NATIONAL TOXICOLOGY PROGRAM
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No. 322

TOXICOLOGY AND CARCINOGENESIS STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

(CAS NO. 61-76-7)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

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

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NOTE TO THE READER

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

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

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

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

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

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

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

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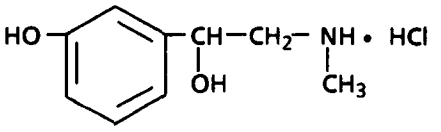

PHENYLEPHRINE HYDROCHLORIDE

CAS No. 61-76-7

$C_9H_{13}NO_2 \cdot HCl$ Molecular weight 203.7

Synonyms: Benzene methanol,3-hydroxy-α-[(methylamino) methyl]hydrochloride (R)-;
(−)-*meta*-Hydroxy-α-[(methylamino) methyl] benzyl alcohol hydrochloride;
meta-Synephrine hydrochloride;
Neo-synephrine®

ABSTRACT

Phenylephrine hydrochloride is a sympathomimetic amine recommended for use as a nasal decongestant and as a mydriatic in ophthalmic applications. In 1977, total U.S. human exposure was estimated at 1.9×10^7 g per year. Phenylephrine hydrochloride was nominated for toxicology and carcinogenesis studies because of a lack of previous long-term studies and because two other sympathomimetic agents (soterenol hydrochloride and mesuprine hydrochloride) produced mesovarial leiomyomas in Sprague-Dawley rats.

Toxicology and carcinogenesis studies of USP-grade phenylephrine hydrochloride were conducted by administering diets containing the chemical (99% pure) to F344/N rats and B6C3F$_1$ mice of each sex in studies of 14 days, 12 weeks, and 2 years. In the 14-day studies, no toxic effects were seen in rats or mice fed diets containing up to 2,000 ppm phenylephrine hydrochloride. Doses were increased in the 12-week studies, and deaths of male rats and male mice were observed in groups fed diets containing 10,000 or 20,000 ppm; 1/10 male rats in the 5,000-ppm group died. Other than inflammatory eye lesions (considered secondary to the pharmacologic drying action of the chemical), no specific organ toxicity was noted. Body weights decreased as concentrations of phenylephrine hydrochloride in the diet were increased, and feed consumption was lower in dosed rats. Doses of 0, 620, and 1,250 ppm for rats and 0, 1,250, and 2,500 ppm for mice were selected for the 2-year studies because of decreased body weight gains in animals given higher doses in the 12-week studies. In the 2-year studies, the approximate amount of phenylephrine hydrochloride consumed per day was 24 mg/kg for low dose rats, 50 mg/kg for high dose rats, 133 mg/kg for low dose mice, and 270 mg/kg for high dose mice.

Body weight differences in rats appeared to be dose related, and dosed animals were 3%-15% lighter than controls. Body weights of dosed mice averaged 3%-14% lower than those of controls throughout the 2-year studies. Survival of high dose male rats was greater than that of the controls (control, 30/50; low dose, 33/50; high dose, 42/50); differences in survival were not significant for female rats (42/50; 34/50; 36/50), male mice (35/50; 38/50; 43/50), or female mice (37/50; 34/50; 34/50).

Few nonneoplastic lesions were related to phenylephrine hydrochloride dosing in rats or mice. Chronic focal inflammation of the liver was observed at increased incidences in dosed rats (male: 2/50; 13/50; 17/50; female: 17/50; 28/50; 35/50). Inflammation of the prostate was seen more frequently in dosed than in control males (10/50; 24/50; 24/50). The incidence of focal cellular change in the liver was increased slightly in high dose male mice (0/50; 2/50; 7/50).

In male rats, mononuclear cell leukemia (24/50; 9/50; 5/50) and pheochromocytomas of the adrenal gland (14/49; 11/50; 2/50) occurred with negative trends, and the incidences in the high dose group were lower than those in the controls. No increases in neoplasia were seen in dosed male or female rats or mice.

Phenylephrine hydrochloride was not mutagenic in four strains of *Salmonella typhimurium* (TA100, TA1535, TA1537, and TA98) with or without Aroclor 1254-induced liver S9 from male Sprague-Dawley rats or male Syrian hamsters. The results of mutagenicity studies of phenylephrine hydrochloride were equivocal in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the absence of S9; it was not tested in the presence of S9. Phenylephrine hydrochloride induced sister-chromatid exchanges (SCEs) but not chromosomal aberrations in Chinese hamster ovary cells. The increase in SCEs was seen only in the absence of metabolic activation with S9.

An audit of the experimental data was conducted for the 2-year studies of phenylephrine hydrochloride. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year studies, there was *no evidence of carcinogenicity** of phenylephrine hydrochloride for male or female F344/N rats given 620 or 1,250 ppm in feed or for male or female B6C3F$_1$ mice given 1,250 or 2,500 ppm in feed. Survival of high dose male rats was greater than that of controls, and the incidences of mononuclear cell leukemia and pheochromocytomas were lower in dosed than in control male rats. Inflammation was observed more frequently in the liver and prostate gland of dosed male rats than in controls.

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*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 8.

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APPENDIXES

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on phenylephrine hydrochloride on March 26, 1986, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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

On March 26, 1986, the draft Technical Report on the toxicology and carcinogenesis studies of phenylephrine hydrochloride received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. J. Bucher, NTP, introduced the studies by reviewing the experimental design, results, and proposed conclusions (no evidence of carcinogenicity for rats or mice).

Dr. Popp, a principal reviewer, agreed with the conclusions as written. He noted that the rationale for studying the chemical was as a response to a recommendation that it be included as part of a class study of benzyl alcohols with sympathomimetic activity. Certain members of this class have been associated with increased incidence of mesovarial leiomyomas. Thus, he asked why the ovary was not handled as a target organ for pathology. Dr. Bucher said that the mesovarial tumors were observed on gross examination in the other studies. A statement would be added indicating that such tumors were not seen grossly or microscopically in the current studies [see p. 43].

As a second principal reviewer, Dr. Sivak agreed with the conclusions and thought that the modest reductions in weight at the high doses in both rats and mice indicated probable attainment of appropriate maximum tolerated doses. He stated that the reduction in adrenal gland lipoid degeneration and focal hyperplasia in dosed male and female rats compared with controls should be reported, since the adrenal glands are likely target organs for the chemical.

As a third principal reviewer, Dr. Perera also agreed with the conclusions and the conduct of the studies. She suggested that some mention might be made in the abstract of the nonneoplastic effects seen in the liver and prostate gland in rats and in the liver in mice.

In other discussion, Dr. Scala expressed concern about the randomization of the animals, noting the variation in initial body weights among animals from various groups. Dr. J. Haseman, NIEHS, said that he had no evidence improper randomization was used and that similar variability also has occurred in other studies. Dr. Mirer said that it would be useful to have survival-adjusted tumor rates also cited in the abstract and discussion, since the life table analysis is based on the adjusted rate. Dr. Haseman agreed that this would be helpful when there were survival differences and when the tumors in question were lethal. Dr. J. Huff, NTP, stated that this would be done for all studies where appropriate and informative.

Dr. Popp moved that the Technical Report on phenylephrine hydrochloride be accepted with the conclusions as written, no evidence of carcinogenicity for rats and mice of each sex. Dr. Swenberg seconded the motion, and it was approved unanimously with 11 affirmative votes.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Phenylephrine Hydrochloride is based on the 12-week studies that began in December 1979 and ended in March 1980 and on the 2-year studies that began in September 1980 and ended in October 1982 at Physiological Research Laboratories.

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I. INTRODUCTION

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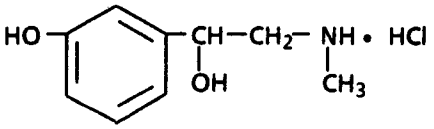

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(−)-*meta*-Hydroxy-α-[(methylamino) methyl] benzyl alcohol hydrochloride;
meta-Synephrine hydrochloride;
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Physical Properties, Uses, Production, and Exposure

Phenylephrine hydrochloride is a sympathomimetic agent used primarily as a nasal decongestant and as a mydriatic in ophthalmic applications. It is a bitter-tasting crystalline material, soluble in water and alcohols, with a melting point of 140°-145° C (Merck, 1976). Phenylephrine hydrochloride is available under a variety of trade names as a sterile solution (10 mg/ml) for parenteral use, as an elixir (1 mg/ml), in tablets (5 mg), and as various nasal (0.125%, 0.25%, 0.5%, and 1.0%) and ophthalmic (2.5% and 10%) solutions (PDR, 1985). In 1974, production of the hydrochloride salt in the United States was estimated at 1.7×10^8 g and of the base, bitartrate salt, and tannate salt at 4.5×10^6 g. The importation of phenylephrine hydrochloride through principal customs districts was reported to be approximately 6.6×10^6 g in 1983 (USITC, 1984), and total U.S. human exposure was estimated at 1.9×10^7 g in 1977 (SRI, 1977). No more recent figures are available.

Doses delivered during use of phenylephrine hydrochloride in nose drops or in ophthalmic solutions can vary widely, but one or two 5-mg tablets are sufficient for a decongestant effect in adult humans. The maximum recommended dose is 12 tablets in 24 hours, or 60 mg (PDR, 1985). Thus, humans could be exposed for short periods of time at approximately 1 mg/kg per day.

Pharmacologic Actions

Phenylephrine differs chemically from the endogenous compound epinephrine in that it lacks a hydroxyl group in position 4 on the benzene ring. Although not a catechol, it exhibits pharmacologic actions resembling several endogenous catecholamines (Meyer and Fraunfelder, 1980). Phenylephrine is an α-receptor agonist and through this mechanism increases systolic and diastolic blood pressure after intravenous, subcutaneous, or oral administration. A rise in blood pressure can trigger a reflex bradycardia; thus, phenylephrine hydrochloride is used to halt episodes of paroxysmal atrial tachycardia. Phenylephrine causes constriction of most vascular beds, which is the basis for its decongestant action. It reduces renal, splanchnic, cutaneous, and limb blood flow, but it increases coronary blood flow. It decreases intestinal motility (Gilman et al., 1985; Eckstein and Abboud, 1962; Aviado, 1959).

Phenylephrine activates α-receptors at low doses and has a weak action on β-receptors at higher doses (Reinhardt and Wagner, 1974; Chiba, 1977). Activation of α1 receptors generally results in the excitatory postsynaptic effect of vasoconstriction. Activation of α2 receptors found on presynaptic nerve terminals inhibits endogenous transmitter release. Stimulation of α2 receptors on cholinergic nerve terminals in the gastrointestinal tract may mediate the inhibitory effects of α-agonists at this site (Gilman et al., 1985; Langer, 1977).

Absorption, Distribution, Metabolism, and Excretion

Phenylephrine hydrochloride is absorbed after oral administration (Bogner and Walsh, 1964), and the drug is rapidly absorbed following inhalation of nasal sprays or topical instillation into the eye (Ibrahim et al., 1983; Meyer and Fraunfelder, 1980). Unlike epinephrine and norepinephrine, phenylephrine does not appear to bind appreciably to albumin (Danon and Sapira, 1972), and the generally short duration of action--20 minutes following intravenous injection (Gilman et al., 1985)--suggests a rather rapid distribution, metabolism, and elimination. When male Wistar rats were given intraperitoneal injections of tritiated phenylephrine, 72% of the label was collected in the urine within 24 hours. Sixteen percent of the dose was unconjugated phenylephrine, the sulfate conjugate, or the glucuronide conjugate, and approximately 56% of the dose was found as *meta*-hydroxymandelic acid (6%), *meta*-hydroxyphenylglycol (50%), or their sulfate or glucuronide conjugates (Ibrahim et al., 1983). Phenylephrine is thought to undergo oxidative deamination by monoamine oxidase to the aldehyde. The aldehyde can be further oxidized by aldehyde oxidase to *meta*-hydroxymandelic acid or reduced by aldehyde dehydrogenase to *meta*-hydroxyphenylglycol. The general pattern of metabolism is similar in humans except that approximately 60% of an inhaled or orally ingested dose of phenylephrine appears in the urine within 24 hours as unchanged or conjugated phenylephrine, 30%-35% of the dose appears as *meta*-hydroxymandelic acid or its conjugates, and 8%-9% appears as *meta*-hydroxyphenylglycol or its sulfate or glucuronide conjugates (Ibrahim et al., 1983). The observation by Midgley et al. (1979) of *meta*-hydroxymandelic acid in the urine of untreated humans suggested that phenylephrine or *meta*-octopamine is an endogenous substance; it was later observed that phenylephrine occurs naturally in bovine and mouse adrenal glands (Midgley et al., 1980; Durden et al., 1980). Crowley et al. (1982) showed that both *meta*-hydroxymandelic acid and *meta*-hydroxyphenylglycol are normal constituents of human and rat urine.

Monoamine oxidase is a component of the outer mitochondrial membrane of a variety of cell types in many tissues (Siegel et al., 1976). It is especially prevalent in the liver and is found in presynaptic adrenergic nerve terminals (Gilman et al., 1985; Finberg and Youdim, 1983). Although this enzyme is important in the metabolic conversion of phenylephrine, the termination of pharmacologic action is due to a decrease in concentration at the receptor site. With endogenous catecholamines, the termination of pharmacologic action is due primarily to reuptake from the synaptic cleft into the presynaptic terminal rather than to enzymatic conversion to an inactive metabolite (Cooper et al., 1982). It is not clear whether phenylephrine is also taken up by the presynaptic nerve terminal (Ibrahim et al., 1983); this action is suggested because tricyclic antidepressants (drugs that inhibit this reuptake process) markedly increase the pressor effects of phenylephrine (PDR, 1985). However, other actions of these drugs may account for this observation.

Toxicity

LD_{50} values for phenylephrine have been determined in several species by various routes of administration. In Wistar rats (sex unspecified), the LD_{50} value by intraperitoneal injection was 17 mg/kg and by subcutaneous injection was 33 mg/kg (Warren and Werner, 1946). Using an unspecified strain and sex of rat, Stockhaus and Wick (1969) reported an oral LD_{50} value of 350 mg/kg; values of 65 and 92 mg/kg were reported for intraperitoneal and subcutaneous injections, respectively. The LD_{50} values in male Swiss mice were 89 mg/kg (intraperitoneal) (Sofia and Knobloch, 1974) and 22 mg/kg (subcutaneous) (Warren and Werner, 1946). New Zealand rabbits (sex unspecified) had LD_{50} values of 0.5 mg/kg (intravenous), 7.2 mg/kg (intramuscular), and 22 mg/kg (subcutaneous) (Warren and Werner, 1946).

Phenylephrine solutions were found not to cause significant corneal edema in rabbits with an intact corneal epithelium, but ocular administration after removal or damage to the epithelium produced a cytotoxic effect to the corneal

endothelium and keratocytes and significant corneal edema (Edelhauser et al., 1979). Phenylephrine has been reported to have an anesthetic effect on the cornea (Reinhardt and Wagner, 1974). No reports of dermal toxicity in animals were found, but several instances of contact dermatitis were reported in humans who used eyedrops containing phenylephrine (Barber, 1983; Camarasa, 1984). These instances followed an initial sensitizing encounter, and repeated dosing produced conjunctival injection, edema, and periorbital eczema.

Human toxicity resulting from systemic absorption of phenylephrine from ocular or nasal preparations has been reported and appears to be related to the pharmacologic action of the drug rather than to an intrinsic cytotoxicity. Side effects of ocular administration are most often associated with the use of 10% solutions and include pain, release of pigment from the iris, elevation of intraocular pressure, and headache (Meyer and Fraunfelder, 1980). The most serious reported sequelae are a marked rise in blood pressure (which has led to subarachnoid hemorrhage), ventricular arrhythmias, and cardiac infarct in susceptible patients (Fraunfelder and Scafidi, 1978). Prinzmetal's angina in one patient was also linked to the use of a 10% ocular solution (Alder et al., 1981). Most of these effects can be related to severe vasoconstriction produced by α-adrenergic stimulation. Intense vasoconstriction can lead to secondary arrhythmias (Papp and Szekeres, 1968); direct β-receptor stimulation, shown with large doses, can have positive chronotropic actions on the sinoatrial node, potentially resulting in primary arrhythmias (Chiba, 1977). Chronic hallucinosis has been related to overuse of nosedrops containing phenylephrine (Escobar and Karno, 1982).

Reproductive Toxicity

Phenylephrine given to pregnant rabbits during the last third of gestation produced fetal growth retardation and the onset of early labor (Shabanah et al., 1969). The use of medications containing phenylephrine during the first 4 months of pregnancy was associated with a greater than expected number of eye, ear, and other minor malformations in humans (Heinonen et al., 1977). Two other epidemiologic studies found no association between congenital disorders and use of phenylephrine during pregnancy (Jick et al., 1981; Colley et al., 1982). β-Sympathomimetic agents consistently caused external and cardiac malformations when administered to chick embryos, but phenylephrine did not cause similar defects (Hodach et al., 1975; Bruyere et al., 1983).

Genetic Toxicology

No studies of the genetic toxicity of phenylephrine hydrochloride were found in the literature. In NTP studies, phenylephrine hydrochloride was not mutagenic in four tester strains of *Salmonella typhimurium* (TA100, TA1535, TA1537, and TA98) in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 (Appendix E). The results of mutagenicity studies of phenylephrine hydrochloride were equivocal in the mouse lymphoma L5178Y/TK$^{+/-}$ assay because a positive response, noted in the first trial without metabolic activation, occurred at high doses that were toxic to the cells (relative total growth of 12.2%) and was not reproduced in the second trial. Phenylephrine hydrochloride was not tested in the presence of S9 in the mouse lymphoma assay.

Phenylephrine hydrochloride induced sister-chromatid exchanges (SCEs) but not chromosomal aberrations in Chinese hamster ovary cells. The increase in SCEs was seen only in the absence of metabolic activation with Aroclor 1254-induced male Sprague-Dawley rat liver S9. In summary, phenylephrine hydrochloride was not mutagenic in bacteria with or without metabolic activation. The evidence for mutagenicity was equivocal in mammalian cells without metabolic activation at nearly toxic doses, and phenylephrine hydrochloride induced SCEs in mammalian cells in the absence of metabolic activation.

Study Rationale

Phenylephrine hydrochloride and three β-agonists (ephedrine, epinephrine, and isoproterenol) were four sympathomimetic agents considered by the National Cancer Institute as part of a benzyl alcohols class study. Interest focused

on these drugs primarily because mesovarial leiomyomas had been reported in Sprague-Dawley rats given the β-agonists soterenol hydrochloride and mesuprine hydrochloride (Nelson et al., 1972; Nelson and Kelly, 1971). Since no reports on the long-term effects of phenylephrine were found in the literature and no such studies have been made available to the Bureau of Drugs of the Food and Drug Administration (FDA), the FDA recommended that the National Cancer Institute nominate phenylephrine hydrochloride to the NTP for toxicology and carcinogenesis studies. The feed route of administration was selected to mimic the oral use of phenylephrine hydrochloride in elixir and tablet form by humans.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PHENYLEPHRINE HYDROCHLORIDE

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II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF PHENYLEPHRINE HYDROCHLORIDE

USP-grade (97.5%-102.5% active ingredient by the USP standard test) phenylephrine hydrochloride was obtained in one lot from Ganes Chemical Company (New York, New York). The identity of phenylephrine hydrochloride was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy (Appendix F).

The purity of phenylephrine hydrochloride was determined to be approximately 99% by elemental analysis, high-performance liquid chromatography, nonaqueous titration of the amine group, and the USP titration method that uses bromination of three aromatic ring positions. Results of the elemental analysis agreed with the theoretical values. Water content was 0.08%. Phenylephrine hydrochloride was 99.3% pure by nonaqueous titration of the amine group and was 101% pure by the USP titration method. Two impurities with a total peak area of 0.09% that of the major peak were detected by high-performance liquid chromatography; these impurities were not identified.

Phenylephrine hydrochloride was stable in storage for at least 2 weeks at 60° C (Appendix F) and was stored at the laboratory in the dark at 25° C. Periodic characterization of phenylephrine hydrochloride by infrared spectroscopy, USP titration method, or high-performance liquid chromatography detected no deterioration over the course of the studies (Appendix F).

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

A formulated diet mixture was homogeneous to ± 1.5% (Appendix G). Phenylephrine hydrochloride at 800 ppm was stable in feed when stored for 2 weeks at temperatures of 4° C or lower. The formulated diets were prepared by adding a dry premix of feed and phenylephrine hydrochloride to the appropriate amount of feed. The mixture was blended for 15 minutes (Table 1). The feed mixtures were analyzed periodically to determine if they contained the correct concentrations of phenylephrine hydrochloride (Appendix H). All of the analyzed feed mixtures were within ± 10% of the target concentrations (Table 2; Appendix I).

TABLE 1. PREPARATION AND STORAGE OF FORMULATED DIETS IN THE FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

Fourteen-Day Studies	Twelve-Week Studies	Two-Year Studies
Preparation		
Premix mixed with bulk feed in Patterson-Kelly® 8-qt twin-shell blender for 5 min with the intensifier bar followed by 10 min without the intensifier bar.	Same as 14-d studies	Premix prepared by mixing weighed quantity of bulk chemical and feed in a mortar. Premix transferred to tared beaker containing approximately 100 g of feed, and an additional portion of feed added to adjust premix weight to 300 g. Premix then thoroughly mixed with spatula. Premix mixed with remainder of the bulk feed in a Patterson-Kelly® twin-shell stainless steel blender. Dietary formulations blended first in 8-qt and then 1-ft^3 blender with the intensifier bar for 5 min and without it for the remaining 10 min.
Maximum Storage Time		
1 wk	1 wk	1 wk
Storage Conditions		
Room temperature	4° C	4° C

TABLE 2. SUMMARY OF RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

	Target Concentration (ppm)		
	620	1,250	2,500
Mean (ppm)	626	1,272	2,531
Standard deviation	11.9	59.1	111.0
Coefficient of variation (percent)	1.9	4.6	4.4
Range (ppm)	600-640	1,130-1,370	2,380-2,690
Number of samples	13	13	13

FOURTEEN-DAY STUDIES

Three- to four-week-old male and female F344/N rats and 4- to 5-week-old B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for approximately 3 weeks before the studies began. Groups of five rats of each sex were fed diets containing 0, 125, 250, 500, 1,000, or 2,000 ppm phenylephrine hydrochloride for 14 consecutive days. Groups of five mice of each sex were fed diets containing 0, 63, 125, 250, 500, or 1,000 ppm.

Rats and mice were observed twice per day and were weighed once per week. Further details on animal maintenance are given in Table 3. A necropsy was performed on all animals.

TWELVE-WEEK STUDIES

Twelve-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of phenylephrine 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 4- to 6-week-old B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 14 days, 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 and 10 mice of each sex were given diets containing 0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm phenylephrine hydrochloride for 12 weeks. Control diets consisted of NIH 07 Rat and Mouse Ration. Formulated diets or control diets and water were available ad libitum. Further experimental details are summarized in Table 3.

Animals were observed two times per day; moribund animals were killed. Feed consumption was measured weekly by cage. Individual animal weights were recorded once per week.

At the end of the 12-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 3. Adrenal glands and hearts were weighed for controls and for the 20,000-ppm groups. Bilateral measurements of pupil diameter were taken for all groups.

TWO-YEAR STUDIES

Study Design

Diets containing 0, 620, or 1,250 ppm phenylephrine hydrochloride were fed to groups of 50 rats of each sex for 103 weeks. Diets containing 0, 1,250, or 2,500 ppm were fed to groups of mice of each sex for 103 weeks.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female, × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

Fourteen-Day Studies	Twelve-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	50 males and 50 females of each species
Doses		
Rats--0, 125, 250, 500, 1,000, or 2,000 ppm phenylephrine hydrochloride in feed; mice--0, 63, 125, 250, 500, or 1,000 ppm phenylephrine hydrochloride in feed	0, 1,250, 2,500, 5,000, 10,000, or 20,000 ppm phenylephrine hydrochloride in feed	Rats--0, 620, or 1,250 ppm phenylephrine hydrochloride in feed; mice--0, 1,250, or 2,500 ppm phenylephrine hydrochloride in feed
Date of First Dose		
5/21/79	12/12/79	Rats--10/7/80; mice--9/22/80
Date of Last Dose		
6/3/79	3/2/80	Rats--9/27/82; mice--9/13/82
Duration of Dosing		
14 d	12 wk	103 wk
Type and Frequency of Observation		
Observed 2 × d; weighed 1 × wk; feed consumption determined 1 × wk	Same as 14-d studies	Observed 2 × d; weighed 1 × wk for 12 wk and 1 × 4 wk thereafter; feed consumption determined 1 × wk; palpation 1 × 4 wk from 9 to 24 mo; ophthalmologic exam of 10 control and 10 high dose animals of each sex at 6, 12, and 18 mo
Necropsy and Histologic Examination		
Necropsy performed on all animals; 10% of the animals, primarily from the highest dose groups, examined histologically. Tissues examined: gross lesions, skin, mandibular lymph nodes, mammary gland, thigh muscle, sciatic nerve, sternebrae or vertebrae or femur including marrow, costochondral junction, rib, oral cavity, thymus, larynx and pharynx, trachea, lungs and bronchi, heart and aorta, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, tongue, ileum, colon, cecum, rectum, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testis/epididymus or ovaries/uterus, nasal cavity, brain, pituitary gland, spinal cord, eyes, preputial or clitoral gland, and zymbal gland	Necropsy performed on all control and 10,000- and 20,000-ppm animals and on all animals that died before the end of the studies. Tissues examined: same as 14-d studies, plus transverse section of nasal bone. Adrenal glands and heart weighed for controls and 20,000-ppm group; pupil diameter of all groups recorded	Necropsy and histologic examination performed on all animals; the following tissues were taken at necropsy: gross lesions, skin, mandibular lymph nodes, mammary gland, salivary gland, sternebrae or vertebrae or femur including marrow, thymus, larynx and pharynx, trachea, lungs and bronchi, heart and aorta, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, tongue, tissue masses and regional lymph nodes, ileum, colon, cecum, rectum, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, urinary bladder, seminal vesicles/prostate/testis/epididymus/vaginal tunics/scrotal sac or ovaries/uterus, brain, pituitary gland, and preputial or clitoral glands. The mesovarium was among those tissues taken for histologic assessment only if a gross lesion was noted.

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

Fourteen-Day Studies	Twelve-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source Charles River Breeding Laboratories (Portage, MI)	Same as 14-d studies	Same as 14-d studies
Study Laboratory Physiological Research Laboratories	Same as 14-d studies	Same as 14-d studies
Method of Animal Identification Rats--tail mark; mice--ear punch	Rats--ear tag; mice--toe clip	Toe and ear clip
Time Held Before Study 20 d	14 d	2 wk
Age When Placed on Study Rats--6-7 wk; mice--7-8 wk	Rats--6-7 wk; mice--6-8 wk	Rats--6-7 wk; mice--7-8 wk
Age When Killed Rats--8-9 wk; mice--9-10 wk	Rats--18-19 wk; mice--18-20 wk	Rats--110-111 wk; mice--111-112 wk
Necropsy Dates Rats--6/6/79-6/8/79; mice--6/5/79-6/8/79	Rats--3/3/80-3/6/80; mice--3/4/80-3/7/80	Rats--10/4/82-10/7/82; mice--9/20/82-9/23/82
Method of Animal Distribution Distributed to weight classes and then to cages according to a table of random numbers	Same as 14-d studies	Same as 14-d studies
Feed Rodent Chow 5001® meal (Ralston Purina Co., St. Louis, MO)	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 12-wk studies
Bedding Aspen Bed (Sawdust and Shavings Co., Anoka, MN)	Aspen wood chips (Sawdust and Shavings Co., Anoka, MN)	Aspen wood shavings that had been washed, screened, and kiln dried (Sawdust and Shavings Co., Anoka, MN)
Water Public water supply softened with sodium zeolite to 21 grains/gal, then filtered through spun polyethylene; automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 14-d studies	Same as 14-d studies
Cages Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Same as 14-d studies	Same as 14-d studies
Cage Filters Reemay spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as 14-d studies	Same as 14-d studies

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

Fourteen-Day Studies	Twelve-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Animals per Cage		
5	5	5
Other Chemicals on Study in the Same Room		
None	None	None
Animal Room Environment		
Temp--22.3°-24.3° C; hum--35%-45%; 12 h light/d; 120 room air changes/h	Temp--20.0°-25.0° C; hum--28%-50%; 12 h light/d; 120 room air changes/h	Temp--22.7° ± 0.4° C; hum--50% ± 10%; 12 h fluorescent light/d; >15 room air changes/h

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 laboratory 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 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 J).

