.3		8
CV (d)	6.8		7.0		19.0	6.7		17.4

(a) Grams of feed removed from the feeder; not corrected for scatter.
(b) Milligrams of diphenhydramine hydrochloride consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX G

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

Meal Diet: December 1980 to January 1983

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

TABLE G1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE G2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE G3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.25 ± 1.04	22.6-26.3	24
Crude fat (percent by weight)	5.10 ± 0.44	4.4-6.0	24
Crude fiber (percent by weight)	3.38 ± 0.38	2.4-4.2	24
Ash (percent by weight)	6.59 ± 0.34	5.97-7.42	24
Amino Acids (percent of total diet)			
Arginine	1.323 ± 0.830	1.21-1.39	4
Cystine	0.310 ± 0.099	0.218-0.400	4
Glycine	1.155 ± 0.069	1.06-1.21	4
Histidine	0.572 ± 0.030	0.530-0.603	4
Isoleucine	0.910 ± 0.033	0.881-0.944	4
Leucine	1.949 ± 0.065	1.85-1.99	4
Lysine	1.275 ± 0.076	1.20-1.37	4
Methionine	0.422 ± 0.187	0.306-0.699	4
Phenylalanine	0.909 ± 0.167	0.665-1.04	4
Threonine	0.844 ± 0.029	0.824-0.886	4
Tryptophan	0.187	0.171-0.211	3
Tyrosine	0.631 ± 0.094	0.566-0.769	4
Valine	1.11 ± 0.050	1.05-1.17	4
Essential Fatty Acids (percent of total diet)			
Linoleic	2.44	2.37-2.52	3
Linolenic	0.274	0.256-0.308	3
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,188 ± 1,239	8,900-1,400	24
Vitamin D (IU/kg)	4,650	3,000-6,300	2
α-Tocopherol (ppm)	41.53 ± 7.52	31.1-48.9	4
Thiamine (ppm)	16.2 ± 2.30	12.0-21.0	(b) 23
Riboflavin (ppm)	7.5 ± 0.96	6.1-8.2	4
Niacin (ppm)	85.0 ± 14.2	65.0-97.0	4
Pantothenic acid (ppm)	29.3 ± 4.6	23.0-34.0	4
Pyridoxine (ppm)	7.6 ± 1.5	5.6-8.8	4
Folic acid (ppm)	2.8 ± 0.88	1.8-3.7	4
Biotin (ppm)	0.27 ± 0.05	0.21-0.32	4
Vitamin B_{12} (ppb)	21.0 ± 11.9	11.0-38.0	4
Choline (ppm)	3,302.0 ± 120.0	3,200.0-3,430.0	4
Minerals			
Calcium (percent)	1.23 ± 0.12	1.10-1.53	24
Phosphorus (percent)	0.97 ± 0.06	0.84-1.10	24
Potassium (percent)	0.862 ± 0.100	0.772-0.974	3
Chloride (percent)	0.546 ± 0.100	0.442-0.635	4
Sodium (percent)	0.311 ± 0.038	0.258-0.350	4
Magnesium (percent)	0.169 ± 0.133	0.151-0.181	4
Sulfur (percent)	0.316 ± 0.070	0.270-0.420	4
Iron (ppm)	447.0 ± 57.3	409.0-523.0	4
Manganese (ppm)	90.6 ± 8.20	81.7-95.5	4
Zinc (ppm)	53.6 ± 5.27	46.1-58.6	4
Copper (ppm)	10.77 ± 3.19	8.09-15.39	4
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.81 ± 0.28	1.44-2.09	4
Cobalt (ppm)	0.68 ± 0.14	0.49-0.80	4

(a) One to four lots of feed analyzed for nutrients reported in this table were manufactured during 1983-85.
(b) One lot (7/22/81) not analyzed for thiamine

TABLE G4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.44 ± 0.14	0.21-0.93	24
Cadmium (ppm) (a)	<0.10		24
Lead (ppm)	1.03 ± 0.75	0.27-2.93	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.27 ± 0.05	0.16-0.40	24
Aflatoxins (ppb) (a,b)	<10	<5.0-10.0	24
Nitrate nitrogen (ppm) (c)	9.35 ± 4.35	0.6-18.0	24
Nitrite nitrogen (ppm) (c)	1.97 ± 1.28	0.4-5.3	24
BHA (ppm) (d)	5.83 ± 5.12	0.4-20.0	24
BHT (ppm) (d)	3.42 ± 2.57	<1.0-13.0	24
Aerobic plate count (CFU/g) (e)	105,438 ± 75,797	7,000-300,000	24
Coliform (MPN/g) (f)	1,046 ± 973	<3-2,400	24
E. coli (MPN/g) (f,g)	8.0 ± 7.91	<3-23	23
E. coli (MPN/g) (f,h)	13.92 ±30.0	<3-150	24
Total nitrosamines (ppb) (i, j)	5.13 ± 4.47	<1.2-18.8	22
Total nitrosamines (ppb) (i,k)	13.11 ± 27.39	<1.2-101.6	24
N-Nitrosodimethylamine (ppb) (i,l)	3.82 ± 4.29	0.6-16.8	22
N-Nitrosodimethylamine (ppb) (i,m)	11.71 ± 27.03	0.6-99	24
N-Nitrosopyrrolidine (ppb)	1.21 ± 0.66	<0.3-2.4	24
Pesticides (ppm)			
α-BHC (a,n)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (o)	<0.01	0.05 (7/14/81)	24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (p)	<0.05	0.13 (8/25/81); 0.6 (6/29/82)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCBs (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (a)	<0.1		24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (q)	0.08 ± 0.05	<0.05-0.25	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

