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TOXICOLOGY AND CARCINOGENESIS STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

(CAS NO. 55-31-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

NTP TECHNICAL REPORT

ON THE

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(CAS NO. 55-31-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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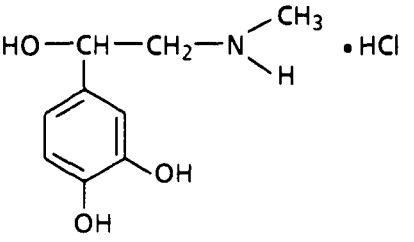
CONTENTS

APPENDIXES



l-EPINEPHRINE HYDROCHLORIDE

CAS No. 55-31-2

$C_9H_{13}NO_3 \cdot HCl$ Molecular weight 219.7

Synonyms for Epinephrine Hydrochloride: Adrenaline hydrochloride; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-benzenediol hydrochloride; (-)3,4-dihydroxy-α-((methylamino) methyl)benzyl alcohol hydrochloride; methylaminoethanol catechol hydrochloride

Trade Names for Epinephrine Formulations: Primatene® Mist; Sus-Phrine®; Epipen®; Supravenin Hydrochloride®; Bronkaid®

ABSTRACT

l-Epinephrine, an endogenous neurotransmitter hormone, is widely used for the treatment of allergic and respiratory disorders. Toxicology and carcinogenesis studies of epinephrine hydrochloride were conducted by exposing groups of F344/N rats and B6C3F$_1$ mice of each sex to an aerosol containing epinephrine hydrochloride for 14 days, 13 weeks, 15 months, or 2 years. During the 14-day and 13-week studies, control animals were exposed to dilute aerosols of hydrochloric acid (pH 2.8), whereas during the 15-month and 2-year studies, controls were exposed to aerosols of water. Genetic toxicology studies of epinephrine were conducted in *Salmonella typhimurium* and Chinese hamster ovary (CHO) cells.

Fourteen-Day Studies: Rats and mice were exposed to 0 or 12.5-200 mg/m^3 epinephrine hydrochloride. Deaths occurred in male rats exposed to 12.5 mg/m^3 or more and in females exposed to 25 mg/m^3 or more. Deaths of mice occurred at concentrations of 50 mg/m^3 or higher. Compound-related clinical signs included an increased respiratory rate in all groups of epinephrine-exposed rats and mice. At higher concentrations (100 and 200 mg/m^3), excessive lacrimation and dyspnea in rats and exaggerated visual and auditory reflexes in mice were observed.

Thirteen-Week Studies: Rats and mice were exposed to 0 or 2.5-40 mg/m^3 epinephrine hydrochloride. Deaths in rats and mice were not concentration related. Final mean body weights of chemically exposed and hydrochloric acid aerosol control rats and mice were generally similar. Increased respiratory rates were noted in rats and mice exposed to 40 mg/m^3. Heart and adrenal gland weights of rats and mice and liver weights of mice exposed to 40 mg/m^3 were greater than those of aerosol controls. Squamous metaplasia occurred in the respiratory epithelium of the nasal mucosa of rats and mice exposed to 40 mg/m^3. Degenerative lesions of the laryngeal muscle were seen in male and female rats exposed to 20 or 40 mg/m^3. Inflammation in the glandular stomach was seen in male and female mice exposed to 10, 20, and 40 mg/m^3, and uterine atrophy was seen in 7/10 female mice exposed to 40 mg/m^3.

Two-year studies were conducted by exposing groups of 60 rats of each sex to 0, 1.5, or 5 mg/m^3 epinephrine hydrochloride, 5 days per week for 103 weeks. Groups of 60 mice of each sex were exposed to 0, 1.5, or 3 mg/m^3 epinephrine hydrochloride, 5 days per week for 104 weeks. Use of these exposure concentrations represented a departure from the usual practice of utilizing doses equivalent to one-half the maximum tolerated dose (MTD) and the MTD for 2-year carcinogenicity studies. Thus, although the dose levels exceeded maximum human therapeutic use levels (normalized to body weight and surface area), they were less than one-half the MTD.

Fifteen-Month Studies: Results of hematologic analyses did not show compound-related changes. Absolute liver weights for exposed mice (3 mg/m^3) and rats (5 mg/m^3) and relative liver weights for exposed rats (5 mg/m^3) were significantly lower than those for controls. The absolute kidney weights for mice exposed to 3 mg/m^3 and the kidney weight to body weight ratio for male mice exposed to 3 mg/m^3 were significantly lower than those for controls. No compound-related lesions were seen in rats or mice.

Body Weights and Survival in the Two-Year Studies: Mean body weights and survival of exposed and control rats and mice were similar (survival, rats--male: control, 33/50; 1.5 mg/m^3, 27/50; 5 mg/m^3, 32/50; female: 32/50; 29/50; 30/50; mice--male: control, 33/50; 1.5 mg/m^3, 34/50; 3 mg/m^3, 36/50; female: 32/50; 35/50; 34/50).

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Suppurative inflammation of the nasal mucosa, dilatation of the nasal glands (Bowman's and septal), and hyperplasia of the respiratory epithelium were seen at increased incidences in male rats exposed to 5 mg/m^3 and in female rats exposed to 1.5 or 5 mg/m^3.

Hyaline degeneration of the olfactory epithelium in male mice and suppurative inflammation of the nasal passage and hyaline degeneration of the respiratory epithelium in female mice were increased in the 1.5 and 3 mg/m^3 groups compared with controls. No neoplasms seen in these studies were considered related to chemical exposure.

Genetic Toxicology: Salmonella gene mutation tests with *l*-epinephrine yielded negative results in strain TA100 in the presence of exogenous metabolic activation (S9) and equivocal results in the absence of S9. No mutagenic activity was observed in strains TA98, TA1535, or TA1537 with or without S9. The responses observed in the CHO cell assay for induction of sister chromatid exchanges were considered to be negative and equivocal in the presence and absence of S9 activation, respectively. *l*-Epinephrine did not induce chromosomal aberrations in CHO cells with or without S9.

Conclusions: Under the conditions of these 2-year studies, no carcinogenic effects were observed in male or female F344/N rats exposed to aerosols containing 1.5 or 5 mg/m^3 *l*-epinephrine hydrochloride for 2 years or in B6C3F$_1$ mice exposed to 1.5 or 3 mg/m^3 *l*-epinephrine hydrochloride for 2 years. However, these studies were considered to be *inadequate studies of carcinogenic activity* because the concentrations used, which were chosen to represent multiples of human therapeutic doses, were considered too low for the animals to have received an adequate systemic challenge from the compound.

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*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

SUMMARY OF THE TWO-YEAR INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Exposure concentrations			
0, 1.5, or 5 mg/m^3 *l*-epinephrine hydrochloride, 6 h/d, 5 d/wk	0, 1.5, or 5 mg/m^3 *l*-epinephrine hydrochloride, 6 h/d, 5 d/wk	0, 1.5, or 3 mg/m^3 *l*-epinephrine hydrochloride, 6 h/d, 5 d/wk	0, 1.5, or 3 mg/m^3 *l*-epinephrine hydrochloride, 6 h/d, 5 d/wk
Body weights in the 2-year study			
Exposed and control groups similar	Exposed and control groups similar	Exposed and control groups similar	Exposed and control groups similar
Survival rates in the 2-year study			
33/50; 27/50; 32/50	32/50; 29/50; 30/50	33/50; 34/50; 36/50	32/50; 35/50; 34/50
Nonneoplastic effects			
Suppurative inflammation of nasal passage; dilatation of nasal gland; hyperplasia of respiratory epithelium	Suppurative inflammation of nasal passage; dilatation of nasal gland; hyperplasia of respiratory epithelium	Hyaline degeneration of olfactory epithelium	Suppurative inflammation of nasal passage; hyaline degeneration of respiratory epithelium
Neoplastic effects			
None	None	None	None
Level of evidence of carcinogenic activity			
Inadequate study	Inadequate study	Inadequate study	Inadequate study

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

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

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of *l*-Epinephrine Hydrochloride is based on 13-week studies that began in November 1981 and ended in February 1982 and on 2-year studies that began in October 1982 and ended in October 1984 at Battelle Pacific Northwest Laboratories (Richland, WA).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on *l*-epinephrine hydrochloride on November 20, 1989, 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 *l*-EPINEPHRINE HYDROCHLORIDE

On November 20, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of *l*-epinephrine hydrochloride received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. D. Dietz, NIEHS, introduced the toxicology and carcinogenesis studies of *l*-epinephrine hydrochloride by reviewing the experimental design and results. He noted that there were no increases in incidence of neoplasia which were judged to be exposure related, although nonneoplastic degenerative inflammatory lesions of the nasal mucosa were seen at higher incidences in exposed rats and mice. Dr. S. Eustis, NIEHS, commented on how exposure concentrations were selected for the 2-year studies. Exposure concentrations were selected to represent approximately 3 and 10 times the doses received by humans given single aerosol exposures for the treatment of asthma and were arrived at on the basis of consultation with the nominating agency. He acknowledged that this rationale was a departure from usual procedures followed in selecting doses for carcinogenesis studies. He asked for the Panel's guidance on how the conclusions should be stated in the Technical Report and on whether the studies constitute a carcinogenicity study or a chronic toxicity study.

Dr. Gold, a principal reviewer, did not agree with the conclusions as originally presented in the Report, no evidence of carcinogenic activity. She said that all four studies should be termed inadequate studies of carcinogenic activity. As noted in the text, the high concentrations in rats and mice were approximately one-fourth and one-eighth, respectively, of the maximum tolerated dose (MTD); Dr. Gold therefore thought that the Report should be designated as something other than a carcinogenicity study. She suggested that a statement should be included in the Abstract and elsewhere emphasizing that the studies were conducted at exposure concentrations considerably below the MTD. Dr. Dietz commented that, on a body weight basis at their respective high concentrations, rats and mice received doses of *l*-epinephrine which were 10 and 20 times that of the human therapeutic dose. He noted that the reason higher concentrations of epinephrine were not used was to avoid the confounding variables associated with the potent pharmacologic action of the compound. He added that microscopic changes in the nasal mucosa were observed in both the 13-week and 2-year studies. Dr. Gold asked for discussion as to whether the occurrences of uterine neoplasms in female mice (endometrial stromal polyps or sarcomas) might be associated with chemical exposure, particularily if three adenocarcinomas of the uterus reported in the Appendix were included in the text table. Dr. Dietz said that the endometrial neoplasms and the adenocarcinomas had different tissues of origin and should not be combined.

Dr. Silbergeld claimed that the exposure concentrations used were insufficient to provide a good toxicology study and questioned how thoroughly nonneoplastic effects were examined, particularly in such target tissues as the adrenal glands and the nervous system. Dr. Eustis said that the target organs for histopathology quality assessment were considered to be the nasal cavity and lungs, although the adrenal glands and other tissues were examined.

Dr. Hayden, the second principal reviewer, thought that the study design appeared adequate because the exposure concentrations chosen were sufficient to cause damage to the nasal epithelium without affecting growth rates or survival for exposed rats or mice. He commented that no evidence of carcinogenesis was found.

SUMMARY OF PEER REVIEW COMMENTS (Continued)

Dr. Zeise moved that the Technical Report on *l*-epinephrine hydrochloride be accepted but with the conclusions for male and female rats and mice changed to inadequate studies of carcinogenic activity; Dr. Garman seconded the motion. Dr. Zeise said that her motion was based on the fact that the exposure concentrations selected were well below the MTD, as well as on uncertainty about whether the concentrations were adequate to represent human therapeutic doses. In the subsequent discussion, Dr. Silbergeld said that she was not convinced that the concentrations used were sufficient to elicit pharmacologic signs analogous to those seen in humans given a therapeutic dose. Dr. Klaassen stated that, according to the current definition of a carcinogenicity study, when negative results are obtained after chemical exposure and the doses are below an MTD, then the study is inadequate for detecting whether there is carcinogenic activity. The motion was accepted by 10 affirmative votes to 1 negative vote (Dr. Carlson).

I. INTRODUCTION

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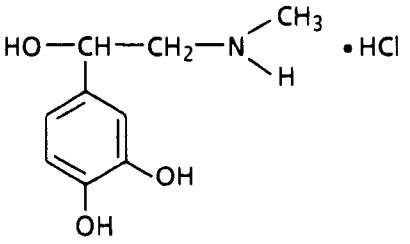

l-EPINEPHRINE HYDROCHLORIDE

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Synonyms for Epinephrine Hydrochloride: Adrenaline hydrochloride; 4-(1-hydroxy-2-(methylamino)ethyl)-1,2-benzenediol hydrochloride; (-)3,4-dihydroxy-α-((methylamino) methyl)benzyl alcohol hydrochloride; methylaminoethanol catechol hydrochloride
Trade Names for Epinephrine Formulations: Primatene® Mist; Sus-Phrine®; Epipen®; Supravenin Hydrochloride®; Bronkaid®

Physical Properties, Uses, Production, and Exposure

Epinephrine is an endogenous hormone derived from the adrenal gland of most animal species and occurring as the *levo*-isomer in mammals, including humans. Pharmacologically, it belongs to a class of β-phenylethylamine derivatives with sympathomimetic activity. Epinephrine is a crystalline material with a melting point of 157° C; it is readily soluble in water and sparingly soluble in absolute alcohol (Merck, 1983). The crystals gradually brown on exposure to light and air, and solutions undergo oxidation in the presence of oxygen and metals (copper, iron, and zinc), especially in neutral and alkaline solutions, to form adrenochrome (McLean, 1980, 1985; Martindale, 1982; Merck, 1983; AHFS, 1988). Stability in solution is increased upon acidification (pH 4.0-4.5), upon the addition of antioxidants (0.1% sodium bisulfite), or under an atmosphere of carbon dioxide or nitrogen (Harvey, 1975).

Epinephrine has a wide range of clinical uses in medicine and surgery based on its actions on blood vessels, the heart, and bronchial muscle (Weiner, 1985). The most common uses of epinephrine hydrochloride are to relieve respiratory distress due to bronchospasm, to provide rapid relief from hypersensitivity reactions to drugs and other allergens, to prolong the action of local anesthetics that possess inherent vasodilator activity, and to maintain arterial pressure during surgical anesthesia (Deterling et al., 1954; Takman et al., 1974; Weiner, 1985; PDR, 1989).

The wide use of epinephrine to treat bronchospasm associated with asthma (Harvey, 1975; Miller, 1978) has been replaced by other drug treatments that utilize epinephrine analogs with greater bronchodilator potency and fewer side effects or by agents that mediate a therapeutic response via different mechanisms (Wilson and McPhillips, 1978; Martindale, 1982; Barnes, 1989). In addition, chronic asthma is now viewed as a chronic inflammatory condition, and current therapy emphasizes the primary use of antiinflammatory agents either alone or in conjunction with other agents, such as epinephrine analogs, which act via bronchodilation (Martindale, 1982; Barnes, 1989). The rationale for this therapeutic approach is to treat the primary inflammatory lesion, which could otherwise result in subepithelial fibrosis, smooth muscle hypertrophy, and even death. Thus, continuous monotherapy with β_2 adrenoceptor agonists such as epinephrine could result in higher allergen doses caused by the

protective effect of such treatment and could develop to aggravated asthmatic reactions (Larsson et al., 1985). Between 1961 and 1966, a correlation between the widespread use of sympathomimetic bronchodialators to treat asthma and an increase in asthma mortality in 10- to 14-year-old children in Great Britian was noted with concern, but the sudden asthma-related deaths were later attributed to the disease instead of the treatment (Martindale, 1982). For severe, acute asthma, nebulized or injectable epinephrine is still indicated (Rakel, 1989). Although the routine, long-term clinical use of epinephrine has been discontinued, it is still available as an over-the-counter agent (Primatene® and Bronkaid®) for symptomatic relief of asthma (AHFS, 1988; PDR, 1989). Other respiratory disorders treated with epinephrine include viral croup, bronchitis, and emphysema (Kay, 1974; AHFS, 1988; Rakel, 1989).

Epinephrine (subcutaneous) is also the drug of choice in treating signs of anaphylactic reactions (hypotension, bronchospasm, and laryngeal edema). It has been used to treat a variety of other allergic disorders, including hay fever, giant urticaria, serum reaction, and serum sickness (Harvey, 1975; Rakel, 1989). Other clinical uses of epinephrine have included topical application to control superficial hemorrhages (hemostatic agent) during surgical procedures on the nose and throat and topical application to the eye in the treatment of primary open-angle glaucoma; in addition, it has been used to restore conduction (enhance cardiac automaticity) during complete heart block, to treat congenital (juvenile) congestive heart failure, to inhibit uterine contractions, to treat hypoglycemic reactions resulting from an overdose of insulin, to control gastrointestinal bleeding, and to increase muscular strength (intra-arterially) in patients with myasthenia gravis (Goldstein et al., 1974; Harvey, 1975; McLean, 1980, 1985; Weiner, 1985; AHFS, 1988; PDR, 1989; Rakel, 1989). Epinephrine has also been used to treat patients suffering from shock (Ellenhorn and Barceloux, 1988); this practice is discouraged because of the potential for an overdose (Weiner, 1985).

The original source of epinephrine for commercial use was bovine adrenal glands (Harvey, 1975; McLean, 1980, 1985). The biosynthesis of epinephrine has been extensively characterized and involves a sequence of five enzymatic reactions, starting with the hydroxylation of phenylalanine to tyrosine and ending with the methylation of norepinephrine to epinephrine (McLean, 1980; Horn, 1981; Cooper et al., 1982). Currently, the primary source for the drug epinephrine is via a synthetic method developed by Stolz in 1904 (Kay, 1974; Harvey, 1975; McLean, 1980, 1985). This Friedel-Crafts acylation reaction involves a condensation between catechol and chloracetyl chloride, followed by a reaction with methylamine to displace chlorine, and then a catalytic reduction of the carbonyl group. The racemic mixture is resolved by reaction with *d*-tartaric acid, followed by fractional crystallization of the diastereomers. Epinephrine hydrochloride is available as an injectable solution (1:1,000 or 1 mg/ml) to be administered subcutaneously or intramuscularly (0.2-1.0 ml) and as an aerosol (0.5% w/w = 5.5 mg/ml) to deliver approximately 0.22-0.25 mg epinephrine per treatment (PDR, 1989).

Total production of epinephrine hydrochloride in the United States during 1972-75 was estimated to exceed 4.5×10^5 g/year, imports are estimated to be 2.1×10^5 g/year, and total human exposure to exogenous epinephrine was estimated to be 5.8×10^5 g/year. More recent figures are not available. A National Occupational Hazard Survey estimated that approximately 7,694 workers were occupationally exposed to epinephrine hydrochloride during 1981-83 (NIOSH, 1989).

Pharmacologic Actions

As an endogenous sympathetic hormone located in the chromaffin cells of the adrenal medulla, epinephrine is involved in the homeostatic regulation of a wide variety of peripheral nervous system functions that include: peripheral excitatory action on smooth muscle (blood vessels and glands), peripheral inhibitory action on smooth muscle (gut, bronchial tree, and blood vessels), cardiac excitatory action, and metabolic and endocrine actions (McLean, 1980; Martindale, 1982; Weiner, 1985; AHFS, 1988). These changes are referred to collectively as the "fight or flight response." They are postulated to be mediated by four receptors (α_1, α_2, β_1, and β_2)

and occur in response to stress, physical activity, or generalized allergic reactions, all of which stimulate the splanchnic nerve innervating the adrenal medulla. The actions of epinephrine are believed to involve primarily the direct interaction of epinephrine with these receptors at pre- and postsynaptic sites; i.e., the pharmacologic effects are not the result of an indirect effect via the modulation of other neurotransmitters. Primary epinephrine-receptor interactions are postulated to result in smooth muscle excitation in cutaneous and pulmonary vessels (postsynaptic α_1); inhibition of epinephrine release from the nerve terminals resulting in depressed uterine and gastrointestinal motility (presynaptic α_2); increased fatty acid metabolism and positive cardiac inotropic and chronotropic stimulation (postsynaptic β_1); and enhanced glycogenolysis and inhibition of smooth muscle resulting in bronchodilation, increased blood flow into skeletal muscle, and depressed uterine and gastrointestinal motility (postsynaptic β_2) (Mayer, 1980; McLean, 1980; Weiner, 1985). The production of cyclic adenosine 3',5'-monophosphate (cyclic AMP) by the stimulation of adenylate cyclase is postulated to be the crucial step linking β_1- and β_2-receptor activation to functional and metabolic changes (Levitzki, 1988). Cyclic AMP is known to activate protein kinase enzymes that phosphorylate other enzymes, thereby altering their activity and changing events in the postsynaptic or effector cell. Although the molecular events following α-receptor stimulation are less well understood, they appear to involve the mobilization of Ca^{++} and/or formation of inositol triphosphate (α_1 receptors) and the inhibition of adenylate cyclase (α_2 receptors) (Weiner, 1985). Low levels of endogenously synthesized epinephrine within the mammalian brain have been confirmed (Cooper et al., 1982; Herregodts et al., 1989).

Major pharmacologic actions produced by epinephrine which have clinical application include the stimulation of heart rate (positive chronotropic action or enhancement of automaticity) and force of contraction (positive inotropic action); relaxation of musculature of the bronchi; dilation of arterioles of splanchnic and skeletal muscle beds; constriction of the vascular beds of the skin, mucosa, gastrointestinal tract, and kidney; increase in blood glucose, lactate, and free fatty acids; inhibition of the secretion of insulin; inhibition of uterine tone and contractions; reduction in intraocular pressure; inhibition of antigen-induced release of histamine; and the facilitation of neuromuscular transmission (Martindale, 1982; Weiner, 1985; AHFS, 1988). Other pharmacologic effects include increased cerebral blood flow, constriction of pulmonary vessels, relaxation of gastrointestinal smooth muscle, contraction of the splenic capsule, urine retention in the bladder, and increased respiratory rate and tidal volume. Antidiuretic effects via epinephrine-stimulated hypothalamic α and β receptors which result in sodium and water retention have also been reported (Smyth et al., 1985; Tsushima et al., 1985, 1986). Because epinephrine affects multiple receptors within and among a variety of tissues and because responses resulting from these receptor interactions may induce reflex responses, the net pharmacologic response is dependent on the dose, the presence of selective receptor blocking agents, and the preexisting physiologic state. Thus, the net effect of epinephrine in humans (0.5-1.5 mg) is to increase blood pressure via direct myocardial stimulation and vasoconstriction of vascular beds in the skin, mucosa, and kidney, which override a decrease in peripheral resistance in the skeletal muscle vasculature. This net pressor effect is later counteracted by a compensatory vagal discharge that brings blood pressure back into the normal range. By contrast, smaller doses (7 μg) elicit a drop in blood pressure, due to the selective action of epinephrine on the more sensitive skeletal muscle vasculature. The pulmonary circulation is an example where the net effect of epinephrine (increase in pulmonary pressure that may evolve to pulmonary edema) is not predictable, based on knowledge of the direct effect of epinephrine on the pulmonary vasculature (vasoconstriction). In this case, the net increase in pulmonary pressure results from the redistribution of blood from systemic to pulmonary circulation because of constriction of the great veins.

Absorption, Distribution, Metabolism, and Excretion

Although epinephrine is absorbed by all routes of exposure, it is not pharmacologically active after oral administration because it is rapidly conjugated and oxidized in the gastrointestinal mucosa and the liver before reaching the systemic circulation (Weiner, 1985; AHFS, 1988). Methyl substitution at the α-carbon ethylamine side chain or the absence of 3-hydroxyl ring substitution results in orally effective derivatives. Absorption from subcutaneous tissue occurs slowly, due to local vasoconstriction, but after intramuscular injection, absorption occurs rapidly, due to localized vasodilation at this site. Although systemic reactions may occur after exposure to large doses of epinephrine aerosols (from 1% solutions), the effects are largely restricted to the respiratory tract. Epinephrine is stable in blood but has a plasma half-life of about 2.5 minutes after intravenous administration, due primarily to its enzymatic destruction in the liver (Harvey, 1975; Weiner, 1985). Epinephrine is distributed throughout all parts of the body, with the exception of the brain (due primarily to the blood-brain barrier), after administration by all parenteral routes. The final enzymatic step in the biosynthesis of epinephrine involves the *N*-methylation of norepinephrine by phenylethanolamine-*N*-methyl transferase. This enzyme is largely restricted to the adrenal medulla; low levels of activity are reported in the heart and mammalian brain (Cooper et al., 1982; Herregodts et al., 1989).

The metabolism of epinephrine is mediated by two enzymes, which together are responsible for the production of six metabolites, including sulfate and glucuronide conjugates (Figure 1) (Crout et al., 1961; Goldstein et al., 1974; Mayer, 1980; McLean, 1980; Cooper et al., 1982; Weiner, 1985). Catechol-*O*-methyltransferase (COMT), a cytoplasmic enzyme located primarily in the liver and kidney, is responsible for extraneuronal metabolism and converts exogenous and endogenous epinephrine and its deaminated metabolites to *O*-methyl derivatives at the 3-hydroxy position of the benzene ring, whereas monoamine oxidase (MAO) located within the outer membrane of neuronal mitochondria of the heart and brain oxidatively deaminates intraneuronal epinephrine to an aldehyde that is either reduced to an alcohol metabolite (3,4-dihydroxyphenylglycol, minor pathway) or oxidized to an acid metabolite (3,4-dihydroxymandelic acid, major pathway). Although significant extraneuronal MAO has been identified, its importance relative to epinephrine metabolism is questionable (Cooper et al., 1982). Enzymatic products of COMT include metanephrine (from epinephrine), 3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid, from 3,4-dihydroxymandelic acid), and 3-methoxy-4-hydroxyphenylglycol (from 3,4-dihydroxyphenylglycol).

Most of the epinephrine that enters the circulation from the adrenal medulla or from exogenous sources is initially methylated by COMT to metanephrine, which may be conjugated to the sulfate or glucuronide (Mayer, 1980). Excretion is primarily via the urine as sulfate conjugates and, to a lesser extent, glucuronide conjugates (AHFS, 1988). A normal 24-hour urine sample from humans usually contains 100-200 µg metanephrine (representing part of the epinephrine released by the adrenal medulla), in addition to 2-5 µg of epinephrine. Metabolic transformation plays a relatively minor role in terminating the actions of endogenously liberated catecholamines, including epinephrine, at neuronal sites. A reuptake mechanism whereby epinephrine reenters the nerve terminal plays a more significant role in this regard (Cooper et al., 1982; Martindale, 1982; Morrow et al., 1987). Approximately 35% of an administered dose of epinephrine undergoes neuronal uptake, with larger amounts undergoing extraneuronal tissue uptake (Morrow et al., 1987).

Toxicity

Acute toxic responses to epinephrine are manifested primarily by exaggerated pharmacologic responses that primarily involve cardiovascular and metabolic function. Thus, the clinical approach to treatment usually involves pharmacologic intervention to counteract the cardiovascular effects of epinephrine with rapidly acting vasodilators such as nitrites (amylnitrite or glyceryl trinitrite) or sodium nitroprusside, α-adrenergic blocking agents such as phentolamine, or β-adrenergic blocking agents such as propanolol (Gleason et al., 1969; Martindale, 1982; Weiner,

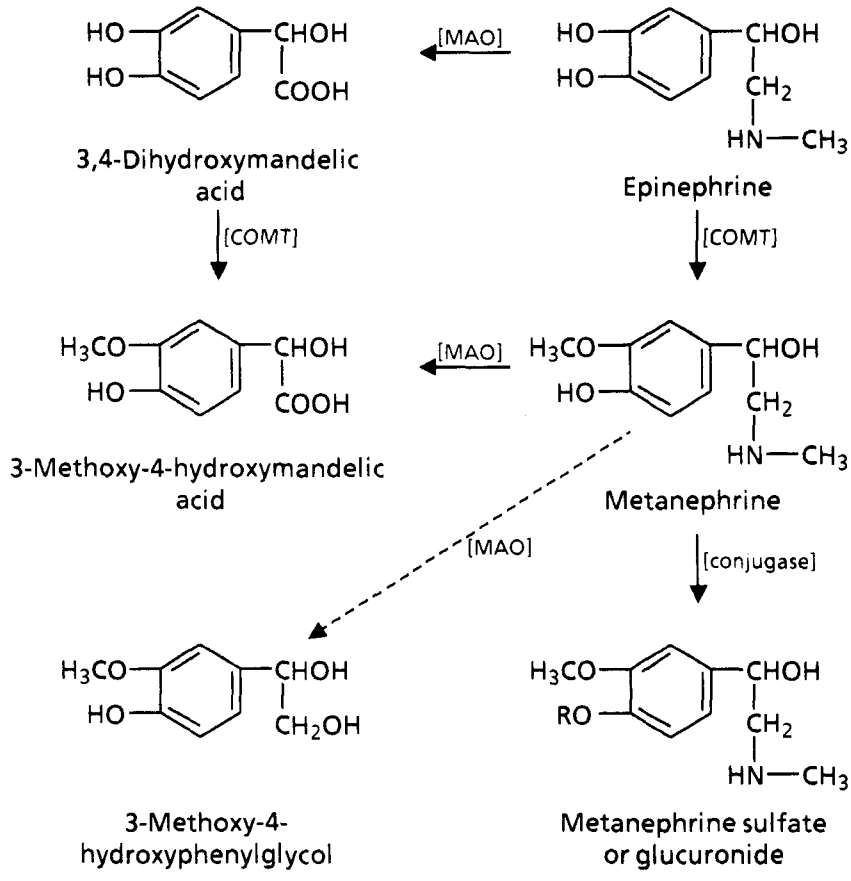

FIGURE 1. STEPS IN THE METABOLIC DISPOSITION OF EPINEPHRINE
(from Mayer, 1980; COMT = catechol-*O*-methyltransferase; MAO = monoamine oxidase)

1985). Brain function may be directly (respiratory stimulation) or indirectly (secondary to peripheral cardiorespiratory and/or metabolic effects) affected by epinephrine. Under normal circumstances, systemic or endogenous epinephrine secreted from the adrenal medulla functions primarily in the maintenance of homeostasis against physiologic stress and does not produce untoward effects (Bard, 1968; Guyton, 1986). This homeostasis can be disrupted, however, when neoplasms of the adrenal medulla develop, during altered metabolic states (hyperthyroidism), when the biologic activity of epinephrine or its metabolism/disposition is affected by other drug exposures, or during clinical states such as acute myocardial infarction resulting in increased levels of endogenous epinephrine (Hickler and Thorn, 1970; Ceremuzynski et al., 1978; Shapiro et al., 1984; Weiner, 1985; AHFS, 1988; Noronha-Dutra et al., 1988; PDR, 1989; Klein et al., 1989).

The subcutaneous and oral LD_{50} values for rats are 5 and 24 mg/kg, respectively (NIOSH, 1983). Epinephrine by the intravenous route was cited as being more lethal to male than to female rats (Astarabadi and Essex, 1952). Kato and Gillette (1965) reported that epinephrine induced a depression in microsomal enzyme activity in male, but not female, rats. Chance (1946) determined epinephrine hydrochloride LD_{50} values by using multiply housed (10 per cage) and singly housed mice and noted that aggregation enhanced the lethality of exogenous epinephrine; i.e., LD_{50} values for singly housed mice were 3.96-4.58 mg/kg compared with values of 1.98-2.17 mg/kg for multiply housed animals.