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

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

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

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 3.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically

varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 3.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

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

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

Statistical Methods

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

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

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

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent

mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with controls and tests for overall dose-response trends.

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

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

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the studies were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and 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 by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

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

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

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

TWELVE-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

TWELVE-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

III. RESULTS: RATS

FOURTEEN-DAY STUDIES

None of the rats died before the end of the studies (Table 4). No clinical signs were associated with phenylephrine hydrochloride dosing. Feed consumption and final mean body weights of dosed rats were not adversely affected by phenylephrine hydrochloride. No compound-related effects were observed at necropsy or upon microscopic examination of tissues from 10% of the study animals. Since no toxic effects were evident in the 14-day studies, doses were increased for the 12-week studies.

TWELVE-WEEK STUDIES

Four of 10 male rats that received 20,000 ppm, 2/10 males that received 10,000 ppm, and 1/10 males that received 5,000 ppm died before the end of the studies (Table 5). Final mean body weights of all groups of dosed males and all but the lowest dose group of female rats were more than 10% lower than those of the controls. The final mean body weights of rats that received 5,000, 10,000, or 20,000 ppm were 57%, 45%, or 35% that of the controls for males and 70%, 58%, or 51% that of the controls for females. Feed consumption by dosed rats was consistently lower than that by the controls and decreased as dose was increased. Rats that received 10,000 or 20,000 ppm were hyperexcitable. Pupil size in dosed groups was generally smaller than that of the controls (Appendix L, Table L1). Absolute adrenal gland weights and heart weights of males and females that received 20,000 ppm were lower than those of the controls (Table L2).

Relative adrenal gland weights and heart weights of males and females that received 20,000 ppm were greater than those of the controls. Pupil size and adrenal gland and heart weights were consistent with the differences in body weight between the dose groups and, because of the large weight differences, were of little value in demonstrating a selective pharmacologic or toxic effect of dosing.

Chronic keratitis of the eye was observed in 4/8 males and 8/10 females at 20,000 ppm and 4/10 males and 6/10 females at 10,000 ppm. Minimal to mild testicular atrophy was observed in 4/8 males, and seminal vesicle atrophy was observed in 5/6 males that received 20,000 ppm; mild to moderate ovarian atrophy was observed in 5/10 females that received 20,000 ppm. No other observed histopathologic effects appeared compound related.

TABLE 4. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Wk 1	Wk 2
MALE							
0	5/5	162 ± 4	197 ± 6	+35 ± 4	--	14.2	20.0
125	5/5	158 ± 5	181 ± 3	+23 ± 4	92	14.2	20.0
250	5/5	167 ± 4	192 ± 5	+25 ± 9	97	14.2	20.0
500	5/5	173 ± 7	196 ± 3	+23 ± 5	99	14.2	20.0
1,000	5/5	160 ± 4	188 ± 5	+28 ± 2	95	14.2	20.0
2,000	5/5	163 ± 6	198 ± 7	+35 ± 2	101	14.2	15.0
FEMALE							
0	5/5	135 ± 4	159 ± 4	+24 ± 2	--	12.8	16.8
125	5/5	136 ± 3	153 ± 8	+17 ± 1	96	12.5	16.4
250	5/5	135 ± 5	155 ± 5	+20 ± 2	97	12.2	16.5
500	5/5	130 ± 3	147 ± 4	+17 ± 2	92	12.5	16.5
1,000	5/5	135 ± 4	145 ± 5	+10 ± 3	91	11.4	16.4
2,000	5/5	133 ± 3	151 ± 4	+18 ± 2	95	10.2	16.0

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Grams of feed per animal per day

TABLE 5. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE TWELVE-WEEK FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Wk 1	Wk 12
MALE							
0	10/10	107 ± 3	363 ± 7	+256 ± 6	--	13.3	14.9
1,250	10/10	107 ± 3	324 ± 6	+217 ± 5	89	12.5	14.2
2,500	10/10	108 ± 3	246 ± 4	+38 ± 5	68	8.4	11.3
5,000	(e) 9/10	108 ± 3	206 ± 5	+98 ± 3	57	7.4	12.1
10,000	(f) 8/10	108 ± 2	165 ± 6	+56 ± 6	45	6.5	10.4
20,000	(g) 6/10	107 ± 2	127 ± 6	+16 ± 6	35	3.5	9.1
FEMALE							
0	10/10	92 ± 1	211 ± 3	+119 ± 3	--	10.0	10.7
1,250	10/10	92 ± 2	202 ± 3	+110 ± 2	96	9.5	9.0
2,500	10/10	95 ± 2	178 ± 2	+83 ± 3	84	8.0	8.5
5,000	10/10	90 ± 3	147 ± 3	+57 ± 3	70	7.0	9.2
10,000	10/10	89 ± 2	122 ± 2	+33 ± 2	58	5.4	8.8
20,000	10/10	91 ± 2	107 ± 3	+16 ± 2	51	3.8	8.4

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams of feed per animal per day
(e) Week of death: 1
(f) Week of death: 3,3
(g) Week of death: 3,5,7,8

Dose Selection Rationale: Because of weight gain depression and the incidence of deaths of males, doses selected for rats for the 2-year studies were 620 and 1,250 ppm phenylephrine hydrochloride in feed.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The initial mean body weight of high dose male rats was 5% lower than that of the controls, and the mean body weights were 4%-15% lower throughout the study (Table 6 and Figure 1). The mean body weight of low dose male rats ranged from 3% to 8% lower than that of the controls. The initial mean body weight of high dose female rats was 4% lower than that of the controls and was 4%-10% lower throughout most of the study. Body weights of low dose females were similar to those of controls. No specific clinical signs of toxicity or ophthalmologic findings noted in any group of dosed rats were attributed to phenylephrine hydrochloride dosing. The average daily feed consumption was similar for dosed and control male and female rats (Appendix K, Tables K1 and K2). The average amount of phenylephrine hydrochloride consumed per day was approximately 22 mg/kg or 47 mg/kg for low dose or high dose male rats and 26 mg/kg or 54 mg/kg for low dose or high dose female rats.

TABLE 6. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

Week on Study	Control		620 ppm			1,250 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	146	50	144	99	50	139	95	50
1	185	50	171	92	50	161	87	50
2	217	50	202	93	50	187	86	50
3	244	50	225	92	50	208	85	50
4	268	50	247	92	50	227	85	50
5	286	50	265	93	50	241	84	50
6	300	50	278	93	50	251	84	50
7	311	50	292	94	50	263	85	50
8	323	50	304	94	50	274	85	50
9	334	50	319	96	50	289	87	50
10	348	50	330	95	50	296	85	50
11	355	50	339	95	50	306	86	50
12	359	50	345	96	50	312	87	50
19	398	50	383	96	50	346	87	49
23	423	50	408	96	50	373	88	49
29	429	50	412	96	50	381	89	49
33	439	50	422	96	50	391	89	48
38	444	50	422	95	50	392	88	48
42	454	50	438	96	50	409	90	48
46	455	50	435	96	50	418	92	46
51	460	50	440	96	50	416	90	46
55	461	50	446	97	50	425	92	46
59	462	50	449	97	50	427	92	46
63	470	50	452	96	50	436	93	46
68	486	50	447	96	50	435	93	46
72	462	49	447	97	50	431	93	46
76	454	47	443	98	47	429	94	46
81	463	44	450	97	45	423	91	46
85	453	44	441	97	43	424	94	45
89	452	40	445	98	41	426	94	44
93	448	37	446	100	40	425	94	43
97	441	36	446	101	34	422	96	43
101	437	31	426	97	34	415	95	42
FEMALE								
0	112	50	111	99	50	107	96	50
1	132	50	129	98	50	122	92	50
2	146	50	143	98	50	134	92	50
3	157	50	153	97	50	144	92	50
4	168	50	164	98	50	153	91	50
5	175	50	172	98	50	160	91	50
6	181	50	178	98	50	167	92	50
7	188	50	184	98	50	172	91	50
8	191	50	188	98	50	177	93	50
9	195	50	192	98	50	181	93	50
10	200	50	198	99	50	186	93	50
11	205	50	203	99	50	190	93	50
12	205	50	204	100	50	192	94	50
19	218	50	215	99	50	206	94	50
23	227	50	225	99	50	216	95	50
29	230	50	226	98	50	215	93	50
33	234	50	232	99	50	223	95	50
38	239	50	236	99	50	229	96	49
42	246	50	242	98	50	232	94	49
46	251	50	244	97	50	237	94	49
51	259	49	249	96	49	240	93	49
55	265	49	256	97	49	246	93	49
59	278	49	264	95	49	253	91	49
63	289	49	274	95	49	260	90	48
68	299	49	283	95	49	266	89	47
72	305	49	291	95	48	276	90	46
76	308	49	295	96	47	278	90	46
81	311	49	298	96	45	284	91	46
85	317	49	279	88	43	293	92	46
89	321	49	310	97	39	300	93	45
93	324	48	317	98	37	311	96	43
97	322	47	316	98	37	314	98	41
101	322	43	317	98	35	312	97	39

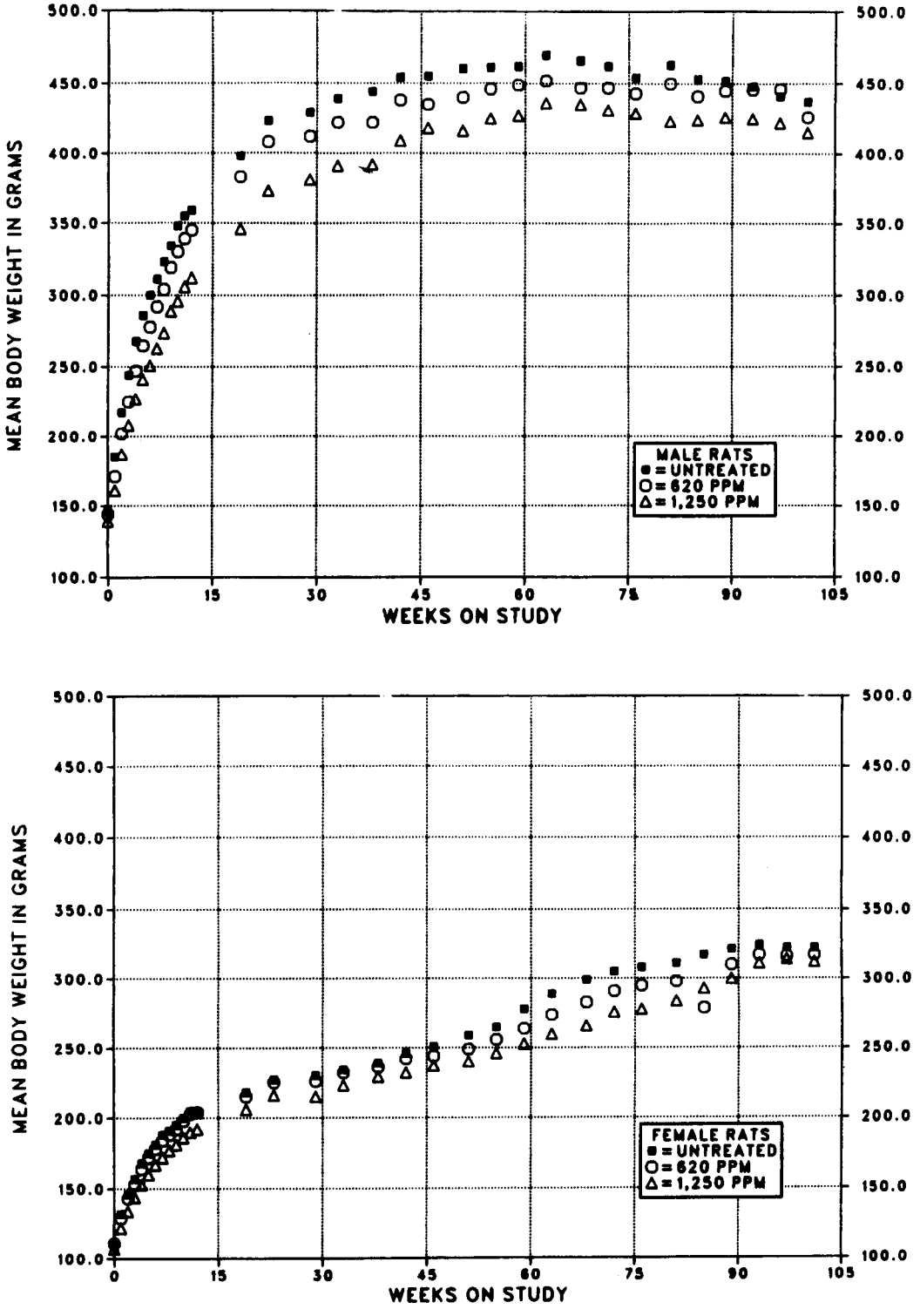

FIGURE 1. GROWTH CURVES FOR RATS FED DIETS CONTAINING PHENYLEPHRINE HYDROCHLORIDE FOR TWO YEARS

III. RESULTS: RATS

Survival

Estimates of the probabilities of survival for male and female rats fed diets containing phenylephrine hydrochloride at the concentrations used in these studies and for controls are shown in the Kaplan and Meier curves in Figure 2. The survival of the high dose group of male rats was significantly greater than that of the controls after week 98 (Table 7).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the liver, lung, hematopoietic system, adrenal gland, and prostate gland.

Lesions in male rats are summarized in Appendix A. Histopathologic findings on neoplasms are summarized in Table A1. Table A2 gives the survival and tumor status for individual male rats. Table A3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table A3 (footnotes). Historical incidences of tumors in control male rats are listed in Table A4. Findings on nonneoplastic lesions are summarized in Table A5.

Lesions in female rats are summarized in Appendix B. Histopathologic findings on neoplasms are summarized in Table B1. Table B2 gives the survival and tumor status for individual female rats. Table B3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table B3 (footnotes). Findings on nonneoplastic lesions are summarized in Table B4.

TABLE 7. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

	Control	620 ppm	1,250 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	20	17	8
Killed at termination	30	33	41
Died during termination period	0	0	1
Survival P values (c)	0.019	0.694	0.021
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	8	16	14
Killed at termination	42	34	35
Died during termination period	0	0	1
Survival P values (c)	0.208	0.071	0.212

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

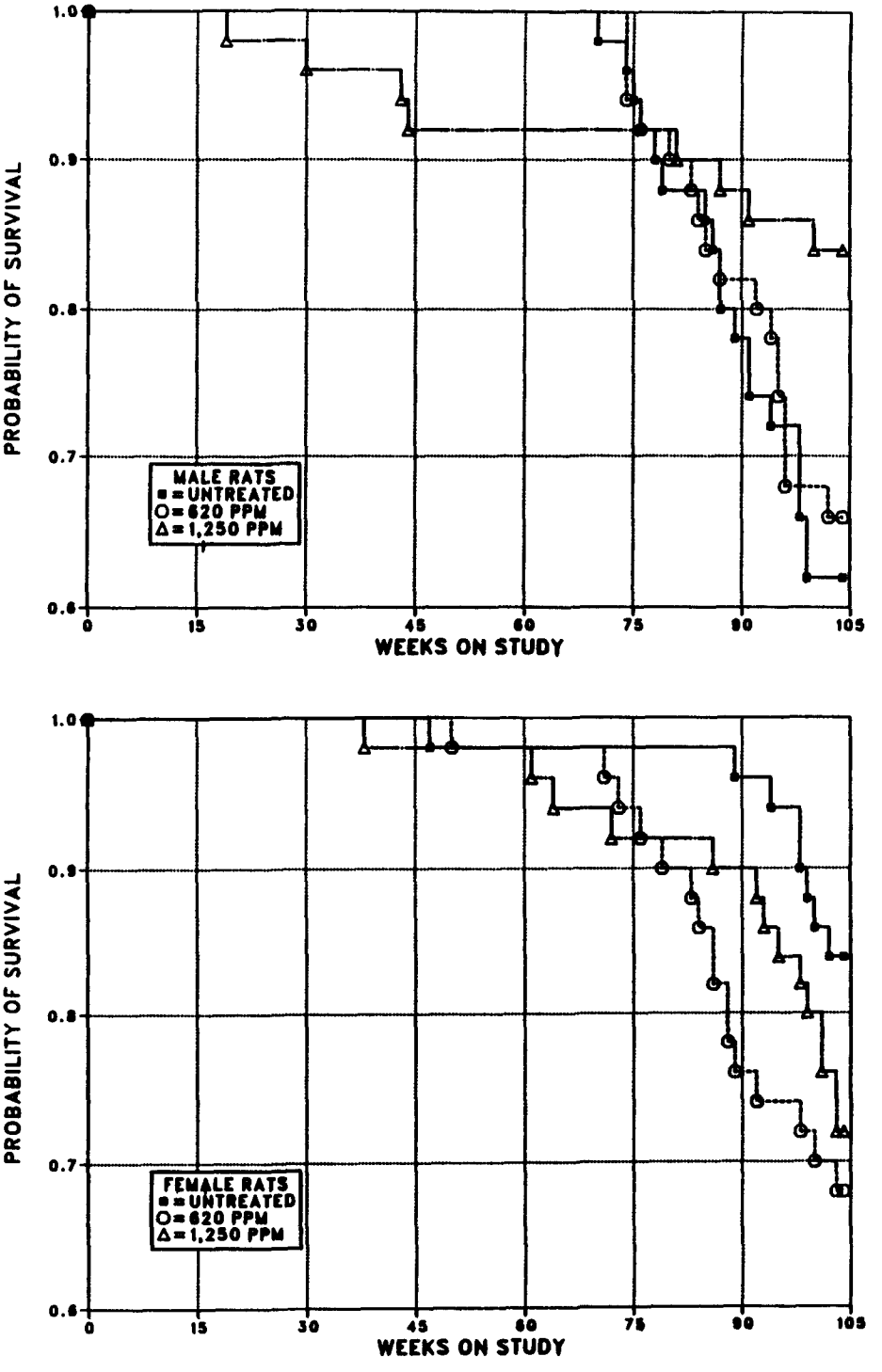

FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING PHENYLEPHRINE HYDROCHLORIDE FOR TWO YEARS

Liver: Chronic focal inflammation was observed at increased incidences in dosed rats (male: control, 2/50; low dose, 13/50; high dose, 17/50; female: 17/50; 28/50; 35/50). The incidence of neoplastic nodules in low dose male rats was significantly lower than that in the controls (5/50; 0/50; 2/50). The incidences of neoplastic nodules or hepatocellular carcinomas (combined) in dosed male rats were not significantly different from that in the controls. Bile duct hyperplasia was observed more frequently in controls than in dosed male rats (46/50; 16/50; 11/50) and female rats (20/50; 5/50; 2/50).

Chronic focal inflammation appeared increased in both incidence and degree in low dose and high dose rats of each sex. The lesion did not differ in character from the lesion that occurs spontaneously in the F344 rat. It was characterized by the presence of mononuclear cells scattered around bile ducts in the portal triad regions of hepatic lobules. Small granulomas were frequently adjacent to or replacing bile ducts in the portal regions. The granulomas appeared to consist entirely of macrophages.

Lung: Perivascular cuffing of the lung was observed at increased incidences in dosed male rats (control, 2/50; low dose, 12/50; high dose, 8/50). The lesion was seen in 4/50 control, 6/50 low dose, and 7/50 high dose females.

Hematopoietic System: Leukemia in male rats occurred with a negative trend, and the incidences in the dosed groups were lower than that in the controls (Table 8). Leukemia was seen in 15/50 control, 14/50 low dose, and 10/50 high dose female rats.

TABLE 8. ANALYSIS OF MONONUCLEAR CELL LEUKEMIA IN MALE RATS IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE (a,b)

	Control	620 ppm (c)	1,250 ppm (c)
Overall Rates	24/50 (48%)	9/50 (18%)	5/50 (10%)
Adjusted Rates	54.9%	21.4%	11.4%
Terminal Rates	11/30 (37%)	3/33 (9%)	3/42 (7%)
Week of First Observation	70	74	91
Life Table Tests	P<0.001N	P=0.003N	P<0.001N
Incidental Tumor Tests	P<0.001N	P=0.002N	P=0.003N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix A, Table A3 (footnotes).
(b) Historical incidence of leukemia in NTP studies (mean ± SD): 458/1,727 (27% ± 9%)
(c) The estimated dose in milligrams per kilograms per day is given in Chapter III (Body Weights and Clinical Signs) and in Appendix K.

Adrenal Gland: The incidence of medullary hyperplasia in dosed male rats was lower than that in the controls. Pheochromocytomas in male rats occurred with a negative trend, and the incidence in the high dose group was lower than that in the controls (Table 9). The incidences of medullary hyperplasia and of pheochromocytomas in dosed female rats were not significantly different from those in the controls (medullary hyperplasia: control, 2/50; low dose, 3/50; high dose, 1/50; pheochromocytomas or malignant pheochromocytomas: 6/50; 6/50; 2/50). Incidences of adrenal cortical hyperplasia and lipoid degeneration in dosed male and female rats were lower than those in the controls (Tables A5 and B4).

Prostate Gland: The incidence of inflammation was increased in dosed versus control male rats (control, 10/50; low dose, 24/50; high dose, 24/50). These lesions were similar to those that spontaneously arise in the F344 rat but were subjectively judged to be more severe in dosed rats than in control rats.

TABLE 9. ANALYSIS OF ADRENAL GLAND LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE

	Control	620 ppm	1,250 ppm
Medullary Hyperplasia			
Overall Rates	10/49 (20%)	4/50 (8%)	6/50 (12%)
Pheochromocytoma			
Overall Rates	13/49 (27%)	10/50 (20%)	2/50 (4%)
Adjusted Rates	39.4%	27.6%	4.8%
Terminal Rates	10/30 (33%)	8/33 (24%)	2/42 (5%)
Week of First Observation	99	76	104
Life Table Tests	P<0.001N	P=0.245N	P<0.001N
Incidental Tumor Tests	P=0.001N	P=0.259N	P=0.002N
Malignant Pheochromocytoma			
Overall Rates	1/49 (2%)	1/50 (2%)	0/50 (0%)
Pheochromocytoma or Malignant Pheochromocytoma (a)			
Overall Rates	14/49 (29%)	11/50 (22%)	2/50 (4%)
Adjusted Rates	42.4%	30.5%	4.8%
Terminal Rates	11/30 (37%)	9/33 (27%)	2/42 (5%)
Week of First Observation	99	76	104
Life Table Tests	P<0.001N	P=0.243N	P<0.001N
Incidental Tumor Tests	P<0.001N	P=0.256N	P<0.001N

(a) Historical incidence in NTP studies (mean ± SD): 358/1,702 (21% ± 10%)

III. RESULTS: MICE

FOURTEEN-DAY STUDIES

None of the mice died before the end of the studies (Table 10). No clinical signs were related to phenylephrine hydrochloride dosing. Final mean body weights and feed consumption were not affected by phenylephrine hydrochloride. No compound-related gross or microscopic pathologic effects were observed. Since no toxic effects were noted in the 14-day studies, doses were increased for the 12-week studies.

TWELVE-WEEK STUDIES

Three of 10 male mice receiving 20,000 ppm and 2/10 males receiving 10,000 ppm died before the end of the study (Table 11). All female mice survived to the end of the study. The final mean body weights of males that received 10,000 or 20,000 ppm were 18% or 25% lower than that of the controls. Final mean body weights of all dosed groups of female mice were 10%-32% lower than that of the controls. Estimated feed consumption by the 20,000-ppm groups was greater than that of the controls.

Rough hair coats and lethargy were considered to be compound-related effects. Pupil size of dosed mice was generally not significantly different from that in controls (Appendix L, Table L3). Inflammatory eye lesions (acute keratitis, panophthalmitis, or phthisis bulbi) were observed in 3/10 males and 2/10 females that received 20,000 ppm. The absolute and relative adrenal gland weights for mice that received 20,000 ppm were greater than those of the controls (Table L4). The relative heart weight for females that received 20,000 ppm was significantly greater than that of the controls. No histopathologic changes were noted in the adrenal gland or heart; no compound-related changes were found in other tissues.

Dose Selection Rationale: Because of decreased weight gain and deaths of male mice at higher doses in the 12-week studies, doses selected for mice for the 2-year studies were 1,250 and 2,500 ppm phenylephrine hydrochloride.

TABLE 10. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Controls (percent)	Feed Consumption (d)	
		Initial (b)	Final	Change (c)		Wk 1	Wk 2
MALE							
0	5/5	25.9 ± 0.7	27.4 ± 0.9	+1.5 ± 0.5	--	2.8	3.6
63	5/5	24.0 ± 0.4	26.1 ± 0.8	+2.1 ± 0.6	95.3	2.9	3.4
125	5/5	25.9 ± 0.6	26.9 ± 0.7	+1.0 ± 1.0	98.2	3.3	3.7
250	5/5	26.0 ± 0.9	28.1 ± 0.9	+2.1 ± 0.3	102.6	2.6	4.0
500	4/4	23.5 ± 1.7	25.8 ± 0.8	+2.3 ± 1.0	94.2	2.5	4.0
1,000	5/5	25.2 ± 1.1	29.5 ± 1.0	+4.3 ± 1.3	107.7	3.3	3.6
FEMALE							
0	5/5	20.1 ± 0.7	21.5 ± 0.4	+1.4 ± 0.4	--	3.4	3.7
63	5/5	19.8 ± 0.6	19.1 ± 0.7	−0.7 ± 0.3	88.8	3.0	3.1
125	5/5	19.7 ± 0.3	18.6 ± 0.3	−1.1 ± 0.3	86.5	2.9	3.5
250	5/5	19.7 ± 0.3	19.5 ± 0.4	−0.2 ± 0.3	90.7	2.8	3.5
500	5/5	20.3 ± 0.5	20.0 ± 0.6	−0.3 ± 0.2	93.0	2.7	3.5
1,000	5/5	19.9 ± 0.5	21.7 ± 0.7	+1.8 ± 0.4	100.9	2.7	3.8

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Grams of feed per animal per day

TABLE 11. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE TWELVE-WEEK FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Wk 1	Wk 12
MALE							
0	10/10	23.2 ± 0.7	33.6 ± 1.1	+10.4 ± 0.9	--	3.0	3.6
1,250	10/10	23.8 ± 1.0	33.2 ± 1.0	+9.4 ± 0.8	98.8	3.1	3.2
2,500	10/10	22.4 ± 1.1	33.6 ± 0.8	+11.2 ± 0.8	100.0	3.1	3.3
5,000	10/10	23.0 ± 0.4	30.8 ± 0.8	+7.8 ± 0.4	91.7	3.2	2.9
10,000	(e) 8/10	22.6 ± 0.7	27.4 ± 0.5	+5.0 ± 0.3	81.5	3.3	3.7
20,000	(f) 7/10	23.9 ± 0.9	25.3 ± 1.4	+0.4 ± 1.9	75.3	3.7	4.2
FEMALE							
0	10/10	19.5 ± 0.7	29.5 ± 1.9	+10.0 ± 1.3	--	3.0	3.5
1,250	10/10	18.6 ± 0.5	26.5 ± 1.2	+7.9 ± 0.8	89.8	2.8	3.1
2,500	10/10	18.1 ± 0.7	25.6 ± 0.5	+7.5 ± 0.7	86.8	2.7	2.8
5,000	10/10	18.8 ± 0.6	23.5 ± 0.6	+4.7 ± 0.4	79.7	2.8	2.9
10,000	10/10	18.1 ± 0.4	22.8 ± 0.3	+4.7 ± 0.3	77.3	3.1	3.5
20,000	10/10	18.0 ± 0.5	20.1 ± 0.5	+2.1 ± 0.3	68.1	3.4	4.3

(a) Number surviving/number initially in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams of feed per animal per day
(e) Week of death: 8,12
(f) Week of death: 3,7,10

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The initial mean body weight of high dose male mice was 5% lower than that of the controls, and the mean body weight was 6%-14% lower throughout the study. The mean body weight of low dose male mice was 4%-10% lower than that of the controls throughout most of the study. The mean body weights of low dose and high dose female mice were approximately 4%-7% and 4%-10% lower than that of the controls after week 25 (Table 12 and Figure 3). The average daily feed consumption by low dose and high dose male mice was 93% and 90% that of the controls and by low dose and high dose female mice, 94% and 93% that of the controls (Appendix K, Tables K3 and K4). The average amount of phenylephrine hydrochloride consumed per day was approximately 130 mg/kg or 260 mg/kg for low dose or high dose male mice and 140 mg/kg or 280 mg/kg for low dose or high dose female mice. No specific clinical signs of toxicity or ophthalmologic findings in any group of dosed mice were attributed to phenylephrine hydrochloride.