TABLE G4. 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) The detection limit was 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) CFU = colony-forming unit
(f) MPN = *most probable number*
(g) Mean, standard deviation, and range exclude one value of 150 obtained for the lot produced on 8/26/82.
(h) Mean, standard deviation, and range include the high value listed in footnote (g).
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range exclude two very high values of 101.6 and 100.3 ppb obtained for the lots produced on 1/26/81 and 4/27/81.
(k) Mean, standard deviation, and range include the high values listed in footnote (j).
(l) Mean, standard deviation, and range exclude two very high values of 97.9 and 99.0 ppb for lots produced on 1/26/81 and 4/27/81.
(m) Mean, standard deviation, and range include the very high values given in footnote (l).
(n) BHC = hexachlorocyclohexane or benzene hexachloride
(o) One observation was above the detection limit; the value and date it was obtained are listed under the range.
(p) Two observations were above the detection limit; the values and dates they were obtained are listed under the range.
(q) Eleven lots contained more than 0.05 ppm.

APPENDIX H

PLASMA CONCENTRATIONS OF DIPHENHYDRAMINE IN RATS

APPENDIX H. PLASMA CONCENTRATIONS

A study of plasma concentrations of diphenhydramine in male F344 rats fed diets containing 313 or 625 ppm diphenhydramine hydrochloride was conducted at Arthur D. Little, Inc., under the sponsorship of the National Toxicology Program (NTP) (NIEHS contract number N01-ES-66138). The laboratory report is on file at NTP, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

I. Methods

Diphenhydramine hydrochloride was mixed with NIH 07 Rat and Mouse Ration (meal) at concentrations of 313 or 625 ppm, and the formulated diets were given to two groups of 15 male F344 rats (290-350 g body weight) for 30 days. Feed, which was replaced once per week, and water were available ad libitum. At 9:00 a.m. at the end of days 1, 3, 10, and 30, and at 2:00 a.m. on day 10, three rats at each concentration were anesthetized with sodium pentobarbital (70-80 mg/kg by intraperitoneal injection), and blood samples were removed by cardiac puncture and transferred into heparinized Vacutainer tubes. At 2:00 a.m. on day 30, a 3-ml blood sample was collected from the orbital sinus of the rats to be killed at 9:00 a.m. Light in the animal room was provided from approximately 6:00 a.m. to 6:00 p.m.

Plasma samples were quantitatively analyzed for diphenhydramine by the method of Abernethy and Greenblatt (1983), using a Hewlett-Packard Model 5830A gas chromatograph equipped with an automatic sampler, an electronic integrator, and a nitrogen-phosphorus detector. Diphenhydramine was extracted by addition of a sodium hydroxide-hexane-isoamyl alcohol mixture to the plasma samples followed by an acid extraction of the organic phase, readjustment of the aqueous phase to pH 11.5, and reextraction with a toluene-isoamyl alcohol mixture. Standard curves of spiked control plasma were linear for diphenhydramine concentrations ranging from 1.0 to 300 ng/ml.

II. Results

Diphenhydramine was detectable only in the 2:00 a.m. plasma samples of rats that received 625 ppm diphenhydramine hydrochloride. At day 30, the concentration of diphenhydramine in the 2:00 a.m. plasma sample was 3.3 ng/ml; this level is nearly at the limit of sensitivity (1 ng/ml) of the analytical method. Results are presented in Table H1.

TABLE H1. CONCENTRATIONS OF DIPHENHYDRAMINE IN PLASMA OF MALE F344 RATS FED DIETS CONTAINING DIPHENHYDRAMINE HYDROCHORIDE FOR UP TO 30 DAYS (a)

Dietary Concentration (ppm)	Day of Study	Time of Bleeding 9:00 a.m.	Time of Bleeding 2:00 a.m.	Plasma Concentration (b) (ng/ml)
313	3	+		(c)
	10		+	(c)
	10	+		(c)
	30		+	(c)
	30	+		(c)
625	3	+		(c)
	10		+	(d)
	10	+		(c)
	30		+	3.3 ± 0.5
	30	+		(c)

(a) The dietary concentration refers to diphenhydramine hydrochloride; the plasma concentration refers to the free base.
(b) The value given is the mean for three rats ± standard deviation.
(c) None detectable
(d) Detectable but not quantifiable

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft (October 1987) NTP Technical Report No. 355 for the 2-year studies of diphenhydramine hydrochloride in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives during October and November 1987 and April 1988 by Argus Research Laboratories, Inc. The audit included review of:

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

Procedures and events during the exposure phase of the studies were documented adequately by the archival records with some minor exceptions. Review of data from the entire exposure phase indicated that husbandry practices were effective and consistent during the course of the studies. Records documented that doses were prepared, stored, analyzed, and administered to animals according to protocols. Recalculation of group mean body weights, collected at 4 different months during the studies, showed five errors of small magnitude (0.3%-4%) out of 48 values checked. Similarly, discrepancies of small magnitude (0.1-0.2 g per animal per day) were found for 6/42 feed consumption measurements recalculated from original data. Clinical observations of signs and masses for individual animals were made consistently, and records showed that they were reviewed at the time of necropsy. Survival data were reviewed and found to be correct.

Review of the pathology specimens showed that identifiers (ears) were saved inconsistently; however, those saved provided correct identification of residual wet tissues for individual animals. Review of data trails provided evidence that the integrity of individual animal identity had been preserved throughout the studies. Inspection of the residual wet tissues for 66 rats and 65 mice detected untrimmed potential lesions in different nontarget organs of 1 rat and 3 mice. All gross observations made at necropsy correlated with microscopic observations. All other aspects of histopathology were complete and accurate.

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