The most serious effects of short-term epinephrine toxicity are rapid and large increases in blood pressure, cerebral hemorrhage, pulmonary arterial hypertension resulting in edema, hyperglycemia, and cardiac arrhythmia with

ventricular fibrillation (Gleason et al., 1969; Harvey, 1975; Horn, 1981; Weiner, 1985; McLean, 1985). Epinephrine-induced hypokalemia resulting from a cyclic AMP-dependent (β_2-receptor-mediated) stimulation of membrane-bound Na^+ and K^+ ATPase can predispose the heart to arrhythmias (Klein et al., 1989). Renal failure has also occasionally been reported as a sequela to primary cardiovascular changes (Levine et al., 1985). All these effects may occur after parenteral administration, whereas none has been reported in humans after oral exposure (Gleason et al., 1969; Harvey, 1975; Weiner, 1985; Arena and Drew, 1986; Ellenhorn and Barceloux, 1988) due to the rapid first pass metabolism of this drug by the liver. Common symptoms associated with these effects include palpitations, vertigo, tremor, tenseness, restlessness, anxiety, fear, throbbing headache, and respiratory difficulty.

Although the excessive use of large doses of aerosols containing sympathomimetic agents have been associated with sudden death (Martindale, 1982), the therapeutically recommended inhalation of relatively concentrated (1%) epinephrine aerosols results in actions that are primarily restricted to the respiratory tract; systemic reactions that include arrhythmia occur only after larger exposures (Weiner, 1985). Other changes associated with epinephrine exposure which could result in toxic responses include the ability of this drug to stimulate platelet aggregation (associated with an increased synthesis of thromboxane B_2, (an agent that is thought to evoke coronary vasospasm) via increases in fibrinogen synthesis, receptor exposure, and binding (Kaplan et al., 1981; Siess et al., 1983; Roy et al., 1985; Carty et al., 1988; Ellenhorn and Barceloux, 1988; Shattil et al., 1989). These epinephrine-induced increases in plasma coagulation factors are important because of potential complications that could develop in conjunction with the ability of this drug to induce hypertension and secondary cerebral hemorrhage (Weiner, 1985).

Repeated local injections of epinephrine can cause injection site necrosis in addition to necrosis in highly perfused organs such as the liver and kidney due to localized tissue hypoxia resulting from vascular constriction (Arena and Drew, 1986; AHFS, 1988). The use of epinephrine to augment local anesthesia at certain anatomic sites, such as the toes and fingers is therefore contraindicated, as tissue necrosis is more likely (PDR, 1989). This warning should be noted in conjunction with the calorigenic action of epinephrine, which results in a 20%-30% increase in oxygen consumption, depressed tissue P_{O_2} or localized hypoxia, and increased blood lactate (Aragno, 1981; Towell et al., 1981; Weiner, 1985). Epinephrine can also induce myocardial and vascular necrosis that is believed to be associated with tissue hypoxia (Weiner, 1985). Both peripheral and coronary artery spasms can be induced by large parenteral doses of epinephrine (Pederson et al., 1989; Karch, 1989). Because of these hypoxic effects, epinephrine should be used with considerable caution in the treatment of shock or circulatory collapse (Harvey, 1975; Weiner, 1985; Ellenhorn and Barceloux, 1988). The multifactorial molecular events underlying the cytotoxic action of epinephrine and its oxidative breakdown product adrenochrome on heart tissue have been ascribed to elevated toxic factors (free radicals) in the blood (Ceremuzynski et al., 1978; Noronha-Dutra et al., 1988; Bindoli et al., 1989). Other morphologic changes in endocardial cells, including alterations in mitochondrial structure and plasma membrane blebs and microvilli, have been associated with epinephrine toxicity. Depressed cellular levels of ATP and reduced glutathione and enzyme activities dependent on sulfhydryl groups are associated with epinephrine cardiotoxicity in addition to changes in plasma membrane permeability. This toxicity is consistent with the cytotoxicity of adrenochrome, which can generate toxic oxygen free radicals that undergo redox cycling involving their transformation to quinonoid compounds (Bindoli et al., 1989).

A variety of drugs and clinical states that exacerbate epinephrine toxicity have been documented (Deterling et al., 1954; Thompson and Harris, 1974; Harvey, 1975; Weiner, 1985; Ellenhorn and Barceloux, 1988; PDR, 1989). Exposure to cardiac glycosides, such as digitalis (Harvey, 1975; PDR, 1989); to mercurial diuretics (PDR, 1989); to propellant gases, such as dichlorodifluoromethane (Thompson and Harris, 1974), and inhalation anesthetic agents, such as cyclopropane (Deterling et al., 1954); and to

halogenated hydrocarbons (Harvey, 1975; Weiner, 1985) can sensitize the heart to the arrhythmic action of epinephrine. Because cervical cordotomy dramatically protects rats from carbon tetrachloride hepatotoxicity, it has been proposed that the halogenated hydrocarbons may manifest their toxicity in part by stimulating the release of catecholamines from the adrenal gland (Calvert and Brody, 1960). This protection was later attributed to factors other than diminished catecholamine release (Larson et al., 1964; Larson and Plaa, 1965). Antidepressant drugs, including MAO inhibitors and tricyclic drugs, may augment epinephrine toxicity by inhibiting its metabolic breakdown and removal (reuptake) from effector sites (Harvey, 1975; Cooper et al., 1982; Weiner, 1985; Ellenhorn and Barceloux, 1988; PDR, 1989). Although the ability of tricyclic antidepressants to block the reuptake of centrally active catecholamines (norepinephrine and dopamine) has been well documented (Coyle and Snyder, 1969; Maxwell et al., 1970; Iversen, 1974; Koe, 1976), this action relative to peripherally active epinephrine has not been described (Baldessarini, 1985). Finally, epinephrine should be avoided in hyperthyroid, hypertensive, and psychoneurotic patients (Harvey, 1975; Weiner, 1985) and used cautiously in diabetics undergoing insulin therapy because of its anti-insulin properties (Horn, 1981; Weiner, 1985; Ellenhorn and Barceloux, 1988).

Although the short-term and long-term toxicity of exogenous epinephrine has not been described, the clinical state resulting from neoplasms of the adrenal medullary chromaffin cells (pheochromocytoma) closely mimics the effects of epinephrine toxicity (Hickler and Thorn, 1970; Shapiro et al., 1984). Thus, the most serious consequences associated with this neoplasm may include paroxysmal or permanent hypertension, pulmonary edema, ventricular fibrillation, and cerebral hemorrhage. Associated clinical signs and symptoms include pallor, nausea, tremor, weakness, nervousness, epigastric pain, dyspnea, flushing, numbness, visual blurring, and dizziness. Progressive weight loss, hyperglycemia, and hypermetabolism are also frequently noted in persons with this condition.

There are reports that the immune system may provide protection against cancer by eliciting an autoimmune response (Anderson, 1964; Old, 1977; Greene et al., 1984; Springer, 1984). These observations are important because physiologic and/or psychologic stress, which results in an increase in systemic epinephrine, is also associated with a decrease in immune function (Keller et al., 1983; Laudenslager et al., 1983). Immune cells change differently in response to epinephrine via catecholamine receptor (within lymphocytes) activation, depending on the type of cell and stage of the cell cycle; therefore, the clinical consequences of these changes are not clear (Marx, 1985). Although cyclic AMP appears to be involved in immune cell proliferation and cycling, the details of this involvement are very complex and are not completely understood (Beckner and Farrar, 1986; Choquet et al., 1987). In addition, any association between stress and cancer mediated by epinephrine has not been substantiated. Indeed, it has been noted that swimming stress provides some protection against carcinogenesis (Anderson, 1964). Finally, it is known that immune suppression is mediated by other adrenal hormones (the corticosteroids) acting through the hypothalmic-pituitary-adrenal pathway (Luster et al., 1982).

Reproductive Toxicity

The placental transfer of epinephrine in humans can be demonstrated indirectly by fetal tachycardia and hyperglycemia that result from the maternal administration of this drug (Zuspan et al., 1966; Asling and Way, 1971). Chernoff and Grabowski (1971) administered pregnant rats 25-100 µg epinephrine by intraperitoneal injection during gestation days 15-21. They noted that this administration resulted in fetal bradycardia (decrease in heart rate from 140 to 180 beats per minute to less than 20 beats per minute), fetal hypotension, and increased fetal serum potassium levels. Because these effects could not be induced by direct fetal injection of epinephrine but could be induced by a reversible interruption of uterine blood flow during clamping of the uterine artery, they attributed these responses to an epinephrine-induced impairment

of uterine blood flow. Misenhimer et al. (1972) showed that epinephrine reduces uteroplacental circulation in monkeys. The response of uterine muscle to epinephrine varies with the species, phase of the sexual cycle, state of gestation, and dose (Weiner, 1985). In humans, epinephrine inhibits uterine tone and contractions during the last months of pregnancy and at parturition.

Chernoff and Grabowski (1971) reported that the intraperitoneal injection of epinephrine to pregnant rats resulted in teratogenic effects (tail deformities and paralysis) in their offspring. Other investigators exposed pregnant rats and mice to either exogenous or endogenous (via stress) epinephrine in an attempt to determine whether exposure can alter neonatal behavior in the offspring (Thompson et al., 1963; Bell et al., 1965; DeFries et al., 1967). The results from these studies, however, failed to demonstrate any convincing epinephrine-mediated alterations in postnatal behavior. Weir (1965) noted that rabbit fetuses and pups were runted (smaller than controls) when epinephrine was administered by intravenous injection to pregnant does. This effect lasted for approximately 3 weeks after birth. Because epinephrine at 25 times the therapeutic human dose is teratogenic in rats, it should only be used during pregnancy only when the potential benefit justifies the risk to the fetus (PDR, 1989).

Several investigators have studied the effects of epinephrine on chick embryos. Gatling (1962) applied 20-200 µg epinephrine to the chorioallantois of 10- to 12-day-old chick embryos and noted cephalic hematomas in addition to skin and extremity hemorrhage after administration of doses as low as 20 µg. In other studies, the structure-activity relationship of several sympathomimetic agents was investigated, and epinephrine was found to be among the more potent agents to produce this effect (5/13 agents) (Gatling, 1965; Becker, 1975). Several possible underlying pharmacologic mechanisms of epinephrine-induced teratogenesis in chick embryos were summarized by Ishikawa et al. (1980). Hodach et al. (1975) exposed chick embryos to 5 µl of 0.4×10^{-9} to 20×10^{-9} M epinephrine in saline and attributed several resulting cardiovascular anomalies (aortic arch defect, ventricular septal defect, double outlet right ventricle, aortic hypoplasia, and truncus arteriosus) to the β-receptor agonist properties of epinephrine. Their conclusion was based on the observation that the frequency of these anomalies was significantly reduced by pretreatment with the β-receptor antagonist propranolol. Gilbert et al. (1976) showed that cocaine (5×10^{-7} M), a reuptake inhibitor, potentiated the ability of epinephrine (5×10^{-10} M) to induce aortic arch malformations in chick embryos. In another study, they showed that methylxanthines (caffeine and theophylline), which mobilize calcium and block the metabolism of cyclic AMP, will potentiate epinephrine-induced aortic arch malformations (Gilbert et al., 1977). Further investigations of the synergistic action of methylxanthines (3.8 mg theophylline) and epinephrine (1 µg) showed that this drug combination produced congestive heart failure and lower limb and beak anomalies in chick embryos (Bruyere et al., 1983). Rajala et al. (1984) suggested that the induction of malformations and decreased probability for survival in epinephrine-exposed chick embryos were related to dysrhythmogenesis and bradycardia in affected embryos.

Genetic Toxicology

There is no information on the mutagenicity of epinephrine hydrochloride per se, but limited information is available on epinephrine (adrenaline) and two of its metabolites. Epinephrine was reported to cause strand breaks in DNA extracted from bacteriophage (Murakami et al., 1979), growth inhibition due to DNA damage in *Bacillus subtilis* (Suter and Matter-Jaeger, 1984), gene mutations in *Salmonella typhimurium* (Yamaguchi, 1981; McGregor et al., 1988), and gene mutation and DNA strand breaks in mammalian cells in vitro (Murakami et al., 1974, 1975; Yamada et al., 1979; McGregor et al., 1988), but the data do not indicate a high level of activity. These findings are consistent with National Toxicology Program (NTP) genotoxicity test results for epinephrine, which showed equivocal responses in the Salmonella gene mutation test (Zeiger et al., 1987; Table J1) and the sister chromatid exchange test in Chinese hamster ovary (CHO) cells (Table J2); negative results were obtained with epinephrine for induction of chromosomal aberrations in CHO cells (Table J3). In vivo tests for induction of

micronuclei (Heddle and Bruce, 1977) and sperm abnormalities (Bruce and Heddle, 1979; Topham, 1980) in mice administered epinephrine were negative. 3-Methoxyepinephrine, a metabolite of epinephrine, was reported to induce DNA strand breaks in *Escherichia coli* (Murakami et al., 1979). Another metabolite, 4-hydroxy-3-methoxymandelic acid, did not inhibit DNA synthesis in human lymphocyctes treated in vitro (Ganeshaguru et al., 1980).

Study Rationale

Epinephrine hydrochloride, phenylephrine hydrochloride, and ephedrine sulfate were three sympathomimetic agents considered by the National Cancer Institute (NCI) as part of a benzyl alcohol class study. Interest has focused on epinephrine and ephedrine primarily because mesovarial leiomyomas have been reported in Sprague Dawley rats given the β-agonists soterenol hydrochloride (Nelson and Kelly, 1971), mesuprine hydrochloride (Nelson et al., 1972), and salbutamol sulfate and terbutaline sulfate (Jack et al., 1983; Gopinath and Gibson, 1987). In addition, benzyl alcohols may act as alkylating agents via formation of electrophilic benzyl carbonium ions. Since no reports on the long-term effects of epinephrine 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 NCI nominate epinephrine hydrochloride to the NTP for toxicology and carcinogenesis studies. The inhalation route of administration was selected because of the extensive clinical use of this drug in aerosol formulations for the treatment of bronchial asthma and respiratory distress (Martindale, 1982; Weiner, 1985; AHFS, 1988; PDR, 1989).

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *l*-EPINEPHRINE, PREPARATION OF *l*-EPINEPHRINE HYDROCHLORIDE, AND CHARACTERIZATION OF *l*-EPINEPHRINE AND *l*-EPINEPHRINE HYDROCHLORIDE

GENERATION AND MONITORING OF CHAMBER CONCENTRATIONS

- Aerosol Generation System
- Aerosol Concentration Monitoring
- Chamber Atmosphere Characterization

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

FIFTEEN-MONTH AND TWO-YEAR STUDIES

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

II. MATERIALS AND METHODS

PROCUREMENT OF *l*-EPINEPHRINE, PREPARATION OF *l*-EPINEPHRINE HYDROCHLORIDE, AND CHARACTERIZATION OF *l*-EPINEPHRINE AND *l*-EPINEPHRINE HYDROCHLORIDE

l-Epinephrine was obtained from Henley and Co., Inc. (New York, NY) in four lots as a white, microcrystalline powder, labeled USP Grade. Purity and identity analyses of all lots were conducted at Midwest Research Institute (MRI) (Appendix I). The conversion of the base to the hydrochloride salt was made at the study laboratory.

All lots of the study chemical were identified as *l*-epinephrine by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity of *l*-epinephrine was estimated to be greater than 98%, as determined by elemental analysis, Karl Fischer water analysis, titration in glacial acetic acid of the amino group with 0.1 N perchloric acid, thin-layer chromatography, and high-performance liquid chromatography. All lots met the USP specification for specific rotation of $-50°$ to $-53.5°$.

Stability studies performed by high-performance liquid chromatography indicated that *l*-epinephrine is stable as a bulk chemical when stored for 2 weeks protected from light at up to 60° C. During the toxicology studies, the bulk chemical was stored at $-20°$ C. Periodic analysis by nonaqueous titration and high-performance liquid chromatography indicated no degradation of the chemical throughout the studies. The hydrochloride salt of *l*-epinephrine was prepared by titration of the free base in water with 3 N hydrochloric acid to a pH of 2.8. Subsequently, the solutions were diluted to a concentration of 2.0 mg/ml for use in the generation system. The solutions were stored at 3°-4° C for a maximum of 3 weeks.

Stability studies of aqueous solutions of *l*-epinephrine hydrochloride prepared in a similar fashion as described above were conducted by MRI. Through the use of polarimetry, it was shown that no racemization had occurred in solutions stored for 21 days at 5° C in the dark. Solutions stored for up to 6 hours at room temperature were also stable. In another study, solutions prepared at pH 1.3 did show significant racemization.

Since the biologic activity is associated with the *levo*-isomer, it was essential to confirm that racemization did not occur during the toxicology studies. Fresh solutions of *l*-epinephrine hydrochloride were prepared every 3 weeks and their specific optical rotations determined before use. The specific optical rotations were within USP specifications for all preparations except one, which was slightly low.

GENERATION AND MONITORING OF CHAMBER CONCENTRATIONS

Aerosol Generation System

An aqueous aerosol of *l*-epinephrine hydrochloride was produced using Model 7301 Retec nebulizers (Cavitron, Englewood Cliffs, NJ). One generator consisting of one to four nebulizers supplied the aerosol for each chamber (Hazleton 2000®, Lab Products, Inc.). The nebulizers were modified by the addition of a baffle to eliminate the larger particles. Air pressure to operate the nebulizers was supplied from the house-pressurized air system. Output of aerosol was related almost directly to operating pressure (Figure I3 and Table I2).

Dilute hydrochloric acid solution (pH 2.8) was prepared for use in generating an acid aerosol for the control chambers in the short-term studies. Controls were not exposed to acid aerosols in the 2-year studies primarily because of wide variability in chloride levels found in samples from the control chambers taken during the short-term studies.

Aerosol Concentration Monitoring

Chamber concentrations were monitored online with a RAM-1 Real-Time Aerosol Monitor, a forward light-scattering photometer that was manually moved from chamber to chamber to sample all exposure chambers approximately once per hour during the exposures. The RAM-1 was calibrated once per week by taking filter samples from each chamber. After determining the concentration from 0.1 N hydrochloric acid

extracts of the filters by spectrophotometry, the RAM-1 response was correlated to the determined calibration concentration. Weekly mean exposure concentrations for the 2-year studies are presented in Figures I4 through I7. A summary of the chamber concentrations is presented in Table I3; Table I4 summarizes the distribution of mean daily concentrations.

Chamber Atmosphere Characterization

Aerodynamic particle size distributions of the aerosol were determined by pulling a chamber sample through an Andersen Cascade Impactor and analyzing the *l*-epinephrine hydrochloride content spectrophotometrically. During the 2-year studies, the particle size distribution was measured once per month. The mass median aerodynamic diameter of the particles ranged from 0.20 to 0.95 μm with a geometric standard deviation ranging from 1.8 to 2.8 μm.

Uniformity of aerosol concentration in each exposure chamber was measured before the start of the studies and was checked at approximately 3-month intervals throughout the studies with a RAM-1. Aerosol concentrations were within 10% of the mean chamber concentration values at all 12 positions sampled within the chamber, and the coefficients of variation of the concentrations determined did not exceed 5%.

During the 2-year studies, a sample of *l*-epinephrine hydrochloride from the 5 mg/m^3 chambers was analyzed by high-performance liquid chromatography for *l*-epinephrine hydrochloride and adrenochrome, thought to be the most likely degradation product. No more than 0.1%, the limit of detection of adrenochrome, was present in the sample.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and were observed for 21 days before exposure began. Groups of five rats and five mice of each sex were exposed to air at target concentrations of 0, 12.5, 25, 50, 100, or 200 mg/m^3 epinephrine hydrochloride, 6 hours per day for 10 exposures over 14 days. Controls were exposed to a hydrochloric acid aerosol (pH 2.8). Rats and mice were observed three times per day and were weighed before exposure, at week 1, and at necropsy. A necropsy was performed on all animals. Histopathologic examinations were performed on selected rats and mice exposed to 12.5, 25, or 50 mg/m^3 epinephrine hydrochloride. Further details are presented in Table 1.

THIRTEEN-WEEK STUDIES

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

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories. Animals were observed for 21 days, distributed to weight classes, and assigned to groups according to tables of random numbers. Feed was available ad libitum during nonexposure periods; water was available at all times. Further experimental details are summarized in Table 1.

Groups of 10 rats and 10 mice of each sex were exposed to air containing target concentrations of 0, 2.5, 5, 10, 20, or 40 mg/m^3 epinephrine hydrochloride, 6 hours per day, 5 days per week for 65 exposures. Controls were exposed to a hydrochloric acid aerosol (pH 2.8). Animals were observed three times per day; moribund animals were killed. Animal weights were recorded once per week.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals. The liver of all animals and the adrenal glands and heart of aerosol controls and groups exposed to 40 mg/m^3 were weighed at necropsy.

Histologic examinations were performed on animals that died before the end of the studies, aerosol controls, and animals exposed to 40 mg/m^3. Selected tissues were examined for other groups. Tissues and groups examined are listed in Table 1.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

Fourteen-Day Studies	Thirteen-Week Studies	Fifteen-Month and 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	15 mo--10 males and 10 females of each species; 2 y--50 males and 50 females of each species
Exposure Concentrations		
0, 12.5, 25, 50, 100, or 200 mg/m^3 *l*-epinephrine hydrochloride by inhalation; controls exposed to a hydrochloric acid aerosol (pH 2.8)	0, 2.5, 5, 10, 20, or 40 mg/m^3 *l*-epinephrine hydrochloride by inhalation; controls exposed to a hydrochloric acid aerosol (pH 2.8)	Rats--0, 1.5, or 5 mg/m^3 *l*-epinephrine hydrochloride by inhalation; mice--0, 1.5, or 3 mg/m^3; controls exposed to aerosols of water
Date of First Exposure		
6/3/81	11/4/81 (20 and 40 mg/m^3 groups), 11/5/81 (5 and 10 mg/m^3 groups), or 11/6/81 (2.5 mg/m^3 groups and controls)	Rats--11/3/82; mice--9/29/82
Date of Last Exposure		
6/16/81	2/2/82 (20 and 40 mg/m^3 groups), 2/3/82 (5 and 10 mg/m^3 groups), or 2/4/82 (2.5 mg/m^3 groups)	15 mo--2/6/84 (rats) or 1/16/84 (mice); 2 y--10/23/84 (rats) or 9/28/84 (mice)
Duration of Exposure		
6 h/d, 5 d/wk for 10 exposures over 14 d	6 h/d, 5 d/wk for 65 exposures	6 h/d, 5 d/wk for 15 mo or 103 (rats) or 104 (mice) wk
Type and Frequency of Observation		
Observed 3 × d; weighed initially and 1 × wk thereafter	Observed 3 × d; weighed 1 × wk	Observed 2 × d; weighed initially, 1 × wk for 12 or 13 wk, and 1 × mo thereafter
Necropsy, Histologic Examinations, and Supplemental Analyses		
Necropsy performed on all animals; histologic exams performed on 1-2 animals from each of the 12.5, 25, and 50 mg/m^3 groups	Necropsy performed on all animals; the following tissues examined histologically for all control and high dose animals and all animals dying before the end of the studies: adrenal glands, bone marrow, brain, colon, duodenum (mice), esophagus, gallbladder (mice), heart, jejunum (rats), mandibular lymph nodes, nasal passage, pancreas, parathyroid glands, pituitary gland, regional lymph nodes (mice), salivary glands, seminal vesicles/prostate/testes or ovaries/uterus, skin, spleen, stomach, thymus, thyroid gland, trachea, tracheobronchial lymph nodes (rats), and urinary bladder (rats); adrenal glands examined for all groups, and anterior nasal passage and heart sections examined for 20 mg/m^3 groups. Organ weights obtained at necropsy include liver for all animals and adrenal glands and heart for control and highest dose groups	Necropsy performed on all animals; the following tissues examined histologically for all control and high dose animals and all animals dying before the end of the studies: adrenal glands, brain, cecum, colon, duodenum, epididymis/prostate/testes or ovaries/uterus, esophagus, gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, heart, ileum, jejunum, kidneys, larynx, liver, lungs and mainstem bronchi, mammary gland, mandibular lymph nodes, nasal passage and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland (rats), rectum, salivary glands, skin, spleen, sternebrae including marrow, stomach, thymus, thyroid gland, trachea, tracheobronchial lymph nodes, and urinary bladder. Tissues examined include gross lesions and nasal passage for low dose rats and pituitary gland for low dose female mice. Blood was collected at 15 mo for hematologic analyses; organ weights obtained at necropsy for animals killed at 15 mo

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

Fourteen-Day Studies	Thirteen-Week Studies	Fifteen-Month and 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 (Kingston, NY)	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory		
Battelle Pacific Northwest Laboratories	Battelle Pacific Northwest Laboratories	Battelle Pacific Northwest Laboratories
Method of Animal Identification		
Ear tags and cage number	Ear tags and cage number	Ear tags and cage number
Time Held Before Study		
21 d	21 d	Rats--22 d; mice--20 d
Age When Placed on Study		
Rats--7-8 wk; mice--8-9 wk	Rats--8 wk; mice--9 wk	Rats--7-8 wk; mice--8-9 wk
Age When Killed		
Rats--9-10 wk; mice--10-11 wk	Rats--21 wk; mice--22 wk	Rats--111-113 wk; mice--114-115 wk
Necropsy or Kill Dates		
6/17/81	2/3/82-2/5/82	15 mo--rats: 2/7/84; mice: 1/17/84; 2 y--rats: 10/31/84-11/2/84; mice: 10/8/84-10/12/84
Method of Animal Distribution		
Assigned to groups according to tables of random numbers	Distributed to weight classes and then assigned to groups according to tables of random numbers	Same as 13-wk studies
Diet		
NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum during nonexposure periods	Same as 14-d studies	Same as 14-d studies
Water		
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 14-d studies	Same as 14-d studies
Cages		
Stainless steel wire bottom cages (Hazleton Systems, Inc., Aberdeen, MD)	Same as 14-d studies	Same as 14-d studies
Animals per Cage		
1	1	1
Other Chemicals on Study in the Same Room		
None	None	None
Chamber Environment		
Temp--69°-76° F; hum--40%-69% (72% for 2 h in one chamber); fluorescent light 12 h/d	Temp--68°-78° F; hum--38%-75%; fluorescent light 12 h/d	Temp--71°-81° F (rats) or 69°-79° F (mice); hum--31%-80% (rats) or 33%-85% (mice); fluorescent light 12 h/d

FIFTEEN-MONTH AND TWO-YEAR STUDIES

Study Design

Groups of 60 rats of each sex were exposed at target concentrations of 0, 1.5, or 5 mg/m^3 *l*-epinephrine hydrochloride, 6 hours per day, 5 days per week for 15 months or for 103 weeks. Groups of 60 mice of each sex were exposed to 0, 1.5, or 3 mg/m^3 *l*-epinephrine hydrochloride, 6 hours per day, 5 days per week for 15 months or for 104 weeks.

Blood samples were taken from the lumbar aorta (rats) or supraorbital sinus (mice) immediately before animals were killed in the 15-month studies. The erythrocyte and leukocyte counts, hemoglobin concentration, hematocrit value, and leukocyte differential count were determined. The brain, liver, and right kidney were weighed at necropsy. Histopathologic examinations were performed on control and high dose animals.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice at 5-6 weeks of age. The animals were quarantined at the study laboratory for 3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 7-8 (rats) or 8-9 (mice) weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix E).

Animal Maintenance

Rats and mice were housed individually. Feed (Appendix F) was removed during exposure; otherwise feed and water were available ad libitum. Cages were rotated to different levels once per week during these studies. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed two times per day. Body weights were recorded once per week for the first 12 weeks (rats) or 13 weeks (mice) of the studies and once per month thereafter. Mean body weights were calculated for each group. Individual animals were examined once per month for abnormalities. 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.

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. Histopathologic examination of tissues was performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 1) were performed on all high dose and control animals and on low dose animals dying before the end of the studies. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs examined in the low dose groups were the nasal passage in rats and mice and the pituitary gland in female mice.

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

10% of the animals were re-evaluated microscopically by a quality assessment pathologist. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target organs and in a 10% random sample of animals.

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

Statistical Methods

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

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

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

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

Tests of significance include pairwise comparisons of each dosed group with controls and a test

for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

Analysis of Continuous Variables: The statistical analysis of organ weight and hematologic data was carried out by using the nonparametric multiple comparison procedures of Dunn (1964) or Shirley (1977) to assess the significance of pairwise comparisons between exposed and control groups. Jonckheere's test (Jonckheere, 1954) was used to evaluate the significance of dose-response trends and to determine whether Dunn's test or Shirley's test should be used for pairwise comparisons.

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

THIRTEEN-WEEK STUDIES

FIFTEEN-MONTH STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

FIFTEEN-MONTH STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

III. RESULTS: RATS

FOURTEEN-DAY STUDIES

All male rats exposed to 50 mg/m^3 epinephrine or greater and all females exposed to 100 mg/m^3 or greater died before the end of the studies. In addition, 3/5 female rats exposed to 50 mg/m^3, 4/5 male rats and 1/5 female rats exposed to 25 mg/ m^3, and 3/5 male rats exposed to 12.5 mg/m^3 died before the end of the studies (Table 2). Surviving female rats exposed to 50 mg/m^3 and surviving male rats exposed to 25 mg/m^3 lost weight. At necropsy, the mean body weight of male rats exposed to 12.5 mg/m^3 was 13% lower than that of hydrochloric acid aerosol controls. Compound-related clinical signs included an increased respiratory rate for all groups of exposed rats and increased lacrimation and dyspnea in the 100 and 200 mg/m^3 groups.