TABLE 12. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

Week on Study	Control		1,250 ppm			2,500 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
1	24.1	50	23.5	98	50	23.0	95	50
2	25.3	50	24.6	97	50	23.9	94	50
3	26.8	50	25.5	95	50	25.3	94	50
4	27.7	50	26.3	95	50	25.7	93	50
5	28.9	50	27.3	94	50	26.5	92	50
6	30.7	50	28.9	94	50	28.1	92	50
7	30.9	50	29.3	95	50	28.7	93	50
8	31.3	50	30.0	96	50	29.3	94	50
9	31.9	50	30.4	95	50	29.5	92	50
10	32.3	50	31.3	97	50	30.2	93	50
11	33.2	50	31.2	94	50	30.4	92	50
12	33.1	50	31.2	94	50	30.3	92	50
19	35.1	50	33.3	95	50	31.4	89	50
21	36.8	48	35.5	96	50	34.1	93	50
25	38.2	48	36.8	96	49	35.1	92	50
30	38.4	48	36.9	96	49	35.8	93	50
35	39.3	48	37.4	95	49	36.1	92	50
40	38.5	48	36.0	94	49	35.0	91	50
44	38.0	48	35.1	92	49	34.8	92	50
48	41.0	47	37.6	92	49	35.4	86	50
53	41.3	47	37.7	91	49	35.7	86	50
57	40.7	46	37.1	91	49	35.9	88	50
61	42.0	46	38.7	92	49	36.4	87	50
65	42.0	45	38.6	92	49	36.7	87	50
70	41.6	45	37.5	90	49	36.2	87	49
74	41.3	45	37.8	92	49	36.6	89	49
78	40.5	45	36.7	91	49	36.5	90	49
83	41.8	41	36.0	86	48	36.4	87	49
87	39.7	41	36.2	91	46	35.8	90	49
91	40.7	39	36.6	90	46	35.8	88	47
95	38.8	37	36.3	94	41	35.2	91	47
99	37.9	37	36.4	96	38	34.6	91	44
103	37.0	35	35.2	95	38	33.3	90	43
FEMALE								
1	19.1	50	18.9	99	50	19.0	99	50
2	19.4	50	19.4	100	50	19.2	99	50
3	19.8	50	19.6	99	50	19.2	97	50
4	20.7	50	20.5	99	50	20.4	99	50
5	21.5	50	21.3	99	50	21.2	99	50
6	22.7	50	22.2	98	50	22.1	97	50
7	23.3	50	22.7	97	50	22.7	97	50
8	23.3	50	22.9	98	50	22.9	98	49
9	23.7	50	23.2	98	50	23.1	97	49
10	24.4	50	23.9	98	50	23.9	98	49
11	24.4	50	24.1	99	50	23.9	98	49
12	25.1	50	24.8	99	50	24.6	98	49
19	27.5	50	26.5	96	50	26.6	97	49
21	30.4	50	28.4	93	50	29.2	96	47
25	32.2	50	29.3	91	50	30.6	95	47
30	32.6	50	30.6	94	50	30.6	94	47
35	34.6	50	33.0	95	50	33.0	95	47
40	34.5	50	32.7	95	50	32.6	94	47
44	34.7	50	33.1	95	50	33.6	97	47
48	37.0	50	35.7	96	50	35.6	96	47
53	37.6	50	36.2	96	50	36.2	96	47
57	37.3	49	35.3	95	50	35.7	96	47
61	39.6	49	37.0	93	50	37.1	94	47
65	40.0	49	37.7	94	50	37.6	94	47
70	39.1	49	36.3	93	50	35.9	92	47
74	39.4	49	37.3	95	49	36.6	93	45
78	39.3	49	37.3	95	47	36.4	93	44
83	40.7	43	38.0	93	47	36.3	89	43
87	38.8	41	37.1	96	45	35.9	93	43
91	38.7	40	36.6	95	44	35.7	92	43
95	39.0	38	36.9	95	40	35.1	90	41
99	39.1	38	37.2	95	35	34.3	88	39
103	37.7	38	35.9	95	35	34.4	91	34

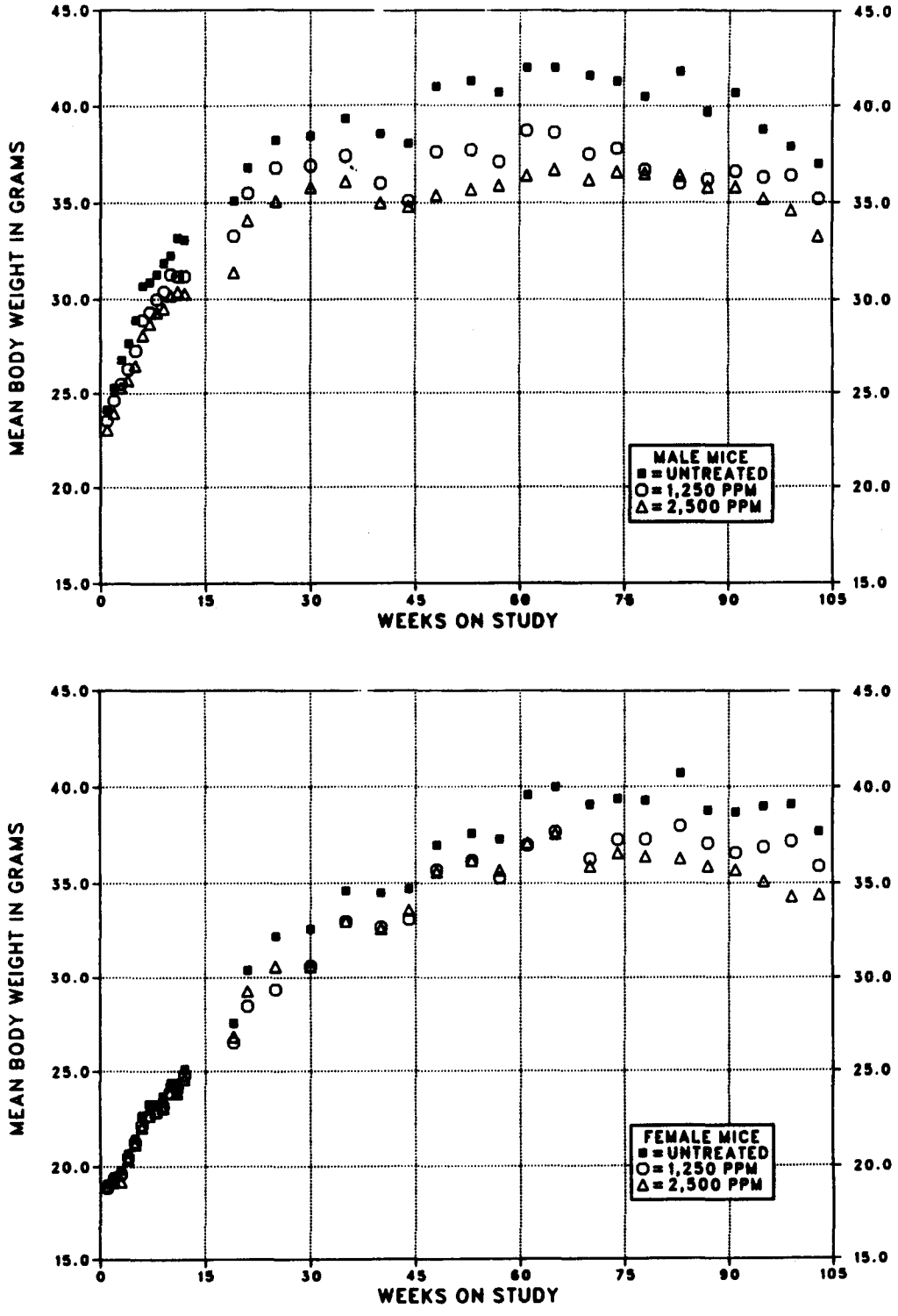

FIGURE 3. GROWTH CURVES FOR MICE FED DIETS CONTAINING PHENYLEPHRINE HYDROCHLORIDE FOR TWO YEARS

III. RESULTS: MICE

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing phenylephrine hydrochloride at the concentrations used in these studies and for controls are shown in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex (Table 13).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver. Lesions in male mice are summarized in Appendix C. Histopathologic findings on neoplasms are summarized in Table C1. Table C2 gives the survival and tumor status for individual male mice. Table C3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table C3 (footnotes). Findings on nonneoplastic lesions are summarized in Table C4.

Lesions in female mice are summarized in Appendix D. Histopathologic findings on neoplasms are summarized in Table D1. Table D2 gives the survival and tumor status for individual female mice. Table D3 contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Table D3 (footnotes). Findings on nonneoplastic lesions are summarized in Table D4.

Liver: Focal cellular change was observed at an increased incidence in high dose male mice (male: control, 0/50; low dose, 2/50; high dose, 7/50); this lesion was not increased in female mice (0/50; 2/50; 1/50).

TABLE 13. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

	Control	1,250 ppm	2,500 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	12	7
Accidentally killed	2	0	0
Killed at termination	35	38	43
Survival P values (c)	0.120	0.820	0.149
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	16	16
Killed at termination	37	34	34
Survival P values (c)	0.664	0.806	0.692

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

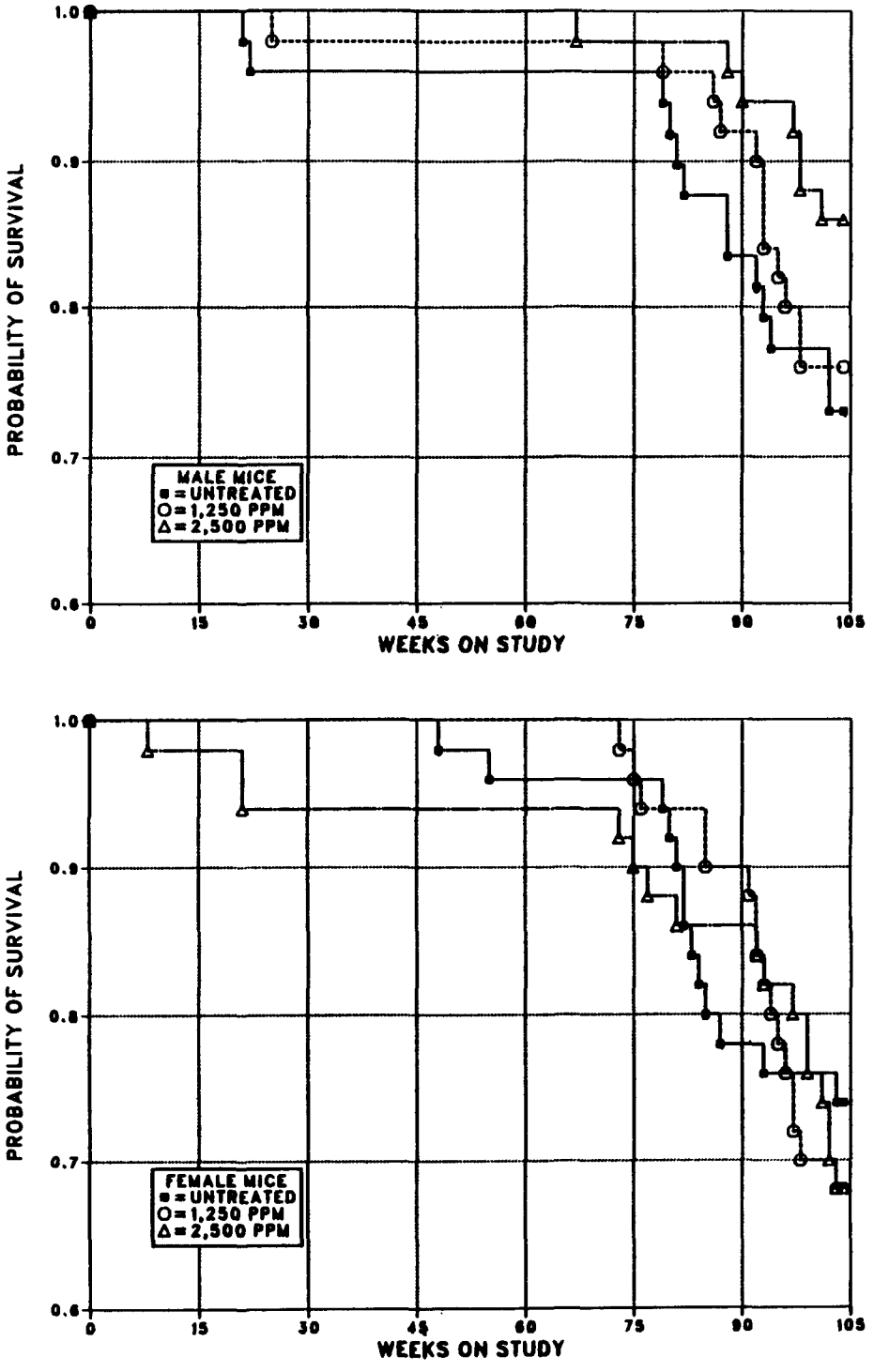

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING PHENYLEPHRINE HYDROCHLORIDE FOR TWO YEARS

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Two-year toxicology and carcinogenesis studies of phenylephrine hydrochloride were conducted on groups of 50 F344/N rats and B6C3F$_1$ mice of each sex. Feed containing 0, 620, or 1,250 ppm phenylephrine hydrochloride was given to rats; mice received feed containing 0, 1,250, or 2,500 ppm. The average daily doses were estimated to be 24 mg/kg for low dose rats, 50 mg/kg for high dose rats, 133 mg/kg for low dose mice, and 270 mg/kg for high dose mice. The concentrations in feed were selected after evaluation of the results of the 12-week studies in which rats and mice received feed containing up to 20,000 ppm phenylephrine hydrochloride.

In the 12-week studies, several male rats and male mice died in the groups fed diets containing 10,000 and 20,000 ppm; one male rat in the 5,000 ppm group died. No female rats or female mice died. A dose-related decrease in body weights was observed. Feed consumption by rats decreased as the concentration of phenylephrine hydrochloride increased, suggesting that formulated diet mixtures were unpalatable. However, feed consumption by mice did not appear to be dose related, and high dose mice apparently consumed more than did controls. No attempts were made to estimate spillage by the various groups. If the feed consumption data are correct, the approximate lethal daily dose was 300 mg/kg for male rats and 1,400 mg/kg for male mice. The dose for rats is similar to the single oral LD_{50} value of 350 mg/kg reported by Stockhaus and Wick (1969).

No specific organ toxicity was seen in the 12-week studies. Mild testicular, seminal vesicle, or ovarian atrophy was observed in mice receiving doses of phenylephrine hydrochloride sufficient to kill several of the male mice, but the cause of the deaths of male rats and male mice could not be determined. Inflammatory eye lesions were observed in higher dose rats and mice. These lesions are probably a secondary effect of the pharmacologic action of phenylephrine hydrochloride, which reduces ocular secretions and thereby predisposes the cornea to irritation and inflammation.

In the 2-year studies, body weights of dosed rats and mice of each sex were slightly lower than those of controls, and this effect was dose related. Feed consumption was not significantly different among dosed and control rats, but dosed mice consumed 6%-10% less feed than did controls. Survival of both dosed and control rats and mice was consistent with that seen in other NTP feed studies. Only 8/50 high dose male rats died before the end of the studies; four of these deaths occurred before week 45. The cause of these four early deaths is unknown, and no neoplastic lesions were found. Nonetheless, survival of high dose male rats was greater than that of the controls, perhaps because of the fewer early deaths from mononuclear cell leukemia in dosed animals (control, 13/20; low dose, 6/17; high dose, 2/8). Three high dose female mice died before week 22. Although these deaths were considered to be natural, two of the animals died on the same day and in the same cage, suggesting that death was associated with some factor other than exposure to phenylephrine hydrochloride. No tumors were observed in these two mice. The other mouse that died early had a benign ovarian teratoma.

Dosed male and female rats had greater incidences of chronic focal inflammation of the liver than did controls (male: control, 2/50; low dose, 13/50; high dose, 17/50; female: 17/50; 28/50; 35/50), and dosed male rats had increased incidences of inflammation of the prostate gland (10/50; 24/50; 24/50) and of inflammation surrounding the vascular tissue in the lung (perivascular cuffing: 2/50; 12/50; 8/50). The liver and prostate gland lesions were similar to those that arise in older, untreated rats, but they were subjectively judged to be more severe and more frequent in dosed animals. The association of perivascular cuffing with administration of phenylephrine hydrochloride was less clear.

No increases in the incidences of neoplastic lesions were found in dosed rats. In fact, significantly lower incidences of several tumors and nonneoplastic proliferative lesions were considered to be associated with phenylephrine hydrochloride dosing. In male rats, mononuclear cell leukemia occurred with a negative trend (control, 24/50; low dose, 9/50; high dose, 5/50). The incidence in high dose males was equal to the lowest incidence observed in historical controls (mean, 27%; range 10%-46%). The incidence in the current control group was greater than the

highest incidence previously seen; thus, the negative trend may be partially explained by the chance occurrence of a much greater incidence of mononuclear cell leukemia than is usually observed in untreated controls. Pheochromocytomas of the adrenal medulla also occurred with a negative trend in male rats (14/49; 11/50; 2/50). This trend appeared to result from an incidence of pheochromocytomas in high dose animals substantially lower than would be expected based on historical control data. Incidences of adrenal medullary hyperplasia were decreased in dosed male rats; decreases in the incidences of proliferative lesions of the adrenal medulla were observed less frequently in female rats. However, dosed male and female rats had slightly lower incidences of adrenal cortical focal hyperplasia than did controls. In addition, bile duct hyperplasia was observed much less frequently in dosed than in control rats (male: control, 46/50; low dose, 16/50; high dose, 11/50; female: 20/50; 5/50; 2/50). Although it is difficult to envision a single mechanism whereby the administration of phenylephrine hydrochloride could decrease the incidence of proliferative lesions in these various organs, the decrease in proliferative lesions of the adrenal gland medulla could have occurred through some type of feedback inhibition, given the similar pharmacologic actions of phenylephrine and of epinephrine, the latter being synthesized and secreted by the adrenal medulla. Differences in body weights or survival are known to influence incidences of neoplasia, but in these studies, body weights were only slightly different between the groups. Survival of high dose male rats, the group that had the fewest proliferative lesions, was greater than that of controls. Mesovarial leiomyomas, observed in rats given β-agonists, were not seen in dosed or control rats in these studies.

In mice, no neoplastic or nonneoplastic lesions were clearly related to dosing with phenylephrine hydrochloride, although the incidence of focal cellular change in the liver was increased slightly in high dose male mice (control, 0/50; low dose, 2/50; high dose, 7/50). The doses of phenylephrine hydrochloride in these studies are considered adequate because higher doses caused marked decreases in body weight in the 12-week studies. No marked increases in the incidences of nonneoplastic lesions resulted from dosing with phenylephrine hydrochloride, and survival of dosed animals was equal to or greater than that of the controls. The doses given to rats and mice were approximately 20-250 times the maximum daily dose recommended for use by humans.

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

Conclusions: Under the conditions of these 2-year studies, there was *no evidence of carcinogenicity** of phenylephrine hydrochloride for male or female F344/N rats given 620 or 1,250 ppm in feed or for male or female B6C3F_1 mice given 1,250 or 2,500 ppm in feed. Survival of high dose male rats was greater than that of controls, and the incidences of mononuclear cell leukemia and pheochromocytomas were lower in dosed than in control male rats. Inflammation was observed more frequently in the liver and prostate gland of dosed male rats than in controls.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 8.

V. REFERENCES

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APPENDIX A

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

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
Squamous cell carcinoma		1 (2%)	
Basal cell tumor		1 (2%)	1 (2%)
Trichoepithelioma	1 (2%)	1 (2%)	
Keratoacanthoma		1 (2%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS		2 (4%)	
Fibroma	3 (6%)	2 (4%)	
Fibrosarcoma	2 (4%)	1 (2%)	
RESPIRATORY SYSTEM			
#Trachea	(50)	(50)	(50)
C-cell carcinoma, invasive	1 (2%)		
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			2 (4%)
C-cell carcinoma, metastatic	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	24 (48%)	9 (18%)	5 (10%)
#Lymph node	(47)	(49)	(49)
C-cell carcinoma, metastatic	1 (2%)		
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
#Liver	(50)	(50)	(50)
Neoplastic nodule	5 (10%)		2 (4%)
Hepatocellular carcinoma	1 (2%)	1 (2%)	
#Colon	(50)	(50)	(49)
Mucinous adenocarcinoma	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(48)	(47)
Adenoma, NOS	11 (23%)	13 (27%)	14 (30%)
#Adrenal medulla	(49)	(50)	(50)
Pheochromocytoma	13 (27%)	10 (20%)	2 (4%)
Pheochromocytoma, malignant	1 (2%)	1 (2%)	
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma		1 (2%)	1 (2%)
Follicular cell carcinoma		1 (2%)	
C-cell adenoma	5 (10%)	5 (10%)	4 (8%)
C-cell carcinoma	2 (4%)	4 (8%)	1 (2%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Parathyroid	(31)	(30)	(32)
Adenoma, NOS	1 (3%)		
#Pancreatic islets	(48)	(49)	(50)
Islet cell adenoma	2 (4%)	2 (4%)	3 (6%)
Islet cell carcinoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	3 (6%)	1 (2%)	
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	2 (4%)	1 (2%)	1 (2%)
Adenoma, NOS		1 (2%)	
#Testis	(50)	(50)	(50)
Interstitial cell tumor	47 (94%)	46 (92%)	45 (90%)
NERVOUS SYSTEM			
#Cerebrum	(50)	(50)	(50)
Glioma, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	2 (4%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	2 (4%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mucinous adenocarcinoma, metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	3	4
Moribund sacrifice	18	14	5
Terminal sacrifice	30	33	41

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	50	49	46
Total primary tumors	128	110	83
Total animals with benign tumors	50	49	46
Total benign tumors	87	86	73
Total animals with malignant tumors	29	21	8
Total malignant tumors	34	24	8
Total animals with secondary tumors##	2	1	
Total secondary tumors	4	1	
Total animals with tumors uncertain--benign or malignant	6		2
Total uncertain tumors	7		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 A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE: UNTREATED CONTROL

ANIMAL NUMBER	109	111	102	120	149	129	147	108	110	121	128	107	136	141	114	131	146	144	145	133	101	103	104	105	108
WEEKS ON STUDY	070	074	075	076	078	079	085	086	087	087	089	091	091	094	098	098	098	099	099	103	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								X	
Fibrosarcoma																	X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell carcinoma, metastatic														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, invasive														X											
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell carcinoma, metastatic														X											
Thymus	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																	X	X		X	X				
Hepatocellular carcinoma																		X							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucinous adenocarcinoma												X													
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X				X							X					X	X	X					
Adrenal	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Pheochromocytoma																	X	X	X		X				X
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																					X				
C-cell carcinoma														X											
Parathyroid	−	−	−	−	+	−	−	+	−	+	+	+	+	−	−	+	+	−	+	+	+	+	+	−	+
Adenoma, NOS																									
Pancreatic islets	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS			X	X																					
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS					X																				
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mucinous adenocarcinoma, metastatic												X													
Leukemia, mononuclear cell	X				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
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

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

ANIMAL NUMBER	112	113	115	116	117	118	119	122	123	124	125	126	127	130	132	134	135	137	138	139	140	142	143	148	150	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Trichoepithelioma				X																						1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma			X					X																		3
Fibrosarcoma					X																					2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, invasive																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C-cell carcinoma, metastatic																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule							X																			5
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucinous adenocarcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																			X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS											X					X					X		X	X		11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma					X			X			X				X			X			X	X	X			13
Pheochromocytoma, malignant																X										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C cell adenoma	X						X				X		X													5
C-cell carcinoma				X																						2
Parathyroid	+	+	+	–	+	–	+	–	+	+	–	+	+	+	+	+	–	–	+	–	+	–	+	+	+	31
Adenoma, NOS		X																								1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma										X			X													2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma											X		X				X									3
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	47
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS							X			X																2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mucinous adenocarcinoma, metastatic																										1
Leukemia, mononuclear cell				X		X			X	X					X		X		X				X			24

* Animals necropsied

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

ANIMAL NUMBER	0038	0043	0045	0117	0112	0114	0004	0040	0026	0041	0029	0013	0119	0115	0116	0033	0042	0001	0002	0003	0005	0008	0007	0008	0009
WEEKS ON STUDY	074	074	074	076	080	083	084	085	087	092	094	095	095	096	096	096	102	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma														X											
Basal cell tumor																									
Trichoepithelioma																									
Keratoacanthoma							X																		
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS	X												X												
Fibroma																									
Fibrosarcoma	X																								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic										X															
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																								X	
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		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma				X					X														X		
Pheochromocytoma, malignant																								X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
C-cell adenoma																	X							X	
C-cell carcinoma										X															
Parathyroid	+	+	+	−	+	−	−	−	−	+	+	−	−	−	−	−	−	+	+	+	+	+	+	−	−
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	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
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS					X																				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	+	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS							X							X											
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X				X			X		X	X					X					X			X

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

ANIMAL NUMBER	0110	0111	0118	0209	0211	0222	0238	0244	0255	0267	0288	0309	0311	0324	0334	0355	0366	0377	0399	0441	0466	0471	0488	0499	0500	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																						X				1
Squamous cell carcinoma																										1
Basal cell tumor																							X			1
Trichoepithelioma	X																									1
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										2
Fibroma																					X		X			2
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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			1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS		X	X	X		X							X					X							X	13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma											X	X		X		X				X				X	X	10
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																		X								1
Follicular cell carcinoma								X																		1
C-cell adenoma				X			X						X													5
C-cell carcinoma					X				X											X						4
Parathyroid	+	+	+	+	–	–	+	–	+	–	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	30
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma							X																	X		2
Islet cell carcinoma																						X				1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	46
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS														X												1
Adenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X																					9

* Animals necropsied

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

ANIMAL NUMBER	057	052	053	099	078	083	082	072	051	054	055	056	058	059	060	061	063	064	065	066	067	068	069	070	071
WEEKS ON STUDY	019	030	043	044	081	087	091	100	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor												X													
Keratoacanthoma															X										
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X		X						X							X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																							X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma																									
C-cell carcinoma																				X					
Parathyroid	+	−	+	+	+	−	+	+	+	−	+	+	−	+	+	−	−	+	+	+	+	+	+	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma										X													X		
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS					X																				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell							X	X	X																

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

ANIMAL NUMBER	073	074	075	076	077	079	080	081	082	084	085	086	087	088	089	090	091	092	093	094	095	096	097	098	100	TOTAL.
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell tumor																										1
Keratoacanthoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																						2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																					X					2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	47
Adenoma, NOS		X			X				X			X	X		X	X		X	X				X			14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma															X											2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																							X			1
C-cell adenoma									X	X				X									X			4
C-cell carcinoma																										1
Parathyroid	+	–	–	–	+	+	+	–	+	+	–	+	–	–	+	+	+	–	+	–	+	–	+	–	+	32
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																X										3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	45
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																					X					1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell						X	X																			5