THIRTEEN-WEEK STUDIES

One of 10 male rats exposed to 40 mg/m^3 died before the end of the studies (Table 3). The final mean body weight of male rats exposed to 40 mg/m^3 was 8% lower than that of the hydrochloric acid aerosol controls. Final mean body weights of exposed and aerosol control female rats were generally similar. Rats exposed to 40 mg/m^3 assumed a ventral recumbent position with limbs extended during exposure and had increased respiratory rates during the first 3 weeks of exposure. Piloerection occurred at 20

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

Concentration (mg/m^3)	Survival (a)	Mean Body Weights (grams) Initial (b)	Necropsy	Change (c)	Necropsy Weight Relative to Controls (percent)
MALE					
(d) 0	5/5	136 ± 8	193 ± 10	+57 ± 3	
12.5	(e) 2/5	143 ± 6	168 ± 18	+39 ± 8	87
25	(f) 1/5	148 ± 2	140	−14	73
50	(g) 0/5	138 ± 6	(h)	(h)	(h)
100	(i) 0/5	147 ± 6	(h)	(h)	(h)
200	(j) 0/5	140 ± 6	(h)	(h)	(h)
FEMALE					
(d) 0	5/5	116 ± 3	136 ± 3	+20 ± 2	
12.5	5/5	118 ± 2	132 ± 3	+14 ± 2	97
25	(k) 4/5	116 ± 4	(l) 128 ± 8	+7 ± 3	94
50	(m) 2/5	114 ± 3	105 ± 3	−6 ± 4	77
100	(n) 0/5	117 ± 3	(h)	(h)	(h)
200	(o) 0/5	115 ± 4	(h)	(h)	(h)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study, unless otherwise specified.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Control animals were exposed to a hydrochloric acid aerosol.
(e) Day of death: all 4
(f) Day of death: 3,3,4,4
(g) Day of death: 3,3,3,9,10
(h) No data are reported due to 100% mortality in this group.
(i) Day of death: 3,3,4,4,11
(j) Day of death: 1,2,2,2,5
(k) Day of death: 4
(l) Body weight of one animal was not recorded at necropsy; weight change is based on remaining three animals.
(m) Day of death: 2,7,9
(n) Day of death: 2,2,2,3,10
(o) Day of death: 2,2,2,2,3

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

Concentration (mg/m^3)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
(d) 0	10/10	164 ± 5	351 ± 6	+187 ± 4	
2.5	10/10	169 ± 5	365 ± 8	+196 ± 9	104
5	10/10	170 ± 5	348 ± 10	+178 ± 7	99
10	10/10	172 ± 5	364 ± 8	+192 ± 5	104
20	10/10	171 ± 5	358 ± 6	+187 ± 4	102
40	(e) 9/10	170 ± 5	324 ± 10	+155 ± 8	92
FEMALE					
(d) 0	10/10	128 ± 2	212 ± 5	+84 ± 3	
2.5	10/10	127 ± 2	215 ± 3	+88 ± 1	101
5	10/10	127 ± 3	204 ± 4	+77 ± 2	96
10	10/10	129 ± 2	214 ± 4	+85 ± 3	101
20	10/10	129 ± 3	213 ± 4	+84 ± 3	100
40	10/10	129 ± 2	204 ± 4	+75 ± 4	96

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Control animals were exposed to a hydrochloric acid aerosol.
(e) Week of death: 1

and 40 mg/m^3. The absolute and relative heart weights for rats exposed to 40 mg/m^3 and the absolute and relative adrenal gland weights for male rats exposed to 40 mg/m^3 were significantly increased (Table 4; data were not collected for rats at lower exposure concentrations). Squamous metaplasia of the respiratory epithelium was seen in the nasal passage of 5/9 males and 4/10 females exposed to 40 mg/m^3. In minimally affected animals, metaplasia consisted only of a slight flattening of the cells, which remained in a single layer. Mild-to-moderate lesions consisted of changes from the single layer of cuboidal epithelium covering the nasal turbinates to several layers of flattened polyhedral cells. Acute inflammation of the nasal mucosa was seen in 6/9 males and 6/10 females exposed to 40 mg/m^3 and 2/10 females exposed to 20 mg/ m^3. Inflammation consisted of cellular debris and neutrophils in the mucosa of the nasal turbinates. Laryngeal myopathy was seen in 9/10 males and 6/10 females exposed to 40 mg/m^3 and in 4/10 males and 1/10 females exposed to 20 mg/m^3 (Figure 2). This lesion was characterized by degeneration, necrosis, and regeneration of myofibers.

Dose Selection Rationale: Epinephrine-induced histologic changes in the nasal mucosa and larynx were the primary findings in the 13-week studies. The primary purpose of these studies was to characterize any pharmacologic and toxic changes associated with reported epinephrine exposure. These changes were noted in groups exposed to 20 or 40 mg/m^3. Because epinephrine is an endogenous hormone with potent and complex pharmacologic activity and because measurable exposures are probably limited to route-specific tissue sites (respiratory and gastrointestinal mucosa), concentrations of epinephrine hydrochloride selected for rats in the 2-year studies were expected to result in daily exposures that exceeded human therapeutic doses (34-69 µg/kg or 0.1-0.3 $µg/cm^2$ per day) but were less than one-half the maximum tolerated dose, the lowest dose commonly used in other NTP 2-year carcinogenicity studies. Rats were thus exposed for 6 hours per day, 5 days per week, to either 1.5 or 5 mg/m^3 epinephrine for a maximum of 2 years. At this level of exposure, anticipated biologic effects were primarily expected at exposure sites in the respiratory and gastrointestinal epithelium.

TABLE 4. ORGAN WEIGHTS FOR RATS IN THE THIRTEEN-WEEK INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE (a)

Organ	Control	2.5 mg/m³	5 mg/m³	10 mg/m³	20 mg/m³	40 mg/m³
MALE						
Number weighed	10	10	10	10	9	9
Body weight (grams)	357 ± 6.1	367 ± 7.3	347 ± 10.1	362 ± 7.2	361 ± 4.9	**309 ± 13.4
Adrenal gland						
Absolute	42.7 ± 1.31	--	--	--	--	**53.2 ± 1.52
Relative	0.120 ± 0.0027	--	--	--	--	**0.176 ± 0.0110
Heart						
Absolute	981 ± 24	--	--	--	--	*1,094 ± 36
Relative	2.74 ± 0.036	--	--	--	--	**3.56 ± 0.127
Liver						
Absolute	13,970 ± 600	13,390 ± 470	12,770 ± 510	14,180 ± 390	13,680 ± 640	12,170 ± 930
Relative	39.1 ± 1.41	36.4 ± 0.58	36.7 ± 0.79	39.2 ± 0.91	37.8 ± 1.51	39.3 ± 2.56
FEMALE						
Number weighed	10	9	10	10	10	10
Body weight (grams)	208 ± 4.6	211 ± 2.7	199 ± 3.6	214 ± 3.9	210 ± 4.5	204 ± 4.1
Adrenal gland						
Absolute	52.9 ± 1.72	--	--	--	--	49.5 ± 1.42
Relative	0.254 ± 0.0048	--	--	--	--	0.243 ± 0.0062
Heart						
Absolute	625 ± 13	--	--	--	--	**695 ± 13
Relative	3.01 ± 0.049	--	--	--	--	**3.42 ± 0.044
Liver						
Absolute	7,386 ± 179	7,922 ± 312	6,907 ± 306	7,911 ± 288	7,377 ± 243	7,691 ± 212
Relative	35.5 ± 0.69	37.5 ± 1.46	34.7 ± 1.21	36.9 ± 0.95	35.2 ± 1.17	37.8 ± 0.72

(a) Mean ± standard error in milligrams (absolute) or milligrams per gram (relative) unless otherwise specified; P values vs. the hydrochloric acid aerosol controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
*P<0.05
**P<0.01

FIFTEEN-MONTH STUDIES

The absolute liver weights and the liver weight to body weight ratios for rats exposed to 5 mg/m³ were significantly lower than those for controls (Table G1). None of the results of hematologic analyses was considered to be compound related (Table H1). No compound-related lesions were seen.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of exposed and control rats were similar throughout most of the studies (Table 5 and Figure 3). No compound-related clinical signs were observed.

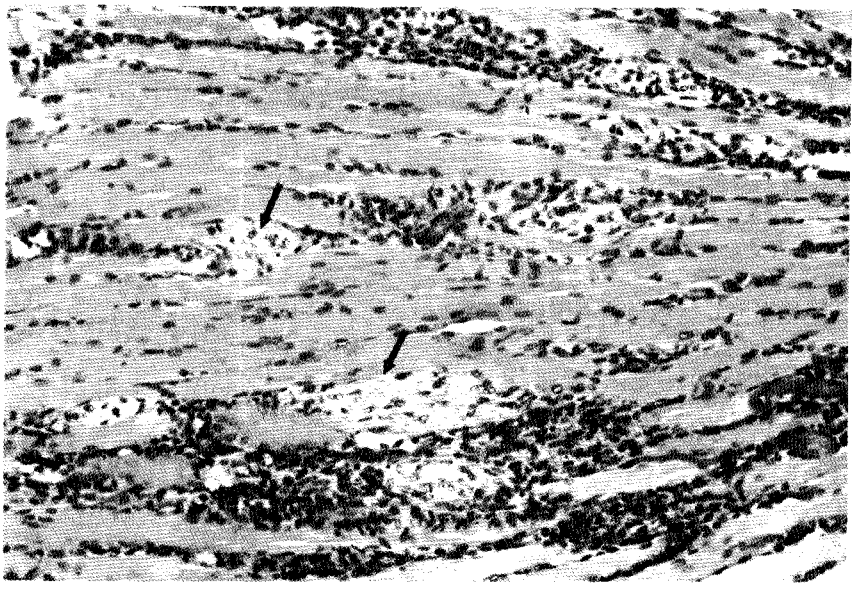

Figure 2. Laryngeal myopathy in a male rat exposed to 40 mg/m^3 *l*-epinephrine hydrochloride by inhalation for 13 weeks. Note focal degeneration of muscle fibers (arrows).

TABLE 5. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

Weeks on Study	Chamber Control		1.5 mg/m^3			5 mg/m^3		
	Av. Wt. (grams)	Number of Survivors	Av. Wt. (grams)	Wt. (percent of chamber controls)	Number of Survivors	Av. Wt. (grams)	Wt. (percent of chamber controls)	Number of Survivors
MALE								
0	141	50	147	104	50	144	102	50
1	180	50	186	103	50	181	101	50
2	197	50	197	100	50	198	101	50
3	211	50	212	100	50	212	100	50
4	227	50	229	101	50	225	99	50
5	235	50	236	100	50	234	100	50
6	242	50	243	100	50	243	100	50
7	248	50	248	100	50	249	100	50
8	260	50	262	101	50	262	101	50
9	266	50	270	102	50	270	102	50
10	275	50	279	101	50	276	100	50
11	281	50	286	102	50	283	101	50
12	290	50	296	102	50	294	101	50
16	315	50	323	103	50	323	103	50
21	344	50	353	103	50	338	98	50
25	362	50	371	102	50	366	101	50
29	375	50	381	102	50	378	101	50
33	386	50	392	102	50	389	101	50
38	397	50	406	102	50	393	99	50
40	384	50	404	105	50	408	106	50
45	401	50	414	103	50	408	102	50
49	410	50	416	101	50	412	100	50
54	416	50	420	101	50	417	100	50
59	426	50	432	101	50	425	100	50
63	436	50	440	101	50	433	99	50
68	441	49	447	101	50	442	100	50
72	444	49	449	101	50	442	100	49
77	450	49	456	101	48	450	100	49
82	463	48	460	99	48	453	98	46
86	467	48	457	98	46	451	97	46
90	465	48	455	98	44	446	96	45
94	461	47	448	97	41	450	98	40
99	455	43	441	97	33	443	97	38
103	449	33	433	96	27	431	96	32
Mean for weeks								
1-12	242.7		245.3	101		243.9	100	
16-49	374.9		384.4	103		379.4	101	
54-103	447.8		444.8	99		440.3	98	
FEMALE								
0	111	50	111	100	50	111	100	50
1	126	50	129	102	50	128	102	50
2	133	50	136	102	50	136	102	50
3	140	50	144	103	50	142	101	50
4	148	50	152	103	50	151	102	50
5	153	50	158	103	50	157	103	50
6	158	50	162	103	50	163	103	50
7	160	50	164	103	50	163	102	50
8	167	50	169	101	50	173	104	50
9	172	50	176	102	50	176	102	50
10	176	50	179	102	50	178	101	50
11	175	50	181	103	50	181	103	50
12	179	50	185	103	50	185	103	50
16	193	50	199	103	50	196	102	50
21	207	50	216	104	49	209	101	50
25	215	50	218	101	49	218	101	50
29	222	50	227	102	49	225	101	50
33	229	50	232	101	49	230	100	50
38	237	49	241	102	49	238	100	50
40	238	49	242	102	49	244	103	50
45	246	49	252	102	49	246	100	50
49	254	49	260	102	49	252	99	50
54	261	49	267	102	49	262	100	49
59	272	49	278	102	49	274	101	49
63	282	49	288	102	48	283	100	49
68	289	49	296	102	48	295	102	49
72	297	47	301	101	48	297	100	49
77	306	47	311	102	45	306	100	49
82	314	47	320	102	43	311	99	48
86	317	45	325	103	42	317	100	47
90	317	43	327	103	41	322	102	44
94	318	40	328	103	39	323	102	40
99	323	35	325	101	37	327	101	35
103	321	32	318	99	29	313	98	32
Mean for weeks								
1-12	157.3		161.3	103		161.1	102	
16-49	226.8		231.9	102		228.7	101	
54-103	301.4		307.0	102		302.5	100	

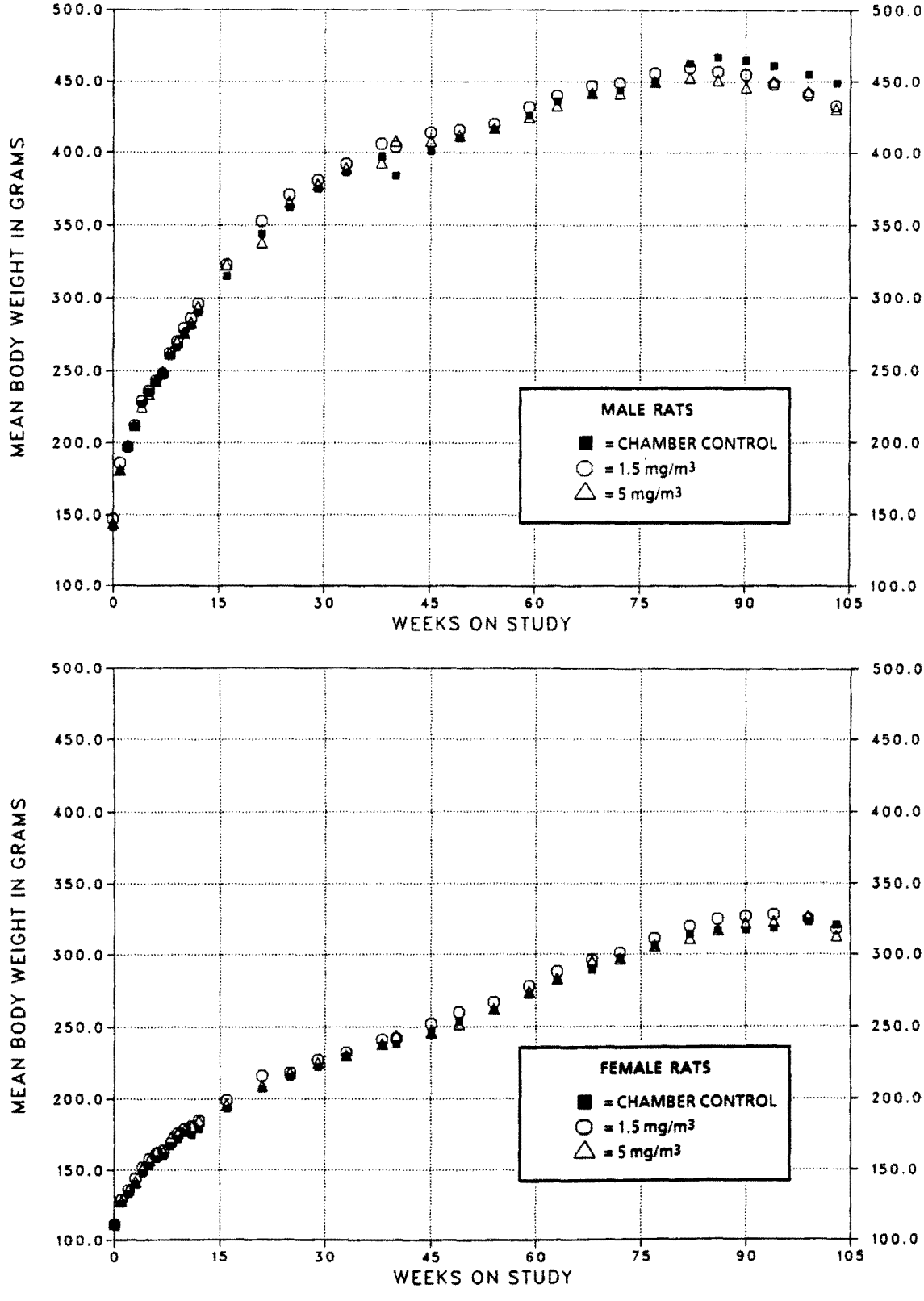

FIGURE 3. GROWTH CURVES FOR RATS EXPOSED TO *l*-EPINEPHRINE HYDROCHLORIDE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats exposed to epinephrine hydrochloride at the concentrations used in these studies and for controls are shown in Table 6 and in the Kaplan and Meier curves in Figure 4. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the nasal passage, thyroid gland, and clitoral gland.

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

TABLE 6. SURVIVAL OF RATS IN THE TWO-YEAR INHALATION STUDIES OF *l*-EPHINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m^3	5 mg/m^3
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	0	6	6
Moribund kills	17	18	12
Animals surviving to study termination	33	(b) 27	32
Mean survival (days)	710	698	698
Survival P values (c)	0.959	0.178	0.773
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	4	3	6
Moribund kills	14	18	14
Animals surviving to study termination	32	29	30
Mean survival (days)	688	680	696
Survival P values (c)	0.962	0.735	0.902

(a) First day of termination period: 729
(b) One animal died or was killed in a moribund condition during the termination period and was combined, for statistical purposes, with those killed at termination.
(c) The result of the life table trend test is in the chamber control column, and the results of the life table pairwise comparisons with the chamber controls are in the dosed columns.

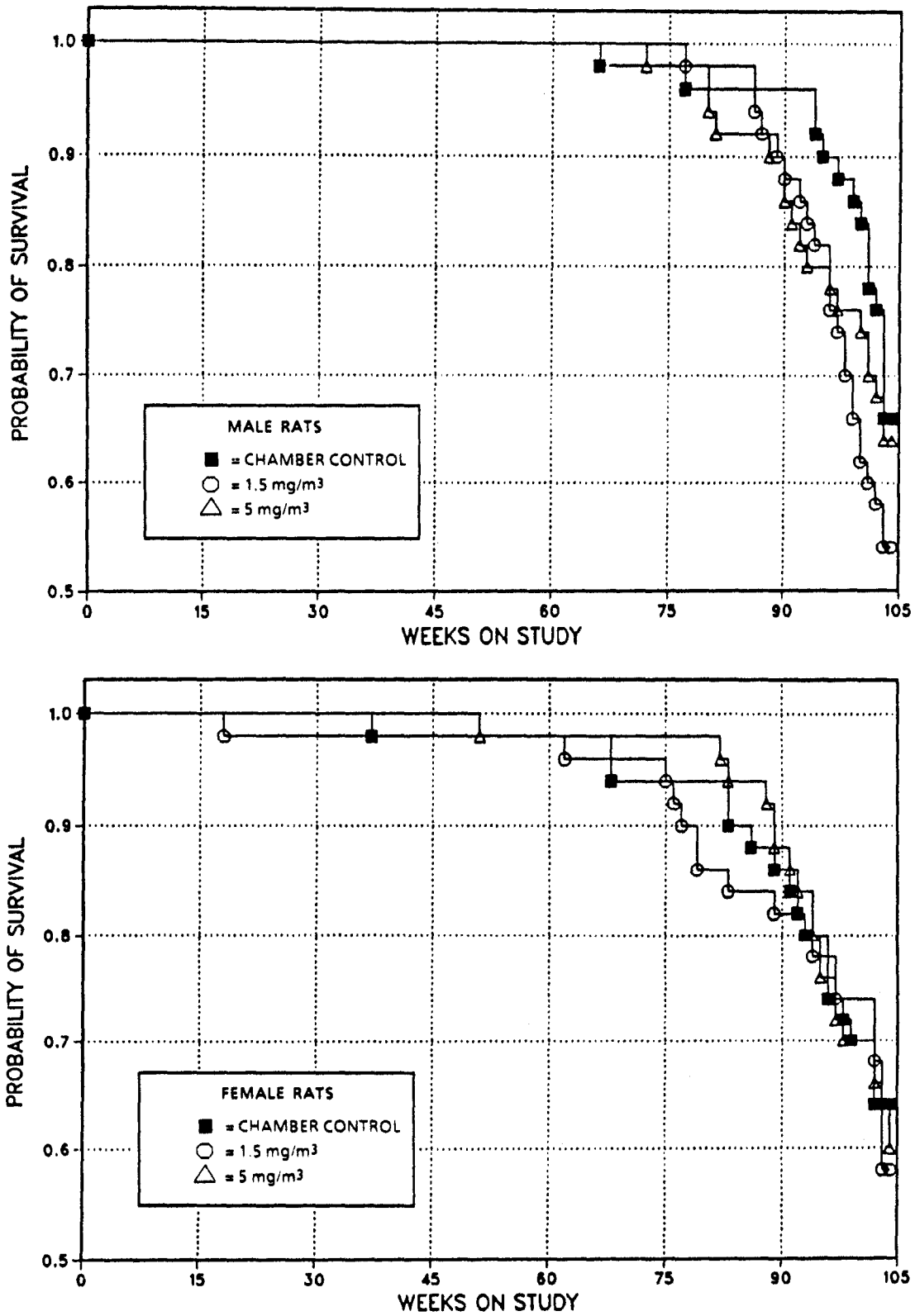

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR RATS EXPOSED TO *l*-EPINEPHRINE HYDROCHLORIDE BY INHALATION FOR TWO YEARS

Nasal Passage: Increased incidences of minimal-to-mild nonneoplastic lesions were seen in exposed male and female rats (Table 7). Lesions observed included suppurative inflammation, dilatation of submucosal nasal glands (Bowman's and septal), and hyperplasia and squamous metaplasia of the respiratory epithelium (Figures 5 and 6). Suppurative inflammation was generally mild in severity and was characterized by accumulation of neutrophils and mucus within the nasal passage lumen or in lumina of nasal glands. In some animals in each of the groups, the inflammation appeared to be associated with the presence of a foreign body (vegetable matter) within the lumen. In a few exposed animals, the inflammation was accompanied by minimal focal squamous metaplasia of the respiratory epithelium in which the normal columnar epithelium was replaced by two or more layers of stratified squamous epithelial cells. The nasal glands were distended with mucus or basophilic mineralized material. Hyperplasia of the respiratory epithelium was extensive but generally mild in severity and was characterized by increased height and cellularity of the epithelium, with increased numbers of goblet cells. An adenoma of the respiratory epithelium occurred in one control male and one control female, but no neoplasms of the nasal passage were found in any of the exposed animals.

Thyroid Gland: The incidence of C-cell adenomas or carcinomas (combined) in male rats exposed to 5 mg/m^3 was significantly lower than that in controls (chamber control, 13/50, 26%; 1.5 mg/m^3, 5/24, 21%; 5 mg/m^3, 5/49, 10%; Table A3). The incidence of these neoplasms in concurrent controls is approximately three times the mean incidence in historical chamber controls at the study laboratory and twice that in historical untreated controls in National Toxicology Program (NTP) studies. Thus, the decreased incidence of C-cell neoplasms is not considered chemical related.

Clitoral Gland: The incidences of adenomas and adenomas or carcinomas (combined) in female rats exposed to 5 mg/m^3 were significantly lower than those in controls (adenomas: chamber control, 5/48, 10%; 1.5 mg/m^3, 1/21, 5%; 5 mg/m^3, 0/47; adenomas or carcinomas, combined: 7/48, 15%; 2/21, 10%; 0/47; Table B3). The incidence of these neoplasms in concurrent controls is approximately three times the mean incidence in historical chamber controls at the study laboratory and twice that of historical untreated controls in NTP studies. Thus, the decreased incidence of clitorial gland neoplasms is not considered chemical related.

TABLE 7. NUMBERS OF RATS WITH SELECTED LESIONS OF THE NASAL PASSAGE IN THE TWO-YEAR INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

Site/Lesion	Male			Female		
	Chamber Control	1.5 mg/m^3	5 mg/m^3	Chamber Control	1.5 mg/m^3	5 mg/m^3
Number examined	50	49	50	50	50	46
Nasal passage						
Suppurative inflammation	8	9	*17	1	**10	*6
Nasal glands						
Dilatation	13	19	**44	4	**15	**37
Respiratory epithelium						
Hyperplasia	1	5	**15	0	**12	**13
Metaplasia	0	3	1	0	2	3
Adenoma	1	0	0	1	0	0

*P<0.05 vs. controls
**P<0.01 vs. controls

III. RESULTS: MICE

FOURTEEN-DAY STUDIES

All mice exposed to 100 or 200 mg/m^3 and 2/5 male mice and 1/5 female mice exposed to 50 mg/m^3 died before the end of the studies (Table 8). At necropsy, the mean body weight of male mice exposed to 25 or 50 mg/m^3 was 10% or 6% lower than that of the hydrochloric acid aerosol controls. The respiratory rate for all groups of epinephrine-exposed mice was increased during exposure, and an exaggerated reflex action in response to visual and auditory stimuli was seen at 100 or 200 mg/m^3.

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

Concentration (mg/m^3)	Survival (a)	Mean Body Weights (grams) Initial (b)	Necropsy	Change (c)	Necropsy Weight Relative to Controls (percent)
MALE					
(d) 0	5/5	23.4 ± 0.2	27.0 ± 0.0	+3.6 ± 0.2	
12.5	5/5	24.0 ± 0.4	26.8 ± 0.4	+2.8 ± 0.2	99
25	5/5	23.8 ± 1.0	24.4 ± 0.5	+0.6 ± 0.8	90
50	(e) 3/5	23.0 ± 0.6	25.3 ± 0.9	+2.3 ± 0.3	94
100	(f) 0/5	23.0 ± 0.9	(g)	(g)	(g)
200	(h) 0/5	23.2 ± 0.6	(g)	(g)	(g)
FEMALE					
(d) 0	5/5	18.8 ± 0.7	22.2 ± 0.7	+3.4 ± 0.5	
12.5	5/5	18.8 ± 0.6	23.0 ± 0.8	+4.2 ± 1.3	104
25	5/5	19.0 ± 0.5	22.0 ± 0.5	+3.0 ± 0.9	99
50	(i) 4/5	20.4 ± 0.6	22.8 ± 0.5	+2.0 ± 0.4	103
100	(j) 0/5	21.0 ± 0.4	(g)	(g)	(g)
200	(k) 0/5	19.0 ± 0.4	(g)	(g)	(g)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Control animals were exposed to a hydrochloric acid aerosol.
(e) Day of death: 6,10
(f) Day of death: 4,5,6,6,6
(g) No data are reported due to 100% mortality in this group.
(h) Day of death: 3,4,5,5,6
(i) Day of death: 6
(j) Day of death: 3,3,4,4,6
(k) Day of death: 3,4,5,5,5

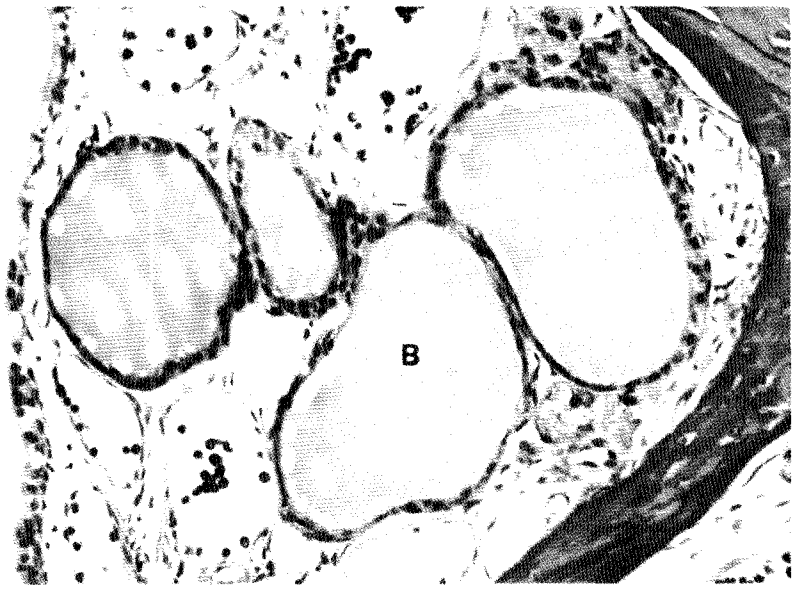

Figure 5. Dilatation of Bowman's glands (B) in the nasal passage of a male rat exposed to 5 mg/m^3 *l*-epinephrine hydrochloride by inhalation for 2 years.

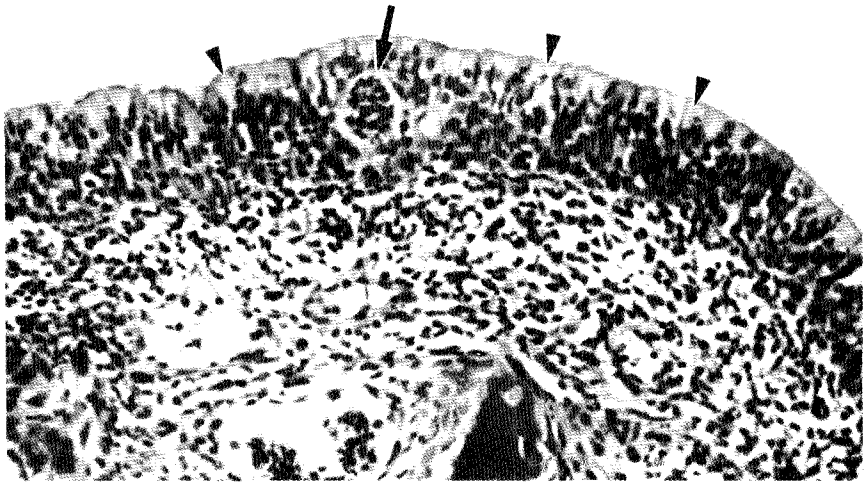

Figure 6. Respiratory epithelial hyperplasia (arrowheads) and inflammation in the nasal passage of a male rat exposed to 5 mg/m^3 *l*-epinephrine hydrochloride by inhalation for 2 years. Note focal accumulation of inflammatory cells in the nasal mucosa (arrow).

THIRTEEN-WEEK STUDIES

One of 10 female mice exposed to 20 mg/m^3, 1/10 male mice exposed to 10 mg/m^3, and 1/10 female mice exposed to 5 mg/m^3 died before the end of the studies (Table 9). Final mean body weights of exposed and hydrochloric acid aerosol control mice were generally similar. At 20 and 40 mg/m^3, the mice assumed a ventral recumbent position with limbs extended during exposure. Inactivity and occasionally increased respiratory rates occurred at 40 mg/m^3. Liver to body weight ratios for mice exposed to 40 mg/m^3 were significantly greater than those for aerosol controls (Table 10). The absolute heart weight and heart to body weight ratios for female mice exposed to 40 mg/m^3 were greater than those for aerosol controls. (Data were not collected for lower exposure groups.) Inflammation in the glandular stomach was seen in 9/10 males and 10/10 females exposed to 40 mg/m^3, 6/10 males and 1/9 females exposed to 20 mg/m^3, and 3/9 males and 2/10 females exposed to 10 mg/m^3. This inflammation (minimal to mild) was characterized by an infiltrate of neutrophils, plasma cells, and mast cells around vessels in the mucosa. Minimal focal squamous metaplasia of the respiratory epithelium in the nasal passage was seen in 3/10 male mice and 1/9 female mice exposed to 40 mg/m^3. Minimal uterine atrophy, characterized by diminished overall size, was seen in 7/10 females exposed to 40 mg/m^3, in addition to an apparent increased number of endometrial stromal cell nuclei per given area. Periportal hepatocellular vacuolization (minimal severity) was seen in 10/10 males and 4/10 females exposed to 40 mg/m^3 and in 2/10 male aerosol controls. This lesion was not clearly exposure related, because it can be associated with extraneous variables such as fasting or bleeding.