* Animals necropsied

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

	Control	620 ppm	1,250 ppm
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	10.0%	6.1%	0.0%
Terminal Rates (c)	3/30 (10%)	2/33 (6%)	0/42 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.044N	P=0.456N	P=0.069N
Incidental Tumor Tests (d)	P=0.044N	P=0.456N	P=0.069N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	16.0%	10.3%	0.0%
Terminal Rates (c)	4/30 (13%)	2/33 (6%)	0/42 (0%)
Week of First Observation	99	74	
Life Table Tests (d)	P=0.014N	P=0.452N	P=0.013N
Incidental Tumor Tests (d)	P=0.040N	P=0.476N	P=0.027N
Cochran-Armitage Trend Test (d)	P=0.029N		
Fisher Exact Test (d)		P=0.500N	P=0.028N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	24/50 (48%)	9/50 (18%)	5/50 (10%)
Adjusted Rates (b)	54.9%	21.4%	11.4%
Terminal Rates (c)	11/30 (37%)	3/33 (9%)	3/42 (7%)
Week of First Observation	70	74	91
Life Table Tests (d)	P<0.001N	P=0.003N	P<0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.002N	P=0.003N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.002N	P<0.001N
Liver: Neoplastic Nodule			
Overall Rates (a)	5/50 (10%)	0/50 (0%)	2/50 (4%)
Adjusted Rates (b)	15.5%	0.0%	4.8%
Terminal Rates (c)	3/30 (10%)	0/33 (0%)	2/42 (5%)
Week of First Observation	99		104
Life Table Tests (d)	P=0.066N	P=0.029N	P=0.113N
Incidental Tumor Tests (d)	P=0.128N	P=0.029N	P=0.282N
Cochran-Armitage Trend Test (d)	P=0.120N		
Fisher Exact Test (d)		P=0.029N	P=0.218N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	5/50 (10%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	15.5%	3.0%	4.8%
Terminal Rates (c)	3/30 (10%)	1/33 (3%)	2/42 (5%)
Week of First Observation	99	104	104
Life Table Tests (d)	P=0.071N	P=0.090N	P=0.113N
Incidental Tumor Tests (d)	P=0.133N	P=0.090N	P=0.282N
Cochran-Armitage Trend Test (d)	P=0.135N		
Fisher Exact Test (d)		P=0.103N	P=0.218N
Pituitary Gland: Adenoma			
Overall Rates (a)	11/48 (23%)	13/48 (27%)	14/47 (30%)
Adjusted Rates (b)	31.2%	35.9%	35.9%
Terminal Rates (c)	6/28 (21%)	9/31 (29%)	14/39 (36%)
Week of First Observation	74	76	104
Life Table Tests (d)	P=0.487N	P=0.491	P=0.536N
Incidental Tumor Tests (d)	P=0.245	P=0.419	P=0.298
Cochran-Armitage Trend Test (d)	P=0.261		
Fisher Exact Test (d)		P=0.407	P=0.299

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

	Control	620 ppm	1,250 ppm
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	13/49 (27%)	10/50 (20%)	2/50 (4%)
Adjusted Rates (b)	39.4%	27.6%	4.8%
Terminal Rates (c)	10/30 (33%)	8/33 (24%)	2/42 (5%)
Week of First Observation	99	76	104
Life Table Tests (d)	P<0.001N	P=0.245N	P<0.001N
Incidental Tumor Tests (d)	P=0.001N	P=0.259N	P=0.002N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test (d)		P=0.298N	P=0.002N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	14/49 (29%)	11/50 (22%)	2/50 (4%)
Adjusted Rates (b)	42.4%	30.5%	4.8%
Terminal Rates (c)	11/30 (37%)	9/33 (27%)	2/42 (5%)
Week of First Observation	99	76	104
Life Table Tests (d)	P<0.001N	P=0.243N	P<0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.256N	P<0.001N
Cochran-Armitage Trend Test (d)	P=0.001N		
Fisher Exact Test (d)		P=0.301N	P<0.001N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	16.7%	14.7%	9.5%
Terminal Rates (c)	5/30 (17%)	4/33 (12%)	4/42 (10%)
Week of First Observation	104	102	104
Life Table Tests (d)	P=0.236N	P=0.570N	P=0.295N
Incidental Tumor Tests (d)	P=0.289N	P=0.576N	P=0.295N
Cochran-Armitage Trend Test (d)	P=0.432N		
Fisher Exact Test (d)		P=0.630	P=0.500N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	5.9%	11.3%	2.4%
Terminal Rates (c)	1/30 (3%)	3/33 (9%)	1/42 (2%)
Week of First Observation	94	92	104
Life Table Tests (d)	P=0.290N	P=0.383	P=0.405N
Incidental Tumor Tests (d)	P=0.425N	P=0.346	P=0.607N
Cochran-Armitage Trend Test (d)	P=0.405N		
Fisher Exact Test (d)		P=0.339	P=0.500N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	7/50 (14%)	9/50 (18%)	5/50 (10%)
Adjusted Rates (b)	22.2%	25.4%	11.9%
Terminal Rates (c)	6/30 (20%)	7/33 (21%)	5/42 (12%)
Week of First Observation	94	92	104
Life Table Tests (d)	P=0.139N	P=0.473	P=0.181N
Incidental Tumor Tests (d)	P=0.232N	P=0.443	P=0.251N
Cochran-Armitage Trend Test (d)	P=0.332N		
Fisher Exact Test (d)		P=0.393	P=0.380N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	2/48 (4%)	2/49 (4%)	3/50 (6%)
Adjusted Rates (b)	6.7%	6.1%	7.1%
Terminal Rates (c)	2/30 (7%)	2/33 (6%)	3/42 (7%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.557	P=0.661N	P=0.651
Incidental Tumor Tests (d)	P=0.557	P=0.661N	P=0.651
Cochran-Armitage Trend Test (d)	P=0.424		
Fisher Exact Test (d)		P=0.684N	P=0.520

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

	Control	620 ppm	1,250 ppm
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	2/48 (4%)	3/49 (6%)	3/50 (6%)
Adjusted Rates (b)	6.7%	9.1%	7.1%
Terminal Rates (c)	2/30 (7%)	3/33 (9%)	3/42 (7%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.575	P=0.544	P=0.651
Incidental Tumor Tests (d)	P=0.575	P=0.544	P=0.651
Cochran-Armitage Trend Test (d)	P=0.432		
Fisher Exact Test (d)		P=0.510	P=0.520
Mammary Gland: Fibroadenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	10.0%	3.0%	0.0%
Terminal Rates (c)	3/30 (10%)	1/33 (3%)	0/42 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.034N	P=0.271N	P=0.069N
Incidental Tumor Tests (d)	P=0.034N	P=0.271N	P=0.069N
Cochran-Armitage Trend Test (d)	P=0.061N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	47/50 (94%)	46/50 (92%)	45/50 (90%)
Adjusted Rates (b)	97.9%	100.0%	97.8%
Terminal Rates (c)	29/30 (97%)	33/33 (100%)	41/42 (98%)
Week of First Observation	70	74	81
Life Table Tests (d)	P=0.002N	P=0.282N	P=0.002N
Incidental Tumor Tests (d)	P=0.495N	P=0.431N	P=0.607
Cochran-Armitage Trend Test (d)	P=0.291N		
Fisher Exact Test (d)		P=0.500N	P=0.358N

(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. N indicates a negative trend or lower incidence in a dosed group.

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

	Incidence in Controls		
	Neoplastic Nodule	Hepatocellular Carcinoma	Neoplastic Nodule or Hepatocellular Carcinoma
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	61/1,719 (3.5%)	12/1,719 (0.7%)	73/1,719 (4.2%)
SD (b)	3.34%	0.98%	3.45%
Range (c)			
High	6/49	1/49	7/49
Low	0/50	0/90	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F334/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Pheochromocytoma	Pheochromocytoma, Malignant	Pheochromocytoma or Pheochromocytoma, Malignant
No 2-year studies by Physiological Research Laboratories are included in the historical data base.			
Overall Historical Incidence			
TOTAL	338/1,702 (19.9%)	20/1,702 (1.2%)	358/1,702 (21.0%)
SD (b)	9.87%	1.49%	9.63%
Range (c)			
High	20/49	3/48	21/49
Low	2/50	0/50	3/50

(a) Data as of August 3, 1984, 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 LEUKEMIA IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Incidence in Controls	
No 2-year studies by Physiological Research Laboratories are included in the historical data base.	
Overall Historical Incidence	
TOTAL	458/1,727 (26.5%)
SD (b)	8.83%
Range (c)	
High	23/50
Low	5/50

(a) Data as of August 3, 1984, 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 PHENYLEPHRINE HYDROCHLORIDE

	CONTROL (UNTR)	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%)	5 (10%)	3 (6%)
Inflammation, NOS			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Atrophy, NOS	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Necrosis, fat	1 (2%)	1 (2%)	2 (4%)
RESPIRATORY SYSTEM			
#Trachea	(50)	(50)	(50)
Inflammation, chronic	1 (2%)	1 (2%)	
#Tracheal submucosa	(50)	(50)	(50)
Inflammation, chronic		2 (4%)	
#Peritracheal tissue	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
#Lung	(50)	(50)	(50)
Congestion, NOS			2 (4%)
Hemorrhage	3 (6%)		1 (2%)
Inflammation, acute	1 (2%)	1 (2%)	
Inflammation, chronic focal	8 (16%)	9 (18%)	8 (16%)
Perivascular cuffing	2 (4%)	12 (24%)	8 (16%)
Alveolar macrophages	4 (8%)	4 (8%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(50)
Hypoplasia, NOS	1 (2%)		
Hyperplasia, NOS	3 (6%)	5 (10%)	1 (2%)
Hyperplasia, reticulum cell	2 (4%)	5 (10%)	2 (4%)
#Spleen	(50)	(50)	(50)
Fibrosis, focal	6 (12%)	3 (6%)	1 (2%)
Hemosiderosis	2 (4%)	2 (4%)	3 (6%)
Hematopoiesis	4 (8%)	2 (4%)	
#Lymph node	(47)	(49)	(49)
Inflammation, acute/chronic			1 (2%)
Hyperplasia, lymphoid	2 (4%)		
#Mandibular lymph node	(47)	(49)	(49)
Plasmacytosis	1 (2%)	3 (6%)	
#Small intestine	(49)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
#Colon	(50)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)
#Thymus	(46)	(49)	(49)
Cyst, NOS	2 (4%)		
Hemorrhage	1 (2%)	2 (4%)	2 (4%)
CIRCULATORY SYSTEM			
#Myocardium	(50)	(50)	(50)
Inflammation, chronic	3 (6%)	1 (2%)	1 (2%)
Degeneration, NOS	40 (80%)	45 (90%)	42 (84%)
*Artery	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
*Pulmonary artery	(50)	(50)	(50)
Calcification, focal		2 (4%)	
*Mediastinal artery	(50)	(50)	(50)
Periarteritis	1 (2%)		
*Portal vein	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		1 (2%)
DIGESTIVE SYSTEM			
*Lip	(50)	(50)	(50)
Inflammation, granulomatous		1 (2%)	
#Salivary gland	(48)	(49)	(50)
Atrophy, NOS		1 (2%)	
#Liver	(50)	(50)	(50)
Hernia, NOS			2 (4%)
Multiple cysts	3 (6%)	1 (2%)	
Congestion, NOS	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, acute		1 (2%)	2 (4%)
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal	2 (4%)	13 (26%)	17 (34%)
Necrosis, NOS	2 (4%)	3 (6%)	2 (4%)
Metamorphosis, fatty	4 (8%)	4 (8%)	5 (10%)
Focal cellular change	36 (72%)	36 (72%)	38 (76%)
Angiectasis	1 (2%)		
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	46 (92%)	16 (32%)	11 (22%)
#Pancreatic acinus	(48)	(49)	(50)
Multiple cysts	4 (8%)		1 (2%)
Inflammation, chronic focal		3 (6%)	
Atrophy, NOS	23 (48%)	19 (39%)	25 (50%)
Hyperplasia, focal	1 (2%)		1 (2%)
#Gastric fundal gland	(50)	(50)	(50)
Dilatation, NOS	8 (16%)	9 (18%)	6 (12%)
#Glandular stomach	(50)	(50)	(50)
Mineralization		1 (2%)	
#Forestomach	(50)	(50)	(50)
Cyst, NOS	1 (2%)		
Inflammation, NOS	3 (6%)		
Ulcer, NOS	1 (2%)		
Hyperplasia, epithelial	16 (32%)	8 (16%)	16 (32%)
#Colon	(50)	(50)	(49)
Inflammation, chronic		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Calculus, gross observation only			1 (2%)
Hydronephrosis	1 (2%)		
Pyelonephritis, NOS			1 (2%)
Inflammation, acute			1 (2%)
Nephropathy	48 (96%)	45 (90%)	43 (86%)
Nephrosis, NOS			1 (2%)
Infarct, NOS		1 (2%)	
Calcification, focal		2 (4%)	
#Kidney/tubule	(50)	(50)	(50)
Atrophy, focal	1 (2%)		

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#Urinary bladder	(48)	(50)	(50)
Calculus, gross observation only			1 (2%)
Cast, NOS			1 (2%)
Edema, NOS	2 (4%)	1 (2%)	
Inflammation, chronic focal		1 (2%)	
Hyperplasia, epithelial			2 (4%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(48)	(47)
Mineralization			1 (2%)
Cyst, NOS	8 (17%)	10 (21%)	6 (13%)
Pigmentation, NOS		1 (2%)	
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	4 (8%)	8 (17%)	7 (15%)
#Adrenal cortex	(49)	(50)	(50)
Hemorrhage	1 (2%)		1 (2%)
Degeneration, lipoid	16 (33%)	14 (28%)	5 (10%)
Necrosis, focal		1 (2%)	
Amyloidosis		1 (2%)	
Lipoidosis		1 (2%)	
Hyperplasia, focal	20 (41%)	12 (24%)	11 (22%)
Angiectasis	17 (35%)	23 (46%)	20 (40%)
#Adrenal medulla	(49)	(50)	(50)
Hyperplasia, NOS	10 (20%)	3 (6%)	1 (2%)
Hyperplasia, focal		1 (2%)	5 (10%)
#Thyroid	(50)	(50)	(50)
Hyperplasia, C-cell	8 (16%)	9 (18%)	7 (14%)
#Thyroid follicle	(50)	(50)	(50)
Dilatation, NOS	2 (4%)		
#Pancreatic islets	(48)	(49)	(50)
Hyperplasia, NOS	2 (4%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Cyst, NOS		2 (4%)	
Inflammation, chronic focal			1 (2%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, cystic	1 (2%)	4 (8%)	3 (6%)
*Preputial gland	(50)	(50)	(50)
Cyst, NOS			3 (6%)
Inflammation, acute/chronic		3 (6%)	1 (2%)
Hyperplasia, cystic			1 (2%)
#Prostate	(50)	(50)	(50)
Multiple cysts			1 (2%)
Inflammation, acute/chronic	10 (20%)	24 (48%)	24 (48%)
*Seminal vesicle	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
Atrophy, NOS	20 (40%)	14 (28%)	17 (34%)
#Testis	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
Calcification, NOS		1 (2%)	2 (4%)
Atrophy, NOS			1 (2%)
Hyperplasia, interstitial cell	16 (32%)	15 (30%)	13 (26%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Gliosis	1 (2%)		
#Corpus callosum	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	
#Cerebellum	(50)	(50)	(50)
Necrosis, cortical		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye/sclera	(50)	(50)	(50)
Calcification, NOS	1 (2%)		
Calcification, focal	1 (2%)		
*Eye/cornea	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS		2 (4%)	1 (2%)
*Eye/lens, capsule	(50)	(50)	(50)
Calcification, NOS		2 (4%)	1 (2%)
*Eye/lens, cortex	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Necrosis, fat	2 (4%)	9 (18%)	8 (16%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX B

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

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

	CONTROL (UNTR)	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)
Papilloma, NOS	1 (2%)		
Squamous cell carcinoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma		1 (2%)	
Fibrosarcoma	1 (2%)	1 (2%)	
Fibrous histiocytoma, malignant	1 (2%)		
Lipoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		
Alveolar/bronchiolar carcinoma	1 (2%)		
C-cell carcinoma, metastatic	1 (2%)		
Pheochromocytoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	15 (30%)	14 (28%)	10 (20%)
#Thymus	(49)	(45)	(48)
Thymoma, benign	1 (2%)		
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Neoplastic nodule	2 (4%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Lipoma		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(49)	(50)
Carcinoma, NOS	2 (4%)		3 (6%)
Adenoma, NOS	27 (55%)	24 (49%)	26 (52%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma	1 (2%)		
Cortical carcinoma		1 (2%)	
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	6 (12%)	5 (10%)	2 (4%)
Pheochromocytoma, malignant		1 (2%)	
#Thyroid	(50)	(48)	(50)
Follicular cell adenoma			1 (2%)
Follicular cell carcinoma	1 (2%)		
C-cell adenoma	8 (16%)	7 (15%)	11 (22%)
C-cell carcinoma	2 (4%)	2 (4%)	3 (6%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Parathyroid	(42)	(37)	(38)
Adenoma, NOS		1 (3%)	
#Pancreatic islets	(50)	(49)	(50)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	2 (4%)
Adenocarcinoma, NOS	1 (2%)	2 (4%)	3 (6%)
Fibroadenoma	11 (22%)	11 (22%)	9 (18%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	
Adenoma, NOS	1 (2%)	3 (6%)	
#Uterus	(50)	(50)	(49)
Endometrial stromal polyp	7 (14%)	6 (12%)	7 (14%)
Endometrial stromal sarcoma	1 (2%)		1 (2%)
#Ovary	(50)	(50)	(49)
Granulosa cell tumor			2 (4%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Carcinoma, NOS, invasive	2 (4%)		1 (2%)
#Cerebellum	(50)	(50)	(50)
Carcinoma, NOS, invasive			1 (2%)
Meningioma		1 (2%)	
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Fibrous histiocytoma, metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death		5	3
Moribund sacrifice	8	11	12
Terminal sacrifice	42	34	35

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	44	45	42
Total primary tumors	92	84	83
Total animals with benign tumors	37	41	39
Total benign tumors	64	61	59
Total animals with malignant tumors	21	21	18
Total malignant tumors	26	23	22
Total animals with secondary tumors##	4	1	2
Total secondary tumors	4	1	2
Total animals with tumors uncertain--benign or malignant	2		2
Total uncertain tumors	2		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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE: UNTREATED CONTROL

ANIMAL NUMBER	13 4	12 4	12 8	10 4	12 5	14 7	13 2	13 3	10 1	10 2	10 3	10 5	10 6	10 7	10 8	10 9	11 0	11 1	11 2	11 3	11 4	11 5	11 6	11 7	11 8
WEEKS ON STUDY	04 7	08 9	09 4	09 8	09 8	09 9	10 0	10 2	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS				X																					
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma						X																			
Fibrous histiocytoma, malignant				X																					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar carcinoma			X																						
C-cell carcinoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma, benign												X													
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule							X			X															
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																				X					
Adenoma, NOS				X	X		X	X	X	X				X	X	X	X	X	X				X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																								X	
Pheochromocytoma																			X						
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma													X	X					X						
C-cell carcinoma																									
Parathyroid	+	−	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma										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			X					X			X			
Endometrial stromal sarcoma	X																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, 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
Fibrous histiocytoma, metastatic				X																					
Leukemia, mononuclear cell		X	X		X		X				X								X	X		X		

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

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

ANIMAL NUMBER	119	120	121	122	123	126	127	129	130	131	135	136	137	138	139	140	141	142	143	144	145	146	148	149	150	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
Fibrous histiocytoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
C-cell carcinoma, metastatic																	X									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma, benign																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS					X																					2
Adenoma, NOS	X	X		X		X	X					X	X	X			X	X	X		X	X		X		27
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma	X								X					X								X	X			6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma												X														1
C-cell adenoma			X	X			X						X								X					8
C-cell carcinoma		X																X								2
Parathyroid	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	42
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS						X																				1
Fibroadenoma				X	X	X	X					X			X							X	X			11
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																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp													X											X		7
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive					X																					2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrous histiocytoma, metastatic																										1
Leukemia, mononuclear cell	X					X			X			X						X			X				X	15

* Animals necropsied

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

ANIMAL NUMBER	0116	0444	0229	0449	0004	0110	0336	0338	0441	0117	0448	0221	0002	0333	0111	0550	0001	0003	0005	0006	0007	0008	0009	0112	0113
WEEKS ON STUDY	050	071	073	076	079	083	084	086	086	088	088	089	092	098	100	103	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, metastatic																									
Trachea	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																								X	
Urinary bladder	+	−	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X			X	X			X	X	X	X		X				X	X			X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma																			X						
Pheochromocytoma																X			X						
Pheochromocytoma, malignant																									
Thyroid	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma						X												X							
C-cell carcinoma																									
Parathyroid	−	−	+	+	−	+	+	+	−	−	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+
Adenoma, NOS																									
Pancreatic islets	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																							X		
Adenocarcinoma, NOS							X													X					
Fibroadenoma								X	X			X							X	X					
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
Adenoma, NOS															X				X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp			X							X												X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Meningioma	X																								
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X	X	X	X	X		X		X				X	X						X		X		

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

ANIMAL NUMBER	0 1 4	0 1 5	0 1 8	0 1 9	0 2 0	0 2 2	0 2 3	0 2 4	0 2 5	0 2 6	0 2 7	0 2 8	0 3 0	0 3 1	0 3 2	0 3 4	0 3 5	0 3 7	0 3 9	0 4 0	0 4 2	0 4 3	0 4 5	0 4 6	0 4 7	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma			X																							1
Fibrosarcoma																						X				1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma, metastatic							X																			1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																										1
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X		X	X						X		X					X		X	X	X	X	X	X		24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical carcinoma																										1
Pheochromocytoma						X		X			X															5
Pheochromocytoma, malignant							X																			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma								X									X		X			X		X		7
C cell carcinoma	X					X																				2
Parathyroid	+	+	+	+	+	–	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	–	+	37
Adenoma, NOS																	X									1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																						X				1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																										1
Adenocarcinoma, NOS																										2
Fibroadenoma	X			X	X	X	X													X						11
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		3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp									X				X	X												6
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Meningioma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X					X									X											14

* Animals necropsied

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

ANIMAL NUMBER	055	068	076	074	066	051	094	062	060	090	056	084	065	078	052	053	054	057	058	059	061	063	064	067	069
WEEKS ON STUDY	038	061	064	072	086	092	093	095	098	099	101	101	103	103	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									X
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS										X													X		
Adenoma, NOS				X	X	X	X	X			X	X			X		X	X	X					X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma										X															
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
C-cell adenoma			X					X					X		X							X	X		
C-cell carcinoma																									
Parathyroid	+	+	+	+	−	+	−	+	+	−	+	−	+	+	+	+	−	−	+	+	−	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																								X	
Adenocarcinoma, NOS	X									X													X		
Fibroadenoma			X				X		X		X		X				X								
Uterus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp															X			X				X			X
Endometrial stromal sarcoma																			X						
Ovary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor											X														X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																							X		
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS													X												
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X			X			X						X			X								X

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

ANIMAL NUMBER	070	071	072	073	075	077	079	080	081	082	083	085	086	087	088	089	091	092	093	095	096	097	098	099	100	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Lipoma																	X									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS												X														3
Adenoma, NOS		X	X	X		X		X								X		X	X	X	X	X	X	X		26
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																									X	2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma											X															1
C-cell adenoma														X					X	X			X		X	11
C-cell carcinoma				X						X								X								3
Parathyroid	+	+	−	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	−	−	+	+	+	+	+	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																						X				2
Adenocarcinoma, NOS																										3
Fibroadenoma							X					X										X				9
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp								X		X										X						7
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive												X														2
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
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		10

* Animals necropsied

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

	Control	620 ppm	1,250 ppm
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	15/50 (30%)	14/50 (28%)	10/50 (20%)
Adjusted Rates (b)	32.3%	31.0%	24.1%
Terminal Rates (c)	11/42 (26%)	5/34 (15%)	6/36 (17%)
Week of First Observation	89	71	61
Life Table Tests (d)	P=0.278N	P=0.451	P=0.304N
Incidental Tumor Tests (d)	P=0.054N	P=0.180N	P=0.114N
Cochran-Armitage Trend Test (d)	P=0.152N		
Fisher Exact Test (d)		P=0.500N	P=0.178N
Pituitary Gland: Adenoma			
Overall Rates (a)	27/49 (55%)	24/49 (49%)	26/50 (52%)
Adjusted Rates (b)	59.9%	57.9%	59.9%
Terminal Rates (c)	23/41 (56%)	16/33 (48%)	19/36 (53%)
Week of First Observation	98	76	72
Life Table Tests (d)	P=0.384	P=0.405	P=0.414
Incidental Tumor Tests (d)	P=0.451N	P=0.433N	P=0.493N
Cochran-Armitage Trend Test (d)	P=0.420N		
Fisher Exact Test (d)		P=0.343N	P=0.457N
Pituitary Gland: Carcinoma			
Overall Rates (a)	2/49 (4%)	0/49 (0%)	3/50 (6%)
Adjusted Rates (b)	4.9%	0.0%	7.9%
Terminal Rates (c)	2/41 (5%)	0/33 (0%)	2/36 (6%)
Week of First Observation	104		99
Life Table Tests (d)	P=0.348	P=0.287N	P=0.445
Incidental Tumor Tests (d)	P=0.380	P=0.287N	P=0.479
Cochran-Armitage Trend Test (d)	P=0.396		
Fisher Exact Test (d)		P=0.247N	P=0.510
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	29/49 (59%)	24/49 (49%)	29/50 (58%)
Adjusted Rates (b)	64.3%	57.9%	65.5%
Terminal Rates (c)	25/41 (61%)	16/33 (48%)	21/36 (58%)
Week of First Observation	98	76	72
Life Table Tests (d)	P=0.307	P=0.533	P=0.326
Incidental Tumor Tests (d)	P=0.538N	P=0.289N	P=0.580
Cochran-Armitage Trend Test (d)	P=0.498N		
Fisher Exact Test (d)		P=0.209N	P=0.534N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	6/50 (12%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	14.3%	14.3%	5.1%
Terminal Rates (c)	6/42 (14%)	4/34 (12%)	1/36 (3%)
Week of First Observation	104	103	99
Life Table Tests (d)	P=0.162N	P=0.608	P=0.188N
Incidental Tumor Tests (d)	P=0.139N	P=0.579	P=0.169N
Cochran-Armitage Trend Test (d)	P=0.107N		
Fisher Exact Test (d)		P=0.500N	P=0.134N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	6/50 (12%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	14.3%	17.1%	5.1%
Terminal Rates (c)	6/42 (14%)	5/34 (15%)	1/36 (3%)
Week of First Observation	104	103	99
Life Table Tests (d)	P=0.174N	P=0.469	P=0.188N
Incidental Tumor Tests (d)	P=0.151N	P=0.439	P=0.169N
Cochran-Armitage Trend Test (d)	P=0.114N		
Fisher Exact Test (d)		P=0.620	P=0.134N

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

	Control	620 ppm	1,250 ppm
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	8/50 (16%)	7/48 (15%)	11/50 (22%)
Adjusted Rates (b)	19.0%	19.5%	27.6%
Terminal Rates (c)	8/42 (19%)	6/34 (18%)	8/36 (22%)
Week of First Observation	104	83	64
Life Table Tests (d)	P=0.166	P=0.555	P=0.201
Incidental Tumor Tests (d)	P=0.233	P=0.578N	P=0.305
Cochran-Armitage Trend Test (d)	P=0.255		
Fisher Exact Test (d)		P=0.535N	P=0.306
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	2/48 (4%)	3/50 (6%)
Adjusted Rates (b)	4.8%	5.9%	8.3%
Terminal Rates (c)	2/42 (5%)	2/34 (6%)	3/36 (8%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.342	P=0.617	P=0.430
Incidental Tumor Tests (d)	P=0.342	P=0.617	P=0.430
Cochran-Armitage Trend Test (d)	P=0.407		
Fisher Exact Test (d)		P=0.676	P=0.500
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	10/50 (20%)	9/48 (19%)	14/50 (28%)
Adjusted Rates (b)	23.8%	25.2%	35.3%
Terminal Rates (c)	10/42 (24%)	8/34 (24%)	11/36 (31%)
Week of First Observation	104	83	64
Life Table Tests (d)	P=0.111	P=0.507	P=0.136
Incidental Tumor Tests (d)	P=0.158	P=0.595	P=0.211
Cochran-Armitage Trend Test (d)	P=0.200		
Fisher Exact Test (d)		P=0.540N	P=0.241
Mammary Gland: Fibroadenoma			
Overall Rates (a)	11/50 (22%)	11/50 (22%)	9/50 (18%)
Adjusted Rates (b)	26.2%	29.0%	21.2%
Terminal Rates (c)	11/42 (26%)	8/34 (24%)	4/36 (11%)
Week of First Observation	104	86	64
Life Table Tests (d)	P=0.494N	P=0.382	P=0.534N
Incidental Tumor Tests (d)	P=0.356N	P=0.561N	P=0.358N
Cochran-Armitage Trend Test (d)	P=0.355N		
Fisher Exact Test (d)		P=0.595	P=0.402N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	11/50 (22%)	12/50 (24%)	10/50 (20%)
Adjusted Rates (b)	26.2%	31.7%	23.6%
Terminal Rates (c)	11/42 (26%)	9/34 (26%)	5/36 (14%)
Week of First Observation	104	86	64
Life Table Tests (d)	P=0.497	P=0.288	P=0.554
Incidental Tumor Tests (d)	P=0.463N	P=0.530	P=0.466N
Cochran-Armitage Trend Test (d)	P=0.452N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	2.4%	5.1%	7.0%
Terminal Rates (c)	1/42 (2%)	1/34 (3%)	1/36 (3%)
Week of First Observation	104	84	38
Life Table Tests (d)	P=0.199	P=0.439	P=0.273
Incidental Tumor Tests (d)	P=0.226	P=0.651	P=0.305
Cochran-Armitage Trend Test (d)	P=0.223		
Fisher Exact Test (d)		P=0.500	P=0.309

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

	Control	620 ppm	1,250 ppm
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (a)	11/50 (22%)	13/50 (26%)	13/50 (26%)
Adjusted Rates (b)	26.2%	33.2%	29.3%
Terminal Rates (c)	11/42 (26%)	9/34 (26%)	6/36 (17%)
Week of First Observation	104	84	38
Life Table Tests (d)	P=0.249	P=0.216	P=0.286
Incidental Tumor Tests (d)	P=0.367	P=0.510	P=0.444
Cochran-Armitage Trend Test (d)	P=0.365		
Fisher Exact Test (d)		P=0.408	P=0.408
Clitoral Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.4%	8.5%	0.0%
Terminal Rates (c)	1/42 (2%)	2/34 (6%)	0/36 (0%)
Week of First Observation	104	100	
Life Table Tests (d)	P=0.424N	P=0.236	P=0.531N
Incidental Tumor Tests (d)	P=0.391N	P=0.198	P=0.531N
Cochran-Armitage Trend Test (d)	P=0.376N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	4.8%	11.4%	0.0%
Terminal Rates (c)	2/42 (5%)	3/34 (9%)	0/36 (0%)
Week of First Observation	104	100	
Life Table Tests (d)	P=0.273N	P=0.247	P=0.273N
Incidental Tumor Tests (d)	P=0.252N	P=0.215	P=0.273N
Cochran-Armitage Trend Test (d)	P=0.220N		
Fisher Exact Test (d)		P=0.339	P=0.247N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	7/50 (14%)	6/50 (12%)	7/49 (14%)
Adjusted Rates (b)	16.1%	15.7%	19.4%
Terminal Rates (c)	6/42 (14%)	4/34 (12%)	7/36 (19%)
Week of First Observation	98	73	104
Life Table Tests (d)	P=0.443	P=0.584	P=0.494
Incidental Tumor Tests (d)	P=0.528	P=0.448N	P=0.509
Cochran-Armitage Trend Test (d)	P=0.543		
Fisher Exact Test (d)		P=0.500N	P=0.597
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	8/50 (16%)	6/50 (12%)	8/49 (16%)
Adjusted Rates (b)	17.8%	15.7%	22.2%
Terminal Rates (c)	6/42 (14%)	4/34 (12%)	8/36 (22%)
Week of First Observation	47	73	104
Life Table Tests (d)	P=0.439	P=0.530N	P=0.484
Incidental Tumor Tests (d)	P=0.520	P=0.335N	P=0.500
Cochran-Armitage Trend Test (d)	P=0.539		
Fisher Exact Test (d)		P=0.387N	P=0.590

(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. N indicates a negative trend or lower incidence in a dosed group.

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Necrosis, fat	1 (2%)		
RESPIRATORY SYSTEM			
#Trachea	(50)	(48)	(50)
Inflammation, chronic		1 (2%)	1 (2%)
#Lung	(50)	(50)	(50)
Congestion, NOS		2 (4%)	
Edema, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic focal	5 (10%)	8 (16%)	5 (10%)
Perivascular cuffing	4 (8%)	6 (12%)	7 (14%)
Alveolar macrophages	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(49)	(49)
Hypoplasia, NOS			1 (2%)
Hyperplasia, NOS		7 (14%)	4 (8%)
Hyperplasia, reticulum cell	10 (20%)	9 (18%)	16 (33%)
#Spleen	(50)	(50)	(50)
Hemosiderosis	5 (10%)	8 (16%)	6 (12%)
Hematopoiesis		1 (2%)	2 (4%)
#Lymph node	(50)	(49)	(49)
Inflammation, acute	1 (2%)		
Hemosiderosis			1 (2%)
Plasmacytosis	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	
#Colon	(49)	(49)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Thymus	(49)	(45)	(48)
Cyst, NOS			2 (4%)
Hemorrhage		1 (2%)	
CIRCULATORY SYSTEM			
#Myocardium	(50)	(50)	(50)
Inflammation, chronic			2 (4%)
Degeneration, NOS	45 (90%)	41 (82%)	39 (78%)
Calcification, focal		1 (2%)	
Hemosiderosis	1 (2%)		
*Pulmonary artery	(50)	(50)	(50)
Calcification, focal	2 (4%)		
#Liver	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
#Thyroid	(50)	(48)	(50)
Perivasculitis	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hernia, NOS	2 (4%)	5 (10%)	1 (2%)
Inflammation, acute			1 (2%)
Inflammation, chronic focal	17 (34%)	28 (56%)	35 (70%)
Cirrhosis, biliary	1 (2%)		

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(50)	(50)
Degeneration, NOS	1 (2%)	2 (4%)	
Necrosis, NOS		2 (4%)	1 (2%)
Amyloidosis			1 (2%)
Metamorphosis, fatty	7 (14%)	6 (12%)	5 (10%)
Pigmentation, NOS			1 (2%)
Focal cellular change	46 (92%)	40 (80%)	44 (88%)
Angiectasis	1 (2%)		
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	20 (40%)	5 (10%)	2 (4%)
#Pancreatic acinus	(50)	(49)	(50)
Inflammation, chronic focal			1 (2%)
Atrophy, NOS	22 (44%)	14 (29%)	14 (28%)
Atrophy, focal			2 (4%)
#Gastric fundal gland	(50)	(50)	(50)
Dilatation, NOS	16 (32%)	6 (12%)	13 (26%)
Degeneration, NOS			1 (2%)
#Forestomach	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	
Inflammation, acute		2 (4%)	
Necrosis, NOS		1 (2%)	
Hyperplasia, epithelial	7 (14%)	10 (20%)	7 (14%)
#Colon	(49)	(49)	(50)
Cyst, NOS		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Nephropathy	41 (82%)	31 (62%)	36 (72%)
Degeneration, hyaline	1 (2%)		
Calcification, NOS			1 (2%)
Calcification, focal	10 (20%)	7 (14%)	6 (12%)
Pigmentation, NOS			1 (2%)
#Urinary bladder	(49)	(46)	(48)
Edema, NOS		1 (2%)	
Inflammation, chronic focal	2 (4%)	1 (2%)	2 (4%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(49)	(50)
Cyst, NOS	29 (59%)	28 (57%)	23 (46%)
Hemorrhagic cyst	1 (2%)		
Pigmentation, NOS		2 (4%)	
Focal cellular change			1 (2%)
Hyperplasia, focal	7 (14%)	8 (16%)	8 (16%)
Angiectasis	1 (2%)		2 (4%)
#Adrenal cortex	(50)	(50)	(50)
Petechia		2 (4%)	
Degeneration, lipoid	31 (62%)	15 (30%)	19 (38%)
Necrosis, NOS		2 (4%)	1 (2%)
Metamorphosis, fatty		1 (2%)	
Calcification, NOS	1 (2%)		
Hyperplasia, focal	18 (36%)	12 (24%)	9 (18%)
Angiectasis	41 (82%)	38 (76%)	42 (84%)
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, NOS	2 (4%)	3 (6%)	1 (2%)
#Thyroid	(50)	(48)	(50)
Hyperplasia, C-cell	21 (42%)	19 (40%)	24 (48%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Thyroid follicle	(50)	(48)	(50)
Dilatation, NOS	1 (2%)		
#Pancreatic islets	(50)	(49)	(50)
Hyperplasia, NOS	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibrosis		1 (2%)	
Hyperplasia, cystic	17 (34%)	12 (24%)	15 (30%)
*Clitoral gland	(50)	(50)	(50)
Multiple cysts		1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	
Hyperplasia, cystic	1 (2%)		
#Uterus	(50)	(50)	(49)
Dilatation, NOS	1 (2%)	2 (4%)	1 (2%)
Cyst, NOS	5 (10%)	2 (4%)	4 (8%)
Hematoma, NOS	1 (2%)		
#Uterus/endometrium	(50)	(50)	(49)
Hyperplasia, cystic	1 (2%)		2 (4%)
#Ovary	(50)	(50)	(49)
Cyst, NOS	1 (2%)		
Parovarian cyst	9 (18%)	6 (12%)	5 (10%)
NERVOUS SYSTEM			
#Cerebrum	(50)	(50)	(50)
Perivascular cuffing			1 (2%)
Degeneration, NOS	1 (2%)		
#Brain	(50)	(50)	(50)
Hydrocephalus, NOS	1 (2%)		1 (2%)
#Cerebral cortex	(50)	(50)	(50)
Degeneration, NOS	2 (4%)		
#Cerebellum	(50)	(50)	(50)
Perivascular cuffing		1 (2%)	
#Cerebellar cortex	(50)	(50)	(50)
Degeneration, NOS	2 (4%)		
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage			1 (2%)
*Eye/cornea	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	1 (2%)
Atrophy, NOS		1 (2%)	
*Eye/lens, cortex	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	
Calcification, NOS		1 (2%)	1 (2%)

TABLE B4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Hematoma, organized		1 (2%)	
Necrosis, fat	6 (12%)	3 (6%)	7 (14%)
ALL OTHER SYSTEMS			
None			
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX C

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

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
Fibroma	2 (4%)		
Fibrosarcoma		4 (8%)	4 (8%)
Lipoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma	4 (8%)	6 (12%)	9 (18%)
Alveolar/bronchiolar carcinoma	3 (6%)	6 (12%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS			1 (2%)
Malignant lymphoma, histiocytic type	2 (4%)		
Malignant lymphoma, mixed type		2 (4%)	4 (8%)
#Spleen	(50)	(50)	(50)
Malignant lymphoma, mixed type			1 (2%)
#Mediastinal lymph node	(40)	(46)	(45)
Malignant lymphoma, undiffer type		1 (2%)	
#Mesenteric lymph node	(40)	(46)	(45)
Malignant lymphoma, histiocytic type	1 (3%)		
CIRCULATORY SYSTEM			
#Liver	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	12 (24%)	10 (20%)	14 (28%)
Hepatocellular carcinoma	4 (8%)	7 (14%)	9 (18%)
#Forestomach	(50)	(49)	(50)
Squamous cell carcinoma			1 (2%)
URINARY SYSTEM			
#Kidney/pelvis	(50)	(50)	(50)
Transitional cell papilloma			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(50)	(50)
Adenoma, NOS		1 (2%)	
#Adrenal	(47)	(49)	(49)
Cortical adenoma	1 (2%)		1 (2%)
#Adrenal medulla	(47)	(49)	(49)
Pheochromocytoma	1 (2%)	1 (2%)	
#Thyroid	(50)	(49)	(50)
Follicular cell adenoma		1 (2%)	
Follicular cell carcinoma			1 (2%)

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
None			
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	3 (6%)		2 (4%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Adenocarcinoma, NOS unclear prim/metastatic	1 (2%)		
Fibrosarcoma, invasive		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	8	2
Moribund sacrifice	4	4	5
Terminal sacrifice	35	38	43
Accidentally killed, nda	2		
TUMOR SUMMARY			
Total animals with primary tumors**	27	30	34
Total primary tumors	35	39	52
Total animals with benign tumors	20	14	23
Total benign tumors	23	19	28
Total animals with malignant tumors	11	18	22
Total malignant tumors	11	20	24
Total animals with secondary tumors##	1	2	
Total secondary tumors	1	2	
Total animals with tumors uncertain--primary or metastatic	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 C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE: UNTREATED CONTROL

ANIMAL NUMBER	11 12	10 08	13 33	13 31	13 37	10 06	11 13	13 36	11 10	11 14	10 05	11 11	10 07	12 20	14 48	10 01	10 02	10 03	10 04	10 09	11 15	11 16	11 17	11 18	11 19
WEEKS ON STUDY	02 21	02 22	05 55	06 33	07 99	08 00	08 11	08 22	08 88	08 88	09 02	09 33	09 94	10 22	10 22	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X														
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma												X													
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	+	+	+	+	−	+	−	−	+	+	−	+	+	+	+	+	+	+	+	+	−	−	+	+
Malignant lymphoma, histiocytic type																									
Thymus	−	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	−	+	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X			X			X		X	X			X	
Hepatocellular carcinoma																						X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+
Adrenal	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	+	+	−	+	−	−	−	+	−	+	−	−	+	+	+	−	−	+	+	+	−	+	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																			X						
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, unclear primary/metastatic															X										
Malignant lymphoma, histiocytic type		X												X											

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

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

ANIMAL NUMBER	121	122	123	124	125	126	127	128	129	130	132	134	135	138	139	140	141	142	143	144	145	146	147	149	150	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma									X														X			2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic			X																							1
Alveolar/bronchiolar adenoma								X		X														X		4
Alveolar/bronchiolar carcinoma																X	X							X		3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	40
Malig lymphoma, histiocytic type																		X								1
Thymus	+	−	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X						X		X		X			X					X						12
Hepatocellular carcinoma			X																X	X						4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	47
Cortical adenoma														X												1
Pheochromocytoma																			X							1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	−	−	−	−	+	−	+	−	−	+	−	+	−	+	+	+	+	+	+	−	+	+	+	−	+	27
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS	X															X										3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS, uncl prim/metas																										1
Malignant lymphoma, histiocytic type																										2

* Animals necropsied

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

ANIMAL NUMBER	0004	0003	0455	0550	0221	0222	0333	0442	0339	0331	0007	0116	0001	0002	0005	0006	0008	0009	0110	0111	0112	0113	0114	0115	0117
WEEKS ON STUDY	0255	0799	0886	0887	0992	0993	0993	0993	0995	0996	0998	0998	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma							X				X						X						X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X																			X			
Alveolar/bronchiolar carcinoma									X																X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, undiffer type																			X						
Thymus	+	−	+	−	−	+	+	+	+	+	−	−	+	+	+	+	+	−	+	+	+	+	−	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	−	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma			X		X													X							
Hepatocellular carcinoma				X								X				X									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS														X											
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma														X											
Thyroid	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	+	−	−	+	+	−	−	−	+	+	−	−	+	+	+	−	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Hepatocellular carcinoma, metastatic												X													
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, invasive																							X		
Malignant lymphoma, mixed type																				X					

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

ANIMAL NUMBER	018	019	020	023	024	025	026	027	028	029	030	032	034	035	036	037	038	040	041	043	044	046	047	048	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										4
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X								X				X					X						6
Alveolar/bronchiolar carcinoma		X								X										X			X			6
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	46
Malignant lymphoma, undiffer type																										1
Thymus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X		X		X					X	X			X					X	10
Hepatocellular carcinoma		X			X						X									X						7
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	N	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma			X																							1
Parathyroid	+	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	–	+	37
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
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hepatocellular carcinoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, invasive																										1
Malignant lymphoma, mixed type														X												2

* Animals necropsied

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

ANIMAL NUMBER	076	064	083	095	071	093	066	051	052	053	054	055	056	057	058	059	060	061	062	063	065	067	068	069	070
WEEKS ON STUDY	067	088	090	097	098	098	101	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma		X		X			X																		
Lipoma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X		X										X	X									
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−
Thymus	+	−	−	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma													X		X	X						X		X	
Hepatocellular carcinoma					X			X							X					X					
Hemangiosarcoma			X																						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma															X										
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma											X														
Urinary bladder	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma														X											
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma													X												
Parathyroid	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	−	+	−	−	−	+	+	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS										X															
Malignant lymphoma, mixed type																							X		

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

ANIMAL NUMBER	072	073	074	075	077	078	079	080	081	082	084	085	086	087	088	089	090	091	092	094	096	097	098	099	100	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma			X																							4
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X				X	X						X			X								9
Alveolar/bronchiolar carcinoma											X										X					2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																X										1
Lymph nodes	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	45
Thymus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	−	+	+	−	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X		X		X			X				X				X		X			X			X		14
Hepatocellular carcinoma				X										X						X	X			X		9
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	−	−	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell papilloma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																										1
Parathyroid	+	+	+	−	−	+	−	+	−	+	−	+	+	−	+	+	−	−	−	+	−	−	+	+	+	32
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS			X																							2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										1
Malignant lymphoma, mixed type					X		X										X									4

* Animals necropsied

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

	Control	1,250 ppm	2,500 ppm
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	0.0%	9.7%	8.5%
Terminal Rates (c)	0/35 (0%)	2/38 (5%)	1/43 (2%)
Week of First Observation		93	88
Life Table Tests (d)	P=0.099	P=0.079	P=0.094
Incidental Tumor Tests (d)	P=0.036	P=0.107	P=0.030
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.059	P=0.059
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	2.5%	9.7%	8.5%
Terminal Rates (c)	0/35 (0%)	2/38 (5%)	1/43 (2%)
Week of First Observation	92	93	88
Life Table Tests (d)	P=0.216	P=0.218	P=0.245
Incidental Tumor Tests (d)	P=0.078	P=0.221	P=0.064
Cochran-Armitage Trend Test (d)	P=0.146		
Fisher Exact Test (d)		P=0.181	P=0.181
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	8.1%	9.7%	8.5%
Terminal Rates (c)	2/35 (6%)	2/38 (5%)	1/43 (2%)
Week of First Observation	92	93	88
Life Table Tests (d)	P=0.533	P=0.552	P=0.601
Incidental Tumor Tests (d)	P=0.352	P=0.568	P=0.370
Cochran-Armitage Trend Test (d)	P=0.424		
Fisher Exact Test (d)		P=0.500	P=0.500
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	9/50 (18%)
Adjusted Rates (b)	10.9%	15.0%	19.8%
Terminal Rates (c)	3/35 (9%)	5/38 (13%)	7/43 (16%)
Week of First Observation	93	86	90
Life Table Tests (d)	P=0.170	P=0.430	P=0.217
Incidental Tumor Tests (d)	P=0.099	P=0.412	P=0.145
Cochran-Armitage Trend Test (d)	P=0.088		
Fisher Exact Test (d)		P=0.370	P=0.117
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	3/50 (6%)	6/50 (12%)	2/50 (4%)
Adjusted Rates (b)	8.6%	15.2%	4.7%
Terminal Rates (c)	3/35 (9%)	5/38 (13%)	2/43 (5%)
Week of First Observation	104	95	104
Life Table Tests (d)	P=0.313N	P=0.287	P=0.406N
Incidental Tumor Tests (d)	P=0.323N	P=0.312	P=0.406N
Cochran-Armitage Trend Test (d)	P=0.424N		
Fisher Exact Test (d)		P=0.243	P=0.500N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	11/50 (22%)	11/50 (22%)
Adjusted Rates (b)	16.5%	27.1%	24.3%
Terminal Rates (c)	5/35 (14%)	9/38 (24%)	9/43 (21%)
Week of First Observation	93	86	90
Life Table Tests (d)	P=0.257	P=0.198	P=0.275
Incidental Tumor Tests (d)	P=0.169	P=0.200	P=0.202
Cochran-Armitage Trend Test (d)	P=0.124		
Fisher Exact Test (d)		P=0.143	P=0.143

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

	Control	1,250 ppm	2,500 ppm
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.4%	0.0%	0.0%
Terminal Rates (c)	1/35 (3%)	0/38 (0%)	0/43 (0%)
Week of First Observation	22		
Life Table Tests (d)	P=0.032N	P=0.117N	P=0.103N
Incidental Tumor Tests (d)	P=0.055N	P=0.119N	P=0.217N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	0.0%	5.3%	11.6%
Terminal Rates (c)	0/35 (0%)	2/38 (5%)	5/43 (12%)
Week of First Observation		104	104
Life Table Tests (d)	P=0.028	P=0.257	P=0.054
Incidental Tumor Tests (d)	P=0.028	P=0.257	P=0.054
Cochran-Armitage Trend Test (d)	P=0.016		
Fisher Exact Test (d)		P=0.247	P=0.028
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	7.4%	7.9%	14.0%
Terminal Rates (c)	1/35 (3%)	3/38 (8%)	6/43 (14%)
Week of First Observation	22	104	104
Life Table Tests (d)	P=0.261	P=0.632N	P=0.340
Incidental Tumor Tests (d)	P=0.173	P=0.647N	P=0.201
Cochran-Armitage Trend Test (d)	P=0.178		
Fisher Exact Test (d)		P=0.661	P=0.243
Liver: Hepatocellular Adenoma			
Overall Rates (a)	12/50 (24%)	10/50 (20%)	14/50 (28%)
Adjusted Rates (b)	32.3%	24.4%	32.6%
Terminal Rates (c)	10/35 (29%)	8/38 (21%)	14/43 (33%)
Week of First Observation	93	86	104
Life Table Tests (d)	P=0.507N	P=0.321N	P=0.534N
Incidental Tumor Tests (d)	P=0.494	P=0.337N	P=0.550N
Cochran-Armitage Trend Test (d)	P=0.363		
Fisher Exact Test (d)		P=0.405N	P=0.410
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	4/50 (8%)	7/50 (14%)	9/50 (18%)
Adjusted Rates (b)	11.4%	17.1%	20.4%
Terminal Rates (c)	4/35 (11%)	5/38 (13%)	8/43 (19%)
Week of First Observation	104	87	98
Life Table Tests (d)	P=0.181	P=0.314	P=0.213
Incidental Tumor Tests (d)	P=0.135	P=0.302	P=0.204
Cochran-Armitage Trend Test (d)	P=0.093		
Fisher Exact Test (d)		P=0.262	P=0.117
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	15/50 (30%)	15/50 (30%)	20/50 (40%)
Adjusted Rates (b)	40.4%	35.1%	45.4%
Terminal Rates (c)	13/35 (37%)	11/38 (29%)	19/43 (44%)
Week of First Observation	93	86	98
Life Table Tests (d)	P=0.407	P=0.474N	P=0.462
Incidental Tumor Tests (d)	P=0.280	P=0.501N	P=0.438
Cochran-Armitage Trend Test (d)	P=0.170		
Fisher Exact Test (d)		P=0.586N	P=0.201

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

	Control	1,250 ppm	2,500 ppm
Harderian Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted Rates (b)	8.6%	0.0%	4.7%
Terminal Rates (c)	3/35 (9%)	0/38 (0%)	2/43 (5%)
Week of First Observation	104		104
Life Table Tests (d)	P=0.319N	P=0.107N	P=0.406N
Incidental Tumor Tests (d)	P=0.319N	P=0.107N	P=0.406N
Cochran-Armitage Trend Test (d)	P=0.390N		
Fisher Exact Test (d)		P=0.121N	P=0.500N

(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. N indicates a negative trend or lower incidence in a dosed group.

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE

	CONTROL (UNTR)	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)
Multiple cysts		1 (2%)	
Inflammation, acute/chronic			2 (4%)
Inflammation, chronic suppurative	1 (2%)		
Inflammation with fibrosis	1 (2%)		1 (2%)
Alopecia			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
Inflammation, granulomatous	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#Tracheal gland	(50)	(50)	(49)
Inflammation, chronic		1 (2%)	1 (2%)
Hyperplasia, adenomatous			1 (2%)
#Lung	(50)	(50)	(50)
Congestion, NOS	1 (2%)		
Hemorrhage	2 (4%)	1 (2%)	
Inflammation, acute		3 (6%)	
Inflammation, acute/chronic	1 (2%)	4 (8%)	2 (4%)
Inflammation, chronic		1 (2%)	3 (6%)
Pneumonia, interstitial chronic	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic focal	2 (4%)	5 (10%)	3 (6%)
Alveolar macrophages	2 (4%)	3 (6%)	3 (6%)
Hyperplasia, alveolar epithelium	1 (2%)	2 (4%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	4 (8%)	1 (2%)	5 (10%)
*Subcutaneous tissue	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
#Bone marrow	(50)	(50)	(50)
Pigmentation, NOS		1 (2%)	
Hyperplasia, granulocytic	10 (20%)	12 (24%)	10 (20%)
Hypoplasia, hematopoietic	1 (2%)		
#Spleen	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Angiectasis	3 (6%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid	12 (24%)	13 (26%)	13 (26%)
Hematopoiesis	1 (2%)	1 (2%)	6 (12%)
#Lymph node	(40)	(46)	(45)
Hyperplasia, lymphoid		1 (2%)	2 (4%)
#Mandibular lymph node	(40)	(46)	(45)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic	1 (3%)		
Pigmentation, NOS		1 (2%)	3 (7%)
Hyperplasia, lymphoid	2 (5%)	4 (9%)	9 (20%)
Mastocytosis	1 (3%)		
#Bronchial lymph node	(40)	(46)	(45)
Hyperplasia, lymphoid			1 (2%)
#Mesenteric lymph node	(40)	(46)	(45)
Inflammation, acute/chronic	1 (3%)	1 (2%)	
Hyperplasia, lymphoid		1 (2%)	2 (4%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Lung	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)	3 (6%)	2 (4%)
#Salivary gland	(49)	(45)	(49)
Hyperplasia, lymphoid	9 (18%)	8 (18%)	11 (22%)
*Gallbladder	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Pancreas	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		
#Forestomach	(50)	(49)	(50)
Hyperplasia, lymphoid			1 (2%)
#Jejunum	(50)	(49)	(49)
Hyperplasia, lymphoid	1 (2%)		
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	10 (20%)	10 (20%)	8 (16%)
#Thymus	(41)	(40)	(40)
Cyst, NOS	1 (2%)	2 (5%)	1 (3%)
Multiple cysts		1 (3%)	2 (5%)
Necrosis, NOS	1 (2%)		
Atrophy, NOS	1 (2%)		
Hyperplasia, lymphoid	2 (5%)	9 (23%)	5 (13%)
CIRCULATORY SYSTEM			
#Myocardium	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
#Liver	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(45)	(49)
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation with fibrosis		1 (2%)	
Atrophy, NOS	2 (4%)	1 (2%)	3 (6%)
#Liver	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, acute focal		1 (2%)	
Inflammation, chronic		1 (2%)	
Inflammation, chronic focal	2 (4%)	1 (2%)	1 (2%)
Degeneration, NOS			1 (2%)
Necrosis, NOS	1 (2%)	1 (2%)	2 (4%)
Cytoplasmic vacuolization	1 (2%)		
Focal cellular change		2 (4%)	7 (14%)
Angiectasis			1 (2%)
*Gallbladder	(50)	(50)	(50)
Cyst, NOS		1 (2%)	1 (2%)
Multiple cysts			1 (2%)
Inflammation, chronic focal		1 (2%)	
Hyperplasia, adenomatous		1 (2%)	
#Bile duct	(50)	(50)	(50)
Distention		1 (2%)	
Hyperplasia, NOS	1 (2%)	1 (2%)	
#Pancreas	(50)	(50)	(50)
Cystic ducts			2 (4%)
Degeneration, NOS		1 (2%)	
Atrophy, NOS		1 (2%)	
#Glandular stomach	(50)	(49)	(50)
Cyst, NOS			1 (2%)
Multiple cysts	1 (2%)	2 (4%)	2 (4%)
Inflammation, acute focal			1 (2%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Glandular stomach (Continued)	(50)	(49)	(50)
Inflammation, acute/chronic	2 (4%)		
Eosinophilic leukocytic infiltrate	2 (4%)	2 (4%)	3 (6%)
Inflammation, chronic focal	3 (6%)		1 (2%)
Hyperplasia, NOS	2 (4%)		
#Duodenum	(50)	(49)	(49)
Diverticulum		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
Hyperplasia, adenomatous			1 (2%)
*Anus	(50)	(50)	(50)
Inflammation, chronic focal			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Multiple cysts	1 (2%)		
Glomerulonephritis, NOS	1 (2%)	2 (4%)	
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic	1 (2%)		
Pyelonephritis, chronic	3 (6%)		
Inflammation, chronic focal	3 (6%)	4 (8%)	1 (2%)
Nephropathy	1 (2%)		
Bacterial septicemia	1 (2%)		
Infarct, NOS	1 (2%)		
Calcification, focal	2 (4%)	1 (2%)	1 (2%)
#Urinary bladder	(49)	(50)	(47)
Calculus, microscopic examination	1 (2%)		
Distention		1 (2%)	
Inflammation, acute	1 (2%)		
Inflammation, chronic	3 (6%)	3 (6%)	
Inflammation, chronic focal	1 (2%)		
Hyperplasia, epithelial		1 (2%)	1 (2%)
Angiectasis	1 (2%)		
#Perivesical tissue	(49)	(50)	(47)
Calcification, focal	1 (2%)		
*Urethra	(50)	(50)	(50)
Inflammation, suppurative	2 (4%)		
*Urethral gland	(50)	(50)	(50)
Hyperplasia, adenomatous			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(50)	(50)
Hyperplasia, adenomatous			1 (2%)
#Anterior pituitary	(48)	(50)	(50)
Cyst, NOS	3 (6%)	3 (6%)	5 (10%)
Multiple cysts		1 (2%)	1 (2%)
Hyperplasia, focal			2 (4%)
#Adrenal/capsule	(47)	(49)	(49)
Hyperplasia, stromal	34 (72%)	42 (86%)	42 (86%)
#Adrenal cortex	(47)	(49)	(49)
Cyst, NOS			1 (2%)
Degeneration, NOS	1 (2%)	3 (6%)	4 (8%)
Focal cellular change	2 (4%)	1 (2%)	1 (2%)
Hypertrophy, focal		1 (2%)	
Hyperplasia, focal	6 (13%)	1 (2%)	2 (4%)
#Adrenal medulla	(47)	(49)	(49)
Inflammation, acute	1 (2%)		
Degeneration, NOS			1 (2%)
Hyperplasia, focal	4 (9%)	1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(49)	(50)
Cystic follicles	1 (2%)	2 (4%)	4 (8%)
Inflammation, chronic focal	1 (2%)		
Atrophy, focal			1 (2%)
Hyperplasia, follicular cell		1 (2%)	
REPRODUCTIVE SYSTEM			
*Prepuce	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
*Preputial gland	(50)	(50)	(50)
Cystic ducts	13 (26%)	1 (2%)	6 (12%)
Inflammation, suppurative		1 (2%)	2 (4%)
Inflammation, acute/chronic	3 (6%)	1 (2%)	1 (2%)
Inflammation, chronic	3 (6%)	5 (10%)	3 (6%)
Inflammation, chronic suppurative	4 (8%)	4 (8%)	4 (8%)
Hyperplasia, cystic			1 (2%)
Hyperplasia, adenomatous	1 (2%)	1 (2%)	3 (6%)
#Prostate	(50)	(49)	(50)
Inflammation, suppurative		1 (2%)	
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	3 (6%)	2 (4%)	
*Seminal vesicle	(50)	(50)	(50)
Distention	11 (22%)	6 (12%)	5 (10%)
Inflammation, chronic	1 (2%)	2 (4%)	
Inflammation, calcified granulomatous		1 (2%)	
#Testis	(49)	(49)	(50)
Degeneration, NOS			1 (2%)
Calcification, focal	4 (8%)	1 (2%)	
Atrophy, NOS	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Inflammation, chronic focal		1 (2%)	
#Brain	(50)	(50)	(50)
Perivascular cuffing			1 (2%)
Calcification, focal	18 (36%)	22 (44%)	17 (34%)
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Bone/lower extremity	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)		
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Necrosis, fat	1 (2%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
Adipose tissue			
Hemorrhage			1
Inflammation, chronic	1	1	
Necrosis, fat	1	2	1
SPECIAL MORPHOLOGY SUMMARY			
None			