Dose Selection Rationale: Epinephrine-induced histologic changes in the nasal mucosa and stomach were the primary findings in the 13-week studies. The primary purpose of these studies was to characterize pharmacologic and

TABLE 9. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

Concentration (mg/m^3)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
(d) 0	10/10	23.7 ± 0.3	28.9 ± 0.3	+5.2 ± 0.3	
2.5	10/10	23.1 ± 0.2	29.1 ± 0.4	+6.0 ± 0.4	101
5	10/10	22.7 ± 0.4	28.6 ± 0.2	+5.9 ± 0.3	99
10	(e) 9/10	22.7 ± 0.3	27.9 ± 0.5	+5.1 ± 0.4	96
20	10/10	23.0 ± 0.5	30.0 ± 0.5	+7.0 ± 0.3	104
40	10/10	23.3 ± 0.4	29.9 ± 0.6	+6.6 ± 0.5	104
FEMALE					
(d) 0	10/10	18.6 ± 0.5	25.2 ± 0.8	+6.6 ± 0.4	
2.5	10/10	18.8 ± 0.6	24.9 ± 0.7	+6.1 ± 0.5	99
5	(f) 9/10	19.1 ± 0.3	25.7 ± 0.3	+6.6 ± 0.2	102
10	10/10	17.6 ± 0.4	24.4 ± 0.5	+6.8 ± 0.4	97
20	(g) 9/10	16.9 ± 0.6	25.8 ± 0.9	+8.7 ± 0.8	102
40	10/10	18.3 ± 0.3	26.6 ± 0.4	+8.3 ± 0.2	106

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Control animals were exposed to a hydrochloric acid aerosol.
(e) Week of death: 6
(f) Week of death: 3
(g) Week of death: 8

TABLE 10. ORGAN WEIGHTS FOR MICE IN THE THIRTEEN-WEEK INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE (a)

Organ	Control	2.5 mg/m³	5 mg/m³	10 mg/m³	20 mg/m³	40 mg/m³
MALE						
Number weighed	9	10	9	9	10	10
Body weight (grams)	29.1 ± 0.28	29.9 ± 0.42	29.6 ± 0.26	29.6 ± 0.43	30.0 ± 0.54	**30.6 ± 0.47
Adrenal gland						
Absolute	5.3 ± 0.20	--	--	--	--	*6.7 ± 0.42
Relative	0.184 ± 0.0078	--	--	--	--	0.220 ± 0.0119
Heart						
Absolute	186 ± 13.9	--	--	--	--	218 ± 10.3
Relative	6.20 ± 0.481	--	--	--	--	7.11 ± 0.286
Liver						
Absolute	1,668 ± 31	1,664 ± 62	1,524 ± 37	1,743 ± 52	1,684 ± 43	*2,060 ± 39
Relative	57.3 ± 0.67	55.7 ± 2.00	51.5 ± 1.03	58.9 ± 1.17	56.0 ± 0.78	**67.4 ± 1.11
FEMALE						
Number weighed	8	10	9	10	9	10
Body weight (grams)	24.7 ± 0.62	25.8 ± 0.66	26.0 ± 0.46	25.9 ± 0.48	*26.3 ± 0.94	**27.1 ± 0.38
Adrenal gland						
Absolute	9.2 ± 0.52	--	--	--	--	*10.3 ± 0.29
Relative	0.374 ± 0.0202	--	--	--	--	0.383 ± 0.0131
Heart						
Absolute	134 ± 7.4	--	--	--	--	**177 ± 8.3
Relative	5.41 ± 0.288	--	--	--	--	*6.53 ± 0.269
Liver						
Absolute	1,363 ± 57	1,458 ± 62	1,361 ± 34	*1,546 ± 53	1,366 ± 57	**1,763 ± 44
Relative	55.1 ± 1.02	56.5 ± 1.75	52.4 ± 0.69	59.7 ± 1.61	51.8 ± 0.66	**65.1 ± 1.20

(a) Mean ± standard error in milligrams (absolute) or milligrams per gram (relative) unless otherwise specified; P values vs. the hydrochloric acid aerosol controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
*P<0.05
**P<0.01

toxic changes associated with repeated epinephrine exposure. These changes were observed at concentrations of 5 mg/m³ or more. Because epinephrine is an endogenous hormone with potent and complex pharmacologic activity and because measurable exposures are probably limited to route-specific tissue sites (respiratory and gastrointestinal mucosa), concentrations for the 2-year studies were expected to result in daily doses that exceeded human therapeutic levels (34-69 µg/kg or 0.1-0.3 µg/cm² per day) but were less than one-half the maximum tolerated dose, the lowest dose commonly used in other NTP 2-year carcinogenicity studies. Mice were thus exposed for 6 hours per day, 5 days per week, to either 1.5 or 3 mg/m³ epinephrine for a maximum of 2 years. At this level of exposure, anticipated biologic effects were primarily expected at exposure sites in the respiratory and gastrointestinal epithelium.

FIFTEEN-MONTH STUDIES

The absolute kidney weights for mice exposed to 3 mg/m³ and the kidney weight to body weight ratio for male mice exposed to 3 mg/m³ were significantly lower than those for controls (Table G2). No differences in hematologic parameters were considered to be compound related (Table H2). No compound-related lesions were seen.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of exposed and control mice were generally similar throughout the studies (Table 11 and Figure 7). Hyperactivity was observed for exposed females for over 2 hours after the exposure period began. This effect was most noticeable for the first 7 months of the studies and was not observed after month 18.

TABLE 11. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

Weeks on Study	Chamber Control Av. Wt. (grams)	Chamber Control Number of Survivors	1.5 mg/m^3 Av. Wt. (grams)	1.5 mg/m^3 Wt. (percent of chamber controls)	1.5 mg/m^3 Number of Survivors	3 mg/m^3 Av. Wt. (grams)	3 mg/m^3 Wt. (percent of chamber controls)	3 mg/m^3 Number of Survivors
MALE								
0	24.8	50	25.4	102	50	25.7	104	50
1	27.2	50	27.8	102	50	27.5	101	50
2	28.5	50	29.7	104	50	29.1	102	50
3	29.8	50	29.7	100	50	29.3	98	50
4	30.2	50	31.5	104	50	28.9	96	50
5	30.1	50	31.2	104	50	30.6	102	50
6	31.1	50	31.5	101	50	31.1	100	50
7	30.9	50	32.6	106	50	30.6	99	50
8	32.0	50	32.7	102	50	31.6	99	50
9	32.4	50	32.2	99	50	31.8	98	50
10	31.9	50	33.3	104	50	31.6	99	50
11	32.0	50	33.6	105	50	31.6	99	50
12	32.4	50	32.0	99	50	31.3	97	50
13	32.0	50	32.0	100	50	32.7	102	50
17	32.3	50	33.7	104	50	33.0	102	50
21	34.0	50	35.1	103	50	34.3	101	50
26	35.5	50	36.4	103	50	35.7	101	50
30	36.0	50	36.4	101	50	35.6	99	50
34	37.1	50	36.4	98	49	36.3	98	49
38	37.0	50	38.7	105	49	37.4	101	49
43	37.0	50	39.3	106	49	39.4	106	49
45	37.3	50	38.9	104	49	39.9	107	49
50	40.2	49	41.5	103	49	38.5	96	48
54	39.3	49	39.7	101	49	39.1	99	48
59	40.3	48	40.1	100	49	39.0	97	47
64	39.9	48	39.4	99	48	37.8	95	46
68	39.4	48	40.3	102	45	39.2	99	46
73	40.9	48	41.3	101	44	40.0	98	45
77	41.0	48	41.3	101	43	40.5	99	44
82	40.4	44	40.9	101	41	40.0	99	42
87	41.1	42	41.1	100	41	40.1	98	41
91	41.7	39	42.3	101	41	41.0	98	41
95	41.2	39	41.8	101	38	39.4	96	40
99	40.2	37	41.8	104	35	39.5	98	40
104	39.6	33	40.8	103	34	38.5	97	37
Mean for weeks								
1-13	30.8		31.5	102		30.6	99	
17-50	36.3		37.4	103		36.7	101	
54-104	40.4		40.9	101		39.5	98	
FEMALE								
0	20.1	50	19.8	99	50	20.3	101	50
1	22.1	50	22.5	102	50	21.2	96	50
2	24.0	50	22.9	95	50	23.9	100	50
3	24.2	50	23.5	97	50	24.4	101	50
4	24.0	50	25.2	105	50	24.8	103	50
5	25.5	50	25.6	100	50	25.9	102	50
6	26.6	50	26.7	100	50	27.0	102	50
7	25.6	50	26.7	104	50	27.3	107	50
8	26.5	50	26.5	100	50	27.7	105	50
9	27.2	50	26.2	96	50	27.6	101	50
10	26.3	50	28.0	106	50	27.0	103	50
11	27.7	50	28.1	101	50	28.2	102	50
12	26.8	50	26.9	100	50	27.4	102	50
13	27.1	50	27.4	101	50	27.7	102	50
17	28.4	50	28.2	99	50	28.7	101	50
21	29.6	50	30.8	104	50	29.6	100	50
26	29.6	50	29.7	100	50	31.2	105	50
30	30.7	50	30.1	98	50	32.6	106	50
34	29.7	49	30.6	103	50	31.6	106	50
38	30.7	49	31.2	102	50	31.7	103	49
43	32.3	49	31.3	97	50	31.7	98	49
45	32.7	49	30.9	94	50	32.4	99	49
50	33.0	48	33.0	100	50	32.5	98	48
54	32.4	48	32.7	101	50	32.9	102	48
59	32.9	48	32.6	99	49	33.3	101	48
64	32.3	48	31.8	98	49	32.6	101	46
68	32.0	48	32.3	101	48	33.1	103	46
73	33.6	47	32.4	96	47	34.1	101	46
77	33.4	47	32.7	98	47	34.3	103	46
82	33.5	45	32.8	98	46	34.7	104	46
87	34.0	44	33.8	99	44	35.3	104	46
91	34.6	43	33.9	98	43	35.9	104	45
95	35.1	43	34.3	98	40	34.8	99	44
99	35.3	39	34.2	97	39	35.1	99	39
104	34.5	34	34.1	99	35	35.1	102	36
Mean for weeks								
1-13	25.7		25.9	101		26.2	102	
17-50	30.7		30.6	100		31.3	102	
54-104	33.6		33.1	99		34.3	102	

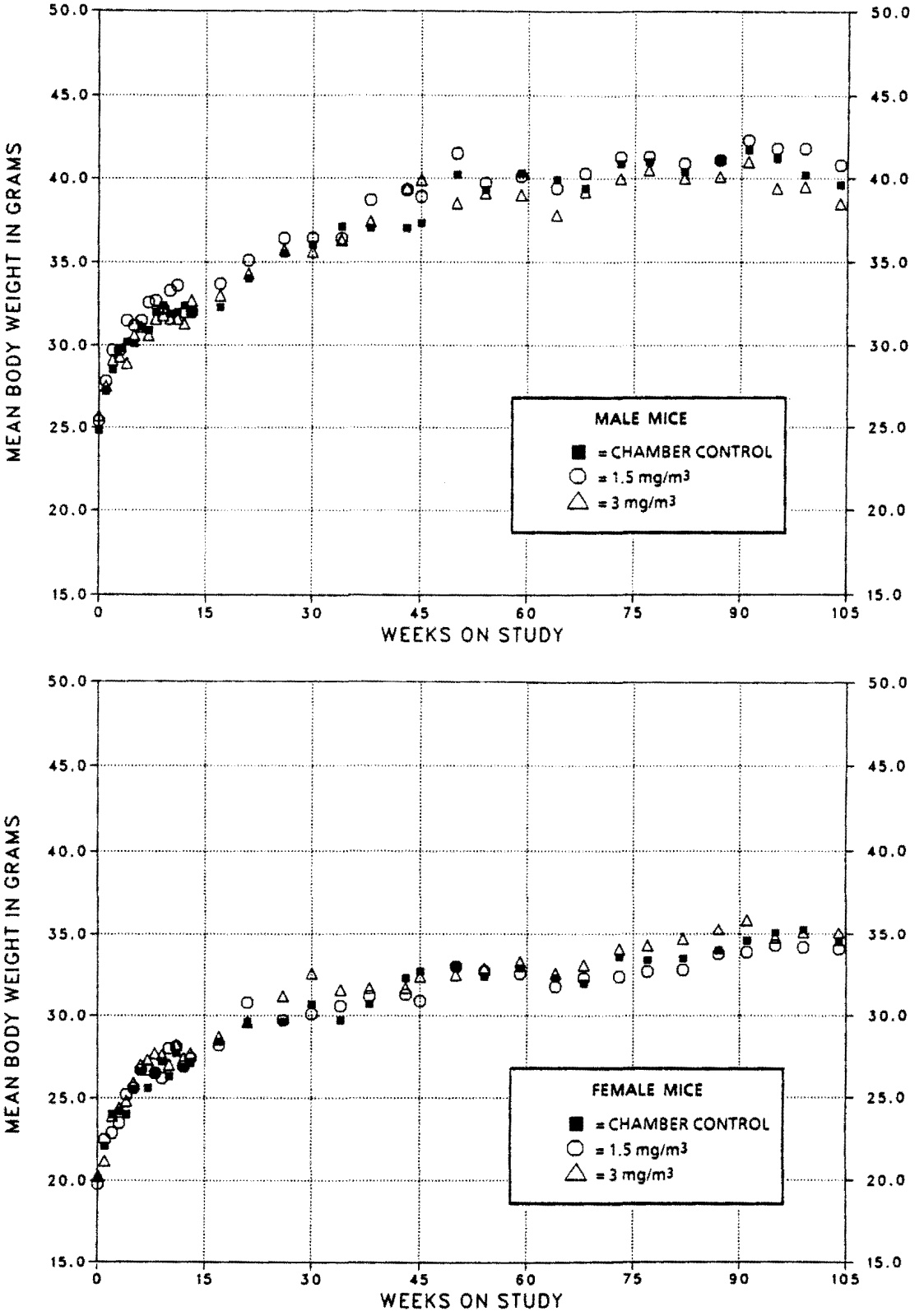

FIGURE 7. GROWTH CURVES FOR MICE EXPOSED TO *l*-EPINEPHRINE HYDROCHLORIDE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice exposed to epinephrine hydrochloride at the concentrations used in these studies and for controls are shown in Table 12 and in the Kaplan and Meier curves in Figure 8. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the nasal passage and uterus.

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

TABLE 12. SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m^3	3 mg/m^3
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	11	4	4
Moribund kills	6	12	10
Animals surviving to study termination	33	34	36
Mean survival (days)	695	680	686
Survival P values (b)	0.666	1.000	0.727
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	11	7	8
Moribund kills	7	8	9
Animals surviving to study termination	32	35	(c) 34
Mean survival (days)	700	702	699
Survival P values (b)	0.781	0.768	0.852

(a) First day of termination period: male--741; female--742
(b) The result of the life table trend test is in the chamber control column, and the results of the life table pairwise comparisons with the chamber controls are in the dosed columns.
(c) One animal died or was killed in a moribund condition during the termination period and was combined, for statistical purposes, with those killed at termination.

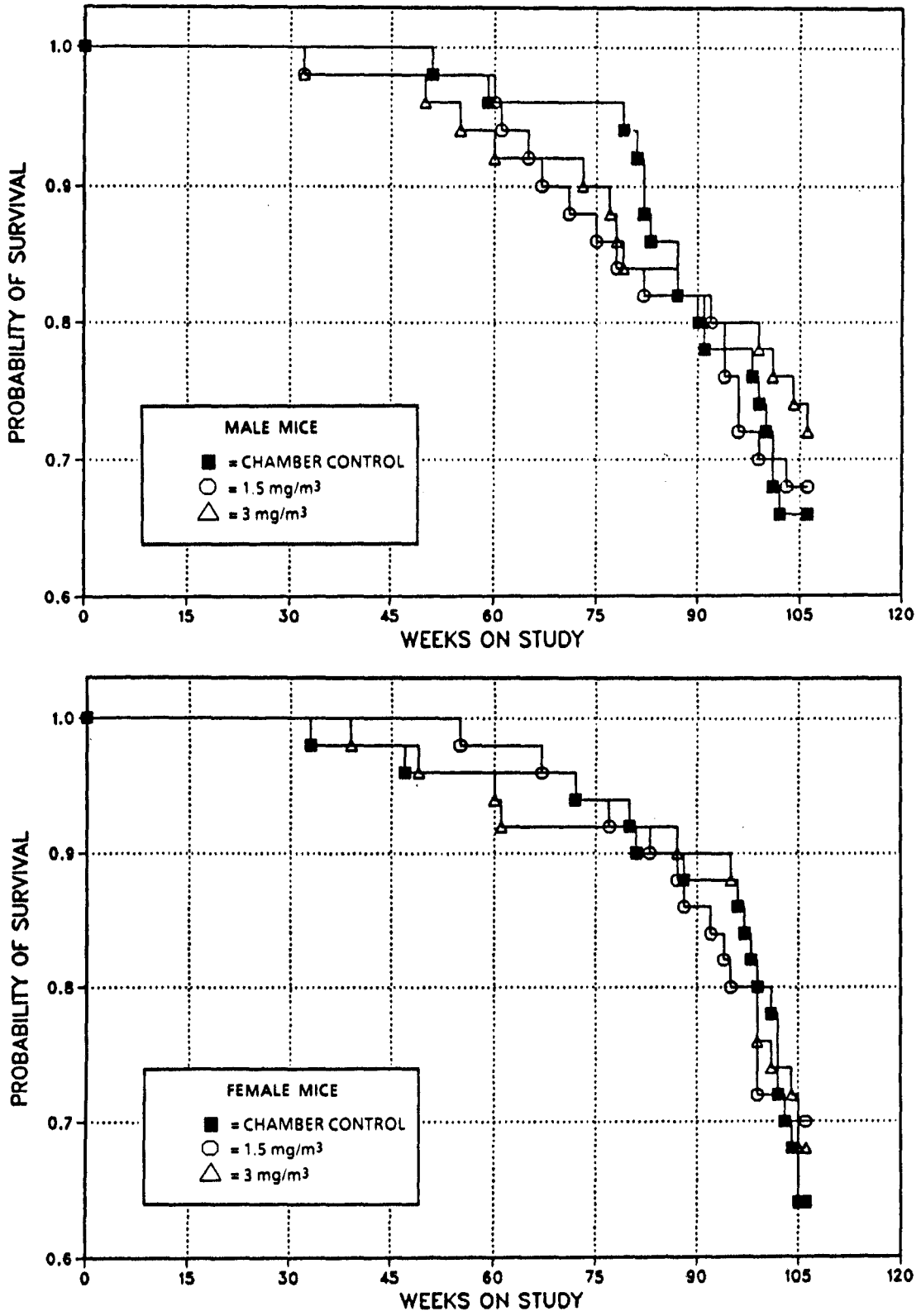

FIGURE 8. KAPLAN-MEIER SURVIVAL CURVES FOR MICE EXPOSED TO *l*-EPINEPHRINE HYDROCHLORIDE BY INHALATION FOR TWO YEARS

Nasal Passage: Increased incidences of usually minimal-to-mild nonneoplastic changes were seen in the nasal passage of exposed male and female mice (Table 13). The incidence of hyaline degeneration of the olfactory epithelium in exposed males and hyaline degeneration of the respiratory epithelium in exposed females was markedly increased compared with that in controls, whereas the incidence of suppurative inflammation was slightly increased in both exposed males and females. Incidences of hyaline degeneration of olfactory epithelium were not different among groups of females, but lesion severity was slightly increased in the high dose female groups (average severity: mild in the control and low dose groups and moderate in the high dose group). The effect was more widespread in females than in males, as both the olfactory epithelium and respiratory epithelium were affected. Hyaline degeneration was characterized by a slight increase in the size of the epithelial cells with accumulation of homogeneous eosinophilic material within the cytoplasm (Figure 9). A small papilloma of the respiratory epithelium occurred in a single high dose male mouse.

Uterus: Endometrial stromal polyps or sarcomas (combined) occurred with a significant positive trend, but the incidences in the exposed groups were not significantly greater than that in controls and were within the range of historical incidences (Table 14).

TABLE 13. NUMBERS OF MICE WITH SELECTED LESIONS OF THE NASAL PASSAGE IN THE TWO-YEAR INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

Site/Lesion	Male			Female		
	Chamber Control	1.5 mg/m^3	3 mg/m^3	Chamber Control	1.5 mg/m^3	3 mg/m^3
Number examined	50	50	50	50	48	50
Nasal passage						
Suppurative inflammation	1	4	3	1	*7	*8
Olfactory epithelium						
Hyaline degeneration	3	**17	**39	44	43	47
Respiratory epithelium						
Hyaline degeneration	5	2	2	7	**28	**19
Papilloma	0	0	1	0	0	0

*P<0.05 vs. controls
**P<0.01 vs. controls

TABLE 14. ENDOMETRIAL STROMAL NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE (a)

	Chamber Control	1.5 mg/m^3	3 mg/m^3
Polyp			
Overall Rates	0/50 (0%)	1/50 (2%)	3/50 (6%)
Sarcoma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Polyp or Sarcoma (b)			
Overall Rates	0/50 (0%)	1/50 (2%)	4/50 (8%)
Terminal Rates	0/32 (0%)	1/35 (3%)	2/34 (6%)
Day of First Observation		742	730
Logistic Regression Tests	P=0.027	P=0.518	P=0.064

(a) For a complete explanation of the entries in this table, see Table D3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence for chamber controls at study laboratory (mean ± SD): 8/385 (2% ± 2%); historical incidence for untreated controls in NTP studies: 39/1,675 (2% ± 2%)

l-Epinephrine was considered to give an equivocal response when tested for mutation induction in *Salmonella typhimurium* strain TA100 in the absence of exogenous metabolic activation; no mutagenic activity was observed in TA100 in the presence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 or in strains TA98, TA1535, or TA1537 with or without S9 (Table J1; Zeiger et al., 1987). In cytogenetic tests with Chinese hamster ovary (CHO) cells, epinephrine gave an equivocal response in the test for sister chromatid exchange (SCE) induction without S9 activation: the first trial was considered negative because the response at the highest dose tested (10 μg/ml) was not statistically significant, but in trial 2, the response produced at this same concentration of epinephrine was significant, and the trial was called weakly positive. Epinephrine was negative for SCE induction in the presence of Aroclor 1254-induced male Sprague Dawley rat S9 (Table J2). Epinephrine did not induce chromosomal aberrations in CHO cells with or without S9 (Table J3). The methodology and full results are presented in Appendix J.

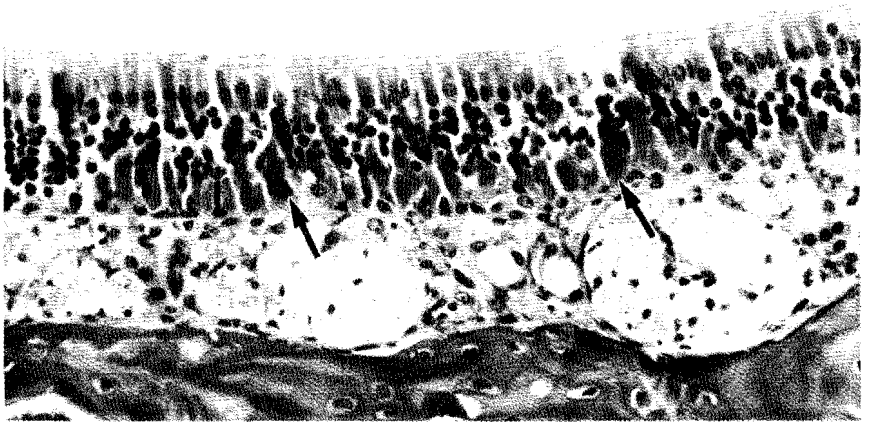

Figure 9. Hyaline degeneration of olfactory epithelium in the nasal passage of a female mouse exposed to 3 mg/m^3 *l*-epinephrine hydrochloride by inhalation for 2 years. Affected cells contain intracytoplasmic droplets (arrows).

IV. DISCUSSION AND CONCLUSIONS

Short-Term Studies
Two-Year Studies
Conclusions

IV. DISCUSSION AND CONCLUSIONS

Toxicity and carcinogenicity studies of *l*-epinephrine hydrochloride were conducted in F344/N rats and $B6C3F_1$ mice as part of a benzyl alcohol class study. Benzyl alcohols were studied because of reports that representatives (soterenol hydrochloride, mesuprine hydrochloride, salbutamol sulfate, and terbutaline sulfate) from this chemical class cause mesovarial leiomyomas in rats (Nelson and Kelly, 1971; Nelson et al., 1972; Jack et al., 1983; Gopinath and Gibson, 1987) and because these chemicals have the potential ability to form electrophilic benzyl carbonium ions. Another benzyl alcohol (medroxalol) was associated with an increased incidence of uterine leiomyomas in mice (Gibson et al., 1987).

The inhalation route of exposure was used for the 14-day, 13-week, and 2-year studies because of the extensive clinical use of this drug in aerosol formulations for the treatment of bronchial asthma and other bronchoconstrictive diseases (Harvey, 1975; Miller, 1978; Martindale, 1982; AHFS, 1988; PDR, 1989). Factors that limit the systemic action of epinephrine after the inhalation of aerosols include the following: (1) When epinephrine aerosols are inhaled, the majority of the drug is either exhaled or deposited in the mouth and swallowed to be rapidly inactivated in the intestinal mucosa and liver before it reaches the systemic circulation. Less than 10% and no more than 15% reaches the lungs where systemic absorption may occur (Warren et al., 1986; Heilborn et al., 1986). Predominant changes in response to the inhalation exposure to epinephrine aerosols would therefore be anticipated in the respiratory and gastrointestinal mucosa. (2) Tolerance or refractoriness may develop after repeated exposures to this drug (Martindale, 1982; Weiner, 1985), and rebound bronchospasm can occur when the drug is withheld during clinical use (AHFS, 1988). Tolerance generally does not affect the therapeutic effect (bronchodilation) but does diminish the toxic side effects (tremor, tachycardia, and palpitations) of β-adrenergic agonists during extended inhalation asthma therapy (Barnes, 1989). (3) The bioavailability of epinephrine following endobronchial instillation in swine (40%) and dogs (80%-85%) indicates the possibility of some in situ binding and/or metabolism by lung tissue (Schuttler et al., 1987; Hornchen et al., 1988). (4) The daily exposures occurred over 6 hours, rather than as a series of bolus exposures as in therapeutic use. Thus, although the overall daily exposures during these animal studies exceed daily therapeutic doses, the blood levels of epinephrine are expected to be lower than those encountered clinically.

Due to these factors, epinephrine-mediated systemic effects reported here were primarily limited to the short-term studies, with changes during the long-term studies primarily restricted to the exposure sites (respiratory and gastrointestinal mucosa).

Short-Term Studies

Results from the 14-day studies showed that rats died after repeated exposure at concentrations of epinephrine hydrochloride lower than those at which the mice died (minimum concentrations for epinephrine-induced deaths: male rats, 12.5 mg/m^3; female rats, 25 mg/m^3; male and female mice, 50 mg/m^3). The results in rats confirm previous observations that lethal doses of epinephrine are lower for males than for females (Astarabadi and Essex, 1952). Male rats also appeared to be more sensitive to the deleterious effects of epinephrine hydrochloride on body weight gain than were female rats. The increased sensitivity of male rats to epinephrine-induced toxicity has not been fully explained; epinephrine depresses liver microsomal enzyme activity from males but not from females (Kato and Gillette, 1965). Rats may be more susceptible than mice to the lethal effects of epinephrine because of the lower normal overall oxygen utilization by rats (0.89 ml/g per hour) compared with that by mice (1.9 ml/g per hour) (Harkness and Wagner, 1989), reflecting differing overall basal metabolic rates (Ganong, 1969).

The observed clinical signs of increased respiratory rate and exaggerated reflex action are consistent with the previously described central nervous system excitatory and pulmonary effects of epinephrine (Harvey, 1975; Weiner, 1985; Arena and Drew, 1986; PDR, 1989). The respiratory rate was increased at all exposure concentrations in both rats and mice, and rats exposed to 100 and 200 mg/m^3 became dyspneic. Labored respiration was reported in rats after

toxic exposure to epinephrine by the subcutaneous and intravenous routes (Voegtlin and Dyer, 1925). In the current studies, exaggerated reflexes to auditory and visual stimuli were limited to mice exposed to 100 or 200 mg/m^3 epinephrine. The increased lacrimation noted in rats exposed to 100 or 200 mg/m^3 could be an irritant response to the acidic aerosol or a pharmacologic response to epinephrine. Although epinephrine by itself can induce lacrimation (Weiner, 1985), this clinical sign is more likely due to the synergistic action of epinephrine and the acidic aerosol vehicle.

In the 13-week studies, epinephrine hydrochloride did not affect the body weight gain or survival of rats or mice at any exposure concentration (0-40 mg/m^3). The nasal mucosa was affected in both the short-term and long-term studies in rats and mice, with epinephrine inducing squamous metaplasia of the anterior nasal mucosa in the 13-week studies. This lesion was found in the anterior dorsal nasal mucosa and was characterized by the change of the normal single layer of cuboidal epithelium covering the nasal turbinates to several layers of squamous epithelium. In the 13-week studies, this lesion was restricted to rats and mice in the 40 mg/m^3 groups. Inflammatory changes in the nasal turbinates of rats exposed to 20 or 40 mg/m^3 epinephrine were also noted. Metaplasia occurs when one adult cell type in a particular tissue is replaced by another cell type (Pitot, 1981; Maronpot, 1990). The most common type of epithelial metaplasia involves the change of pseudostratified columnar epithelium of the respiratory mucosa to squamous epithelium. It commonly occurs in response to long-term irritation and inflammation and can also result from vitamin A deficiency. Neoplastic transformation occasionally occurs at a site of metaplasia. Formaldehyde is an example of a widely used irritant (Jaeger and Gearhart, 1982) which has been shown to cause squamous cell metaplasia in the nasal turbinates in rats (Rusch et al., 1983), monkeys (Rusch et al., 1983), and mice (Maronpot et al., 1986) and squamous cell carcinomas of the nasal mucosa in rats (Chang et al., 1983). The pathogenesis of epinephrine-induced changes in the nasal turbinates observed in the current studies may involve a direct action of epinephrine, which is known to cause localized necrotic reactions at exposure sites, arterial walls, and the myocardium (Weiner, 1985; Arena and Drew, 1986; AHFS, 1988), or by an indirect action whereby epinephrine may decrease the irritant threshold to the acidic aerosol to which all groups were exposed during these short-term studies.

As in the 14-day studies, increased and labored respiration resulted from epinephrine hydrochloride exposure in the 13-week studies, but this was limited to rats and mice exposed to 40 mg/m^3. Such labored respiration could be due to the pharmacologic action of epinephrine (stimulation of central respiratory centers) or be a result of a toxic effect (pulmonary edema) (Harvey, 1975; Weiner, 1985; Arena and Drew, 1986; Ellenhorn and Barceloux, 1988). The increased respiratory rates observed in the 13-week studies were probably the result of a pharmacologic action of epinephrine because no abnormal histologic changes in the lung were observed. Labored respiration occurred primarily during the first 3 weeks of exposure. This diminishing effect is characteristic of sympathomimetic amines, which show a tolerance to many pharmacologic effects (Goldstein et al., 1974; Martindale, 1982; Weiner, 1985).

In the 13-week studies, laryngeal myopathy was noted in 9/10 male and 6/10 female rats exposed to 40 mg/m^3 and in 4/10 males and 1/10 females exposed to 20 mg/m^3. This lesion was characterized by mild-to-moderate multifocal myofiber necrosis with mononuclear inflammatory cell accumulation, increased numbers of satellite cell nuclei, regenerative fibers, and minimal fibrosis. The lesion was limited to rats and was more severe in the male rat that died during week 1, when labored respiration was observed. Other investigators have noted that subcutaneous injections of epinephrine cause skeletal muscle necrosis in rats, due to vascular constriction (Benoit, 1978). The laryngeal myopathy observed in these studies is most likely due to exertion of the laryngeal muscles associated with epinephrine-induced labored respiration. The degenerative changes occurring in exertional myopathies are thought to result from the rapid utilization of glycogen, which generates heat and lactic acid (Hulland, 1985). These metabolic products are postulated to initiate a sequence of

destructive changes in contractile proteins. Epinephrine stimulates the same changes (glycogenolysis and increased tissue lactate) (Mayer, 1980; Weiner, 1985; Ellenhorn and Barceloux, 1988).

Finally, inflammatory changes of the glandular stomach were noted in mice exposed to 10, 20, or 40 mg/m^3 epinephrine hydrochloride in the 13-week studies. The incidence and severity were dose related. Although the pathogenesis for these inflammatory changes is unclear, it is known that epinephrine affects gastrointestinal circulation (Schnitzlein, 1957; Kerr and Swan, 1981; Yano et al., 1981; Randall et al., 1989) and motility (Lands et al., 1947; Harvey, 1975; Weiner, 1985). Recently, Randall et al. (1989) administered epinephrine via arteries supplying the small intestine of dogs and noted hemostasis and associated mucosal damage (observed grossly).

The primary microscopic changes associated with epinephrine administration as outlined above involved exposure sites in the respiratory and gastrointestinal epithelium. Several other incidental changes occurred which were either attributable to or associated with the systemic pharmacologic action of epinephrine (piloerection in rats and uterine atrophy in mice) (Weiner, 1985) or which were not clearly dose related (hepatocellular vacuolization in mice). Organ weight changes were observed in the adrenal gland and heart in rats and mice and liver in mice, but these changes were not clearly associated with dose-related microscopic changes.

Two-Year Studies

Dose selection for the 2-year studies was based on a review of the results of the 13-week studies, with consideration given to any pharmacologic change that could confound the primary objective of carcinogenicity evaluation and on considerations of human levels of exposure to this endogenous hormone. The primary purpose of the short-term studies was to establish no-effect concentrations for any pharmacologic or toxic effects due to repeated epinephrine exposure. High concentrations for the 2-year studies were considerably lower than the estimated maximum tolerated dose (MTD) of 20 mg/m^3 for rats and mice. The estimated MTD was based on epinephrine-induced microscopic changes because epinephrine hydrochloride did not affect growth and because pharmacologic effects such as labored respiration were primarily limited to the 40 mg/m^3 dose group. In the 14-day studies, however, labored respiration was observed for rats and mice at all exposure concentrations, including the lowest concentration (12.5 mg/m^3). High exposure concentrations were therefore set at a level lower than this pharmacologic concentration.

Because epinephrine is an endogenous hormone and because aerosolized preparations are expected to induce selected changes at target sites where localized concentrations are relatively high, primary consideration was placed on selecting concentrations for the current 2-year studies which would be equivalent to those used during prolonged therapeutic use of the aerosolized drug by humans. Thus, the high concentration for mice (3 mg/m^3) was approximately one-seventh the MTD, whereas the high concentration for rats (5 mg/m^3) was approximately one-fourth the MTD. The selection of doses for these studies, therefore, represents a departure from the normal practice of utilizing doses that represent the MTD and one-half the MTD based on body weight changes during the 13-week studies (Gart et al., 1979; Bernstein et al., 1985). Tables 15 and 16 summarize exposure concentrations to epinephrine hydrochloride aerosols normalized to body weight and surface area of rats and mice in the studies reported here.

Each mist or spray of aerolized epinephrine formulations for human use delivers approximately 200-300 µg epinephrine hydrochloride per exposure by oral inhalation (Martindale, 1982; AHFS, 1988; PDR, 1989). The recommended maximum use for symptomatic relief of bronchoconstriction is one exposure every 3 hours for a total of eight exposures, although followup second exposures are permitted 1 minute after the initial exposure for a total of 16 possible exposures per 24 hours. Thus, under normal use conditions, a maximum exposure of 2.4-4.8 mg epinephrine hydrochloride per 24 hours would be expected. Corresponding daily exposure ranges normalized for body weight, metabolic body weight, and body surface area are 34-69 µg/kg, 99-198 µg/kg, and 0.1-0.3 µg/cm^2.

TABLE 15. SUMMARY OF DAILY EXPOSURES TO AEROSOLIZED *l*-EPINEPHRINE HYDROCHLORIDE IN THE TWO-YEAR INHALATION STUDIES IN RATS (a)

	Aerosol Concentration		Biologic Units Used to Normalize Exposures (b)
	1.5 mg/m³	5.0 mg/m³	
MALE			
Week 1	407 µg/kg	1,392 µg/kg	BW
Week 103	175 µg/kg	585 µg/kg	BW
TWA (c)	194 µg/kg	656 µg/kg	BW
TWA	153 µg/kg	516 µg/kg	MBW
TWA	0.1 µg/cm²	0.5 µg/cm²	SA
FEMALE			
Week 1	586 µg/kg	1,969 µg/kg	BW
Week 103	238 µg/kg	805 µg/kg	BW
TWA	295 µg/kg	996 µg/kg	BW
TWA	210 µg/kg	706 µg/kg	MBW
TWA	0.2 µg/cm²	0.7 µg/cm²	SA

(a) Daily exposures were calculated with the following assumptions: The respiratory rate and tidal volume of naive F344 rats are 129 breaths per minute and 1.09 ml per breath (Chang et al., 1981). All rats respired normally during each daily 6-hour exposure session.
(b) BW = body weight; MBW = metabolic body weight (NAS/NRC, 1966); SA = surface area
(c) TWA = time-weighted average

TABLE 16. SUMMARY OF DAILY EXPOSURES TO AEROSOLIZED *l*-EPINEPHRINE HYDROCHLORIDE IN THE TWO-YEAR INHALATION STUDIES IN MICE (a)

	Aerosol Concentration		Biologic Units Used to Normalize Exposures (b)
	1.5 mg/m³	3.0 mg/m³	
MALE			
Week 1	435 µg/kg	876 µg/kg	BW
Week 104	297 µg/kg	626 µg/kg	BW
TWA (c)	319 µg/kg	657 µg/kg	BW
TWA	141 µg/kg	286 µg/kg	MBW
TWA	0.2 µg/cm²	0.4 µg/cm²	SA
FEMALE			
Week 1	538 µg/kg	1,137 µg/kg	BW
Week 104	355 µg/kg	687 µg/kg	BW
TWA	392 µg/kg	760 µg/kg	BW
TWA	164 µg/kg	318 µg/kg	MBW
TWA	0.3 µg/cm²	0.5 µg/cm²	SA

(a) Daily exposures were calculated with the following assumptions: The respiratory rate and tidal volume of naive laboratory mice are 140 breaths per minute and 0.16 ml per breath (Harkness and Wagner, 1989). All mice respired normally during each daily 6-hour exposure session.
(b) BW = body weight; MBW = metabolic body weight (NAS/NRC, 1966); SA = surface area
(c) TWA = time-weighted average

Thus, the high concentrations used in the 2-year rat and mouse studies reported here either exceed maximum human therapeutic levels by approximately a factor of 10 (doses normalized for body weight) or 2 (doses normalized for body surface area).

Epinephrine did not affect growth or survival of rats or mice in the 2-year studies; no compound-related clinical signs were noted. The only deleterious changes noted in either the rat or mouse studies involved the nasal epithelium. For rats, this change involved increased incidences of

suppurative inflammation, dilatation of the nasal glands (Bowman's and septal), and hyperplasia of the respiratory epithelium in epinephrine-exposed animals (see Table 7). The minimally effective concentrations for these changes were 1.5 mg/m^3 and 5 mg/m^3 for females and males, respectively. The hyperplasia was characterized by transformation of the normal columnar epithelium into a pseudostratified type with increased thickness and number of goblet cells. Epinephrine was also associated with a nonsignificant increase in squamous metaplasia, which was focal and minimal in severity. This involved the replacement of normal columnar epithelium by two or more layers of stratified squamous epithelium. Although the nasal epithelium was also affected in mice, the microscopic changes were different. As with the rats, suppurative inflammation was noted, but only in 1.5 and 3 mg/m^3 females. Hyperplasia and metaplasia were not observed. Instead, hyaline degeneration of the olfactory (males) and respiratory (females) epithelium were noted at increased incidences in exposed mice in the 1.5 and 3 mg/m^3 groups. Since the same site (nasal turbinates) was involved in chemical-mediated nonneoplastic changes by the same route of exposure in both the 13-week and 2-year studies, it is hypothesized that similar etiologic factors (direct necrotic action of epinephrine and/or epinephrine-induced depression of the irritant threshold to acidic aerosol) may be causative for these nasal changes (Weiner, 1985; Arena and Drew, 1986).

Administration of epinephrine by inhalation for 2 years to F344/N rats was not associated with increased incidences of neoplasms at any site. The incidences of thyroid C-cell neoplasms in control male rats and clitoral gland neoplasms in control female rats were high relative to the mean incidence in historical controls. Thus, the marginally decreased incidences of these neoplasms in the respective exposed groups were not considered chemically related.

In B6C3F$_1$ mice exposed to epinephrine for 2 years, the only noteworthy observation was the occurrence of stromal polyps in the uterus of females (chamber control, 0/50; 1.5 mg/m^3, 1/50; 3 mg/m^3, 3/50) and a stromal sarcoma in the 3 mg/m^3 group. The incidence of stromal polyps or sarcomas (combined) occurred with a statistically significant positive trend, but the incidences in the exposed groups were not statistically greater than that in controls. Furthermore, the incidences of these neoplasms did not exceed the range in historical controls (dosed feed studies) for all National Toxicology Program (NTP) laboratories (0%-8% for polyps and 0%-4% for sarcomas).

Concern about the potential carcinogenic effects of β-adrenergic agents and sympathomimetic amines developed after reports that soterenol hydrochloride and mesuprine hydrochloride induced mesovarial leiomyomas in Charles River CD (Sprague Dawley-derived) rats (Nelson and Kelly, 1971; Nelson et al., 1972). Soterenol and mesuprine are structurally related compounds with similar pharmacologic activities, both acting as selective β_2-adrenergic stimulants (β_2-agonists). Since then, additional studies have shown that similar β_2-agonists, terbutaline and salbutamol, also cause mesovarial leiomyomas in rats (Jack et al., 1983) and that the concurrent administration of propranolol (a specific β-antagonist or β-blocker) completely prevented the induction of leiomyomas in rats given salbutamol. The mesovarium is a peritoneal fold containing a small amount of smooth muscle that suspends the ovary within the peritoneal cavity. Apperley et al. (1978) demonstrated that isolated mesovarial strips contain primarily β_2-adrenergic receptors.

More recently, another β-adrenergic agonist, medroxalol hydrochloride, was shown to cause uterine leiomyomas in CD-1 mice (Sells and Gibson, 1987; Gibson et al., 1987). However, it did not induce mesovarial leiomyomas in Long Evans rats. Propranolol, given concurrently to mice, prevented the induction of the uterine neoplasms by medroxalol. Because of the selective pharmacologic effects of these agents and the ability of propranolol to prevent the development of leiomyomas, it has been proposed that the β-stimulation is an important part of the causal mechanism. The differences in the response of rats and mice to these agents may be related to the relative abundance of the receptor subtypes in tissues and the relative receptor selectivity of these agents.

Since epinephrine has β-stimulatory effects, it is important to note that epinephrine administered by inhalation did not cause the development of mesovarial leiomyomas in rats or uterine leiomyomas in mice in these current studies. This may be due to differences in strain susceptibility, differences in the relative α- and β-stimulatory effects, or differences in the effective dose at the target sites. Although epinephrine stimulates β_2 receptors, it also stimulates β_1, postsynaptic α_1, and presynaptic α_2 receptors; the latter inhibits the release of endogenous epinephrine from the nerve terminals. Further, down-regulation of receptor sites is known to occur with the prolonged administration of adrenergic compounds. It is not known whether or how these factors might affect the ability of β_2-agonists to induce leiomyomas in susceptible organs.

Although uterine leiomyomas were not increased in female mice exposed to epinephrine, stromal polyps and a stromal sarcoma occurred only in exposed females as noted above. However, the β_2-agonist medroxalol did not induce uterine stromal neoplasms in mice and no other β_2-agonists or sympathomimetic agents were reported to cause uterine stromal neoplasms. Thus, it is difficult to attribute the small increase in uterine stromal neoplasms in mice in the current study to the administration of epinephrine.

Previously reported studies of ephedrine sulfate, a sympathomimetic amine believed to exert its effects indirectly through the release of norepinephrine from nerve terminals, and phenylephrine, a sympathomimetic amine that is a selective α-agonist at low doses, demonstrated no evidence of carcinogenicity for F344/N rats or $B6C3F_1$ mice (NTP, 1986, 1987). Further, a related indirectly acting sympathomimetic amine studied by the NTP, *dl*-amphetamine sulfate, is also negative for carcinogenicity (NTP, 1990). None of these compounds produced mesovarial leiomyomas in rats or uterine leiomyomas in mice.

Maximum exposure concentrations for the 2-year studies, after equilibration for body weight or surface area, represented daily exposures that were approximately 2-20 times those maximally encountered by humans during prolonged therapeutic use. Due to the route of exposure (inhalation of aerosol) and the relatively complete and rapid metabolism of this endogenous neurotransmitter hormone, the primary anticipated and observed changes during the short-term and 2-year studies reported here were limited to the respiratory and gastrointestinal mucosa. Epinephrine concentrations at the respiratory epithelium induced cellular changes (metaplasia) in the nasal mucosa of both species in the 13-week studies and other nonneoplastic changes (hyperplasia) at this same route-specific target site in the short-term and 2-year studies. Other changes interpreted to be exposure-site specific for epinephrine were laryngeal myopathy (13-week rat studies) and inflammatory changes of the glandular stomach (13-week mouse studies). Because the concentrations selected for the 2-year studies were not set at one-half the MTD and the MTD according to routine NTP practice (Gart et al., 1979; Bernstein et al., 1985), the 2-year study results are not considered adequate for assessing the carcinogenic activity of this compound. Even though epinephrine concentrations were probably adequate at the primary exposure site (respiratory epithelium) as evidenced by proliferative changes at this site, exposure concentrations at other sites were probably not sufficient to induce such changes.

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

IV. DISCUSSION AND CONCLUSIONS

Conclusions

Under the conditions of these 2-year studies, no carcinogenic effects were observed in male or female F344/N rats exposed to aerosols containing 1.5 or 5 mg/m^3 *l*-epinephrine hydrochloride for 2 years or in B6C3F$_1$ mice exposed to 1.5 or 3 mg/m^3 *l*-epinephrine hydrochloride for 2 years. However, these studies were considered to be *inadequate studies of carcinogenic activity* because the concentrations used, which were chosen to represent multiples of human therapeutic doses, were considered too low for the animals to have received an adequate systemic challenge from the compound.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 6.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on pages 9-10.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m^3	5 mg/m^3
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(48)	*(50)	(49)
Leukemia mononuclear			1 (2%)
Intestine large, cecum	(49)	*(50)	(46)
Leukemia mononuclear			2 (4%)
Intestine large, colon	(50)	*(50)	(47)
Leukemia mononuclear			2 (4%)
Intestine large, rectum	(50)	*(50)	(45)
Leukemia mononuclear			1 (2%)
Intestine small, duodenum	(50)	*(50)	(47)
Leukemia mononuclear			1 (2%)
Intestine small, ileum	(49)	*(50)	(44)
Leukemia mononuclear			1 (2%)
Intestine small, jejunum	(50)	*(50)	(45)
Leukemia mononuclear			1 (2%)
Liver	(50)	*(50)	(49)
Leukemia monocytic		1 (2%)	
Leukemia mononuclear	18 (36%)	19 (38%)	21 (43%)
Neoplastic nodule	1 (2%)	1 (2%)	
Mesentery	*(50)	*(50)	*(50)
Sarcoma		1 (2%)	
Schwannoma, NOS		1 (2%)	
Pancreas	(50)	*(50)	(49)
Leukemia mononuclear	3 (6%)	5 (10%)	5 (10%)
Salivary glands	(50)	*(50)	(49)
Leukemia mononuclear	3 (6%)	4 (8%)	1 (2%)
Stomach, forestomach	(49)	*(50)	(48)
Leukemia mononuclear	2 (4%)	2 (4%)	1 (2%)
Sarcoma	1 (2%)		
Stomach, glandular	(50)	*(50)	(48)
Leukemia mononuclear	2 (4%)	2 (4%)	1 (2%)
Tongue	*(50)	*(50)	*(50)
Papilloma squamous	1 (2%)		
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Leukemia mononuclear	3 (6%)	3 (6%)	5 (10%)
Schwannoma, NOS	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	*(50)	(49)
Leukemia mononuclear	6 (12%)	4 (8%)	11 (22%)
Osteosarcoma, metastatic, bone		1 (2%)	
Adrenal gland, medulla	(50)	*(50)	(48)
Leukemia mononuclear	7 (14%)	3 (6%)	10 (21%)
Pheochromocytoma malignant		1 (2%)	1 (2%)
Pheochromocytoma benign	9 (18%)	2 (4%)	14 (29%)
Pheochromocytoma benign, multiple	2 (4%)	1 (2%)	2 (4%)
Islets, pancreatic	(50)	*(50)	(49)
Adenoma	5 (10%)	1 (2%)	1 (2%)
Carcinoma	1 (2%)	1 (2%)	
Parathyroid gland	(43)	*(50)	(37)
Leukemia mononuclear	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
ENDOCRINE SYSTEM (Continued)			
Pituitary gland	(50)	*(50)	(48)
Leukemia mononuclear	2 (4%)	6 (12%)	5 (10%)
Pars distalis, adenoma	34 (68%)	29 (58%)	25 (52%)
Pars distalis, carcinoma		1 (2%)	
Thyroid gland	(50)	*(50)	(49)
Leukemia mononuclear	2 (4%)		
C-cell, adenoma	7 (14%)	2 (4%)	5 (10%)
C-cell, adenoma, multiple	2 (4%)	1 (2%)	
C-cell, carcinoma	4 (8%)	2 (4%)	
Follicular cell, carcinoma	2 (4%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(46)	*(50)	(39)
Leukemia mononuclear			2 (5%)
Mesothelioma malignant	1 (2%)	2 (4%)	2 (5%)
Preputial gland	(49)	*(50)	(49)
Adenoma	3 (6%)		2 (4%)
Carcinoma		1 (2%)	2 (4%)
Leukemia mononuclear			1 (2%)
Prostate	(50)	*(50)	(49)
Adenoma			1 (2%)
Leukemia mononuclear		1 (2%)	2 (4%)
Seminal vesicle	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	2 (4%)
Mesothelioma malignant		1 (2%)	
Testes	(50)	*(50)	(50)
Leukemia mononuclear	2 (4%)	3 (6%)	2 (4%)
Mesothelioma malignant	1 (2%)	2 (4%)	2 (4%)
Interstitial cell, adenoma	14 (28%)	10 (20%)	8 (16%)
Interstitial cell, adenoma, multiple	25 (50%)	22 (44%)	34 (68%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(50)	(49)
Leukemia mononuclear	6 (12%)	11 (22%)	11 (22%)
Lymph node	(50)	*(50)	(50)
Iliac, leukemia mononuclear	1 (2%)		
Mediastinal, leukemia mononuclear	1 (2%)	2 (4%)	
Mesenteric, leukemia mononuclear	2 (4%)	1 (2%)	
Pancreatic, leukemia mononuclear	1 (2%)		
Renal, leukemia mononuclear		1 (2%)	
Lymph node, bronchial	(44)	*(50)	(45)
Leukemia mononuclear	13 (30%)	9 (18%)	11 (24%)
Lymph node, mandibular	(48)	*(50)	(42)
Leukemia mononuclear	11 (23%)	10 (20%)	11 (26%)
Spleen	(50)	*(50)	(49)
Leukemia mononuclear	18 (36%)	21 (42%)	21 (43%)
Osteosarcoma, metastatic, bone		1 (2%)	
Thymus	(46)	*(50)	(49)
Leukemia mononuclear	5 (11%)	4 (8%)	7 (14%)
INTEGUMENTARY SYSTEM			
Mammary gland	(35)	*(50)	(41)
Fibroadenoma	2 (6%)		1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
INTEGUMENTARY SYSTEM (Continued)			
Skin	(50)	*(50)	(50)
Fibroma	5 (10%)		1 (2%)
Keratoacanthoma	2 (4%)		1 (2%)
Lipoma			1 (2%)
Papilloma			2 (4%)
Sarcoma			1 (2%)
Trichoepithelioma	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	*(50)	(50)
Osteosarcoma		1 (2%)	
Skeletal muscle	*(50)	*(50)	*(50)
Osteosarcoma, metastatic, bone		1 (2%)	
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Leukemia mononuclear	2 (4%)	2 (4%)	4 (8%)
Oligodendroglioma benign	1 (2%)	1 (2%)	
Cerebrum, astrocytoma, NOS			1 (2%)
Spinal cord	*(50)	*(50)	*(50)
Leukemia mononuclear		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(49)
Alveolar/bronchiolar adenoma	4 (8%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	1 (2%)		
Carcinoma, metastatic, preputial gland			1 (2%)
Leukemia mononuclear	18 (36%)	13 (26%)	15 (31%)
Osteosarcoma, metastatic, bone		1 (2%)	
Nose	(50)	(49)	(50)
Adenoma	1 (2%)		
Leukemia mononuclear	2 (4%)		1 (2%)
Sarcoma	1 (2%)		
SPECIAL SENSES SYSTEM			
Ear	*(50)	*(50)	*(50)
Neurofibroma			1 (2%)
Eye	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		
URINARY SYSTEM			
Kidney	(50)	*(50)	(49)
Leukemia mononuclear	7 (14%)	4 (8%)	6 (12%)
Pelvis, transitional epithelium, carcinoma			1 (2%)
Urinary bladder	(50)	*(50)	(49)
Leukemia mononuclear	3 (6%)	2 (4%)	2 (4%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	19 (38%)	21 (42%)	22 (44%)
Mesothelioma malignant	1 (2%)	2 (4%)	3 (6%)
Leukemia monocytic		1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	33	26	32
Moribund	17	18	13
Dead		6	5
TUMOR SUMMARY			
Total animals with primary neoplasms **	50	49	50
Total primary neoplasms	150	104	133
Total animals with benign neoplasms	50	47	50
Total benign neoplasms	119	71	102
Total animals with malignant neoplasms	25	27	26
Total malignant neoplasms	30	32	30
Total animals with secondary neoplasms ***		1	1
Total secondary neoplasms		4	1
Total animals with neoplasms--uncertain benign or malignant	1	1	1
Total uncertain neoplasms	1	1	1

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: CHAMBER CONTROL

WEEKS ON STUDY	06 7	07 8	09 4	09 5	09 5	09 7	09 9	10 0	10 1	10 1	10 1	10 2	10 3	10 3	10 3	10 3	10 3	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5
CARCASS ID	04 1	03 1	14 1	08 1	31 1	43 1	23 1	36 1	41 1	17 1	48 1	49 1	18 1	21 1	24 1	38 1	46 1	01 1	02 1	05 1	06 1	07 1	09 1	10 1	11 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X	X						X	X					X				X			X	X
Neoplastic nodule																									
Mesentery					+			+							+			+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X							X	X													
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X							X	X													
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X							X														
Sarcoma																						X			
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X							X														
Tongue																									
Papilloma squamous																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X							X	X													
Schwannoma, NOS																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X						X										X			X	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X						X	X					X							X	
Pheochromocytoma benign					X					X					X							X	X		
Pheochromocytoma benign, multiple																					X				
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma									X																
Parathyroid gland	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	M	+	+	M	+	+	+	+	+	+
Leukemia mononuclear											X														
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X								X													
Pars distalis, adenoma		X	X			X	X	X	X	X		X	X	X	X			X	X		X	X	X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X	X													
C-cell, adenoma	X																							X	
C-cell, adenoma, multiple			X																						
C-cell, carcinoma		X										X					X								
Follicular cell, carcinoma													X												
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Mesothelioma malignant																									
Preputial gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X					X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X							X														
Mesothelioma malignant																									
Interstitial cell, adenoma				X	X		X	X					X	X											
Interstitial cell, adenoma, multiple			X								X	X			X	X	X	X	X	X			X	X	X

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	121	131	151	161	191	201	221	251	261	271	281	291	301	321	331	341	351	371	391	401	421	441	451	471	501	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X					X		X			X		X		X	X			X	X						18
Neoplastic nodule																							X			1
Mesentery																				+						5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Sarcoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Tongue																+										1
Papilloma squamous																X										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3
Schwannoma, NOS	X																									1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X															6
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X															7
Pheochromocytoma benign	X									X		X							X							9
Pheochromocytoma benign, multiple																								X		2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X		X																X		X				5
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	43
Leukemia mononuclear																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Pars distalis, adenoma	X	X		X		X	X	X	X			X	X	X	X	X	X			X		X	X	X		34
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
C-cell, adenoma	X					X					X							X							X	7
C-cell, adenoma, multiple																								X		2
C-cell, carcinoma								X																		4
Follicular cell, carcinoma	X																									2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	46
Mesothelioma malignant																								X		1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X																								3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Mesothelioma malignant																								X		1
Interstitial cell, adenoma						X	X	X					X		X		X		X					X		14
Interstitial cell, adenoma, multiple		X	X	X	X				X	X	X			X				X		X		X	X		X	25

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

WEEKS ON STUDY	067	078	094	095	095	097	099	100	101	101	101	102	103	103	103	103	103	105	105	105	105	105	105	105	105
CARCASS ID	041	031	141	081	311	431	231	361	411	171	481	491	181	211	241	381	461	011	021	051	061	071	091	101	111
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X						X	X					X								
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, leukemia mononuclear																									
Mediastinal, leukemia mononuclear																					X				
Mesenteric, leukemia mononuclear											X														
Pancreatic, leukemia mononuclear																									
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X						X	X					X				X			X	X
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X			X	X						X	X									X			X	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+
Leukemia mononuclear	X			X	X						X	X					X				X			X	X
Thymus	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X	X						X	X									X				
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M	M	+	+	+	+	M	+	+
Fibroadenoma																	X			X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma							X									X	X								
Keratoacanthoma													X												
Trichoepithelioma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X							X														
Oligodendroglioma benign			X																						
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X						X										
Alveolar/bronchiolar carcinoma																									
Leukemia mononuclear	X			X	X						X	X					X				X			X	X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																				X					
Leukemia mononuclear											X	X													
Sarcoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye											+									+					
Leukemia mononuclear											X														
Harderian gland																			●						
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X							X	X												X	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X							X	X													

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	121	131	151	161	191	201	221	251	261	271	281	291	301	321	331	341	351	371	391	401	421	441	451	471	501	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X																									6
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Iliac, leukemia mononuclear	X																									1
Mediastinal, leukemia mononuclear																										1
Mesenteric, leukemia mononuclear																				X						2
Pancreatic, leukemia mononuclear	X																									1
Lymph node, bronchial	+	+	+	+	+	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	44
Leukemia mononuclear	X										X		X						X	X						13
Lymph node, mandibular	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear	X					X					X									X						11
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X					X		X			X		X		X	X			X	X						18
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	46
Leukemia mononuclear																										5
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	M	M	M	+	M	35
Fibroadenoma																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																				X					X	5
Keratoacanthoma													X													2
Trichoepithelioma																					X					1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle							+						+													2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Oligodendroglioma benign																										1
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X	X													4
Alveolar/bronchiolar carcinoma																					X					1
Leukemia mononuclear	X							X			X		X	X	X	X			X	X						18
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Leukemia mononuclear																										2
Sarcoma																					X					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye				+																		+				4
Leukemia mononuclear																										1
Harderian gland																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X			X						X						7
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										3

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: 1.5 mg/m³

WEEKS ON STUDY	0 7 7	0 8 6	0 8 6	0 8 7	0 8 9	0 9 0	0 9 2	0 9 3	0 9 5	0 9 6	0 9 6	0 9 6	0 9 7	0 9 8	0 9 8	0 9 9	0 9 9	1 0 0	1 0 0	1 0 1	1 0 2	1 0 3	1 0 3	1 0 5	1 0 5
CARCASS ID	1 4 1 1	1 3 8 1	1 4 3 1	1 3 1 1	1 4 6 1	1 5 0 1	1 3 2 1	1 0 3 1	1 1 0 1	1 1 9 1	1 0 2 1	1 0 6 1	1 0 4 1	1 5 1 1	1 2 4 1	1 2 1 1	1 3 7 1	1 3 5 1	1 4 8 1	1 1 3 1	1 0 5 1	1 2 9 1	1 4 4 1	1 4 5 1	1 4 9 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Intestine large, cecum	+	+	A	M	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	
Intestine large, colon	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Intestine large, rectum	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Intestine small	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Intestine small, duodenum	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Intestine small, ileum	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	A	+	+	+	
Intestine small, jejunum	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	A	+	+	+	
Liver	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia monocytic																									X
Leukemia mononuclear	X	X				X	X	X	X	X		X					X	X			X	X	X		
Neoplastic nodule																	X								
Mesentery	+		+														+								
Sarcoma																									
Schwannoma, NOS	X																								
Pancreas	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear	X					X			X			X										X			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear						X			X			X										X			
Stomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear								X				X													
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear								X				X													
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear						X		X				X													
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal gland, cortex	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear						X	X		X			X													
Osteosarcoma, metastatic, bone					X																				
Adrenal gland, medulla	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear						X		X				X													
Pheochromocytoma malignant																									
Pheochromocytoma benign																					X				
Pheochromocytoma benign, multiple																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Adenoma																						X			
Carcinoma													X												
Parathyroid gland	+	M	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X	X			X										X			
Pars distalis, adenoma			X			X		X	X	X	X		X	X			X	X	X	X	X	X	X	X	X
Pars distalis, carcinoma		X																							
Thyroid gland	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
C cell, adenoma														X							X				
C cell, adenoma, multiple																			X						
C cell, carcinoma																								X	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant							X																		
Preputial gland	+	+	+	M	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Carcinoma											X														
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Leukemia mononuclear						X																			
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear						X																			
Mesothelioma malignant							X																		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X				X													
Mesothelioma malignant							X																		
Interstitial cell adenoma					X																X	X			X
Interstitial cell, adenoma multiple	X											X			X	X			X				X	X	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	10111	10711	10811	10911	11111	11211	11411	11611	11711	11811	12011	12211	12311	12511	12611	12711	12811	13011	13311	13411	13611	13911	14011	14211	14711		TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus																											24
Intestine large		+							+				+														23
Intestine large, cecum		+							+				+														22
Intestine large, colon																											20
Intestine large, rectum																											20
Intestine small																											21
Intestine small, duodenum																											21
Intestine small, ileum																											19
Intestine small, jejunum																											20
Liver						+		+		+	+		+		+		+	+		+							33
Leukemia monocytic																											1
Leukemia mononuclear						X					X		X				X	X		X							19
Neoplastic nodule																											1
Mesentery								+								+											5
Sarcoma																X											1
Schwannoma, NOS																											1
Pancreas																											23
Leukemia mononuclear																											5
Salivary glands																											24
Leukemia mononuclear																											4
Stomach									+		+		+									+					27
Stomach, forestomach									+		+		+														26
Leukemia mononuclear																											2
Stomach, glandular									+													+					25
Leukemia mononuclear																											2
CARDIOVASCULAR SYSTEM																											
Heart																											24
Leukemia mononuclear																											3
ENDOCRINE SYSTEM																											
Adrenal gland						+								+				+									26
Adrenal gland, cortex																											23
Leukemia mononuclear																											4
Osteosarcoma, metastatic, bone																											1
Adrenal gland, medulla						+												+									25
Leukemia mononuclear																											3
Pheochromocytoma malignant																		X									1
Pheochromocytoma benign						X																					2
Pheochromocytoma benign, multiple																											1
Islets, pancreatic																											24
Adenoma																											1
Carcinoma																											1
Parathyroid gland																											19
Pituitary gland	+	+	+			+	+						+				+	+	+			+	+		+		36
Leukemia mononuclear						X																					6
Pars distalis, adenoma	X	X	X			X	X						X				X	X	X			X	X		X		29
Pars distalis, carcinoma																											1
Thyroid gland									+																		24
C cell, adenoma																											2
C cell, adenoma, multiple																											1
C-cell, carcinoma									X																		2
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Epididymis							+		+																		27
Mesothelioma malignant									X																		2
Preputial gland											+							+									25
Carcinoma																											1
Prostate																		+									25
Leukemia mononuclear																											1
Seminal vesicle																											24
Leukemia mononuclear																											1
Mesothelioma malignant																											1
Testes	+	+		+	+	+	+	+	+	+	+	+		+	+	+	+		+	+	+	+	+	+	+			47
Leukemia mononuclear																											3
Mesothelioma malignant									X																		2
Interstitial cell, adenoma	X	X		X			X												X						X		10
Interstitial cell, adenoma, multiple					X	X		X	X	X	X	X		X	X	X				X	X	X	X	X			22