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

APPENDIX D

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

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	49
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(49)	(50)	(49)
Fibrosarcoma	1 (2%)	1 (2%)	2 (4%)
RESPIRATORY SYSTEM			
#Lung	(49)	(50)	(49)
Adenocarcinoma, NOS, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	1 (2%)	3 (6%)	5 (10%)
Alveolar/bronchiolar carcinoma	1 (2%)	3 (6%)	1 (2%)
Fibrosarcoma, metastatic		1 (2%)	
Osteosarcoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(49)
Malignant lymphoma, undiffer type		1 (2%)	2 (4%)
Malignant lymphoma, lymphocytic type	1 (2%)	7 (14%)	1 (2%)
Malignant lymphoma, histiocytic type	2 (4%)	3 (6%)	2 (4%)
Malignant lymphoma, mixed type	5 (10%)	5 (10%)	8 (16%)
#Spleen	(49)	(50)	(49)
Malignant lymphoma, mixed type	5 (10%)	2 (4%)	2 (4%)
#Mediastinal lymph node	(42)	(45)	(46)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
#Liver	(49)	(50)	(49)
Kupffer cell sarcoma		1 (2%)	
#Kidney	(49)	(50)	(49)
Malignant lymphoma, mixed type			1 (2%)
#Uterus	(49)	(50)	(49)
Malignant lymphoma, histiocytic type			1 (2%)
#Thymus	(46)	(48)	(44)
Malignant lymphoma, lymphocytic type	1 (2%)		
Malignant lymphoma, mixed type			1 (2%)
CIRCULATORY SYSTEM			
#Spleen	(49)	(50)	(49)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(49)
Hepatocellular adenoma	3 (6%)	2 (4%)	4 (8%)
#Duodenum	(47)	(48)	(46)
Adenoma, NOS			1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(48)	(49)
Adenoma, NOS	1 (2%)		
#Anterior pituitary	(48)	(48)	(49)
Adenoma, NOS		3 (6%)	

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(49)	(50)	(48)
Pheochromocytoma		1 (2%)	1 (2%)
#Thyroid	(49)	(50)	(48)
Follicular cell adenoma			2 (4%)
#Pancreatic islets	(49)	(49)	(49)
Islet cell adenoma		1 (2%)	
Islet cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(49)
Adenocarcinoma, NOS		1 (2%)	1 (2%)
Fibroadenoma		1 (2%)	
#Uterus	(49)	(50)	(49)
Leiomyosarcoma	1 (2%)	1 (2%)	1 (2%)
Endometrial stromal polyp		1 (2%)	
#Ovary	(49)	(43)	(48)
Teratoma, benign			1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(49)	(50)	(49)
Adenoma, NOS	2 (4%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Muscle of leg	(49)	(50)	(49)
Fibrosarcoma		1 (2%)	
BODY CAVITIES			
*Mediastinum	(49)	(50)	(49)
Fibrosarcoma, metastatic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(49)
Islet cell carcinoma, metastatic	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	6	8	8
Moribund sacrifice	7	8	8
Terminal sacrifice	37	34	34

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	21	31	27
Total primary tumors	26	39	37
Total animals with benign tumors	6	13	12
Total benign tumors	8	13	14
Total animals with malignant tumors	18	23	21
Total malignant tumors	18	26	23
Total animals with secondary tumors##	2	1	2
Total secondary tumors	2	2	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 PHENYLEPHRINE HYDROCHLORIDE: UNTREATED CONTROL

ANIMAL NUMBER	12 28	12 22	11 12	13 32	11 10	13 36	15 50	14 44	11 13	10 05	13 39	14 46	10 01	10 02	10 03	10 04	10 06	10 07	10 08	10 09	11 11	11 14	11 15	11 16	11 17
WEEKS ON STUDY	04 8	05 5	07 9	08 0	08 1	08 2	08 2	08 3	08 4	08 5	08 7	09 3	10 3	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma												X													
RESPIRATORY SYSTEM																									
Lungs and bronchi	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X																
Alveolar/bronchiolar carcinoma																			X						
Osteosarcoma, metastatic		X																							
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Malignant lymphoma, mixed type													X												
Lymph nodes	A	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	–	+	–	+	–	+	+
Thymus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–
Malignant lymphoma, lymphocytic type																									
CIRCULATORY SYSTEM																									
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	A	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X				
Bile duct	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	A	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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																									
Adrenal	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	A	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Pancreatic islets	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma						X																			
REPRODUCTIVE SYSTEM																									
Mammary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
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									X					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
Islet cell carcinoma, metastatic						X																			
Malignant lymphoma, lymphocytic type							X																		
Malignant lymphoma, histiocytic type											X					X									
Malignant lymphoma, mixed type														X	X										

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

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

ANIMAL NUMBER	118	119	120	121	123	124	125	126	127	129	130	131	133	134	135	137	138	140	141	142	143	145	147	148	149	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																										1
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma													X													1
Malignant lymphoma, mixed type						X						X					X								X	5
Lymph nodes	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	46
Malignant lymphoma, lymphocytic type													X													1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma						X		X																		3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	47
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	48
Adenoma, NOS								X																		1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	−	+	+	−	−	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma									X																	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Islet cell carcinoma, metastatic																										1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, histiocytic type																										2
Malignant lymphoma, mixed type		X	X																				X			5

* Animals necropsied

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

ANIMAL NUMBER	0161	0151	0255	0288	0335	0271	0330	0448	0411	0499	0003	0044	0223	0550	0088	0441	0011	0022	0055	0066	0077	0099	0110	0111	0122
WEEKS ON STUDY	073	075	076	085	085	091	092	092	093	094	095	096	097	097	098	103	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma			X																						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar carcinoma							X								X										
Fibrosarcoma, metastatic			X																						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																	X								
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+
Thymus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X																
Kupffer cell sarcoma										X															
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X			X										
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	–	+	+	+	+	–	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma				X																					
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																		X							
Fibroadenoma																X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Endometrial stromal polyp																									
Ovary	+	+	+	–	–	+	+	–	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma																							X		
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fibrosarcoma, metastatic			X																						
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undiffer type											X														
Malignant lymphoma, lymphocytic type	X						X																X		
Malignant lymphoma, histiocytic type																X									
Malignant lymphoma, mixed type																			X						

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

ANIMAL NUMBER	013	014	017	018	019	020	021	022	024	026	029	031	032	033	034	036	037	038	039	040	042	043	045	046	047	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																	X						3
Alveolar/bronchiolar carcinoma	X																									3
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type										X																2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	45
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X																									2
Kupffer cell sarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS														X												3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	+	–	+	–	–	–	+	+	+	+	+	+	+	+	–	+	–	–	–	+	+	+	+	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma														X												1
Endometrial stromal polyp																		X								1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	43
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS							X																			1
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Fibrosarcoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, undiffer type																										1
Malignant lymphoma, lymphocytic type		X			X						X							X								7
Malignant lymphoma, histiocytic type																				X					X	3
Malignant lymphoma, mixed type						X								X		X						X				5

* Animals necropsied

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

ANIMAL NUMBER	0669	0556	0559	0991	0666	0554	0773	0992	0662	0886	0664	0889	0882	0770	0883	0668	0551	0552	0553	0555	0557	0558	0660	0661	0663
WEEKS ON STUDY	008	021	021	073	075	077	081	092	093	097	099	099	101	102	102	103	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic								X																	
Alveolar/bronchiolar adenoma															X										
Alveolar/bronchiolar carcinoma				X																					
Trachea	+	+	A	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									X
Lymph nodes	+	–	A	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic				X																					
Thymus	+	–	A	–	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																								X	
CIRCULATORY SYSTEM																									
Heart	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	A	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X										X						
Bile duct	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	A	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N
Pancreas	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	A	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	A	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS															X										
Large intestine	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Urinary bladder	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	A	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	A	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	–	–	A	–	+	+	–	–	+	+	+	–	–	+	+	+	+	–	+	+	+	–	–	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	A	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS								X																	
Uterus	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																								X	
Malignant lymphoma, histiocytic type																									
Ovary	+	+	A	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Teratoma, benign	X																								
NERVOUS SYSTEM																									
Brain	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, undiffer type														X											
Malignant lymphoma, lymphocytic type																X									
Malignant lymphoma, histiocytic type																		X	X						
Malignant lymphoma, mixed type																							X		

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

ANIMAL NUMBER	065	067	071	072	074	075	076	077	078	079	080	081	084	085	087	088	090	093	094	095	096	097	098	099	100	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibrosarcoma						X																				2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, metastatic																										1
Alveolar/bronchiolar adenoma				X		X	X	X																		5
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type													X													2
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Alveolar/bronchiolar carcinoma, meta																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Malignant lymphoma, mixed type																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																						X	X			4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type												X														1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma																							X			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma	X																			X						2
Parathyroid	+	+	−	+	−	−	+	+	−	−	+	+	−	+	+	−	−	+	+	−	−	+	−	+	+	27
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma																										1
Malignant lymphoma, histiocytic type	X																									1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Teratoma, benign																										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	*49
Malignant lymphoma, undiffer type														X												2
Malignant lymphoma, lymphocytic type																				X						1
Malignant lymphoma, histiocytic type																			X							2
Malignant lymphoma, mixed type						X	X				X					X							X			8

* Animals necropsied

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

	Control	1,250 ppm	2,500 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/49 (2%)	3/50 (6%)	5/49 (10%)
Adjusted Rates (b)	2.4%	8.8%	14.1%
Terminal Rates (c)	0/37 (0%)	3/34 (9%)	4/34 (12%)
Week of First Observation	84	104	102
Life Table Tests (d)	P=0.062	P=0.294	P=0.094
Incidental Tumor Tests (d)	P=0.051	P=0.235	P=0.077
Cochran-Armitage Trend Test (d)	P=0.070		
Fisher Exact Test (d)		P=0.316	P=0.102
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	1/49 (2%)	3/50 (6%)	1/49 (2%)
Adjusted Rates (b)	2.7%	7.8%	2.1%
Terminal Rates (c)	1/37 (3%)	1/34 (3%)	0/34 (0%)
Week of First Observation	104	92	73
Life Table Tests (d)	P=0.605	P=0.299	P=0.749
Incidental Tumor Tests (d)	P=0.589N	P=0.341	P=0.659N
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.316	P=0.753N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	2/49 (4%)	6/50 (12%)	6/49 (12%)
Adjusted Rates (b)	5.0%	16.2%	16.0%
Terminal Rates (c)	1/37 (3%)	4/34 (12%)	4/34 (12%)
Week of First Observation	84	92	73
Life Table Tests (d)	P=0.107	P=0.130	P=0.123
Incidental Tumor Tests (d)	P=0.095	P=0.115	P=0.144
Cochran-Armitage Trend Test (d)	P=0.114		
Fisher Exact Test (d)		P=0.141	P=0.134
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	2/49 (4%)	7/50 (14%)	1/49 (2%)
Adjusted Rates (b)	4.9%	18.3%	2.9%
Terminal Rates (c)	1/37 (3%)	5/34 (15%)	1/34 (3%)
Week of First Observation	82	73	104
Life Table Tests (d)	P=0.451N	P=0.078	P=0.525N
Incidental Tumor Tests (d)	P=0.548N	P=0.063	P=0.674N
Cochran-Armitage Trend Test (d)	P=0.420N		
Fisher Exact Test (d)		P=0.084	P=0.500N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	2/49 (4%)	3/50 (6%)	3/49 (6%)
Adjusted Rates (b)	5.1%	8.6%	8.6%
Terminal Rates (c)	1/37 (3%)	2/34 (6%)	2/34 (6%)
Week of First Observation	87	103	103
Life Table Tests (d)	P=0.384	P=0.480	P=0.476
Incidental Tumor Tests (d)	P=0.423	P=0.535	P=0.468
Cochran-Armitage Trend Test (d)	P=0.412		
Fisher Exact Test (d)		P=0.509	P=0.500
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	10/49 (20%)	7/50 (14%)	12/49 (24%)
Adjusted Rates (b)	26.3%	20.6%	35.3%
Terminal Rates (c)	9/37 (24%)	7/34 (21%)	12/34 (35%)
Week of First Observation	103	104	104
Life Table Tests (d)	P=0.272	P=0.364N	P=0.315
Incidental Tumor Tests (d)	P=0.302	P=0.298N	P=0.372
Cochran-Armitage Trend Test (d)	P=0.351		
Fisher Exact Test (d)		P=0.282N	P=0.405

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

	Control	1,250 ppm	2,500 ppm
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	14/49 (29%)	18/50 (36%)	18/49 (37%)
Adjusted Rates (b)	34.8%	46.6%	50.0%
Terminal Rates (c)	11/37 (30%)	14/34 (41%)	16/34 (47%)
Week of First Observation	82	73	102
Life Table Tests (d)	P=0.163	P=0.207	P=0.183
Incidental Tumor Tests (d)	P=0.187	P=0.284	P=0.207
Cochran-Armitage Trend Test (d)	P=0.227		
Fisher Exact Test (d)		P=0.283	P=0.259
Liver: Hepatocellular Adenoma			
Overall Rates (a)	3/49 (6%)	2/50 (4%)	4/49 (8%)
Adjusted Rates (b)	8.1%	5.3%	11.0%
Terminal Rates (c)	3/37 (8%)	1/34 (3%)	3/34 (9%)
Week of First Observation	104	93	93
Life Table Tests (d)	P=0.393	P=0.524N	P=0.466
Incidental Tumor Tests (d)	P=0.494	P=0.419N	P=0.555
Cochran-Armitage Trend Test (d)	P=0.416		
Fisher Exact Test (d)		P=0.419N	P=0.500
Pituitary Gland: Adenoma			
Overall Rates (a)	1/48 (2%)	3/48 (6%)	0/49 (0%)
Adjusted Rates (b)	2.8%	8.1%	0.0%
Terminal Rates (c)	1/36 (3%)	1/34 (3%)	0/34 (0%)
Week of First Observation	104	96	
Life Table Tests (d)	P=0.379N	P=0.295	P=0.511N
Incidental Tumor Tests (d)	P=0.216N	P=0.512	P=0.511N
Cochran-Armitage Trend Test (d)	P=0.372N		
Fisher Exact Test (d)		P=0.308	P=0.495N

(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. N indicates a negative trend or lower incidence in a dosed group.

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	49
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(49)
Multiple cysts		1 (2%)	
RESPIRATORY SYSTEM			
#Trachea	(49)	(50)	(48)
Hyperplasia, epithelial			1 (2%)
#Tracheal gland	(49)	(50)	(48)
Multiple cysts			1 (2%)
#Lung	(49)	(50)	(49)
Hemorrhage		1 (2%)	
Inflammation, acute	2 (4%)	1 (2%)	1 (2%)
Inflammation, acute/chronic	3 (6%)		1 (2%)
Inflammation, chronic	2 (4%)	5 (10%)	4 (8%)
Alveolar macrophages		3 (6%)	1 (2%)
Hyperplasia, alveolar epithelium	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(49)
Hyperplasia, lymphoid	12 (24%)	12 (24%)	7 (14%)
*Blood	(49)	(50)	(49)
Leukocytosis, NOS			1 (2%)
#Bone marrow	(48)	(50)	(49)
Hyperplasia, erythroid			1 (2%)
Hyperplasia, granulocytic	13 (27%)	15 (30%)	6 (12%)
Hyperplasia, eosinophilic			1 (2%)
Hypoplasia, hematopoietic			1 (2%)
#Spleen	(49)	(50)	(49)
Inflammation, acute		1 (2%)	
Amyloidosis			1 (2%)
Atrophy, NOS			1 (2%)
Angiectasis	1 (2%)		
Hyperplasia, lymphoid	12 (24%)	8 (16%)	12 (24%)
Hematopoiesis	6 (12%)	3 (6%)	6 (12%)
#Splenic capsule	(49)	(50)	(49)
Inflammation, chronic diffuse		1 (2%)	
#Lymph node	(42)	(45)	(46)
Inflammation, acute/chronic		1 (2%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)	
#Mandibular lymph node	(42)	(45)	(46)
Hyperplasia, lymphoid	6 (14%)	3 (7%)	5 (11%)
#Mesenteric lymph node	(42)	(45)	(46)
Inflammation, acute/chronic		1 (2%)	
Angiectasis			1 (2%)
#Renal lymph node	(42)	(45)	(46)
Inflammation, acute		1 (2%)	
Hyperplasia, plasma cell	1 (2%)		
*Perilymphatic tissue	(49)	(50)	(49)
Hyperplasia, plasma cell			1 (2%)
#Lung	(49)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)	4 (8%)	1 (2%)
#Salivary gland	(48)	(47)	(48)
Hyperplasia, lymphoid	7 (15%)	3 (6%)	4 (8%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Liver	(49)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	2 (4%)
Hematopoiesis	1 (2%)		2 (4%)
#Pancreas	(49)	(49)	(49)
Hyperplasia, lymphoid		4 (8%)	
#Kidney	(49)	(50)	(49)
Hyperplasia, lymphoid	7 (14%)	5 (10%)	9 (18%)
#Perirenal tissue	(49)	(50)	(49)
Hyperplasia, lymphoid		1 (2%)	
#Urinary bladder	(49)	(48)	(47)
Hyperplasia, lymphoid	3 (6%)	3 (6%)	3 (6%)
#Adrenal cortex	(49)	(50)	(48)
Hematopoiesis			1 (2%)
#Thymus	(46)	(48)	(44)
Multiple cysts		2 (4%)	1 (2%)
Atrophy, NOS			1 (2%)
Angiectasis			1 (2%)
Hyperplasia, lymphoid	10 (22%)	8 (17%)	12 (27%)
CIRCULATORY SYSTEM			
*Multiple organs	(49)	(50)	(49)
Polyangiitis	1 (2%)		
#Mediastinal lymph node	(42)	(45)	(46)
Lymphangiectasis			1 (2%)
#Myocardium	(49)	(50)	(49)
Inflammation, acute focal			1 (2%)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Inflammation, chronic focal	2 (4%)	1 (2%)	
Degeneration, NOS		1 (2%)	
Calcification, focal	1 (2%)	1 (2%)	
Pigmentation, NOS			2 (4%)
Hyperplasia, focal	1 (2%)	1 (2%)	
#Mitral valve	(49)	(50)	(49)
Pigmentation, NOS			1 (2%)
*Artery/tunica adventitia	(49)	(50)	(49)
Inflammation, acute		1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(48)	(47)	(48)
Multiple cysts	1 (2%)		
Atrophy, NOS			1 (2%)
#Liver	(49)	(50)	(49)
Multiple cysts		1 (2%)	
Inflammation, acute focal	1 (2%)		
Inflammation, acute/chronic	3 (6%)	2 (4%)	
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal		2 (4%)	2 (4%)
Necrosis, NOS	1 (2%)	1 (2%)	
Focal cellular change		2 (4%)	1 (2%)
Angiectasis	2 (4%)		
*Gallbladder	(49)	(50)	(49)
Cyst, NOS		1 (2%)	
Inflammation, suppurative		1 (2%)	
Inflammation with fibrosis	1 (2%)		
Hyperplasia, epithelial	1 (2%)		

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(49)	(49)	(49)
Cyst, NOS			1 (2%)
Cystic ducts	1 (2%)		2 (4%)
Inflammation, necrotizing		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal			1 (2%)
Atrophy, NOS	2 (4%)	1 (2%)	3 (6%)
Hyperplasia, intraductal			1 (2%)
#Glandular stomach	(49)	(50)	(48)
Cyst, NOS	1 (2%)	1 (2%)	4 (8%)
Multiple cysts	7 (14%)	2 (4%)	1 (2%)
Inflammation, acute/chronic	1 (2%)	2 (4%)	
Eosinophilic leukocytic infiltrate	1 (2%)	4 (8%)	2 (4%)
Inflammation, chronic focal	5 (10%)		2 (4%)
Necrosis, focal			1 (2%)
Pigmentation, NOS			1 (2%)
Hyperplasia, NOS		1 (2%)	1 (2%)
#Forestomach	(49)	(50)	(48)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Inflammation, chronic suppurative		1 (2%)	
Hyperplasia, epithelial		1 (2%)	
URINARY SYSTEM			
#Kidney	(49)	(50)	(49)
Multiple cysts	1 (2%)		
Glomerulonephritis, NOS	1 (2%)		2 (4%)
Pyelonephritis, chronic		1 (2%)	1 (2%)
Inflammation, chronic focal	3 (6%)	3 (6%)	3 (6%)
Calcification, focal	1 (2%)		
#Perirenal tissue	(49)	(50)	(49)
Inflammation, acute/chronic		1 (2%)	
#Kidney/glomerulus	(49)	(50)	(49)
Amyloidosis		2 (4%)	1 (2%)
#Kidney/tubule	(49)	(50)	(49)
Cast, NOS	1 (2%)	1 (2%)	
Regeneration, NOS	2 (4%)		
#Urinary bladder	(49)	(48)	(47)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic	2 (4%)		
Inflammation, chronic focal			1 (2%)
Hyperplasia, epithelial		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(48)	(49)
Cyst, NOS	3 (6%)	1 (2%)	3 (6%)
Multiple cysts		1 (2%)	1 (2%)
Hyperplasia, focal	8 (17%)	5 (10%)	9 (18%)
Angiectasis	5 (10%)	2 (4%)	
#Adrenal/capsule	(49)	(50)	(48)
Hyperplasia, stromal	46 (94%)	48 (96%)	46 (96%)
#Adrenal cortex	(49)	(50)	(48)
Cyst, NOS	3 (6%)		2 (4%)
Hemorrhage	1 (2%)		
Degeneration, NOS	2 (4%)	2 (4%)	1 (2%)
Focal cellular change	3 (6%)	2 (4%)	5 (10%)
Hyperplasia, focal	1 (2%)	1 (2%)	
Angiectasis	1 (2%)		2 (4%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Adrenal medulla	(49)	(50)	(48)
Degeneration, NOS		1 (2%)	
Hyperplasia, focal		1 (2%)	1 (2%)
Angiectasis			1 (2%)
#Periadrenal tissue	(49)	(50)	(48)
Inflammation, suppurative	1 (2%)		
#Thyroid	(49)	(50)	(48)
Cyst, NOS	1 (2%)		1 (2%)
Cystic follicles	3 (6%)	3 (6%)	3 (6%)
Hyperplasia, follicular cell	3 (6%)	1 (2%)	2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(49)
Multiple cysts	1 (2%)		
*Clitoral gland	(49)	(50)	(49)
Distention	2 (4%)	1 (2%)	1 (2%)
#Uterus	(49)	(50)	(49)
Distention	1 (2%)		2 (4%)
Multiple cysts		1 (2%)	
Edema, NOS		1 (2%)	
Inflammation, suppurative	3 (6%)	4 (8%)	
Inflammation, chronic necrotizing	1 (2%)		
Angiectasis	1 (2%)		1 (2%)
#Uterus/endometrium	(49)	(50)	(49)
Multiple cysts			1 (2%)
Hyperplasia, cystic	43 (88%)	43 (86%)	40 (82%)
#Ovary	(49)	(43)	(48)
Cyst, NOS	9 (18%)	6 (14%)	9 (19%)
Multiple cysts			3 (6%)
Inflammation, suppurative	1 (2%)	1 (2%)	
Inflammation, chronic suppurative	1 (2%)		
Degeneration, NOS			1 (2%)
Atrophy, NOS		1 (2%)	
Angiectasis			2 (4%)
NERVOUS SYSTEM			
#Brain/meninges	(49)	(50)	(49)
Perivascular cuffing	1 (2%)		2 (4%)
#Brain	(49)	(50)	(49)
Perivascular cuffing	3 (6%)	3 (6%)	
Calcification, NOS		1 (2%)	
Calcification, focal	18 (37%)	22 (44%)	21 (43%)
*Spinal cord	(49)	(50)	(49)
Degeneration, myelin		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(49)	(50)	(49)
Inflammation, chronic		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE *TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE* (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Mesentery	(49)	(50)	(49)
Inflammation, acute/chronic		1 (2%)	
Inflammation with fibrosis		1 (2%)	
Necrosis, fat		1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(49)
Inflammation, suppurative			1 (2%)
Inflammation, acute/chronic	1 (2%)		
Bacterial septicemia		1 (2%)	
Adipose tissue			
Hematoma, organized			1
Necrosis, fat	7	2	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

GENETIC TOXICOLOGY OF

PHENYLEPHRINE HYDROCHLORIDE

TABLE E1. MUTAGENICITY OF PHENYLEPHRINE HYDROCHLORIDE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (μg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	114 ± 1.5	141 ± 3.8	137 ± 3.3
	100	107 ± 16.8	137 ± 11.5	128 ± 8.7
	333	129 ± 9.9	142 ± 2.8	129 ± 10.4
	1,000	117 ± 4.3	123 ± 16.1	131 ± 5.7
	3,333	111 ± 10.0	123 ± 14.4	133 ± 3.6
	10,000	108 ± 6.3	144 ± 2.3	120 ± 9.1
TA1535	0	19 ± 0.7	5 ± 0.3	9 ± 2.0
	100	17 ± 1.2	7 ± 0.6	6 ± 0.9
	333	18 ± 3.5	8 ± 2.0	8 ± 2.1
	1,000	16 ± 4.2	9 ± 1.9	6 ± 0.9
	3,333	14 ± 0.6	8 ± 1.9	7 ± 1.2
	10,000	11 ± 1.2	6 ± 0.9	6 ± 0.9
TA1537	0	4 ± 2.0	4 ± 0.7	7 ± 1.7
	100	3 ± 1.3	8 ± 2.3	5 ± 1.2
	333	4 ± 0.9	5 ± 1.3	6 ± 0.7
	1,000	3 ± 1.5	5 ± 1.5	7 ± 1.0
	3,333	3 ± 1.3	7 ± 0.3	5 ± 1.2
	10,000	4 ± 1.5	6 ± 1.0	4 ± 0.7
TA98	0	16 ± 1.7	25 ± 4.0	28 ± 2.1
	100	15 ± 6.0	21 ± 3.7	30 ± 2.8
	333	17 ± 1.5	23 ± 1.8	35 ± 1.5
	1,000	15 ± 1.5	15 ± 0.3	31 ± 0.9
	3,333	15 ± 1.0	24 ± 3.7	30 ± 3.6
	10,000	17 ± 1.2	20 ± 1.2	27 ± 3.0

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

TABLE E2. MUTAGENICITY OF PHENYLEPHRINE HYDROCHLORIDE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

Compound	Concentration (μg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
Distilled water					
		84	100.7	118.0	28
		75	94.0	95.0	27
		101	73.0	89.0	46
		88	90.7	96.0	(b) 32 (33)
Methyl methanesulfonate					
	5	527	62.5	38.9	281
		627	72.0	42.4	290
		635	65.3	33.4	324 (298)
Phenylephrine hydrochloride					
	125	99	83.3	89.8	40
		74	82.7	92.2	30
		88	85.0	86.2	35 (35)
	250	85	68.5	68.3	41
		103	80.8	79.6	42
		99	77.2	82.7	43 (42)
	500	94	62.3	45.1	50
		64	49.7	50.3	43
		72	102.8	56.4	23 (39)
	750	108	80.5	44.8	45
		83	93.3	46.2	30
		92	96.7	42.6	32 (35)
	1,000	120	84.2	33.0	48
		121	62.0	19.9	65
		125	86.5	26.9	48 (54)
	1,500	151	62.2	13.0	81
		162	65.3	11.2	83
		149	70.5	12.3	70 (78)

(a) Experiments were performed twice, all doses were tested in duplicate or triplicate. Because the results from the two experiments were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). 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 supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.
(b) The mean of the results of replicate determinations is the number in parentheses.