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	077	086	086	087	089	090	092	093	095	096	096	096	097	098	098	099	099	100	100	101	102	103	103	105	105
CARCASS ID	14111	13811	14311	13111	14611	15011	13211	10311	11011	11911	10211	10611	10411	11511	12411	12111	13711	13511	14811	11311	10511	12911	14411	14511	14911
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear	X	X				X	X	X	X			X						X			X	X	X		
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mediastinal, leukemia mononuclear																									
Mesenteric, leukemia mononuclear								X																	
Renal, leukemia mononuclear																									
Lymph node, bronchial	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	
Leukemia mononuclear		X				X		X	X			X					X	X				X	X		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	
Leukemia mononuclear	X					X	X	X	X			X					X	X				X			
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X				X	X	X	X	X		X					X	X			X	X	X		X
Osteosarcoma, metastatic, bone					X																				
Thymus	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear						X		X	X			X													
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	M	+	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	
Osteosarcoma					X																				
Skeletal muscle					+																				
Osteosarcoma, metastatic, bone					X																				
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear								X				X													
Oligodendroglioma benign																X									
Spinal cord								+																	
Leukemia mononuclear								X																	
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Lung	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma																									
Leukemia mononuclear	X	X				X	X	X	X	X		X					X	X			X	X	X		
Osteosarcoma, metastatic, bone					X																				
Nose	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSES SYSTEM																									
Ear																									
Eye																									
URINARY SYSTEM																									
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X	X			X													
Urinary bladder	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear						X						X													

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	10111	10711	10811	10911	11111	11211	11411	11611	11711	11811	12011	12211	12311	12511	12611	12711	12811	13011	13311	13411	13611	13911	14011	14211	14711			TISSUES TUMORS
HEMATOPOIETIC SYSTEM																												
Bone marrow																												23
Leukemia mononuclear																												11
Lymph node													+				+	+						+				28
Mediastinal, leukemia mononuclear																	X							X				2
Mesenteric, leukemia mononuclear																												1
Renal, leukemia mononuclear																		X										1
Lymph node, bronchial																												22
Leukemia mononuclear																												9
Lymph node, mandibular													+															24
Leukemia mononuclear													X															10
Spleen						+					+		+		+		+	+		+				+				32
Leukemia mononuclear						X					X		X				X	X		X				X				21
Osteosarcoma, metastatic, bone																												1
Thymus																												22
Leukemia mononuclear																												4
INTEGUMENTARY SYSTEM																												
Mammary gland																												20
Skin					+																		+					26
MUSCULOSKELETAL SYSTEM																												
Bone																												24
Osteosarcoma																												1
Skeletal muscle																												1
Osteosarcoma, metastatic, bone																												1
NERVOUS SYSTEM																												
Brain																												24
Leukemia mononuclear																												2
Oligodendroglioma benign																												1
Spinal cord																												1
Leukemia mononuclear																												1
RESPIRATORY SYSTEM																												
Larynx																												24
Lung	+	+						+		+												+			+			29
Alveolar/bronchiolar adenoma		X																										1
Leukemia mononuclear																												13
Osteosarcoma, metastatic, bone																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			49
Trachea																												24
SPECIAL SENSES SYSTEM																												
Ear	+																											1
Eye			+			+				+																		3
URINARY SYSTEM																												
Kidney		+																+										26
Leukemia mononuclear																												4
Urinary bladder																												22
Leukemia mononuclear																												2

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: 5 mg/m³

WEEKS ON STUDY	072	080	080	081	088	090	090	091	092	093	096	097	100	101	101	102	103	103	105	105	105	105	105	105	105
CARCASS ID	22051	22081	20031	21111	22261	21141	25001	24611	24111	24771	24411	23111	24511	21131	24211	21151	23611	23811	20111	20211	20411	20511	20611	20711	20911
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Intestine large	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X					X												
Intestine large, colon	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X					X												
Intestine large, rectum	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	M	+	+
Leukemia mononuclear								X																	
Intestine small	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Intestine small, ileum	A	+	+	A	A	+	+	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Intestine small, jejunum	A	+	+	A	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X			X	X		X		X	X	X	X	X			X		X	X		X
Mesentery																									
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X					X					X		X										
Salivary glands	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X						X					X	X											X
ENDOCRINE SYSTEM																									
Adrenal gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X			X					X	X	X	X						X			X
Adrenal gland, medulla	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X			X			X		X	X	X		X					X			
Pheochromocytoma malignant													X												
Pheochromocytoma benign		X		X						X						X	X				X				
Pheochromocytoma benign, multiple																									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Parathyroid gland	M	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+
Pituitary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Leukemia mononuclear								X					X		X										X
Pars distalis, adenoma			X	X		X		X	X	X	X			X			X		X	X					X
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	A	+	M	+	M	+	+	+	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	M	+
Leukemia mononuclear								X														X			
Mesothelioma malignant		X																							
Preputial gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Carcinoma											X														
Leukemia mononuclear								X																	
Prostate	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear								X					X												
Seminal vesicle	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X					X												
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Mesothelioma malignant		X																X							
Interstitial cell, adenoma	X		X						X					X											X
Interstitial cell, adenoma multiple		X			X		X					X	X		X	X	X	X		X	X	X	X	X	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 5 mg/m³ (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	21101	21201	21611	21711	21811	21911	22011	22111	22211	22311	22411	22711	22811	22911	23011	23211	23311	23411	23511	23711	23911	24011	24311	24811	24911	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leukemia mononuclear																										2
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										2
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		45
Leukemia mononuclear																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Leukemia mononuclear																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Leukemia mononuclear																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
Leukemia mononuclear																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Leukemia mononuclear				X					X				X							X			X	X		21
Mesentery																+									+	2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Leukemia mononuclear									X																	5
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Leukemia mononuclear																										1
Stomach, glandular	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Leukemia mononuclear																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																										5
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Leukemia mononuclear																							X			11
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Leukemia mononuclear																							X			10
Pheochromocytoma malignant																										1
Pheochromocytoma benign					X	X		X		X								X				X	X	X		14
Pheochromocytoma benign, multiple			X						X																	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenoma																										1
Parathyroid gland	+	+	+	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M		37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Leukemia mononuclear																								X		5
Pars distalis, adenoma	X	X	X		X	X	X	X			X	X				X		X					X	X		25
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
C cell, adenoma		X						X	X							X		X								5
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	M	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+		39
Leukemia mononuclear																										2
Mesothelioma malignant								X																		2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenoma																	X									2
Carcinoma														X												2
Leukemia mononuclear																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenoma																X										1
Leukemia mononuclear																										2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Leukemia mononuclear																										2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																								X		2
Mesothelioma malignant																										2
Interstitial cell, adenoma	X															X				X						8
Interstitial cell, adenoma, multiple		X		X	X	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X	X	X	34

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 5 mg/m³
(Continued)

WEEKS ON STUDY	072	080	080	081	088	090	090	091	092	093	096	097	100	101	101	102	103	103	105	105	105	105	105	105	105	105
CARCASS ID	22051	20811	20311	21111	22261	21411	25011	24611	24111	24711	24411	23111	24511	21311	24211	21511	23611	23811	20111	20211	20411	20051	20061	20071	20091
HEMATOPOIETIC SYSTEM																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X			X			X		X	X		X						X			X
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X			X					X	X	X	X						X			X
Lymph node, mandibular	A	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M
Leukemia mononuclear		X	X		X			X					X	X	X	X						X			
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X			X	X		X		X	X	X	X	X			X		X	X		X
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X		X			X					X	X	X										
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	M	+	+	M	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma												X													
Keratoacanthoma																	X								
Lipoma																		X							
Papilloma											X														
Sarcoma																	X								
Trichoepithelioma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X					X	X											
Cerebrum, astrocytoma, NOS																									
RESPIRATORY SYSTEM																									
Larynx	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X						X				
Carcinoma, metastatic, preputial gland																									
Leukemia mononuclear		X	X		X			X					X	X	X	X	X					X			X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear				+																					
Neurofibroma				X																					
Eye																			+						
URINARY SYSTEM																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X			X					X	X	X	X									
Pelvis, transitional epithelium, carcinoma																									
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X					X												

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 5 mg/m³ (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	21101	21201	21601	21701	21801	21901	22001	22101	22201	22301	22401	22701	22801	22901	23001	23201	23301	23401	23501	23701	23901	24001	24301	24801	24901	TOTAL: TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear									X															X		11
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	M	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	45
Leukemia mononuclear									X																	11
Lymph node, mandibular	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	42
Leukemia mononuclear									X															X		11
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear				X					X				X							X			X	X		21
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	49
Leukemia mononuclear									X																	7
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	41
Fibroadenoma			X																							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Keratoacanthoma																										1
Lipoma																										1
Papilloma												X														2
Sarcoma																										1
Trichoepithelioma																X										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Cerebrum, astrocytoma, NOS																			X							1
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																										2
Carcinoma, metastatic, preputial gland														X												1
Leukemia mononuclear									X				X											X	X	15
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Ear																										1
Neurofibroma																										1
Eye									+								+									3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										6
Pelvis, transitional epithelium, carcinoma																						X				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2

TABLE A3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m^3	5 mg/m^3
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	11/50 (22%)	(b) 3/25 (12%)	16/48 (33%)
Adjusted Rates (c)	29 6%		43 1%
Terminal Rates (d)	8/33 (24%)		11/31 (35%)
Day of First Observation	661		556
Life Table Test (e)			P=0 142
Logistic Regression Test (e)			P=0 143
Fisher Exact Test (e)			P=0 152
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	11/50 (22%)	(b) 4/25 (16%)	17/48 (35%)
Adjusted Rates (c)	29 6%		44 6%
Terminal Rates (d)	8/33 (24%)		11/31 (35%)
Day of First Observation	661		556
Life Table Test (e)			P=0 102
Logistic Regression Test (e)			P=0 100
Fisher Exact Test (e)			P=0 106
Preputial Gland: Adenoma			
Overall Rates (a)	3/49 (6%)	(b) 0/25 (0%)	2/49 (4%)
Adjusted Rates (c)	7 9%		5 3%
Terminal Rates (d)	1/33 (3%)		1/32 (3%)
Day of First Observation	707		630
Life Table Test (e)			P=0 533N
Logistic Regression Test (e)			P=0 494N
Fisher Exact Test (e)			P=0 500N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	(b) 1/25 (4%)	4/49 (8%)
Adjusted Rates (c)	7 9%		10 6%
Terminal Rates (d)	1/33 (3%)		2/32 (6%)
Day of First Observation	707		630
Life Table Test (e)			P=0 461
Logistic Regression Test (e)			P=0 508
Fisher Exact Test (e)			P=0 500
Pancreatic Islets: Adenoma			
Overall Rates (a)	5/50 (10%)	(b) 1/24 (4%)	1/49 (2%)
Adjusted Rates (c)	14 4%		2 9%
Terminal Rates (d)	4/33 (12%)		0/32 (0%)
Day of First Observation	714		714
Life Table Test (e)			P=0 120N
Logistic Regression Test (e)			P=0 126N
Fisher Exact Test (e)			P=0 107N
Pancreatic Islets. Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	(b) 2/24 (8%)	1/49 (2%)
Adjusted Rates (c)	16 4%		2 9%
Terminal Rates (d)	4/33 (12%)		0/32 (0%)
Day of First Observation	702		714
Life Table Test (e)			P=0 074N
Logistic Regression Test (e)			P=0 073N
Fisher Exact Test (e)			P=0 059N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	(b) 1/29 (3%)	2/49 (4%)
Adjusted Rates (c)	10 7%		5 8%
Terminal Rates (d)	2/33 (6%)		1/32 (3%)
Day of First Observation	702		707
Life Table Test (e)			P=0 376N
Logistic Regression Test (e)			P=0 373N
Fisher Exact Test (e)			P=0 349N

TABLE A3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	(b) 1/29 (3%)	2/49 (4%)
Adjusted Rates (c)	13.6%		5.8%
Terminal Rates (d)	3/33 (9%)		1/32 (3%)
Day of First Observation	702		707
Life Table Test (e)			P=0.251N
Logistic Regression Test (e)			P=0.251N
Fisher Exact Test (e)			P=0.226N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	34/50 (68%)	(b) 29/36 (81%)	25/48 (52%)
Adjusted Rates (c)	76.8%		61.2%
Terminal Rates (d)	23/33 (70%)		16/31 (52%)
Day of First Observation	540		560
Life Table Test (e)			P=0.168N
Logistic Regression Test (e)			P=0.084N
Fisher Exact Test (e)			P=0.080N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	34/50 (68%)	(b) 30/36 (83%)	25/48 (52%)
Adjusted Rates (c)	76.8%		61.2%
Terminal Rates (d)	23/33 (70%)		16/31 (52%)
Day of First Observation	540		560
Life Table Test (e)			P=0.168N
Logistic Regression Test (e)			P=0.084N
Fisher Exact Test (e)			P=0.080N
Subcutaneous Tissue: Fibroma			
Overall Rates (f)	5/50 (10%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (c)	13.0%	0.0%	2.6%
Terminal Rates (d)	2/33 (6%)	0/27 (0%)	0/32 (0%)
Day of First Observation	693		674
Life Table Tests (e)	P=0.120N	P=0.061N	P=0.132N
Logistic Regression Tests (e)	P=0.113N	P=0.041N	P=0.108N
Cochran-Armitage Trend Test (e)	P=0.107N		
Fisher Exact Test (e)		P=0.028N	P=0.102N
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	39/50 (78%)	32/47 (68%)	42/50 (84%)
Adjusted Rates (c)	86.6%	96.8%	93.2%
Terminal Rates (d)	27/33 (82%)	23/24 (96%)	29/32 (91%)
Day of First Observation	653	535	500
Life Table Tests (e)	P=0.224	P=0.345	P=0.235
Logistic Regression Tests (e)	P=0.073	P=0.513N	P=0.192
Cochran Armitage Trend Test (e)	P=0.180		
Fisher Exact Test (e)		P=0.192N	P=0.306
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	9/50 (18%)	(b) 3/24 (13%)	5/49 (10%)
Adjusted Rates (c)	24.4%		15.6%
Terminal Rates (d)	7/33 (21%)		5/32 (16%)
Day of First Observation	463		729
Life Table Test (e)			P=0.215N
Logistic Regression Test (e)			P=0.201N
Fisher Exact Test (e)			P=0.205N

TABLE A3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	4/50 (8%)	(b) 2/24 (8%)	0/49 (0%)
Adjusted Rates (c)	9 9%		0.0%
Terminal Rates (d)	1/33 (3%)		0/32 (0%)
Day of First Observation	540		
Life Table Test (e)			P=0 075N
Logistic Regression Test (e)			P=0 058N
Fisher Exact Test (e)			P=0 061N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	13/50 (26%)	(b) 5/24 (21%)	5/49 (10%)
Adjusted Rates (c)	32 4%		15 6%
Terminal Rates (d)	8/33 (24%)		5/32 (16%)
Day of First Observation	463		729
Life Table Test (e)			P=0 047N
Logistic Regression Test (e)			P=0 032N
Fisher Exact Test (e)			P=0 037N
Hematopoietic System: Mononuclear or Monocytic Leukemia			
Overall Rates (f)	19/50 (38%)	(b,g) 21/50 (42%)	22/50 (44%)
Adjusted Rates (c)	47 4%	50 4%	50 3%
Terminal Rates (d)	13/33 (39%)	8/27 (30%)	11/32 (34%)
Day of First Observation	463	535	556
Life Table Tests (e)	P=0 325	P=0 215	P=0 288
Logistic Regression Tests (e)	P=0 384	P=0 500	P=0 382
Cochran-Armitage Trend Test (e)	P=0 334		
Fisher Exact Test (e)		P=0 419	P=0 342
All Sites: Mesothelioma			
Overall Rates (f)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (c)	3 0%	5 9%	8.0%
Terminal Rates (d)	1/33 (3%)	1/27 (4%)	1/32 (3%)
Day of First Observation	729	644	556
Life Table Tests (e)	P=0 264	P=0 444	P=0 304
Logistic Regression Tests (e)	P=0 281	P=0 506	P=0.331
Cochran-Armitage Trend Test (e)	P=0 259		
Fisher Exact Test (e)		P=0 500	P=0 309
All Sites: Benign Tumors			
Overall Rates (f)	50/50 (100%)	47/50 (94%)	50/50 (100%)
Adjusted Rates (c)	100 0%	100 0%	100 0%
Terminal Rates (d)	33/33 (100%)	27/27 (100%)	32/32 (100%)
Day of First Observation	463	535	500
Life Table Tests (e)	P=0 433	P=0 186	P=0 386
Logistic Regression Tests (e)	P=0 417	P=0 094N	P=1 000
Cochran Armitage Trend Test (e)	P=0 472		
Fisher Exact Test (e)		P=0 121N	P=1 000
All Sites: Malignant Tumors			
Overall Rates (f)	25/50 (50%)	27/50 (54%)	26/50 (52%)
Adjusted Rates (c)	58 4%	61 2%	58 7%
Terminal Rates (d)	16/33 (48%)	11/27 (41%)	14/32 (44%)
Day of First Observation	463	535	556
Life Table Tests (e)	P=0 465	P=0 189	P=0 410
Logistic Regression Tests (e)	P=0 543N	P=0 567	P=0 543
Cochran Armitage Trend Test (e)	P=0 508		
Fisher Exact Test (e)		P=0 421	P=0 500

TABLE A3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
All Sites: All Tumors			
Overall Rates (f)	50/50 (100%)	49/50 (98%)	50/50 (100%)
Adjusted Rates (c)	100.0%	100.0%	100.0%
Terminal Rates (d)	33/33 (100%)	27/27 (100%)	32/32 (100%)
Day of First Observation	463	535	500
Life Table Tests (e)	P=0.464	P=0 115	P=0.386
Logistic Regression Tests (e)	P=0.676	P=0.465N	P=1.000
Cochran-Armitage Trend Test (e)	P=0.698		
Fisher Exact Test (e)		P=0.500N	P=1.000

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence in animals killed at the end of the study
(e) 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 logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in controls is indicated by (N).
(f) Number of tumor-bearing animals/number of animals examined grossly at the site
(g) Thirty-two spleens were examined microscopically.

TABLE A4. HISTORICAL INCIDENCE OF THYROID C-CELL NEOPLASMS IN MALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	1/44	0/44	1/44
Methyl methacrylate	2/50	2/50	4/50
Propylene	2/45	2/45	4/45
1,2-Epoxybutane	4/49	0/49	4/49
Dichloromethane	1/49	1/49	2/49
Tetrachloroethylene	3/47	4/47	7/47
Bromoethane	4/46	0/46	4/46
TOTAL	17/330 (5.2%)	9/330 (2.7%)	26/330 (7.9%)
SD (b)	2.68%	3.18%	4.02%
Range (c)			
High	4/46	4/47	7/47
Low	1/49	0/49	1/44
Overall Historical Incidence for Untreated Controls in NTP Studies			
TOTAL	155/1,576 (9.8%)	51/1,576 (3.2%)	205/1,576 (13.0%)
SD (b)	5.94%	3.70%	6.55%
Range (c)			
High	11/49	6/49	15/50
Low	0/49	0/50	1/50

(a) Data as of March 1, 1989, 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 INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m^3	5 mg/m^3
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(49)	(22)	(46)
Hemorrhage	1 (2%)	3 (14%)	
Parasite metazoan	5 (10%)		2 (4%)
Artery, inflammation, chronic	1 (2%)		
Intestine large, colon	(50)	(20)	(47)
Parasite metazoan	4 (8%)	4 (20%)	
Intestine large, rectum	(50)	(20)	(45)
Parasite metazoan	7 (14%)		4 (9%)
Liver	(50)	(33)	(49)
Angiectasis	2 (4%)		
Angiectasis, focal			1 (2%)
Basophilic focus	17 (34%)	5 (15%)	22 (45%)
Clear cell focus	18 (36%)	1 (3%)	7 (14%)
Developmental malformation	5 (10%)	4 (12%)	2 (4%)
Eosinophilic focus	1 (2%)		
Fibrosis	1 (2%)		
Inflammation, granulomatous	10 (20%)	3 (9%)	9 (18%)
Inflammation, suppurative			1 (2%)
Necrosis	1 (2%)	5 (15%)	2 (4%)
Thrombus, multiple	1 (2%)		
Bile duct, fibrosis	7 (14%)		2 (4%)
Bile duct, hyperplasia	33 (66%)	14 (42%)	27 (55%)
Hepatocyte, vacuolization cytoplasmic	5 (10%)	5 (15%)	7 (14%)
Mesentery	(5)	(5)	(2)
Fibrosis	1 (20%)		
Hemorrhage	1 (20%)		
Inflammation, chronic	4 (80%)	2 (40%)	2 (100%)
Necrosis		1 (20%)	
Fat, necrosis			1 (50%)
Pancreas	(50)	(23)	(49)
Fibrosis	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
Acinus, atrophy	19 (38%)	11 (48%)	18 (37%)
Artery, inflammation		1 (4%)	
Salivary glands	(50)	(24)	(49)
Hemorrhage		1 (4%)	
Inflammation, chronic	3 (6%)		3 (6%)
Karyomegaly	3 (6%)		4 (8%)
Stomach, forestomach	(49)	(26)	(48)
Acanthosis	2 (4%)	3 (12%)	3 (6%)
Diverticulum		1 (4%)	
Fibrosis		1 (4%)	
Hyperkeratosis	2 (4%)		3 (6%)
Inflammation, suppurative	5 (10%)	2 (8%)	4 (8%)
Ulcer	2 (4%)	2 (8%)	1 (2%)
Muscularis, hyperplasia			1 (2%)
Stomach, glandular	(50)	(25)	(48)
Atrophy	1 (2%)		
Cyst	1 (2%)		
Erosion	3 (6%)		
Fibrosis	2 (4%)		2 (4%)
Hyperplasia, lymphoid	1 (2%)		
Inflammation, chronic	3 (6%)		2 (4%)
Inflammation, suppurative	1 (2%)	2 (8%)	2 (4%)
Epithelium, hyperplasia		1 (4%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m³	5 mg/m³
CARDIOVASCULAR SYSTEM			
Heart	(50)	(24)	(50)
Cardiomyopathy	24 (48%)	7 (29%)	28 (56%)
Thrombus	1 (2%)		2 (4%)
Atrium, dilatation	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(26)	(49)
Hyperplasia	1 (2%)		
Adrenal gland, cortex	(50)	(23)	(49)
Developmental malformation			1 (2%)
Hemorrhage			1 (2%)
Hyperplasia	7 (14%)		5 (10%)
Mineralization	1 (2%)		
Vacuolization cytoplasmic	19 (38%)	8 (35%)	13 (27%)
Vacuolization nuclear	1 (2%)		
Adrenal gland, medulla	(50)	(25)	(48)
Hyperplasia	14 (28%)	2 (8%)	12 (25%)
Hyperplasia, focal			1 (2%)
Necrosis	1 (2%)		
Islets, pancreatic	(50)	(24)	(49)
Hyperplasia	2 (4%)		
Parathyroid gland	(43)	(19)	(37)
Hyperplasia	1 (2%)		1 (3%)
Pituitary gland	(50)	(36)	(48)
Cyst		2 (6%)	
Pars distalis, angiectasis			1 (2%)
Pars distalis, hyperplasia	3 (6%)	1 (3%)	1 (2%)
Thyroid gland	(50)	(24)	(49)
C-cell, hyperplasia	9 (18%)	3 (13%)	6 (12%)
Follicular cell, cyst	1 (2%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(46)	(27)	(39)
Angiectasis		1 (4%)	
Inflammation, chronic			1 (3%)
Preputial gland	(49)	(25)	(49)
Cyst	3 (6%)	2 (8%)	4 (8%)
Inflammation, suppurative	9 (18%)	1 (4%)	10 (20%)
Prostate	(50)	(25)	(49)
Hyperplasia	2 (4%)		
Inflammation, suppurative	12 (24%)	6 (24%)	8 (16%)
Seminal vesicle	(50)	(24)	(49)
Inflammation, suppurative	8 (16%)	3 (13%)	7 (14%)
Testes	(50)	(47)	(50)
Atrophy	35 (70%)	23 (49%)	41 (82%)
Mineralization	1 (2%)		1 (2%)
Artery, inflammation	5 (10%)	2 (4%)	3 (6%)
Interstitial cell, hyperplasia	4 (8%)		1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(23)	(49)
Atrophy	1 (2%)		
Fibrosis	1 (2%)		
Lymph node	(50)	(28)	(50)
Renal, hyperplasia		1 (4%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(50)	(32)	(49)
Developmental malformation			1 (2%)
Fibrosis	3 (6%)	3 (9%)	2 (4%)
Hematopoietic cell proliferation	1 (2%)		1 (2%)
Hemorrhage			1 (2%)
Infarct	2 (4%)		3 (6%)
Pigmentation, hemosiderin			1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(35)	(20)	(41)
Galactocele	1 (3%)		
Hyperplasia			1 (2%)
Skin	(50)	(26)	(50)
Acanthosis			1 (2%)
Cyst epithelial inclusion	1 (2%)	3 (12%)	2 (4%)
Hyperkeratosis			1 (2%)
Inflammation, chronic	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	(2)	(1)	(1)
Diaphragm, developmental malformation	1 (50%)		1 (100%)
Diaphragm, fibrosis	1 (50%)		
NERVOUS SYSTEM			
Brain	(50)	(24)	(50)
Compression	9 (18%)	11 (46%)	3 (6%)
Congestion	1 (2%)		
Gliosis	1 (2%)		
Hemorrhage	3 (6%)	6 (25%)	6 (12%)
Mineralization			1 (2%)
Necrosis			1 (2%)
Thrombus			1 (2%)
Ventricle, dilatation	4 (8%)	1 (4%)	
Spinal cord		(1)	
Hemorrhage		1 (100%)	
RESPIRATORY SYSTEM			
Larynx	(50)	(24)	(48)
Foreign body	5 (10%)		3 (6%)
Hemorrhage		1 (4%)	
Inflammation, chronic	3 (6%)		
Inflammation, suppurative	14 (28%)	6 (25%)	13 (27%)
Epithelium, hyperplasia		1 (4%)	
Lung	(50)	(29)	(49)
Foreign body	1 (2%)		
Hemorrhage	2 (4%)	2 (7%)	3 (6%)
Alveolar epithelium, hyperplasia	2 (4%)	4 (14%)	1 (2%)
Alveolus, edema	1 (2%)	1 (3%)	
Alveolus, fibrosis	1 (2%)		
Alveolus, infiltration cellular, histiocytic	6 (12%)	4 (14%)	2 (4%)
Alveolus, inflammation, suppurative	1 (2%)	1 (3%)	5 (10%)
Artery, mediastinum, inflammation			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
RESPIRATORY SYSTEM (Continued)			
Nose	(50)	(49)	(50)
Foreign body	4 (8%)	5 (10%)	10 (20%)
Hemorrhage	1 (2%)		
Inflammation, suppurative	8 (16%)	9 (18%)	17 (34%)
Necrosis	1 (2%)		
Glands, dilatation	13 (26%)	19 (39%)	44 (88%)
Glands, hyperplasia	2 (4%)		
Nasolacrimal duct, inflammation, suppurative	2 (4%)	1 (2%)	1 (2%)
Olfactory epithelium, metaplasia			1 (2%)
Respiratory epithelium, hyperplasia		5 (10%)	15 (30%)
Respiratory epithelium, hyperplasia, focal	1 (2%)		
Respiratory epithelium, metaplasia, squamous		3 (6%)	1 (2%)
Trachea	(50)	(24)	(49)
Inflammation, chronic		1 (4%)	
Inflammation, suppurative	1 (2%)		
Epithelium, hyperplasia		1 (4%)	
SPECIAL SENSES SYSTEM			
Eye	(4)	(3)	(3)
Cataract		1 (33%)	
Lens, cataract	4 (100%)	1 (33%)	3 (100%)
Harderian gland	(1)		
Hyperplasia	1 (100%)		
URINARY SYSTEM			
Kidney	(50)	(26)	(49)
Infarct		1 (4%)	
Nephropathy, chronic	49 (98%)	26 (100%)	49 (100%)
Pelvis, hyperplasia	1 (2%)		
Pelvis, inflammation, suppurative	2 (4%)		
Urinary bladder	(50)	(22)	(49)
Hyperplasia	1 (2%)		
Inflammation, suppurative	2 (4%)		

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m^3	5 mg/m^3
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine small, ileum	(45)	*(50)	(44)
Adenocarcinoma			1 (2%)
Leukemia mononuclear	1 (2%)		
Liver	(50)	*(50)	(47)
Leukemia mononuclear	24 (48%)	18 (36%)	16 (34%)
Neoplastic nodule	1 (2%)		1 (2%)
Neoplastic nodule, multiple	1 (2%)		
Mesentery	*(50)	*(50)	*(50)
Hemangioma	1 (2%)		
Pancreas	(49)	*(50)	(47)
Leukemia mononuclear	8 (16%)	6 (12%)	3 (6%)
Salivary glands	(50)	*(50)	(48)
Leukemia mononuclear	1 (2%)		1 (2%)
Stomach, forestomach	(50)	*(50)	(48)
Leukemia mononuclear	1 (2%)		
Stomach, glandular	(49)	*(50)	(47)
Leukemia mononuclear	1 (2%)		
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(49)
Leukemia mononuclear	9 (18%)	2 (4%)	2 (4%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	*(50)	(47)
Adenoma			1 (2%)
Leukemia mononuclear	10 (20%)	12 (24%)	4 (9%)
Adrenal gland, medulla	(50)	*(50)	(47)
Leukemia mononuclear	10 (20%)	8 (16%)	5 (11%)
Pheochromocytoma benign	1 (2%)	1 (2%)	4 (9%)
Islets, pancreatic	(49)	*(50)	(47)
Adenoma	1 (2%)		
Adenoma, multiple		1 (2%)	
Leukemia mononuclear	1 (2%)		1 (2%)
Pituitary gland	(49)	*(50)	(47)
Leukemia mononuclear	9 (18%)	6 (12%)	3 (6%)
Pars distalis, adenoma	30 (61%)	25 (50%)	32 (68%)
Pars distalis, carcinoma	1 (2%)	1 (2%)	1 (2%)
Pars intermedia, adenoma	1 (2%)		
Thyroid gland	(50)	*(50)	(47)
Leukemia mononuclear	1 (2%)		
C-cell, adenoma	4 (8%)	3 (6%)	4 (9%)
C-cell, adenoma, multiple			1 (2%)
C-cell, carcinoma	2 (4%)		2 (4%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(48)	*(50)	(47)
Adenoma	5 (10%)	1 (2%)	
Carcinoma	2 (4%)	1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m³	5 mg/m³
GENITAL SYSTEM (Continued)			
Ovary	(50)	*(50)	(47)
Granulosa cell tumor, NOS		1 (2%)	
Granulosa cell tumor malignant	2 (4%)		
Leukemia mononuclear	3 (6%)	4 (8%)	2 (4%)
Uterus	(50)	*(50)	(48)
Carcinoma			1 (2%)
Leiomyoma		1 (2%)	
Leukemia mononuclear	5 (10%)	1 (2%)	
Endometrium, deciduoma malignant	1 (2%)		
Endometrium, polyp	1 (2%)		
Endometrium, polyp stromal	8 (16%)	4 (8%)	4 (8%)
Endometrium, polyp stromal, multiple	1 (2%)		
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(50)	(47)
Leukemia mononuclear	7 (14%)	7 (14%)	2 (4%)
Lymph node	(48)	*(50)	(48)
Mediastinal, leukemia mononuclear	2 (4%)	1 (2%)	
Mesenteric, leukemia mononuclear	3 (6%)	2 (4%)	
Pancreatic, leukemia mononuclear	2 (4%)		
Renal, leukemia mononuclear	1 (2%)	1 (2%)	1 (2%)
Lymph node, bronchial	(37)	*(50)	(39)
Leukemia mononuclear	12 (32%)	11 (22%)	8 (21%)
Lymph node, mandibular	(48)	*(50)	(45)
Leukemia mononuclear	14 (29%)	8 (16%)	7 (16%)
Spleen	(50)	*(50)	(47)
Leukemia mononuclear	24 (48%)	18 (36%)	16 (34%)
Thymus	(50)	*(50)	(47)
Leukemia mononuclear	11 (22%)	4 (8%)	5 (11%)
Thymoma benign	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(49)	*(50)	(49)
Adenocarcinoma	2 (4%)	3 (6%)	4 (8%)
Fibroadenoma	9 (18%)	11 (22%)	9 (18%)
Fibroadenoma, multiple	1 (2%)		2 (4%)
Skin	(48)	*(50)	(48)
Fibroma	1 (2%)	1 (2%)	1 (2%)
Fibrous histiocytoma		1 (2%)	
Squamous cell carcinoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Bone	(50)	*(50)	(48)
Leukemia mononuclear		1 (2%)	
NERVOUS SYSTEM			
Brain	(50)	*(50)	(49)
Carcinoma, metastatic, pituitary gland		1 (2%)	
Glioma, NOS, marked		1 (2%)	
Glioma, NOS, moderate			1 (2%)
Leukemia mononuclear	5 (10%)	1 (2%)	
Oligodendroglioma malignant			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(48)
Alveolar/bronchiolar adenoma		1 (2%)	
Carcinoma, metastatic, thyroid gland	1 (2%)		
Leukemia mononuclear	19 (38%)	15 (30%)	11 (23%)
Bronchus, carcinoma			1 (2%)
Nose	(50)	(50)	(46)
Leukemia mononuclear	1 (2%)		
Respiratory epithelium, adenoma	1 (2%)		
SPECIAL SENSES SYSTEM			
Zymbal gland	*(50)	*(50)	*(50)
Squamous cell carcinoma		1 (2%)	
URINARY SYSTEM			
Kidney	(50)	*(50)	(48)
Leukemia mononuclear	6 (12%)	5 (10%)	3 (6%)
Urinary bladder	(49)	*(50)	(47)
Leukemia mononuclear	2 (4%)	1 (2%)	
Papilloma	2 (4%)		
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	24 (48%)	18 (36%)	16 (32%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	32	29	30
Moribund	14	16	14
Dead	4	5	6
TUMOR SUMMARY			
Total animals with primary neoplasms **	49	41	43
Total primary neoplasms	105	76	87
Total animals with benign neoplasms	43	35	38
Total benign neoplasms	70	49	59
Total animals with malignant neoplasms	29	22	23
Total malignant neoplasms	35	25	27
Total animals with secondary neoplasms ***	1	1	
Total secondary neoplasms	1	1	
Total animals with neoplasms--uncertain benign or malignant		2	1
Total uncertain neoplasms		2	1

* Number of animals receiving complete necropsy examinations, all gross lesions including masses examined microscopically
** Primary tumors: all tumors except secondary tumors
*** Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: CHAMBER CONTROL

WEEKS ON STUDY	037	068	068	083	084	087	090	091	092	093	096	096	096	098	099	102	103	103	105	105	105	105	105	105	105
CARCASS ID	06551	05511	07511	09111	09711	07611	06811	06611	08211	08811	05711	05311	09311	05811	08311	08111	09911	10011	05111	05521	05441	05561	05591	06011	06111
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	M	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	M	+	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X			X	X	X		X	X	X			X	X	X	X	X			X	X		
Neoplastic nodule																									
Neoplastic nodule multiple																									
Mesentery									+																
Hemangioma									X																
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X		X		X		X				X			X						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X																			
Stomach, glandular	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X																			
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X			X	X	X					X			X						
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X			X		X					X			X				X		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X			X	X	X					X			X						
Pheochromocytoma benign																	X								
Islets, pancreatic	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear										X															
Parathyroid gland	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X					X				X	X				X	X		X	X						
Pars distalis, adenoma					X				X		X		X		X	X	X	X	X		X	X	X	X	X
Pars distalis, carcinoma								X																	
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
C cell, adenoma																								X	
C cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Adenoma				X			X												X						
Carcinoma														X											X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																X									
Leukemia mononuclear										X	X								X						
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X													X			X						
Endometrium, deciduoma malignant							X																		
Endometrium, polyp															X										
Endometrium, polyp stromal																	X		X	X			X		
Endometrium, polyp stromal, multiple																X									

\+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A Autolysis precludes examination
X Incidence of listed morphology

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	06621	06631	06641	06671	06691	07001	07111	07211	07331	07411	07711	07811	07911	08001	08441	08511	08611	08711	08911	09001	09221	09411	09511	09661	09881	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear																										1
Intestine small jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X				X		X			X		X				X		X	X		24
Neoplastic nodule						X																				1
Neoplastic nodule multiple																									X	1
Mesentery																										1
Hemangioma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear															X											8
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X											9
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X									X		10
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X									X		10
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																									X	1
Leukemia mononuclear																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	M	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear															X											9
Pars distalis, adenoma	X		X	X	X		X	X				X	X	X	X		X	X	X		X	X		X		30
Pars distalis, carcinoma																										1
Pars intermedia, adenoma		X																								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
C cell, adenoma									X				X												X	4
C cell, carcinoma									X													X				2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma		X																	X							5
Carcinoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant																						X				2
Leukemia mononuclear																										3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear															X											5
Endometrium, deciduoma malignant																										1
Endometrium, polyp																										1
Endometrium, polyp stromal								X	X	X							X									8
Endometrium, polyp stromal multiple																										1

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

WEEKS ON STUDY	037	068	068	083	084	087	090	091	092	093	096	096	096	098	099	102	103	103	105	105	105	105	105	105	105
CARCASS ID	06511	05511	07511	09111	09711	07611	06811	06611	08211	08811	05711	05311	09311	05811	08311	08111	09911	10011	05111	05211	05541	05561	05591	06011	06111
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X					X				X	X	X				X									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear																			X						
Mesenteric, leukemia mononuclear			X									X							X						
Pancreatic, leukemia mononuclear			X																X						
Renal, leukemia mononuclear	X																								
Lymph node, bronchial	M	+	+	+	+	+	M	M	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+
Leukemia mononuclear			X			X				X	X	X				X		X	X				X		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X	X	X			X	X			X	X		X	X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X	X			X	X	X		X	X	X			X	X	X	X	X			X	X		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X				X	X	X				X			X						
Thymoma benign																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									X
Fibroadenoma			X		X																X	X	X		
Fibroadenoma, multiple								X																	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma				X																					
Squamous cell carcinoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X					X					X					X			X						
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Leukemia mononuclear	X	X	X			X	X	X		X	X	X			X	X		X	X			X	X		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Respiratory epithelium, adenoma		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									+
Eye					+																		+		
Lacrimal gland				+													+								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X					X					X			X						
Urinary bladder	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X																X						
Papilloma																									

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	06621	06631	06641	06671	06691	07701	07711	07721	07731	07741	07771	07781	07791	08001	08441	08551	08661	08671	08891	09001	09211	09441	09551	09661	09881	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																								X		7
Lymph node	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Mediastinal, leukemia mononuclear															X											2
Mesenteric, leukemia mononuclear																										3
Pancreatic, leukemia mononuclear																										2
Renal, leukemia mononuclear																										1
Lymph node, bronchial	+	+	M	+	M	M	+	+	+	+	M	+	M	+	+	+	M	M	+	+	+	+	+	+	+	37
Leukemia mononuclear										X					X									X		12
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Leukemia mononuclear						X															X			X		14
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X				X		X			X		X				X		X	X		24
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	50
Leukemia mononuclear						X									X									X		11
Thymoma benign																				X						1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma																	X									2
Fibroadenoma					X	X											X					X				9
Fibroadenoma, multiple																										1
Skin	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Fibroma																										1
Squamous cell carcinoma				X																						1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										5
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																						X				1
Leukemia mononuclear						X				X					X									X		19
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Respiratory epithelium, adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										1
Eye							+									+		+								5
Lacrimal gland																				+						3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										6
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Papilloma											X											X				2

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: 1.5 mg/m³

WEEKS ON STUDY	0 1 8	0 6 2	0 7 5	0 7 6	0 7 7	0 7 9	0 7 9	0 8 3	0 8 9	0 9 3	0 9 4	0 9 7	0 9 7	1 0 2	1 0 2	1 0 2	1 0 3	1 0 3	1 0 3	1 0 3	1 0 3	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	1 8 2 1	1 8 6 1	1 5 7 1	1 7 8 1	1 8 3 1	1 7 6 1	1 8 5 1	1 7 5 1	1 7 2 1	2 0 0 1	1 9 8 1	1 5 9 1	1 9 1 1	1 6 6 1	1 8 4 1	1 9 5 1	1 5 6 1	1 6 1 1	1 6 5 1	1 8 1 1	1 9 9 1	1 5 1 1	1 5 2 1	1 5 3 1	1 5 4 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large, cecum	M	M	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+				
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Intestine small, ileum	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+				
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	
Leukemia mononuclear	X				X	X		X			X	X	X	X	X	X	X		X	X	X				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Leukemia mononuclear												X	X	X	X				X		X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Leukemia mononuclear																X			X						
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	
Leukemia mononuclear	X					X		X					X	X	X	X	X		X	X	X				
Adrenal gland, medulla	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	
Leukemia mononuclear						X		X					X	X	X					X	X				
Pheochromocytoma benign															X										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Adenoma, multiple																									
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear					X			X					X		X				X		X				
Pars distalis, adenoma		X			X		X		X		X	X		X			X	X		X	X	X	X	X	
Pars distalis, carcinoma																X									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
C cell, adenoma									X				X		X										
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+				
Adenoma																									
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Granulosa cell tumor, NOS																									
Leukemia mononuclear	X							X											X		X				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Leiomyoma			X																						
Leukemia mononuclear																			X						
Endometrium, polyp stromal																X									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	15551	15581	16001	16021	16631	16441	16671	16881	16991	17001	17111	17331	17441	17771	17991	18001	18771	18881	18991	19091	19211	19331	19441	19661	19771		TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus																											21
Intestine large																											20
Intestine large, cecum																											17
Intestine large, colon																											20
Intestine large, rectum																											20
Intestine small																											20
Intestine small, duodenum																											20
Intestine small, ileum																											18
Intestine small, jejunum																											19
Liver		+			+	+	+			+		+												+	+		31
Leukemia mononuclear		X				X				X														X			18
Pancreas																											21
Leukemia mononuclear																											6
Salivary glands																											21
Stomach																											21
Stomach, forestomach																											21
Stomach, glandular																											21
CARDIOVASCULAR SYSTEM																											
Heart																											21
Leukemia mononuclear																											2
ENDOCRINE SYSTEM																											
Adrenal gland																								+			23
Adrenal gland, cortex																								+			23
Leukemia mononuclear																								X			12
Adrenal gland, medulla																								+			22
Leukemia mononuclear																								X			8
Pheochromocytoma benign																											1
Islets, pancreatic																								+			22
Adenoma, multiple																								X			1
Parathyroid gland																											20
Pituitary gland	+	+			+	+	+	+	+	+					+		+		+		+	+	+				38
Leukemia mononuclear																											6
Pars distalis, adenoma	X	X			X	X	X	X	X	X											X	X	X				25
Pars distalis, carcinoma																											1
Thyroid gland																											21
C-cell, adenoma																											3
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Clitoral gland						+						+										+					21
Adenoma												X															1
Carcinoma																						X					1
Ovary			+																								22
Granulosa cell tumor, NOS			X																								1
Leukemia mononuclear																											4
Uterus	+					+											+					+					25
Leiomyoma																											1
Leukemia mononuclear																											1
Endometrium, polyp stromal						X											X					X					4

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	018	062	075	076	077	079	079	083	089	093	094	097	097	102	102	102	103	103	103	103	103	105	105	105	105
CARCASS ID	18211	18611	15711	17811	18311	17611	18511	17511	17211	20011	19811	15911	19111	16611	18411	19511	15611	16111	16511	18111	19911	15111	15211	15311	15411
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Leukemia mononuclear	X					X		X						X		X			X		X				
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Mediastinal, leukemia mononuclear																					X				
Mesenteric, leukemia mononuclear	X										X														
Renal, leukemia mononuclear	X																								
Lymph node, bronchial	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+				
Leukemia mononuclear	X					X		X			X	X	X	X	X		X		X		X				
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	M	+	+	+	+				
Leukemia mononuclear	X				X	X		X					X						X	X	X				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Leukemia mononuclear	X				X	X		X			X	X	X	X	X	X	X		X	X	X				
Thymus	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+				
Leukemia mononuclear	X				X	X															X				
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		
Adenocarcinoma																X		X							
Fibroadenoma													X		X	X	X		X				X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Fibroma																									
Fibrous histiocytoma														X											
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Leukemia mononuclear																					X				
Skeletal muscle																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Carcinoma, metastatic, pituitary gland																X									
Glioma, NOS, marked										X															
Leukemia mononuclear	X																								
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	
Alveolar/bronchiolar adenoma																X									
Leukemia mononuclear	X				X	X		X			X	X	X	X	X	X	X		X	X	X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
SPECIAL SENSES SYSTEM																									
Eye								+				+	+	+											
Lacrimal gland														+											
Zymbal gland				+																					
Squamous cell carcinoma				X																					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			
Leukemia mononuclear	X					X		X					X			X									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				
Leukemia mononuclear																			X						

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL
CARCASS ID	15551	15581	16001	16021	16031	16041	16071	16081	16091	17001	17011	17031	17041	17071	17091	18001	18071	18081	18091	19001	19021	19031	19041	19061	19071		TISSUES TUMORS
HEMATOPOIETIC SYSTEM																											
Bone marrow																											21
Leukemia mononuclear																											7
Lymph node																											22
Mediastinal, leukemia mononuclear																											1
Mesenteric, leukemia mononuclear																											2
Renal, leukemia mononuclear																											1
Lymph node, bronchial																											18
Leukemia mononuclear																											11
Lymph node, mandibular																											17
Leukemia mononuclear																											8
Spleen		+				+				+	-													+			26
Leukemia mononuclear		X				X				X														X			18
Thymus																											19
Leukemia mononuclear																											4
INTEGUMENTARY SYSTEM																											
Mammary gland					+							+		+	+		+							+			28
Adenocarcinoma					X																						3
Fibroadenoma												X		X	X		X							X			11
Skin		+																									22
Fibroma		X																									1
Fibrous histiocytoma																											1
MUSCULOSKELETAL SYSTEM																											
Bone																											21
Leukemia mononuclear																											1
Skeletal muscle					+																						1
NERVOUS SYSTEM																											
Brain																											21
Carcinoma, metastatic, pituitary gland																											1
Glioma, NOS, marked																											1
Leukemia mononuclear																											1
RESPIRATORY SYSTEM																											
Larynx																											21
Lung						+																					23
Alveolar/bronchiolar adenoma																											1
Leukemia mononuclear						X																					15
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea																											21
SPECIAL SENSES SYSTEM																											
Eye			+																		+				+		7
Lacrimal gland																											1
Zymbal gland																											1
Squamous cell carcinoma																											1
URINARY SYSTEM																											
Kidney																					+						23
Leukemia mononuclear																											5
Urinary bladder																											21
Leukemia mononuclear																											1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: 5 mg/m³

WEEKS ON STUDY	051	082	083	088	089	089	091	092	094	094	095	095	097	097	098	103	103	103	104	104	105	105	105	105	105
CARCASS ID	26991	26881	25581	25361	26761	27911	25511	27111	25411	26211	27811	29911	28911	29961	28111	26411	27311	29711	29941	28611	25511	25521	25561	25671	25991
ALIMENTARY SYSTEM																									
Esophagus	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+
Intestine large, colon	A	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Intestine small	A	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+
Intestine small, ileum	A	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+
Adenocarcinoma																									
Intestine small, jejunum	A	+	+	+	A	+	A	+	+	A	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+
Liver	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X	X					X			X	X							X
Neoplastic nodule																									
Mesentery																									
Pancreas	M	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X																		X
Salivary glands	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X																					
Stomach	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		X
ENDOCRINE SYSTEM																									
Adrenal gland	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Leukemia mononuclear				X			X	X	X																
Adrenal gland, medulla	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X	X																
Pheochromocytoma benign			X									X											X		
Islets, pancreatic	M	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Parathyroid gland	M	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X		X																
Pars distalis, adenoma						X	X		X	X				X	X	X			X	X	X	X	X	X	
Pars distalis, carcinoma																	X								
Thyroid gland	M	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																						X			
C cell, adenoma, multiple																X									
C-cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Ovary	A	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X																		
Uterus	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma										X															
Endometrium, polyp stromal																							X		
Vagina						+																			

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 5 mg/m³ (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	26011	26111	26311	26511	26711	27011	27211	27411	27511	27611	27711	28011	28211	28311	28411	28511	28711	28811	29011	29111	29211	29311	29511	29811	30101	
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma					X																					1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear					X			X		X	X	X						X	X	X						16
Neoplastic nodule										X																1
Mesentery		+																					+			2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma									X																	1
Leukemia mononuclear																										4
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear											X															5
Pheochromocytoma benign		X																								4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										1
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	47
Leukemia mononuclear											X															3
Pars distalis, adenoma		X		X	X	X	X	X		X		X	X	X	X	X		X	X	X	X	X	X		X	32
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
C cell, adenoma							X	X														X				4
C cell, adenoma, multiple																										1
C cell, carcinoma		X		X																						2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																										1
Endometrium, polyp stromal		X		X							X															4
Vagina													+													2

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 5 mg/m³ (Continued)

WEEKS ON STUDY	051	082	083	088	089	089	091	092	094	094	095	095	097	097	098	103	103	103	104	104	105	105	105	105	105
CARCASS ID	26691	26881	25881	25331	26661	27991	25551	27111	25441	26221	27881	29991	28991	29661	28111	26441	27331	29771	29441	28661	25111	25221	25661	25771	25991
HEMATOPOIETIC SYSTEM																									
Blood		+																							
Bone marrow	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X											X							
Lymph node	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal, leukemia mononuclear																	X								
Lymph node, bronchial	M	+	+	+	A	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	M	+
Leukemia mononuclear				X			X	X	X									X							X
Lymph node, mandibular	A	+	+	+	M	+	+	+	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X		X								X	X							X
Spleen	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X	X					X			X	X							X
Thymus	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X		X																X
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma							X									X									
Fibroadenoma						X							X		X			X				X			
Fibroadenoma, multiple																X									
Skin	+	+	+	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma													X												
MUSCULOSKELETAL SYSTEM																									
Bone	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									+
NERVOUS SYSTEM																									
Brain	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS, moderate																							X		
Oligodendroglioma malignant											X														
RESPIRATORY SYSTEM																									
Larynx	A	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X	X	X									X							X
Bronchus, carcinoma				X																					
Nose	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Trachea	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
Lacrimal gland																+									
URINARY SYSTEM																									
Kidney	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X			X																		X
Urinary bladder	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 5 mg/m³
(Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
CARCASS ID	26011	26111	26311	26511	26711	27011	27211	27411	27511	27611	27711	28011	28211	28311	28411	28511	28711	28811	29011	29111	29211	29311	29511	29811	30011	TOTAL TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										2
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Renal, leukemia mononuclear																										1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	M	39
Leukemia mononuclear											X									X						8
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear																			X							7
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear					X			X		X	X	X						X	X	X						16
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear											X															5
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma							X																		X	4
Fibroadenoma												X	X					X					X			9
Fibroadenoma, multiple		X																								2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Fibroma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skeletal muscle																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Glioma, NOS, moderate																										1
Oligodendroglioma malignant																										1
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear					X			X			X							X		X						11
Bronchus, carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPECIAL SENSES SYSTEM																										
Eye		+																			+					2
Lacrimal gland																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47

TABLE B3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m^3	5 mg/m^3
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	1/50 (2%)	(b) 1/22 (5%)	4/47 (9%)
Adjusted Rates (c)	2.9%		11.0%
Terminal Rates (d)	0/32 (0%)		2/30 (7%)
Day of First Observation	715		581
Life Table Test (e)			P=0.180
Logistic Regression Test (e)			P=0.143
Fisher Exact Test (e)			P=0.162
Clitoral Gland: Adenoma			
Overall Rates (a)	5/48 (10%)	(b) 1/21 (5%)	0/47 (0%)
Adjusted Rates (c)	13.6%		0.0%
Terminal Rates (d)	3/31 (10%)		0/29 (0%)
Day of First Observation	577		
Life Table Test (e)			P=0.039N
Logistic Regression Test (e)			P=0.036N
Fisher Exact Test (e)			P=0.030N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	7/48 (15%)	(b) 2/21 (10%)	0/47 (0%)
Adjusted Rates (c)	18.9%		0.0%
Terminal Rates (d)	4/31 (13%)		0/29 (0%)
Day of First Observation	577		
Life Table Test (e)			P=0.012N
Logistic Regression Test (e)			P=0.010N
Fisher Exact Test (e)			P=0.007N
Mammary Gland: Fibroadenoma			
Overall Rates (f)	10/50 (20%)	11/50 (22%)	11/50 (22%)
Adjusted Rates (c)	26.9%	31.2%	30.2%
Terminal Rates (d)	7/32 (22%)	6/29 (21%)	6/30 (20%)
Day of First Observation	476	679	622
Life Table Tests (e)	P=0.465	P=0.446	P=0.468
Logistic Regression Tests (e)	P=0.504	P=0.487	P=0.504
Cochran-Armitage Trend Test (e)	P=0.484		
Fisher Exact Test (e)		P=0.500	P=0.500
Mammary Gland: Adenocarcinoma			
Overall Rates (f)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (c)	6.3%	8.8%	11.4%
Terminal Rates (d)	2/32 (6%)	1/29 (3%)	2/30 (7%)
Day of First Observation	729	714	637
Life Table Tests (e)	P=0.293	P=0.484	P=0.323
Logistic Regression Tests (e)	P=0.307	P=0.497	P=0.344
Cochran-Armitage Trend Test (e)	P=0.297		
Fisher Exact Test (e)		P=0.500	P=0.339
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (f)	11/50 (22%)	13/50 (26%)	14/50 (28%)
Adjusted Rates (c)	29.8%	36.2%	37.5%
Terminal Rates (d)	8/32 (25%)	7/29 (24%)	8/30 (27%)
Day of First Observation	476	679	622
Life Table Tests (e)	P=0.305	P=0.358	P=0.298
Logistic Regression Tests (e)	P=0.335	P=0.392	P=0.328
Cochran-Armitage Trend Test (e)	P=0.314		
Fisher Exact Test (e)		P=0.408	P=0.322

TABLE B3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	30/49 (61%)	(b) 25/38 (66%)	32/47 (68%)
Adjusted Rates (c)	74.8%		83.8%
Terminal Rates (d)	22/32 (69%)		23/29 (79%)
Day of First Observation	582		622
Life Table Test (e)			P=0.278
Logistic Regression Test (e)			P=0.405
Fisher Exact Test (e)			P=0.313
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	31/49 (63%)	(b) 26/38 (68%)	33/47 (70%)
Adjusted Rates (c)	75.4%		84.2%
Terminal Rates (d)	22/32 (69%)		23/29 (79%)
Day of First Observation	582		622
Life Table Test (e)			P=0.286
Logistic Regression Test (e)			P=0.407
Fisher Exact Test (e)			P=0.307
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	4/50 (8%)	(b) 3/21 (14%)	5/47 (11%)
Adjusted Rates (c)	12.5%		15.8%
Terminal Rates (d)	4/32 (13%)		4/30 (13%)
Day of First Observation	729		715
Life Table Test (e)			P=0.466
Logistic Regression Test (e)			P=0.497
Fisher Exact Test (e)			P=0.460
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	(b) 3/21 (14%)	7/47 (15%)
Adjusted Rates (c)	15.6%		22.3%
Terminal Rates (d)	5/32 (16%)		6/30 (20%)
Day of First Observation	729		715
Life Table Test (e)			P=0.337
Logistic Regression Test (e)			P=0.372
Fisher Exact Test (e)			P=0.336
Uterus/Endometrium: Stromal Polyp			
Overall Rates (f)	10/50 (20%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (c)	28.4%	12.8%	13.3%
Terminal Rates (d)	7/32 (22%)	3/29 (10%)	4/30 (13%)
Day of First Observation	693	714	729
Life Table Tests (e)	P=0.102N	P=0.097N	P=0.092N
Logistic Regression Tests (e)	P=0.083N	P=0.072N	P=0.069N
Cochran-Armitage Trend Test (e)	P=0.089N		
Fisher Exact Test (e)		P=0.074N	P=0.074N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (f)	24/50 (48%)	(b,g) 18/50 (36%)	16/50 (32%)
Adjusted Rates (c)	52.6%	40.9%	41.4%
Terminal Rates (d)	11/32 (34%)	4/29 (14%)	9/30 (30%)
Day of First Observation	258	126	615
Life Table Tests (e)	P=0.136N	P=0.245N	P=0.131N
Logistic Regression Tests (e)	P=0.102N	P=0.131N	P=0.086N
Cochran-Armitage Trend Test (e)	P=0.088N		
Fisher Exact Test (e)		P=0.156N	P=0.076N

TABLE B3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
All Sites: Benign Tumors			
Overall Rates (f)	43/50 (86%)	35/50 (70%)	38/50 (76%)
Adjusted Rates (c)	95.5%	77.6%	88.2%
Terminal Rates (d)	30/32 (94%)	19/29 (66%)	25/30 (83%)
Day of First Observation	476	430	581
Life Table Tests (e)	P=0.380N	P=0.230N	P=0.339N
Logistic Regression Tests (e)	P=0.189N	P=0.050N	P=0.098N
Cochran-Armitage Trend Test (e)	P=0.255N		
Fisher Exact Test (e)		P=0.045N	P=0.154N
All Sites: Malignant Tumors			
Overall Rates (f)	29/50 (58%)	22/50 (44%)	23/50 (46%)
Adjusted Rates (c)	62.6%	48.5%	56.2%
Terminal Rates (d)	15/32 (47%)	6/29 (21%)	13/30 (43%)
Day of First Observation	258	126	615
Life Table Tests (e)	P=0.273N	P=0.224N	P=0.249N
Logistic Regression Tests (e)	P=0.224N	P=0.098N	P=0.167N
Cochran-Armitage Trend Test (e)	P=0.205N		
Fisher Exact Test (e)		P=0.115N	P=0.158N
All Sites: All Tumors			
Overall Rates (f)	49/50 (98%)	41/50 (82%)	43/50 (86%)
Adjusted Rates (c)	98.0%	82.0%	91.5%
Terminal Rates (d)	31/32 (97%)	20/29 (69%)	26/30 (87%)
Day of First Observation	258	126	581
Life Table Tests (e)	P=0.325N	P=0.261N	P=0.296N
Logistic Regression Tests (e)	P=0.113N	P=0.005N	P=0.023N
Cochran-Armitage Trend Test (e)	P=0.111N		
Fisher Exact Test (e)		P=0.008N	P=0.030N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence in animals killed at the end of the study
(e) 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 logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in controls is indicated by (N).
(f) Number of tumor-bearing animals/number of animals examined grossly at the site
(g) Twenty-six spleens were examined microscopically.