TABLE E3. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY PHENYLEPHRINE HYDROCHLORIDE (a)

−S9 (b)		+S9 (c)	
Dose (μg/ml)	SCE/Cell (d)	Dose (μg/ml)	SCE/Cell (d)
Medium	9.1	Medium	10.2
Phenylephrine hydrochloride		Phenylephrine hydrochloride	
1,500	12.1	8,500	10.6
2,000	11.4	9,000	11.1
2,500	11.9	10,000	11.8
Mitomycin C		Cyclophosphamide	
0.001	15.3	0.400	13.5
0.010	48.8	2.000	27.0

(a) SCE = sister-chromatid exchange
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent (medium) for 2 hours at 37° C; 2 hours after initiation of treatment, 10 μM BrdU was added, and incubation was continued for an additional 22-24 hours. (Due to chemically induced cell cycle delay, cells treated with study compound were allowed to incubate an additional 6 hours to accumulate sufficient metaphases for analysis.) Cells were washed, fresh medium containing BrdU (10 μM) and colcemid (0.1 μg/ml) was added, and incubation was continued for 2-3 hours (Galloway et al., 1985).
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 μM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 μg/ml) present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).
(d) Cells were collected by mitotic shake-off, tested for 3 minutes with potassium chloride (75 mM), washed twice with fixative, and dropped onto slides and air dried (Galloway et al., 1985).

TABLE E4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY PHENYLEPHRINE HYDROCHLORIDE (a)

−S9 (b)		+S9 (c)	
Dose (μg/ml)	Abs/100 Cells (percent cells with Abs)	Dose (μg/ml)	Abs/100 Cells (percent cells with Abs)
Medium	2 (2)	Medium	1 (1)
Phenylephrine hydrochloride		Phenylephrine hydrochloride	
1,500	1 (1)	9,000	3 (3)
2,000	1 (1)	9,500	1 (1)
2,500	4 (3)	10,000	1 (1)
Mitomycin C		Cyclophosphamide	
0.150	14 (12)	5.0	12 (12)
0.500	28 (28)	37.5	36 (32)

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

APPENDIX F

CHEMICAL CHARACTERIZATION OF PHENYLEPHRINE HYDROCHLORIDE

APPENDIX F. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Phenylephrine Hydrochloride Lot No. 160-XX-177 Performed by the Analytical Chemistry Laboratory

A. Physical properties	Determined	Literature Values
1. Appearance:	White, microcrystalline powder	
2. Melting point:	139°-141° C (visual, capillary)	140°-145° C (Hawley, 1977)

B. Spectral data

1. Infrared

Instrument:	Beckman IR-12	
Phase:	2% in potassium bromide pellet	
Results:	See Figure 5	Spectrum consistent with literature reference (Sammul et al., 1964)

2. Ultraviolet/visible

Instrument:	Cary 118 No absorbance from 800 to 350 nm	
Solvent:	95% Ethanol	
Results:	λ_{max} (nm) $\quad \varepsilon \times 10^{-3}$ 283 $\quad 1.891 \pm 0.011(\delta)$ 276 $\quad 2.122 \pm 0.006(\delta)$	No literature reference found. Spectrum consistent with structure.

3. Nuclear magnetic resonance

Instrument:	Varian EM-360A	
Solvent:	Deuterium oxide with internal sodium-3-trimethylsilylpropionate-2,2,3,3,$-d_4$	
Assignments:	See Figure 6	No literature reference found. Spectrum consistent with structure of phenylephrine hydrochloride

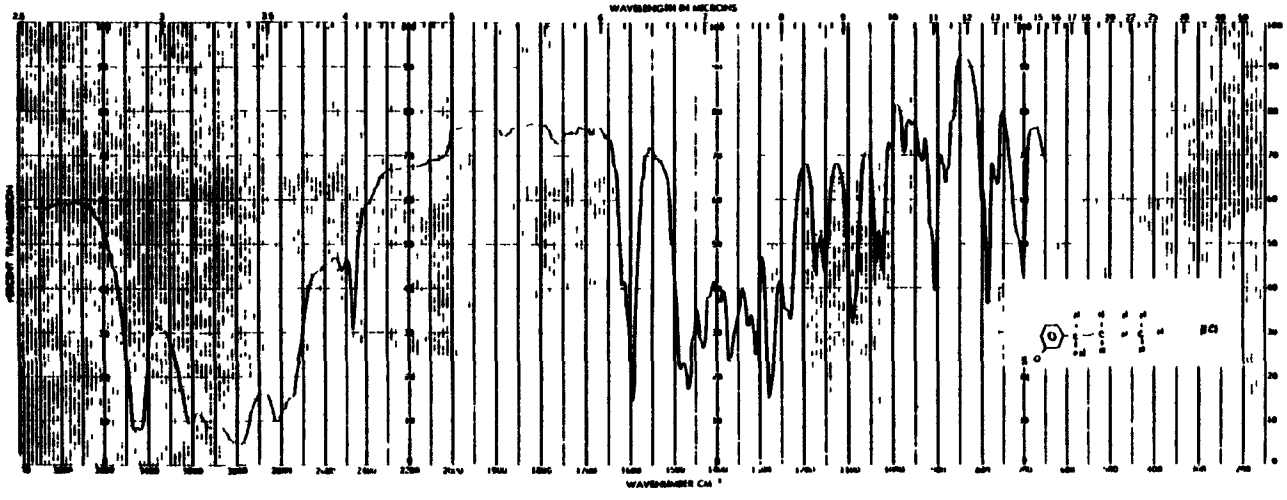

FIGURE 5. INFRARED ABSORPTION SPECTRUM OF PHENYLEPHRINE HYDROCHLORIDE (LOT NO. 160-XX-177)

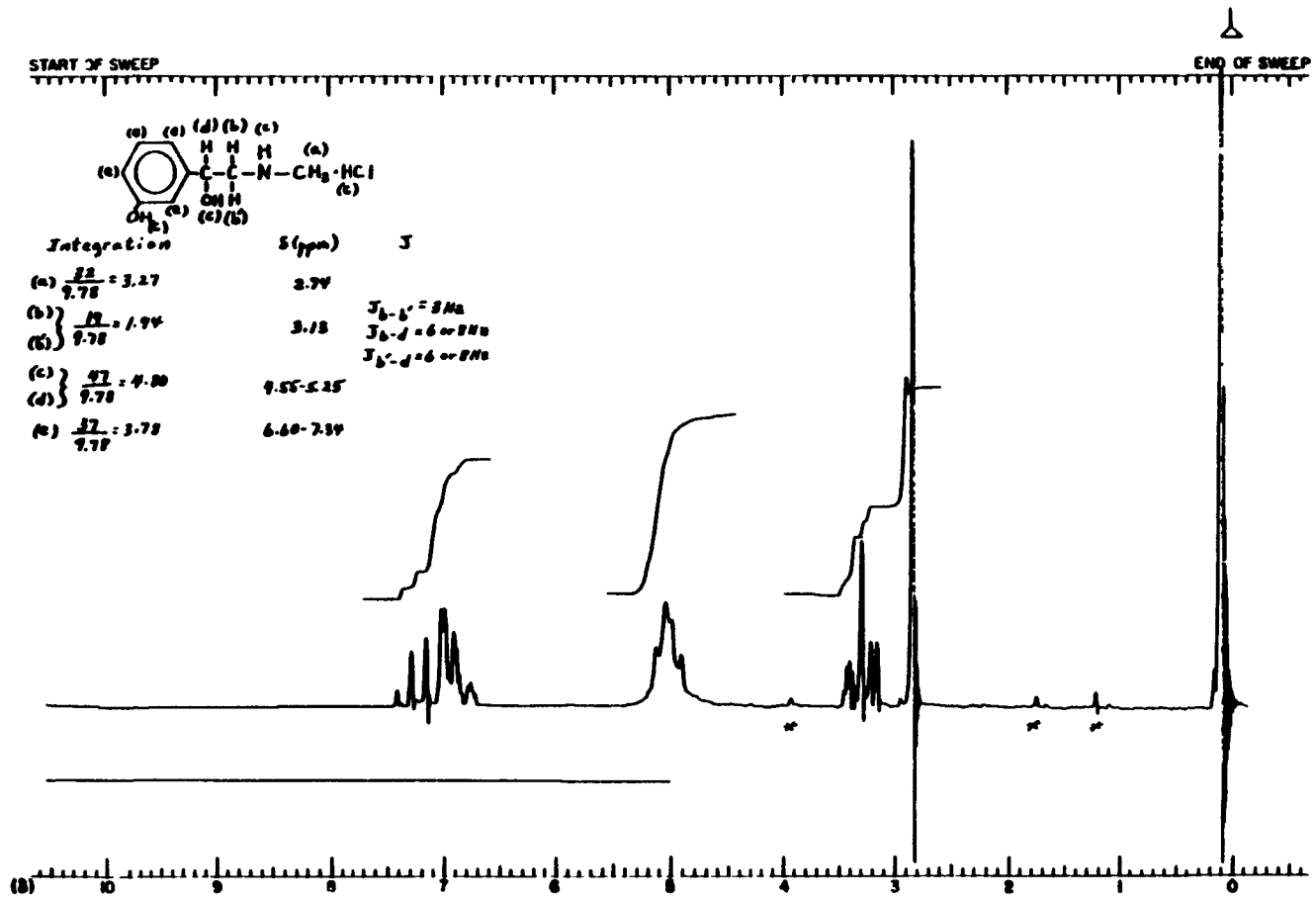

FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF PHENYLEPHRINE HYDROCHLORIDE (LOT NO. 160-XX-177)

	Determined	
Chemical shift (δ):	a	3.27 ppm
	b, b'	d of d, 3.13 ppm
	c, d	broad absorbance, 4.55-5.25 ppm
	e	m, 6.60-7.34 ppm
Coupling constants:	$J_{b\text{-}b'}$	= 3 Hz
	$J_{b\text{-}d}$	= 6 or 8 Hz
	$J_{b'\text{-}d}$	= 6 or 9 Hz
Integration ratios:	a	3.27
	b, b'	1.94
	c, d	4.80
	e	3.78

C. Titration

1. USP assay--bromination of three aromatic positions *ortho* and *para* to the phenolic hydroxyl group: 101.04% ± 0.37(δ)%
2. Nonaqueous titration of the amine group with perchloric acid: 99.25% ± 0.39(δ)%

D. Water analysis (Karl Fischer): 0.08% ± 0.03(δ)%

E. Elemental analysis

Element	C	H	N	Cl
Theory (T)	53.07	6.93	6.88	17.41
Determined (D)	53.34	7.19	6.85	17.31
	53.12	7.00	6.82	17.33
Percent D/T	100.30	102.38	99.34	99.48

F. Ketone analysis (USP, 1975): Meets USP specifications of <500 ppm compared with acetone standard

G. Chromatographic analysis

1. Thin-layer chromatography

Plates: Silica Gel 60 F-254
Reference standard: *o*-Aminophenol, 10 µg (10 µg/µl methanol)
Amount spotted: 100 and 300 µg (10 µg/µl methanol)
Visualization: Ultraviolet (254 nm) and 0.2% ninhydrin in butanol (spray)
Solvent
System 1: acetone:chloroform:ammonium hydroxide (58:40:2)
System 2: methanol:hydrochloric acid (99:1)

Results

Spot Intensity	R_f	R_{st}
System 1		
Major	0.26	0.52
System 2		
Major	0.36	0.54

2. High-performance liquid chromatography

Instrument system
Pump: Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Column: µBondapak C_{18}, 300 mm × 3.9 mm ID
Detection: Ultraviolet, 280 nm
Guard column: CO:PELL ODS, 72 mm × 2.3 mm ID
Solvent system
A: Water with 5 mM heptane sulfonic acid sodium salt and 1% (v/v) acetic acid
B: Methanol with 5 mM heptane sulfonic acid sodium salt and 1% (v/v) acetic acid

System 1

Solvent program: 40% A:60% B, isocratic
Flow rate: 1 ml/min
Samples injected: Solution (20 µl) of 1.4 mg phenylephrine hydrochloride per ml water, filtered

Results: Major peak and two impurities before the major peak. Impurities totaled 0.08% of the major peak.

Peak No.	Retention Time (min)	Retention Time (relative to major peak)	Area (percent of major peak)
1	3.0	0.55	0.01
2	3.5	0.64	0.07
3	5.5	1.00	100

System 2

Solvent program: 80% A:20% B, isocratic
Flow rate: 1 ml/min
Samples injected: Solution (10µl) of 3.5 mg phenylephrine hydrochloride per ml water, filtered

Results: Major peak and two impurities before the major peak. Impurities totaled 0.9%.

Peak No.	Retention Time (min)	Retention Time (relative to major peak)	Area (percent of major peak)
1	2.5	0.20	0.01
2	3.5	0.20	0.08
3	17.4	1.00	100

Peak 2 in each system was difficult to quantitate accurately because it appeared very close to the solvent front. An injection of sample solution from System 1 exhibited no additional impurities up to 65 minutes when run at 100% B. Peaks no. 1 and no. 2 in System 1 correspond to peak no. 1 and no. 2 in System 2.

H. **Conclusions:** The results of the elemental analysis for carbon, hydrogen, nitrogen, and chlorine were in agreement with the theoretical values. Assay using the USP method (bromination of three aromatic positions on the phenol) indicated a purity of 101.04% ± 0.37(δ)%. (The USP specifications are not less than 97.5% and not more than 102.5% based on this assay.) Nonaqueous titration of the amine group with perchloric acid indicated a purity of 99.25% ± 0.39(δ)%. The sample passed the USP test for ketones (<500 ppm compared with acetone standard). Thin-layer chromatography indicated a single major spot in each of two systems. Two high-performance liquid chromatographic systems each indicated two impurities before the major peak totaling 0.08% of the major peak in one system and 0.09% in the other. The impurity peaks in one system corresponded to those in the other system. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of phenylephrine hydrochloride.

II. Stability Study of Phenylephrine Hydrochloride Lot No. 160-XX-077 Performed by the Analytical Chemistry Laboratory

A. Sample preparation and storage: Samples of phenylephrine hydrochloride were stored for 2 weeks at temperatures of −20°, 5°, 25°, or 60° C in glass tubes with Teflon®-lined caps.

B. Analytical method: Samples from each storage temperature were analyzed by high-performance liquid chromatography

Instrumental system
Pump: Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Detection: Ultraviolet, 280 nm
Column: μBondapak C_{18}, 300 mm × 3.9 mm ID
Guard column: CO:PELL ODS, 72 mm × 2.3 mm ID
Solvent system
A: Water with 5 mM lauryl sulfate and 1% (v/v) acetic acid
B: Methanol with 5 mM lauryl sulfate and 1% (v/v) acetic acid
Program: 30% A:70% B, isocratic
Flow rate: 2 ml/min
Samples injected: Solutions (25 μl) of 0.14% phenylephrine hydrochloride, from each storage temperature, in water containing 0.1% uracil as an internal standard
Retention times
Phenylephrine hydrochloride--3.5 min
Uracil (internal standard)--1.8 min

C. Results: Sample peak heights were compared with internal standard peak heights, and the recovery of phenylephrine hydrochloride from each storage temperature was compared with the recovery of the −20° C sample.

Storage Temperature	Percent Compound (normalized to −20° C sample)
−20° C	100.0 ± 2.0(δ)
5° C	101.2 ± 2.0(δ)
25° C	99.2 ± 2.0(δ)
60° C	98.9 ± 2.0(δ)

D. Conclusions: Phenylephrine hydrochloride is stable as the bulk chemical, within the limits of experimental error, when stored for 2 weeks at temperatures up to 60° C.

III. Stability Study of Phenylephrine Hydrochloride Lot. No. 160-XX-177 at the Study Laboratory

A. Storage conditions

Bulk: 25° C
Reference: −20° C

B. Analytical method

1. Infrared spectroscopy

Instrument: Perkin-Elmer 283 or Beckman Acculab 8
Phase: 1% or 2% in potassium bromide pellet

2. **USP titration:** Approximately 0.1 g of phenylephrine hydrochloride was accurately weighed into a 250-ml iodine flask. The phenylephrine hydrochloride was dissolved in 20 ml of distilled water. Fifty milliliters of 0.100 N bromine and then 5.0 ml of concentrated hydrochloric acid was added. The mixture was allowed to stand 15 minutes. Then 10.0 ml of potassium iodide (10% w/v) was added, and that mixture was allowed to stand 5 minutes. The mixture was then titrated with 0.1 N sodium thiosulfate with 3.0 ml starch indicator solution added as the end point was approached.

3. High-performance liquid chromatography

Instrument: Varian 5060 with Vista 401
Detection: Ultraviolet at 280 nm
Column: μBondapak C_{18}, 300 mm × 3.9 mm ID
Guard column: CO:PELL ODS, 72 mm × 2.3 mm ID
Solvent system
A: Water with 5 mM sodium lauryl sulfate and 1% (v/v) acetic acid
B: Methanol with 5 mM sodium lauryl sulfate and 1% (v/v) acetic acid
Program: 70% B
Flow rate: 2.0 ml/min
Retention volume: 3.5 ml--uracil (internal standard)
7.0 ml--phenylephrine hydrochloride

C. Results

1. **Infrared spectroscopy:** All bulk spectra were comparable to the reference spectra and to the spectra supplied by the analytical chemistry laboratory.

2. Titration

Date of Analysis	Percent Purity (a) Bulk	Reference
11/79	102	104
02/80	100	100
06/80	99	99
09/80	99	99
10/80	97	97
02/81	101	100
06/81	100	100
10/81	100	99
02/82	101	101
06/82	101	102
10/82	102	102

(a) Results of duplicate analysis

3. High-performance liquid chromatography

Date of Analysis	Relative Weight Ratio (a) Bulk	Reference	Percent Purity (b)
02/81	(c) 7.91×10^{-3}	(c) 8.04×10^{-3}	98
06/81	(c) 5.37×10^{-3}	(d) 5.29×10^{-3}	102
10/81	(d) 7.61×10^{-3}	(d) 7.65×10^{-3}	100
02/82	(d) 1.34×10^{-2}	(d) 1.33×10^{-2}	101
06/82	(d) 5.75×10^{-3}	(d) 5.70×10^{-3}	101
10/82	(d) 7.00×10^{-3}	(d) 6.95×10^{-3}	101

(a) (Area compound + area internal standard) × weight compound
(b) Bulk relative weight ratio + reference relative weight ratio × 100
(c) Results of duplicate analysis
(d) Results of triplicate analysis

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

APPENDIX G

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

APPENDIX G. PREPARATION AND CHARACTERIZATION

I. Studies Conducted at the Analytical Chemistry Laboratory

A. Formulated diet homogeneity

1. **Preparation and sampling procedure:** A 1.2012-g weight of phenylephrine hydrochloride was transferred to a tared 250-ml beaker and thoroughly mixed by spatula with 25 g of feed. About 25 g more feed was added to the beaker, and the contents were again thoroughly mixed.

   This operation was repeated with two additional 25-g batches of feed so that the final weight of the premix was 100 g.

   Undosed rodent feed (700 g) was layered in the bottom of a Patterson-Kelly® blender; the 100-g premix was added in roughly equal amounts to both sides of the blender. The fine residue adhering to the beaker was taken up by 100 g of feed stirred in the beaker for a few seconds and added to the blender. After an additional 600 g of feed was layered over the premix, the blender ports were sealed. The target concentration of phenylephrine hydrochloride in the finished blend was 800.8 ppm.

   Mixing was conducted for 15 minutes with the intensifier bar for the first 5 minutes. At the end of the 15-minute mixing period, about 50 g of blended feed was sampled from the upper left- and right-hand ports and from the bottom discharge port.

   Duplicate weighings (20 ± 0.01 g) of each sample were transferred to individual 200-ml centrifuge bottles.

2. **Analysis:** Samples were extracted with 100 ml of a methanol:acetic acid (99:1) mixture by sonication for 30 seconds and shaken for 15 minutes on a New Brunswick® gyrotory shaker set at 300 rpm. After the extract was clarified by centrifugation at 2,000 rpm for 5 minutes, a few milliliters of solution was filtered through a 0.5-µ Millipore syringe filter. The phenylephrine hydrochloride content of the filtrate was determined with the high-performance liquid chromatographic system described below:

   Instrument: Waters Associates ALC202 Liquid Chromatograph
   Attenuation: 0.05 AU full scale
   Column: µBondapak C_{18}; 300 mm × 4 mm ID stainless steel
   Mobile phase
   Pump A: 5 mM sodium lauryl sulfate in methanol:acetic acid (99:1)
   Pump B: 5 mM sodium lauryl sulfate in water:acetic acid (99:1)
   Mobile phase ratio: 40% A:60% B
   Detector: Waters Model 440, 280 nm filter
   Volume injected: 16 µl
   Flow rate: 1 ml/min
   Retention time: 10.3 min

3. **Quality control:** Duplicate injections of duplicate extracts were analyzed. Recovery of chemical was determined in triplicate, with freshly spiked feed at the same level as the samples and assayed with the samples. Linearity of detector response was evaluated with standard solutions prepared in blank feed extract.

4. **Results**

Sampling Location	Concentration of Phenylephrine Hydrochloride (ppm) (a,b)	Percent Recovery
Right	800	
	803	(c) 100.0 ± 0.2(δ)
Left	827	
	797	101.2 ± 1.9(δ)
Bottom	777	
	802	98.5 ± 1.5(δ)

(a) Results corrected for zero-time recovery yield of 98.2% ± 3.2(δ)% (n=6)
(b) Target concentration of chemical in feed, 800.8 ppm
(c) Error values are deviations from the mean.

5. **Conclusions:** The results of analysis of phenylephrine hydrochloride blended with rodent feed at a concentration of 800 ppm showed a variation in actual concentration of ± 1.5% of target concentration between three sampling points after being mixed by the technique described.

B. Formulated diet stability

1. **Sample preparation and storage:** From the phenylephrine hydrochloride feed blend described in Sections I.A.2. and I.A.3. of this appendix, eight samples (20 g ± 0.01 g) were transferred to individual 200-ml centrifuge bottles and sealed with screw caps. Duplicate bottles were stored at −20°, 5°, 25°, or 45° C for 2 weeks.

2. **Extraction and analysis:** The analysis procedure was the same as in Section I.A.2. of this appendix except the extracting solvent was methanol:acetic acid (95:5), and a Burrell Wrist-Action® shaker was used instead of the gyrotory shaker.

3. **Quality control:** Duplicate weighed samples were analyzed. Recovery of phenylephrine hydrochloride was determined in triplicate with freshly spiked feed at the same concentration as samples and assayed with the samples. Linearity of the detector response was evaluated with standard solutions prepared in blank feed extract.

4. **Results: Two-week stability in feed**

Storage Temperature	Concentration of Phenylephrine Hydrochloride (ppm) (a,b)	Percent Recovery
−20° C	808	
	813	(c) 101.2 ± 0.3
5° C	810	
	803	100.8 ± 0.5
25° C	775	
	775	96.8 ± 0
45° C	784	
	780	97.7 ± 0.3

(a) No recovery correction was applied to the analysis values, since the spiked recovery yield of 101.1% ± 0.5% was within the analytical error of the test.
(b) Target concentration of chemical in feed was 800.8 ppm.
(c) Error values are deviations from the mean.

5. **Conclusions:** Phenylephrine hydrochloride at 800 ppm in feed exhibited no measurable loss in stability after 2 weeks at temperatures up to 5° C. Although there was a slight downward trend (3%) in stability under 25° C and 45° C storage, the decrease was not considered significant because of the analytical error (± 2%).

II. Analysis of Formulated Diets for Mixing Homogeneity at the Study Laboratory

A. Preparation and sampling: For each dietary concentration, the premix was prepared by weighing a quantity of the bulk chemical (a 1-week supply of formulated diet) and transferring the weighed chemical to a mortar containing 25-50 g feed. The compound and feed were thoroughly mixed and then transferred to a tared beaker containing approximately 100 g of feed. An additional portion of feed was added to adjust the premix weight to 300 g. The premix was mixed thoroughly with a spatula.

Bulk mixing was performed in a Patterson-Kelly® twin-shell stainless steel blender fitted with an intensifier bar. The 2,500-ppm and 1,250-ppm formulated diets were blended in an 8-qt and a 1-ft^3 blender, respectively. For each formulation, the appropriate weight of undosed feed (4,000 g and 16,200 g for the 2,500-ppm and 1,250-ppm formulations, respectively) was accurately weighed and transferred in four portions to both sides of the blender. The premix was added in roughly equal amounts to both sides of the blender. For the 2,500-ppm formulation, the fine residue adhering to the beaker was taken up by using the premix beaker to transfer equal amounts of the remaining feed to both sides of the blender. The blender ports were sealed, and mixing was conducted for 15 minutes with the intensifier bar for the first 5 minutes.

Three samples were taken from each of the 1,250-ppm and 2,500-ppm diets. About 50 g of subsurface mixture was taken from the upper left- and right-hand ports and from the discharge port of the twin-shell blender. Duplicate 10-g samples were analyzed.

B. Analysis: Samples were extracted with 100.0 ml of methanol:acetic acid (99:1) by being shaken for 20 minutes on a Kraft shaker and centrifuged for 10 minutes in a Beckman Centrifuge at 2,000 rpm. The extract was filtered and loaded into sampling vials and analyzed by high-performance liquid chromatography.

Instrument: Varian 5000 HPLC with 8000 auto sampler UV 500 variable wavelength detector and Varian recorder
Detector: 276 nm
Solvent system: 5 mM sodium dodecyl sulfate in a mixture of 1% acetic acid, 39.5% methanol, and 59.5% water
Flow rate: 1.6 ml/min
Retention time: 28 min

C. Quality control measures: Duplicate injections of duplicate extracts were analyzed. Recovery was determined in duplicate, with freshly spiked NIH 07 Rat and Mouse Ration at the same concentration as the samples and assayed with the samples. Linearity of detector response was evaluated with standard solutions prepared in blank feed extract.

D. Results

Sample Location	Target Concentration (ppm)	Determined Concentration (ppm) (a)	Percent of Target
Bottom	2,500	2,310	92.4
Upper right	2,500	2,380	95.2
Upper left	2,500	2,570	102.8
Batch	2,500	2,510	100.4
Bottom	1,250	1,200	96.0
Upper right	1,250	1,200	96.0
Upper left	1,250	1,190	94.8
Batch	1,250	1,210	96.8

(a) Results of duplicate analysis

E. Conclusions: All dietary concentrations were within ± 10% of the target value.

APPENDIX H

METHODS OF ANALYSIS OF FORMULATED DIETS

APPENDIX H. METHODS OF ANALYSIS

I. Study Laboratory

Procedure: Approximately 10 g of accurately weighed feed was placed in a 250-ml centrifuge bottle and extracted with 100 ml of methanol:acetic acid (95:5) by being shaken for 15 minutes on a Kraft shaker. The extracts were clarified by centrifugation for 10 minutes at 2,000 rpm on a Beckman TJ-6 centrifuge. The extracts were then filtered through 0.45-μ swinny-type filters directly into 2.0-ml auto sampling vials and injected in triplicate on a high-performance liquid chromatograph under the following conditions:

Instrument: Varian 5030 or Varian 5060 with Vista 401
Column: Waters μBondapak C_{18} 300 mm × 4 mm with a Whatman CO:PELL C_{18} guard column or ALTEX Ultrasphere ODS 5 μ 150 mm× 4.6 mm with a Whatman CO:PELL 70 mm × 4.9 mm guard column
Detector: 250 or 280 nm
Mobile phase: Water with 1% acetic acid:methanol with 1% acetic acid, (90:10, 80:20, or 60:40) or methanol:water (50:50) with 1% acetic acid and 5 mM sodium lauryl sulfate added

II. Analytical Chemistry Laboratory

A. Preparation of spiked feed standards: An extractant solution was prepared by diluting 50 ml of reagent-grade glacial acetic acid to 1,000 ml of methanol in a volumetric flask.

Two standard solutions of phenylephrine hydrochloride were prepared independently in extractant solution. These solutions were diluted with extractant solution to make four additional standards. Aliquots (10 or 20 ml) of the six standard solutions were pipetted into individual 200-ml centrifuge bottles containing 10 g of undosed feed to make spiked feed standards bracketing the specified concentration range of the referee sample. One 200-ml centrifuge bottle containing 10 g of undosed feed was treated with 10 or 20 ml of extractant solution for use as a blank. The spiked feed standards and the feed blank were sealed and allowed to stand overnight at room temperature before analysis.

B. Preparation of formulated diet sample: Triplicate weights of the referee feed sample (approximately 10 g weighed to the nearest 0.001 g) were transferred to individual 200-ml centrifuge bottles. Extractant solution (10 or 20 ml) was pipetted into each sample; the bottles were sealed and allowed to stand overnight at room temperature before analysis.

C. Analysis: Extractant solution was pipetted into each blank, standard, and referee sample bottle; the bottles were shaken at maximum stroke for 30 minutes on a wrist-action shaker. After centrifugation for 10 minutes, an aliquot of each extract was filtered through a 0.5-μ Millipore filter. The concentration of phenylephrine hydrochloride in the filtered solutions was determined by the high-performance liquid chromatographic system described below.

System: Waters Model 6000A Pump or Varian Model 5020 Solvent Delivery System
WISP Model 710 or Rheodyne Model 7125 Injector
Waters Model 440 Detector at 280 nm, 0.1 AUFS
Column: Waters μBondapak C_{18}, 300 mm × 3.9 mm ID, with a Whatman CO:PELL ODS guard column, 72 mm × 2.3 mm ID
Mobile phase: A:B, 20:80 or 60:40
A: 5 mM sodium lauryl sulfate in methanol:acetic acid (99:1)
B: 5 mM sodium lauryl sulfate in water:acetic acid (99:1)
Flow rate: 1.0 ml/min
Volume injected: 20 or 25 μl

D. **Quality assurance measures:** The referee feed sample was analyzed in triplicate, and the undosed feed sample was analyzed once. Individually spiked portions of the diet (six levels bracketing the specified concentration range of the referee sample) were prepared from two independently weighed standards and were used to obtain standard data. Duplicate injections of each standard and sample were made into the chromatograph in a random order.

APPENDIX I

RESULTS OF ANALYSIS OF FORMULATED DIETS

TABLE I1. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

Date Mixed	Determined Concentration (a) of Phenylephrine Hydrochloride in Feed for Target Concentration (ppm) 620	1,250	2,500
11/03/80	620	1,240	2,500
12/15/80	(b) 610	1,290	2,420
01/12/81	620	1,130	2,540
04/20/81	640	1,250	2,400
06/01/81	630	1,240	2,380
07/13/81	620	1,270	2,520
10/05/81	630	1,370	2,640
11/02/81	640	1,340	2,680
01/18/82	600	1,290	2,400
02/08/82	630	1,270	2,560
04/12/82	640	1,330	2,660
06/07/82	630	1,240	2,510
07/19/82	630	1,270	2,690
Mean (ppm)	626	1,272	2,531
Standard deviation	11.9	59.1	111.0
Coefficient of variation (percent)	1.9	4.6	4.4
Range (ppm)	600-640	1,130-1,370	2,380-2,690
Number of samples	13	13	13

(a) Average of results of duplicate analysis
(b) Result of a single analysis

TABLE I2. RESULTS OF REFEREE ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm) Study Laboratory (a)	Referee Laboratory (b)
11/03/80	620	620	610
10/05/81	620	630	610
06/07/82	2,500	2,510	2,510
07/19/82	1,250	1,270	1,230

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

APPENDIX J

SENTINEL ANIMAL PROGRAM

APPENDIX J. SENTINEL ANIMAL PROGRAM

I. Methods

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

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

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

II. Results

Results are presented in Table J1.

TABLE J1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE (a)

Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS		
6	--	None positive
12	--	None positive
18	7/9	Sendai
24	8/10	Sendai
MICE		
6	--	None positive
12	--	None positive
18	5/10	Sendai
	2/10	MHV
24	6/8	Sendai

(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, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX K

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

TABLE K1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE

	Control		620 ppm				1,250 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
6	15	300	13	278	0.9	29	14	251	0.9	70
11	16	355	16	339	1.0	29	15	306	0.9	61
12	15	359	16	345	1.1	29	15	312	1.0	60
19	15	398	15	383	1.0	24	14	346	0.9	51
23	16	423	15	408	0.9	23	14	373	0.9	47
29	16	429	16	412	1.0	24	15	381	0.9	49
33	16	439	16	422	1.0	24	16	391	1.0	51
38	17	444	16	422	0.9	24	14	392	0.8	45
42	15	454	15	438	1.0	21	17	409	1.1	52
46	16	455	15	435	0.9	21	16	418	1.0	48
51	16	460	15	440	0.9	21	14	416	0.9	42
55	15	461	16	446	1.1	22	16	425	1.1	47
59	17	462	17	449	1.0	23	17	427	1.0	50
63	14	470	15	452	1.1	21	15	436	1.1	43
68	15	466	14	447	0.9	19	15	435	1.0	43
72	14	462	14	447	1.0	19	14	431	1.0	41
76	14	454	14	443	1.0	20	14	429	1.0	41
81	14	463	14	450	1.0	19	14	423	1.0	41
85	14	453	14	441	1.0	20	15	424	1.1	44
89	14	452	15	445	1.1	21	15	426	1.1	44
93	15	448	15	446	1.0	21	15	425	1.0	44
97	14	441	14	446	1.0	19	12	422	0.9	36
101	13	437	13	426	1.0	19	13	415	1.0	39
Mean	15.0	434	14.9	420	1.0	22	14.7	396	1.0	47
SD (d)	1.1		1.0		0.1	3	1.2		0.1	8
CV (e)	7.3		6.7		10.0	13.6	8.2		10.0	17.0

(a) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Milligrams of phenylephrine hydrochloride consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE K2. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE

	Control		620 ppm				1,250 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
6	9	181	10	178	1.1	35	9	167	1.0	67
11	11	205	11	203	1.0	34	10	190	0.9	66
12	10	205	10	204	1.0	30	10	192	1.0	65
19	10	218	10	215	1.0	29	10	206	1.0	61
23	10	227	10	225	1.0	28	10	216	1.0	58
29	10	230	10	226	1.0	27	10	215	1.0	58
33	10	234	10	232	1.0	27	10	223	1.0	56
38	11	239	10	236	0.9	26	10	229	0.9	55
42	10	246	12	242	1.2	31	10	232	1.0	54
46	11	251	10	244	0.9	25	10	237	0.9	53
51	11	259	10	249	0.9	25	11	240	1.0	57
55	12	265	12	256	1.0	29	12	246	1.0	61
59	12	278	12	264	1.0	28	11	253	0.9	54
63	11	289	11	274	1.0	25	11	260	1.0	53
68	12	299	11	283	0.9	24	11	266	0.9	52
72	11	305	9	291	0.8	19	11	276	1.0	50
76	11	308	11	295	1.0	23	11	278	1.0	49
81	11	311	11	298	1.0	23	12	284	1.1	53
85	10	317	10	279	1.0	22	11	293	1.1	47
89	11	321	11	310	1.0	22	12	300	1.1	50
93	10	324	12	317	1.2	23	12	311	1.2	48
97	11	322	10	316	0.9	20	10	314	0.9	40
101	10	322	11	317	1.1	22	11	312	1.1	44
Mean	10.7	268	10.6	259	1.0	26	10.7	250	1.0	54
SD (d)	0.8		0.8		0.1	4	0.8		0.1	7
CV (e)	7.5		7.5		10.0	15.4	7.5		10.0	13.0

(a) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Estimate milligrams of phenylephrine hydrochloride consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE K3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE

	Control		1,250 ppm				2,500 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
2	3	25.3	3	24.6	1.0	152	3	23.9	1.0	314
8	4	31.3	3	30.0	0.8	125	4	29.3	1.0	341
12	4	33.1	3	31.2	0.8	120	3	30.3	0.8	248
19	4	35.1	3	33.3	0.8	113	3	31.4	0.8	239
21	4	36.8	4	35.5	1.0	141	3	34.1	0.8	220
25	4	38.2	4	36.8	1.0	136	4	35.1	1.0	285
30	4	38.4	4	36.9	1.0	136	3	35.8	0.8	209
35	4	39.3	4	37.4	1.0	134	4	36.1	1.0	277
40	5	38.5	4	36.0	0.8	139	3	35.0	0.6	214
44	4	38.0	4	35.1	1.0	142	4	34.8	1.0	287
48	4	41.0	4	37.6	1.0	133	2	35.4	0.5	141
53	5	41.3	4	37.7	0.8	133	4	35.7	0.8	280
57	6	40.7	4	37.1	0.7	135	4	35.9	0.7	279
61	5	42.0	4	38.7	0.8	129	4	36.4	0.8	275
65	4	42.0	4	38.6	1.0	130	4	36.7	1.0	272
70	4	41.6	4	37.5	1.0	133	4	36.2	1.0	276
74	4	41.3	4	37.8	1.0	132	4	36.6	1.0	273
78	4	40.5	4	36.7	1.0	136	4	36.5	1.0	274
83	4	41.8	4	36.0	1.0	139	4	36.4	1.0	275
87	2	39.7	3	36.2	1.5	104	3	35.8	1.5	209
91	4	40.7	4	36.6	1.0	137	4	35.8	1.0	279
95	4	38.8	4	36.3	1.0	138	4	35.2	1.0	284
99	4	37.9	4	36.4	1.0	137	4	34.6	1.0	289
103	4	37.0	3	35.2	0.8	107	4	33.3	1.0	300
Mean	4.1	38.3	3.8	35.6	0.9	132	3.6	34.4	0.9	264
SD (d)	0.7		0.4		0.2	11	0.6		0.2	42
CV (e)	17.1		10.5		22.2	8.3	16.7		22.2	15.9

(a) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Milligrams of phenylephrine hydrochloride consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE K4. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF PHENYLEPHRINE HYDROCHLORIDE

	Control		1,250 ppm				2,500 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
2	3	19.4	3	19.4	1.0	193	4	19.2	1.3	521
8	3	23.3	4	22.9	1.3	218	3	22.9	1.0	328
12	3	25.1	3	24.8	1.0	151	3	24.6	1.0	305
19	3	27.5	3	26.5	1.0	142	3	26.8	1.0	280
21	3	30.4	3	28.4	1.0	132	4	29.2	1.3	342
25	3	32.2	4	29.3	1.3	171	3	30.6	1.0	245
30	3	32.6	3	30.6	1.0	123	3	30.6	1.0	245
35	4	34.6	4	33.0	1.0	152	4	33.0	1.0	303
40	2	34.5	3	32.7	1.5	115	3	32.6	1.5	230
44	3	34.7	3	33.1	1.0	113	4	33.6	1.3	298
48	4	37.0	4	35.7	1.0	140	4	35.6	1.0	281
53	3	37.6	4	36.2	1.3	138	4	36.2	1.3	276
57	3	37.3	3	35.3	1.0	106	3	35.7	1.0	210
61	4	39.6	4	37.0	1.0	135	4	37.1	1.0	270
65	4	40.0	4	37.7	1.0	133	4	37.6	1.0	266
70	3	39.1	3	36.3	1.0	103	3	35.9	1.0	209
74	4	39.4	4	37.3	1.0	134	4	36.6	0.9	239
78	3	39.3	3	37.3	1.0	101	4	36.4	1.3	275
83	3	40.7	4	38.0	1.3	132	3	36.3	1.0	207
87	4	38.8	3	37.1	0.8	101	3	35.9	0.8	209
91	3	38.7	4	36.6	1.3	137	4	35.7	1.3	280
95	4	39.0	4	36.9	1.0	136	3	35.1	0.8	214
99	4	39.1	4	37.2	1.0	134	4	34.3	1.0	292
103	3	37.7	3	35.9	1.0	104	4	34.4	1.3	291
Mean	3.3	34.9	3.5	33.1	1.1	135	3.5	32.7	1.1	276
SD (d)	0.6		0.5		0.2	28	0.5		0.2	65
CV (e)	18.2		14.3		18.2	20.7	14.3		18.2	23.6

(a) Grams of feed removed from feed hopper per animal per day. Not corrected for scatter.
(b) Grams of feed per day for the dosed group divided by that for the controls
(c) Milligrams of phenylephrine hydrochloride consumed per day per kilogram of body weight
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

APPENDIX L

PUPIL MEASUREMENTS AND SELECTED ORGAN WEIGHTS IN THE TWELVE-WEEK FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

TABLE L1. PUPIL MEASUREMENTS FOR RATS IN THE TWELVE-WEEK FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE (a)

Concentration (ppm)	Pupil Size (mm) Left	Right	Combined
MALE			
0	1.82 ± 0.35 (9)	1.41 ± 0.29 (9)	1.62 ± 0.37
1,250	(b) 1.35 ± 0.22 (10)	1.32 ± 0.34 (10)	1.34 ± 0.28
2,500	(b) 1.18 ± 0.18 (10)	1.33 ± 0.26 (10)	(c) 1.26 ± 0.23
5,000	1.53 ± 0.44 (9)	1.40 ± 0.37 (9)	1.48 ± 0.40
10,000	1.41 ± 0.41 (7)	1.31 ± 0.63 (8)	1.36 ± 0.52
20,000	(b) 0.78 ± 0.21 (4)	1.06 ± 0.60 (5)	(b) 0.93 ± 0.32
FEMALE			
0	1.63 ± 0.62 (10)	1.37 ± 0.60 (10)	1.50 ± 0.61
1,250	1.37 ± 0.32 (10)	1.28 ± 0.27 (10)	1.33 ± 0.30
2,500	1.44 ± 0.18 (9)	1.28 ± 0.25 (9)	1.36 ± 0.23
5,000	1.70 ± 0.16 (9)	(d) 1.26 ± 0.13 (9)	(d) 1.48 ± 0.27
10,000	(b) 0.99 ± 0.24 (7)	(c) 0.91 ± 0.08 (8)	(b) 0.95 ± 0.17
20,000	1.27 ± 0.06 (3)	1.03 ± 0.53 (8)	(c) 1.09 ± 0.46

(a) Mean in millimeters ± standard deviation (number of observations); n for the combined = sum of the n's for the left and right. P values are versus the controls by Dunnett's test. Pupil size was determined by measuring pupil diameter on photographs of animals taken during week 12 of the study.
(b) $P<0.01$
(c) $P<0.05$
(d) Excludes one value of 5.0 mm in an eye regarded as diseased

TABLE L2. ABSOLUTE AND RELATIVE ADRENAL GLAND AND HEART WEIGHTS OF RATS IN THE TWELVE-WEEK FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE

Concentration (ppm)	Adrenal Gland Absolute (a)	Relative (b)	Heart Absolute (a)	Relative (b)
MALE				
0	41.1 ± 4.75 (10)	0.11 ± 0.01 (10)	950 ± 83.0 (10)	2.62 ± 0.20 (10)
20,000	35.4 ± 6.95 (6)	(c) 0.28 ± 0.06 (6)	(c) 652 ± 48.5 (6)	(c) 5.21 ± 0.74 (6)
FEMALE				
0	54.0 ± 7.32 (10)	0.26 ± 0.04 (10)	613 ± 31.0 (10)	2.90 ± 0.09 (10)
20,000	(c) 36.3 ± 8.83 (10)	(d) 0.34 ± 0.07 (10)	(c) 531 ± 38.3 (10)	(c) 4.98 ± 0.35 (10)

(a) Mean in milligrams ± standard deviation (number of observations)
(b) Mean in milligrams per gram ± standard deviation
(c) $P<0.001$ in a *t*-test comparison with the controls
(d) $P=0.006$ in a *t*-test comparison with the controls

TABLE L3. PUPIL MEASUREMENTS FOR MICE IN THE TWELVE-WEEK FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE (a)

Concentration (ppm)	Pupil Size (mm)		
	Left	Right	Combined
MALE			
0	1.20 ± 0.31 (10)	1.07 ± 0.19 (9)	1.14 ± 0.27
1,250	1.41 ± 0.85 (10)	1.68 ± 0.92 (10)	1.54 ± 0.87
2,500	1.07 ± 0.24 (10)	1.37 ± 0.33 (10)	1.22 ± 0.32
5,000	1.59 ± 0.77 (10)	(b) 1.95 ± 0.83 (10)	(b) 1.77 ± 0.80
10,000	1.65 ± 0.48 (8)	1.59 ± 0.22 (7)	1.62 ± 0.37
20,000	1.05 ± 0.21 (2)	1.54 ± 0.23 (5)	1.40 ± 0.32
FEMALE			
0	1.05 ± 0.27 (6)	1.31 ± 0.46 (10)	1.18 ± 0.39
1,250	1.04 ± 0.29 (10)	1.09 ± 0.23 (9)	1.06 ± 0.26
2,500	1.06 ± 0.14 (10)	1.21 ± 0.19 (10)	1.14 ± 0.18
5,000	1.36 ± 0.80 (10)	1.63 ± 0.85 (10)	1.49 ± 0.82
10,000	1.26 ± 0.22 (10)	1.45 ± 0.36 (10)	1.35 ± 0.31
20,000	1.39 ± 0.15 (8)	1.57 ± 0.27 (7)	1.47 ± 0.23

(a) Mean in millimeters ± standard deviation (number of observations); n for the combined = sum of the n's for the left and right. P values are versus the controls by Dunnett's test. Pupil size was determined by measuring pupil diameter on photographs of animals taken during week 12 of the study.
(b) $P<0.01$; all other comparisons were not significant.

TABLE L4. ABSOLUTE AND RELATIVE ADRENAL GLAND AND HEART WEIGHTS OF MICE IN THE TWELVE-WEEK FEED STUDIES OF PHENYLEPHRINE HYDROCHLORIDE (a)

Concentration (ppm)	Adrenal Gland		Heart	
	Absolute (a)	Relative (b)	Absolute (a)	Relative (b)
MALE				
0	4.33 ± 1.07 (10)	0.13 ± 0.03 (10)	159.8 ± 17.89 (10)	4.79 ± 0.63 (10)
20,000	(c) 9.07 ± 1.33 (7)	(c) 0.37 ± 0.08 (7)	(d) 139.3 ± 20.28 (7)	5.65 ± 1.38 (7)
FEMALE				
0	8.82 ± 1.99 (10)	0.34 ± 0.08 (10)	125.5 ± 10.98 (10)	4.37 ± 0.74 (10)
20,000	9.98 ± 2.75 (10)	(d) 0.44 ± 0.10 (10)	116.4 ± 12.01 (10)	(c) 5.81 ± 0.58 (10)

(a) Mean in milligrams ± standard deviation (number of observations)
(b) Mean in milligrams per gram ± standard deviation
(c) $P<0.001$ in a *t*-test comparison with the controls
(d) $P<0.05$ in a *t*-test comparison with the controls

APPENDIX M

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

Meal Diet: September 1980 to October 1982

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

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

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

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

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

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

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

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

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.22 ± 1.07	22.6-26.3	24
Crude fat (percent by weight)	5.09 ± 0.46	4.2-6.0	24
Crude fiber (percent by weight)	3.42 ± 0.39	2.4-4.2	24
Ash (percent by weight)	6.63 ± 0.38	5.97-7.42	24
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,108 ± 1,093	9,100-14,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	19.0 ± 2.73	16.0-26.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.25 ± 0.15	1.10-1.53	24
Phosphorus (percent)	0.99 ± 0.08	0.84-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

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

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

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.41 ± 0.15	0.13-0.93	24
Cadmium (ppm) (a)	<0.1		24
Lead (ppm)	1.07 ± 0.73	0.27-2.93	24
Mercury (ppm) (a)	< 0.05		24
Selenium (ppm)	0.29 ± 0.07	0.16-0.48	24
Aflatoxins (ppb) (a,b)	<10	<5.0-<10.0	24
Nitrate nitrogen (ppm) (c)	9.18 ± 4.33	0.6-18.0	24
Nitrite nitrogen (ppm) (c)	1.99 ± 1.30	0.4-5.3	24
BHA (ppm) (d,e)	5.10 ± 4.19	<0.4-15.0	24
BHT (ppm) (d)	3.05 ± 1.52	1.2-6.0	24
Aerobic plate count (CFU/g)	80,604 ± 48,850	7,000-210,000	24
Coliform (MPN/g) (f)	883 ± 908	<3-2,400	24
E. coli (MPN/g) (g)	8.0 ± 7.91	<3-23	23
E. coli (MPN/g) (h)	13.88 ± 30.00	<3-150	24
Total nitrosamines (ppb) (i,j)	6.69 ± 5.60	1.2-18.8	22
Total nitrosamines (ppb) (i,k)	14.55 ± 27.15	1.2-101.6	24
N-Nitrosodimethylamine (ppb) (i,l)	5.25 ± 5.33	0.6-16.8	22
N-Nitrosodimethylamine (ppb) (i,m)	13.02 ± 26.80	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 M4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) Detection limit 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) One batch contained less than 0.5 ppm. The value was <0.04 and it was produced on 4/27/81.
(f) MPN = most probable number
(g) Mean, standard deviation, and range exclude one value of 150 produced on 8/26/82.
(h) Mean, standard deviation, and range include the high value given 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 for batches produced on 1/26/81 and 4/27/81.
(k) Mean, standard deviation, and range include the very high values given in footnote j.
(l) Mean, standard deviation, and range exclude two very high values of 97.9 and 99 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) There was one observation above the detection limit. The value and the date it was obtained are given under the range.
(p) There were two observations above the detection limit. The values and the dates they were obtained are given under the range.
(q) Ten batches contained more than 0.05 ppm.

APPENDIX N

DATA AUDIT SUMMARY

APPENDIX N. DATA AUDIT SUMMARY

The experimental data, pathology materials, and tables for the NTP Technical Report on the toxicology and carcinogenesis studies of phenylephrine hydrochloride were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The audit was conducted during May and June of 1985 at the NTP Archives, Research Triangle Park, North Carolina, and at Dynamac Corporation, Rockville, Maryland, by the following Argus Research Laboratories, Inc., personnel: Jane E. Goeke, Ph.D.; Elizabeth L. Feussner, V.M.D., D.A.B.T.; Alan M. Hoberman, Ph.D.; Vanette M. Everline, B.S.; David M. Willet, B.S.; and Carol L. Veigle, HTL. Diana S. Copeland, D.V.M., D.A.C.V.P., Pathology Associates, Inc., also participated. The 2-year studies in F344/N rats and B6C3F$_1$ mice were conducted from September 1980 to October 1982 at Physiological Research Laboratories, under a subcontract with Tracor Jitco, Inc., for the National Toxicology Program. The full audit report has been reviewed by the NTP and is on file at the NTP Archives, Research Triangle Park, North Carolina.

The audit involved a review of all prestudy data (i.e., receipt, quarantine, randomization, animal identification) and a complete review of inlife data (body weights, clinical observations, dosing) for a random 10% of the animals in each group. In addition, all records of study animal deaths, moribund or terminal kills, tumors, lesions, and masses were verified. All available chemistry data were audited, and 10% of the dose calculations were verified. For the pathology portion of the audit, a slide/block match was conducted for all high dose and control animals; wet tissue examination and animal identification were performed on a random 10% sample of rats and mice, and gross observations and microscopic diagnoses were compared on Individual Animal Data Records of all rats and mice.

The inlife data for the 2-year studies of phenylephrine hydrochloride were found to be in generally good order. Minor discrepancies were noted concerning start and stop dates for dosing, calculations of body weights and feed consumption, and recording of the size and presence of masses in clinical observation and gross necropsy records. Essentially all chemistry data were present and verified.

In the audit of pathology data, untrimmed lesions were found in the wet tissues of 14/54 rats and 14/51 mice. Few of these were considered probable neoplasia, but this finding prompted a review for untrimmed lesions of the lung and liver from all groups of male and female mice. The results of this review have been incorporated into the pathology tables shown in this Technical Report. Lesions undiagnosed on slides were found in 11/67 rats and 13/47 mice. Each case consisted of more than 40 tissues on 10-13 slides, and most missed lesions were restricted to 1 tissue on 1 slide of each animal. Three of the undiagnosed rat lesions and two of the undiagnosed mouse lesions involved neoplasms in nontarget organs. Missed lesions were distributed between tissues and dose groups such that resolution would have no impact on the results of the studies; therefore, no further action was taken.

In summary, the audit of the data for the 2-year feed studies of phenylephrine hydrochloride revealed numerous minor discrepancies in records from the inlife portion of the studies and several untrimmed or undiagnosed lesions in the pathology materials. Those problems considered minor were not necessarily pursued to final conclusion but are listed in the full audit report. In conclusion, the data presented in the Technical Report are considered adequate to meet the objectives of these studies.

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