TABLE B4. HISTORICAL INCIDENCE OF CLITORAL GLAND NEOPLASMS IN FEMALE F344/N RATS (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
Propylene oxide	0/50	0/50	0/50
Methyl methacrylate	0/50	2/50	2/50
Propylene	0/49	0/49	0/49
1,2-Epoxybutane	1/50	2/50	3/50
Dichloromethane	0/50	1/50	1/50
Tetrachloroethylene	3/50	2/50	5/50
Bromoethane	1/50	0/50	1/50
TOTAL	5/349 (1.4%)	7/349 (2.0%)	12/349 (3.4%)
SD (b)	2.23%	2.00%	3.60%
Range (c)			
High	3/50	2/50	5/50
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls in NTP Studies			
TOTAL	62/1,643 (3.8%)	(d) 53/1,643 (3.2%)	(d) 115/1,643 (7.0%)
SD (b)	4.36%	3.49%	4.86%
Range (c)			
High	10/50	6/49	10/50
Low	0/50	0/50	0/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes four adenocarcinomas, NOS, and three squamous cell carcinomas

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m³	5 mg/m³
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(45)	(17)	(44)
Parasite metazoan	3 (7%)	1 (6%)	1 (2%)
Artery, inflammation			2 (5%)
Intestine large, colon	(49)	(20)	(45)
Hemorrhage			1 (2%)
Parasite metazoan	3 (6%)		1 (2%)
Intestine large, rectum	(49)	(20)	(46)
Parasite metazoan	1 (2%)		
Intestine small	(50)	(20)	(44)
Muscularis, hyperplasia			1 (2%)
Intestine small, duodenum	(50)	(20)	(44)
Artery, inflammation			1 (2%)
Intestine small, ileum	(45)	(18)	(44)
Inflammation, chronic	1 (2%)		
Artery, inflammation			1 (2%)
Intestine small, jejunum	(48)	(19)	(44)
Inflammation, chronic	1 (2%)		
Artery, inflammation			1 (2%)
Liver	(50)	(31)	(47)
Angiectasis	2 (4%)	1 (3%)	2 (4%)
Basophilic focus	21 (42%)	9 (29%)	22 (47%)
Basophilic focus, multiple		1 (3%)	
Clear cell focus	3 (6%)	2 (6%)	3 (6%)
Developmental malformation	2 (4%)	9 (29%)	6 (13%)
Eosinophilic focus	3 (6%)	1 (3%)	1 (2%)
Eosinophilic focus, multiple			1 (2%)
Hematopoietic cell proliferation			2 (4%)
Hyperplasia, focal		1 (3%)	
Inflammation, granulomatous	19 (38%)	6 (19%)	21 (45%)
Inflammation, suppurative			2 (4%)
Mixed cell focus			1 (2%)
Necrosis	7 (14%)	3 (10%)	3 (6%)
Artery, inflammation			1 (2%)
Artery, mineralization			1 (2%)
Bile duct, hyperplasia	10 (20%)	9 (29%)	8 (17%)
Hepatocyte, cytomegaly	1 (2%)		
Hepatocyte, vacuolization cytoplasmic	11 (22%)	7 (23%)	11 (23%)
Mesentery	(1)		(2)
Inflammation, chronic			1 (50%)
Necrosis			1 (50%)
Pancreas	(49)	(21)	(47)
Fibrosis			1 (2%)
Acinus, atrophy	7 (14%)	7 (33%)	11 (23%)
Artery, inflammation			2 (4%)
Salivary glands	(50)	(21)	(48)
Inflammation, suppurative	1 (2%)		
Karyomegaly	1 (2%)		
Duct, hyperplasia	1 (2%)		
Stomach, forestomach	(50)	(21)	(48)
Acanthosis	1 (2%)	1 (5%)	4 (8%)
Developmental malformation			1 (2%)
Hyperkeratosis			1 (2%)
Inflammation, suppurative	2 (4%)		4 (8%)
Ulcer	2 (4%)	1 (5%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
ALIMENTARY SYSTEM (Continued)			
Stomach, glandular	(49)	(21)	(47)
Inflammation, chronic			1 (2%)
Inflammation, suppurative			1 (2%)
Mineralization		1 (5%)	2 (4%)
Artery, inflammation			1 (2%)
Epithelium, hyperplasia	1 (2%)		1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(21)	(49)
Cardiomyopathy	13 (26%)	6 (29%)	20 (41%)
Mineralization		1 (5%)	2 (4%)
Thrombus	2 (4%)		4 (8%)
Artery, inflammation			1 (2%)
Artery, mineralization		1 (5%)	
Myocardium, hemorrhage	1 (2%)		
Myocardium, necrosis		1 (5%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(23)	(47)
Angiectasis			1 (2%)
Hemorrhage		1 (4%)	2 (4%)
Hyperplasia	13 (26%)		8 (17%)
Necrosis		2 (9%)	1 (2%)
Thrombus			1 (2%)
Vacuolization cytoplasmic	21 (42%)	9 (39%)	17 (36%)
Adrenal gland, medulla	(50)	(22)	(47)
Hyperplasia	7 (14%)	2 (9%)	4 (9%)
Hyperplasia, focal	1 (2%)		
Vacuolization cytoplasmic	1 (2%		
Parathyroid gland	(41)	(20)	(44)
Hyperplasia		1 (5%)	5 (11%)
Pituitary gland	(49)	(38)	(47)
Cyst		3 (8%)	1 (2%)
Pars distalis, angiectasis	3 (6%)		1 (2%)
Pars distalis, hyperplasia	3 (6%)	1 (3%)	3 (6%)
Pars distalis, hyperplasia, focal		1 (3%)	
Pars intermedia, angiectasis			1 (2%)
Thyroid gland	(50)	(21)	(47)
Ultimobranchial cyst	1 (2%)	1 (5%)	1 (2%)
C-cell, hyperplasia	17 (34%)	9 (43%)	11 (23%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(48)	(21)	(47)
Cyst	2 (4%)		
Hyperplasia	5 (10%)	2 (10%)	1 (2%)
Inflammation, suppurative	5 (10%)	3 (14%)	4 (9%)
Metaplasia, squamous			1 (2%)
Ovary	(50)	(22)	(47)
Cyst	7 (14%)		5 (11%)
Inflammation, chronic	1 (2%)		1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
GENITAL SYSTEM (Continued)			
Uterus	(50)	(25)	(48)
Decidual reaction	1 (2%)		
Dilatation	3 (6%)	1 (4%)	1 (2%)
Hemorrhage	1 (2%)	1 (4%)	
Inflammation, suppurative	1 (2%)	2 (8%)	
Metaplasia, squamous	1 (2%)		
Prolapse		1 (4%)	
Endometrium, hyperplasia	2 (4%)	1 (4%)	
Vagina			(2)
Inflammation, suppurative			1 (50%)
HEMATOPOIETIC SYSTEM			
Blood			(1)
Neutrophilia			1 (100%)
Bone marrow	(50)	(21)	(47)
Fibrosis		1 (5%)	
Hyperplasia			1 (2%)
Lymph node	(48)	(22)	(48)
Mediastinal, hyperplasia		1 (5%)	
Lymph node, mandibular	(48)	(17)	(45)
Hyperplasia		1 (6%)	2 (4%)
Spleen	(50)	(26)	(47)
Developmental malformation		1 (4%)	
Fibrosis	1 (2%)	2 (8%)	3 (6%)
Hematopoietic cell proliferation	3 (6%)	1 (4%)	5 (11%)
Infarct			1 (2%)
Pigmentation		1 (4%)	
Thymus	(50)	(19)	(47)
Cyst	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(49)	(28)	(49)
Galactocele	1 (2%)	1 (4%)	
Hyperplasia		1 (4%)	
Skin	(48)	(22)	(48)
Acanthosis	1 (2%)		
Inflammation, chronic	1 (2%)		
Inflammation, suppurative		1 (5%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
Skeletal muscle		(1)	(1)
Diaphragm, developmental malformation		1 (100%)	1 (100%)
NERVOUS SYSTEM			
Brain	(50)	(21)	(49)
Compression	10 (20%)	6 (29%)	9 (18%)
Congestion	1 (2%)		
Hemorrhage	6 (12%)		
Thrombus			1 (2%)
Ventricle, dilatation	1 (2%)	1 (5%)	1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	5 mg/m^3
RESPIRATORY SYSTEM			
Larynx	(50)	(21)	(47)
Foreign body		1 (5%)	5 (11%)
Inflammation, chronic		2 (10%)	4 (9%)
Inflammation, suppurative	12 (24%)	4 (19%)	17 (36%)
Mineralization		1 (5%)	
Epithelium, hyperplasia	2 (4%)	2 (10%)	1 (2%)
Lung	(50)	(23)	(48)
Foreign body		1 (4%)	1 (2%)
Hemorrhage	2 (4%)		
Inflammation, granulomatous			1 (2%)
Mineralization		1 (4%)	2 (4%)
Alveolar epithelium, hyperplasia			2 (4%)
Alveolus, edema		1 (4%)	
Alveolus, infiltration cellular, histiocytic	5 (10%)	7 (30%)	6 (13%)
Alveolus, inflammation, suppurative	3 (6%)	1 (4%)	5 (10%)
Artery, inflammation			2 (4%)
Bronchiole, inflammation, suppurative		1 (4%)	
Nose	(50)	(50)	(46)
Dilatation		1 (2%)	
Foreign body	1 (2%)	5 (10%)	1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, suppurative	1 (2%)	10 (20%)	6 (13%)
Parasite metazoan	1 (2%)		
Glands, dilatation	4 (8%)	15 (30%)	37 (80%)
Nasolacrimal duct, inflammation, suppurative		1 (2%)	1 (2%)
Respiratory epithelium, hyperplasia		12 (24%)	13 (28%)
Respiratory epithelium, metaplasia, squamous		2 (4%)	3 (7%)
Trachea	(50)	(21)	(47)
Inflammation, suppurative		1 (5%)	
SPECIAL SENSES SYSTEM			
Ear	(1)		
Acanthosis	1 (100%)		
Inflammation, granulomatous	1 (100%)		
Eye	(5)	(7)	(2)
Atrophy	1 (20%)		
Lens, cataract	3 (60%)	7 (100%)	2 (100%)
Lacrimal gland	(3)	(1)	(1)
Degeneration			1 (100%)
Inflammation, chronic	3 (100%)	1 (100%)	1 (100%)
URINARY SYSTEM			
Kidney	(50)	(23)	(48)
Cyst	1 (2%)		
Infarct	1 (2%)		
Mineralization	1 (2%)	1 (4%)	3 (6%)
Nephropathy, chronic	49 (98%)	21 (91%)	47 (98%)
Pelvis, dilatation			1 (2%)

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m³	3 mg/m³
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Liver	(50)	*(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)
Hemangiosarcoma, metastatic, spleen	1 (2%)		1 (2%)
Hepatocellular carcinoma	11 (22%)	7 (14%)	10 (20%)
Hepatocellular carcinoma, multiple	1 (2%)		
Hepatocellular adenoma	10 (20%)	5 (10%)	6 (12%)
Hepatocellular adenoma, multiple		2 (4%)	
Histiocytic sarcoma, metastatic, skin	1 (2%)		
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	1 (2%)	1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (2%)		
Stomach	(50)	*(50)	(50)
Sarcoma, poorly differentiated		1 (2%)	
Stomach, forestomach	(47)	*(50)	(50)
Mast cell tumor malignant, metastatic, bone marrow			1 (2%)
Papilloma squamous		1 (2%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	*(50)	(48)
Adenoma			1 (2%)
Lymphoma malignant mixed	1 (2%)		
Adrenal gland, medulla	(48)	*(50)	(45)
Lymphoma malignant mixed	1 (2%)		
Pituitary gland	(50)	*(50)	(48)
Lymphoma malignant mixed	1 (2%)		
Thyroid gland	(49)	*(50)	(50)
Follicular cell, adenoma			1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Prostate	(48)	*(50)	(49)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	1 (2%)		
Testes	(50)	*(50)	(50)
Hemangioma	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	3 mg/m^3
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(50)	(50)
Hemangiosarcoma, metastatic, spleen	1 (2%)		1 (2%)
Calvarium, mast cell tumor malignant			1 (2%)
Lymph node	(49)	*(50)	(50)
Axillary, lymphoma malignant mixed		1 (2%)	
Iliac, lymphoma malignant mixed		1 (2%)	
Iliac, lymphoma malignant undifferentiated cell type	1 (2%)		
Inguinal, lymphoma malignant lymphocytic		1 (2%)	
Mediastinal, lymphoma malignant mixed		2 (4%)	
Mesenteric, lymphoma malignant lymphocytic		1 (2%)	
Mesenteric, lymphoma malignant mixed	4 (8%)	3 (6%)	
Mesenteric, lymphoma malignant undifferentiated cell type	1 (2%)		
Pancreatic, lymphoma malignant mixed		1 (2%)	
Renal, lymphoma malignant lymphocytic		1 (2%)	
Renal, lymphoma malignant mixed	1 (2%)	3 (6%)	
Renal, lymphoma malignant undifferentiated cell type	1 (2%)		
Lymph node, bronchial	(43)	*(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	2 (5%)	2 (4%)	1 (2%)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)		
Lymph node, mandibular	(43)	*(50)	(41)
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	2 (5%)	1 (2%)	
Lymphoma malignant undifferentiated cell type	1 (2%)		
Mast cell tumor malignant, metastatic, bone marrow			1 (2%)
Spleen	(50)	*(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	3 (6%)
Hemangiosarcoma, metastatic, skin	2 (4%)		
Lymphoma malignant lymphocytic		1 (2%)	
Lymphoma malignant mixed	6 (12%)	4 (8%)	2 (4%)
Lymphoma malignant undifferentiated cell type	1 (2%)		
Mast cell tumor malignant, metastatic, bone marrow			1 (2%)
Thymus	(41)	*(50)	(33)
Osteosarcoma, metastatic, bone	1 (2%)		
INTEGUMENTARY SYSTEM			
Skin	(48)	*(50)	(49)
Basal cell carcinoma		1 (2%)	
Subcutaneous tissue, fibrosarcoma	1 (2%)		
Subcutaneous tissue, hemangiosarcoma	2 (4%)		
Subcutaneous tissue, histiocytic sarcoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Bone	(50)	*(50)	(50)
Osteosarcoma	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Lymphoma malignant lymphocytic		1 (2%)	1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m³	3 mg/m³
RESPIRATORY SYSTEM			
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	10 (20%)	8 (16%)	8 (16%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)	2 (4%)
Alveolar/bronchiolar carcinoma	5 (10%)	3 (6%)	5 (10%)
Alveolar/bronchiolar carcinoma, multiple			1 (2%)
Carcinoma, metastatic, harderian gland		1 (2%)	
Hepatocellular carcinoma, metastatic, liver	2 (4%)	2 (4%)	2 (4%)
Hepatocellular carcinoma, metastatic, multiple, liver			1 (2%)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed		1 (2%)	2 (4%)
Osteosarcoma, metastatic, bone	1 (2%)		
Mediastinum, hemangioma			1 (2%)
Nose	(50)	*(50)	(50)
Lymphoma malignant mixed	1 (2%)		
Respiratory epithelium, papilloma			1 (2%)
SPECIAL SENSES SYSTEM			
Ear	*(50)	*(50)	*(50)
Fibrosarcoma		1 (2%)	
Eye	*(50)	*(50)	*(50)
Fibrosarcoma		1 (2%)	
Harderian gland	*(50)	*(50)	*(50)
Adenoma	2 (4%)	1 (2%)	2 (4%)
Carcinoma		1 (2%)	1 (2%)
URINARY SYSTEM			
Kidney	(50)	*(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Lymphoma malignant lymphocytic			2 (4%)
Lymphoma malignant mixed			2 (4%)
Urinary bladder	(50)	*(50)	(50)
Lymphoma malignant mixed			1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant mixed	7 (14%)	5 (10%)	3 (6%)
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant undifferentiated cell	1 (2%)		
Lymphoma malignant lymphocytic		1 (2%)	2 (4%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Terminal sacrifice	33	34	36
Dead	10	4	4
Moribund	7	12	10

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	3 mg/m^3
TUMOR SUMMARY			
Total animals with primary neoplasms **	38	33	33
Total primary neoplasms	56	41	49
Total animals with benign neoplasms	20	17	19
Total benign neoplasms	24	18	22
Total animals with malignant neoplasms	25	21	20
Total malignant neoplasms	32	23	27
Total animals with secondary neoplasms ***	8	4	7
Total secondary neoplasms	10	5	9

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: CHAMBER CONTROL

WEEKS ON STUDY	051	059	079	081	082	082	083	087	088	090	091	098	099	100	102	102	102	106	106	106	106	106	106	106
CARCASS ID	181	191	211	341	501	311	261	331	071	431	491	121	381	251	021	481	461	011	031	041	051	061	081	091	101
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, spleen																									
Hepatocellular carcinoma					X		X			X	X		X			X			X			X			
Hepatocellular carcinoma, multiple								X																	
Hepatocellular adenoma		X										X							X						
Histiocytic sarcoma, metastatic, skin			X																						
Lymphoma malignant mixed						X																			
Lymphoma malignant undifferentiated cell type																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed						X																			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymphoma malignant mixed						X																			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	+	+	+	M	M	M	M	M	M	+	M	M	M	M	+	M	M	M	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed						X																			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+								+	+			+	+		+	+							+	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed						X																			
Seminal vesicle										+															
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma									X																
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, lymphoma malignant undifferentiated cell type																									
Mesenteric, lymphoma malignant mixed						X										X									
Mesenteric, lymphoma malignant undifferentiated cell type																									
Renal, lymphoma malignant mixed																				X					
Renal, lymphoma malignant undifferentiated cell type																									
Lymph node, bronchial	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymphoma malignant mixed						X														X					
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																									
Lymph node, mandibular	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Lymphoma malignant mixed													X			X									
Lymphoma malignant undifferentiated cell type																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, skin											X				X										
Lymphoma malignant mixed						X							X				X			X					
Lymphoma malignant undifferentiated cell type																									
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Osteosarcoma, metastatic, bone																	X								

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL
CARCASS ID	111	131	141	151	161	171	201	221	231	241	271	281	291	301	321	351	361	371	391	401	411	421	441	451	471	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	M	43
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma										X																1
Hemangiosarcoma, metastatic, spleen								X																		1
Hepatocellular carcinoma							X						X							X						11
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma					X							X				X	X			X			X		X	10
Histiocytic sarcoma, metastatic, skin																										1
Lymphoma malignant mixed																										1
Lymphoma malignant undifferentiated cell type															X											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth								+												+						2
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Adrenal gland, medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	M	M	+	+	M	+	M	+	+	+	M	+	+	M	M	+	M	M	M	M	+	+	M	20
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland							+						+			+			+				+			13
Prostate	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																										1
Seminal vesicle																			+							2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen								X																		1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Iliac, lymphoma malignant undifferentiated cell type															X											1
Mesenteric, lymphoma malig mixed						X																			X	4
Mesenteric, lymphoma malignant undifferentiated cell type															X											1
Renal, lymphoma malignant mixed																										1
Renal, lymphoma malignant undifferentiated cell type															X											1
Lymph node, bronchial	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	43
Lymphoma malignant mixed																										2
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung							X																			1
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	43
Lymphoma malignant mixed																										2
Lymphoma malignant undifferentiated cell type															X											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma								X																		1
Hemangiosarcoma, metastatic, skin																										2
Lymphoma malignant mixed						X																			X	6
Lymphoma malignant undifferentiated cell type															X											1
Thymus	+	M	+	+	M	M	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	41
Osteosarcoma, metastatic, bone																										1

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

WEEKS ON STUDY	051	059	079	081	082	082	083	087	088	090	091	098	099	100	102	102	102	106	106	106	106	106	106	106	106
CARCASS ID	181	191	211	341	501	311	261	331	071	431	491	121	381	251	021	481	461	011	031	041	051	061	081	091	101
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	+	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma				X																					
Subcutaneous tissue, hemangiosarcoma											X				X										
Subcutaneous tissue, histiocytic sarcoma			X																						
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																	X								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X				X	X				X													X	
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																	X								
Hepatocellular carcinoma, metastatic, liver					X			X																	
Osteosarcoma, metastatic, bone																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland											+														
Adenoma											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
CARCASS ID	111	131	141	151	161	171	201	221	231	241	271	281	291	301	321	351	361	371	391	401	411	421	441	451	471	TOTAL: TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	48
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																										2
Subcutaneous tissue, histiocytic sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X			X			X													X					X	10
Alveolar/bronchiolar adenoma, multiple																						X				1
Alveolar/bronchiolar carcinoma							X								X			X			X					5
Hepatocellular carcinoma, metastatic, liver																										2
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland														+												2
Adenoma														X												2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: 1.5 mg/m³

WEEKS ON STUDY	032	060	061	066	067	072	075	078	082	092	094	095	096	096	099	103	107	107	107	107	107	107	107	107	107
CARCASS ID	1101	1071	1471	1051	1391	1451	1251	1501	1491	1221	1081	1031	1091	1121	1401	1351	1011	1021	1041	1061	1111	1131	1141	1151	1161
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Gallbladder	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Intestine large, cecum	M	+	M	+	M	M	+	+	+	+	+	+	+	+	+	+									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Intestine large, rectum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+						
Hemangiosarcoma																									
Hepatocellular carcinoma					X		X			X			X	X				X							
Hepatocellular adenoma				X															X						
Hepatocellular adenoma, multiple																									
Lymphoma malignant lymphocytic											X														
Lymphoma malignant mixed																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Salivary glands	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Sarcoma, poorly differentiated																X									
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+		+	+	+	+	+	+										
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Alveolar/bronchiolar carcinoma, metastatic, lung												X													
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						+			
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						+			
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Parathyroid gland	M	M	+	M	M	+	+	+	+	M	M	M	M	M	M	M									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Thyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Penis															+									+	
Preputial gland						+	+	+		+		+	+									+			
Prostate	+	+	M	+	+	M		+	+	+	+	+	+	+	+	+									
Lymphoma malignant lymphocytic											X														
Seminal vesicle	+			+	+					+															
Testes	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Lymph node	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+								+	
Axillary, lymphoma malignant mixed																									
Iliac, lymphoma malignant mixed																									
Inguinal, lymphoma malignant lymphocytic											X														
Mediastinal, lymphoma malignant mixed																								X	
Mesenteric, lymphoma malignant lymphocytic											X														
Mesenteric, lymphoma malignant mixed															X									X	
Pancreatic, lymphoma malignant mixed																								X	
Renal, lymphoma malignant lymphocytic											X														
Renal, lymphoma malignant mixed															X									X	
Lymph node, bronchial	M	+	M	M	+	+	+	+	+	+	+	+	+		+	M									
Lymphoma malignant lymphocytic											X														
Lymphoma malignant mixed															X										
Lymph node, mandibular	M	+	+	M	+	+	+	+	+	+	+		+		+	+									
Lymphoma malignant lymphocytic											X														
Lymphoma malignant mixed															X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+						
Hemangiosarcoma																									
Lymphoma malignant lymphocytic											X														
Lymphoma malignant mixed															X				X						
Thymus	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TOTAL TISSUES TUMORS
CARCASS ID	11171	11181	11191	12201	12211	12231	12241	12261	12271	12281	12291	13301	13311	13321	13331	13341	13361	13371	13381	14411	14421	14431	14441	14461	14481		
ALIMENTARY SYSTEM																											
Esophagus																											16
Gallbladder																											14
Intestine large																											16
Intestine large, cecum																											12
Intestine large, colon																											16
Intestine large, rectum																											15
Intestine small												+								+							18
Intestine small, duodenum																											16
Intestine small, ileum																				+							17
Intestine small, jejunum												+															17
Liver				+								+			+				+				−	+	+	25
Hemangiosarcoma																			X								1
Hepatocellular carcinoma				X																							7
Hepatocellular adenoma																							X	X	X		5
Hepatocellular adenoma, multiple												X			X												2
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed				X																							1
Pancreas																											16
Salivary glands																											15
Stomach						+													+								18
Sarcoma, poorly differentiated																											1
Stomach, forestomach						+																					16
Papilloma squamous						X																					1
Stomach, glandular																			+								15
Tooth																											
CARDIOVASCULAR SYSTEM																											
Heart																											16
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
ENDOCRINE SYSTEM																											
Adrenal gland	+				+			+	+	+	+	+		+	+	+	+	+		+	+	+					32
Adrenal gland, cortex	+				+			+	+	+	+	+		+	+	+	+	+		+	+	+					32
Adrenal gland, medulla																											16
Islets, pancreatic																											16
Parathyroid gland																											5
Pituitary gland																											16
Thyroid gland																											15
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Epididymis																											15
Penis																			.								2
Preputial gland		+																	+								9
Prostate																											13
Lymphoma malignant lymphocytic																											1
Seminal vesicle																											4
Testes																											15
HEMATOPOIETIC SYSTEM																											
Bone marrow																											16
Lymph node				+	+										+						+		+				20
Axillary, lymphoma malignant mixed				X																							1
Iliac, lymphoma malignant mixed				X																							1
Inguinal, lymphoma malignant lymphocytic																											1
Mediastinal, lymphoma malig mixed				X																							2
Mesenteric, lymphoma malignant lymphocytic																											1
Mesenteric, lymphoma malignant mixed				X																							3
Pancreatic, lymphoma malignant mixed																											1
Renal, lymphoma malig lymphocytic																											1
Renal, lymphoma malignant mixed				X																							3
Lymph node, bronchial					+																+						13
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed																					X						2
Lymph node, mandibular																											12
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed																											1
Spleen				+																	+		+				20
Hemangiosarcoma																							(				1
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed				X																	X						4
Thymus																											12

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	032	060	061	066	067	072	075	078	082	092	094	095	096	096	099	103	107	107	107	107	107	107	107	107	107
CARCASS ID	11011	10711	14711	10511	13911	14511	12511	15011	14911	12211	10811	10311	10911	11211	14011	13511	10111	10211	10411	10611	11111	11311	11411	11511	11611
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M		M	M	M	+	+	M	M	M	M									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M									+
Basal cell carcinoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Lymphoma malignant lymphocytic											X														
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+			+	
Alveolar/bronchiolar adenoma				X						X							X				X				
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma												X													
Carcinoma, metastatic, harderian gland								X																	
Hepatocellular carcinoma, metastatic, liver													X	X											
Lymphoma malignant mixed																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+					+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
SPECIAL SENSES SYSTEM																									
Ear																									
Fibrosarcoma																									
Eye																									
Fibrosarcoma																									
Harderian gland								+																	
Adenoma																									
Carcinoma								X																	
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									
Alveolar/bronchiolar carcinoma, metastatic, lung												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TOTAL:
CARCASS ID	11171	11181	11191	12201	12211	12231	12241	12261	12271	12281	12291	13301	13111	13211	13311	13411	13611	13711	13811	14111	14211	14311	14411	14611	14811		TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Mammary gland									+																		3
Skin								+	+				+						+				+				21
Basal cell carcinoma									X																		1
MUSCULOSKELETAL SYSTEM																											
Bone																											16
NERVOUS SYSTEM																											
Brain																											16
Lymphoma malignant lymphocytic																											1
RESPIRATORY SYSTEM																											
Larynx																											16
Lung		+		+			+	+	+	+	+	+				+	+					+		+			32
Alveolar/bronchiolar adenoma				X				X		X	X																8
Alveolar/bronchiolar adenoma, multiple							X																				1
Alveolar/bronchiolar carcinoma							X										X										3
Carcinoma, metastatic, harderian gland																											1
Hepatocellular carcinoma, metastatic, liver																											2
Lymphoma malignant mixed				X																							1
Nose	+		+			+	+	+	+	+	+	+			+			+	+		+			+			34
Trachea																											16
SPECIAL SENSES SYSTEM																											
Ear		+																									1
Fibrosarcoma		X																									1
Eye		+																									1
Fibrosarcoma		X																									1
Harderian gland																+											2
Adenoma																X											1
Carcinoma																											1
URINARY SYSTEM																											
Kidney																											16
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Urinary bladder																											16

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: 3 mg/m³

WEEKS ON STUDY	0 3 3	0 5 0	0 5 5	0 6 1	0 7 3	0 7 7	0 7 8	0 7 9	0 8 7	0 9 1	1 0 0	1 0 1	1 0 4	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6
CARCASS ID	2 4 3 1	2 0 6 1	2 1 5 1	2 1 3 1	2 5 0 1	2 1 8 1	2 4 9 1	2 0 1 1	2 2 2 1	2 0 8 1	2 0 3 1	2 1 4 1	2 4 2 1	2 4 5 1	2 0 2 1	2 0 4 1	2 0 5 1	2 0 7 1	2 0 9 1	2 1 0 1	2 1 1 1	2 1 1 2	2 1 1 6	2 1 7 1	2 1 9 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, spleen																	X								
Hepatocellular carcinoma					X		X	X	X				X	X											
Hepatocellular adenoma			X	X		X		X															X		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mast cell tumor malignant, metastatic, bone marrow																			X						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Islets, pancreatic		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	M	M	M	+	+	M	+	+	+	+	M	M	+	+	M	+	+	M	+	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland				+		+			+	+			+							+					
Prostate	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle				+																					
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen										X															
Calvarium, mast cell tumor malignant																			X						
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung									X																
Lymphoma malignant mixed																									
Lymph node, mandibular	+	M	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+
Mast cell tumor malignant, metastatic, bone marrow																			X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X	X						X								
Lymphoma malignant mixed																									
Mast cell tumor malignant, metastatic, bone marrow																			X						
Thymus	M	M	+	+	+	+	M	+	+	M	+	+	M	M	+	+	+	M	+	+	+	+	+	M	M

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 3 mg/m³ (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL
CARCASS ID	22201	22211	22231	22241	22251	22261	22271	22281	22291	23301	23311	23321	23331	23341	23351	23361	23371	23381	23391	24401	24411	24441	24461	24471	24481	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma		X																								1
Hemangiosarcoma, metastatic, spleen																										1
Hepatocellular carcinoma							X			X								X	X							10
Hepatocellular adenoma											X															6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mast cell tumor malignant, metastatic, bone marrow																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth														+												1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Adenoma		X																								1
Adrenal gland, medulla	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	45
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	+	+	M	+	+	+	M	M	M	+	M	+	M	+	M	+	+	+	+	M	M	+	M	+	27
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																						X				1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland							+																			7
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																										1
Calvarium, mast cell tumor malignant																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Lymphoma malignant mixed					X																					1
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	41
Mast cell tumor malignant, metastatic, bone marrow																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										3
Lymphoma malignant mixed																	X						X			2
Mast cell tumor malignant, metastatic, bone marrow																										1
Thymus	+	+	+	M	+	+	M	M	+	M	+	+	+	+	+	+	+	M	+	M	M	M	+	+	+	33

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 3 mg/m³ (Continued)

WEEKS ON STUDY	033	050	055	061	073	077	078	079	087	091	100	101	104	106	106	106	106	106	106	106	106	106	106	106
CARCASS ID	24311	20611	21511	21311	25011	21811	24911	20111	22211	20811	20311	21411	24211	24511	20211	20411	20511	20711	20911	21011	21111	21211	21161	21711	21911
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M
Skin	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																			X						
RESPIRATORY SYSTEM																									
Larynx	M	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X				X						X		X			
Alveolar/bronchiolar adenoma, multiple																			X						
Alveolar/bronchiolar carcinoma									X								X							X	
Alveolar/bronchiolar carcinoma, multiple										X															
Hepatocellular carcinoma, metastatic, liver							X																		
Hepatocellular carcinoma, metastatic, multiple, liver								X																	
Lymphoma malignant lymphocytic																					X				
Lymphoma malignant mixed																									
Mediastinum, hemangioma																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, papilloma				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland														+										+	
Adenoma														X										X	
Carcinoma														X											
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																			X		X				
Lymphoma malignant mixed																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 3 mg/m³ (Continued)

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL.
CARCASS ID	22201	22211	22231	22241	22251	22261	22271	22281	22291	23301	23311	23321	23331	23341	23351	23361	23371	23381	23391	24401	24411	24421	24461	24471	24481	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	+	M	+	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X					X							X		X											8
Alveolar/bronchiolar adenoma, multiple																				X						2
Alveolar/bronchiolar carcinoma		X								X																5
Alveolar/bronchiolar carcinoma, multiple																										1
Hepatocellular carcinoma, metastatic, liver																		X								2
Hepatocellular carcinoma, metastatic, multiple, liver																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed					X																		X			2
Mediastinum, hemangioma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory epithelium, papilloma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland																										2
Adenoma																										2
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed					X																		X			2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																							X			1

TABLE C3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m^3	3 mg/m^3
Liver: Hepatocellular Adenoma			
Overall Rates (a)	10/50 (20%)	(b) 7/25 (28%)	6/50 (12%)
Adjusted Rates (c)	27 7%		13 6%
Terminal Rates (d)	8/33 (24%)		2/36 (6%)
Day of First Observation	409		381
Life Table Test (e)			P=0 192N
Logistic Regression Test (e)			P=0 174N
Fisher Exact Test (e)			P=0 207N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	12/50 (24%)	(b) 7/25 (28%)	10/50 (20%)
Adjusted Rates (c)	28 7%		23 2%
Terminal Rates (d)	5/33 (15%)		4/36 (11%)
Day of First Observation	570		510
Life Table Test (e)			P=0 382N
Logistic Regression Test (e)			P=0 384N
Fisher Exact Test (e)			P=0 405N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	20/50 (40%)	(b) 14/25 (56%)	15/50 (30%)
Adjusted Rates (c)	46 5%		32 6%
Terminal Rates (d)	11/33 (33%)		6/36 (17%)
Day of First Observation	409		381
Life Table Test (e)			P=0 201N
Logistic Regression Test (e)			P=0 171N
Fisher Exact Test (e)			P=0 201N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	11/50 (22%)	(b) 9/32 (28%)	10/50 (20%)
Adjusted Rates (c)	28 1%		26 2%
Terminal Rates (d)	7/33 (21%)		8/36 (22%)
Day of First Observation	409		694
Life Table Test (e)			P=0 436N
Logistic Regression Test (e)			P=0 507N
Fisher Exact Test (e)			P=0 500N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	5/50 (10%)	(b) 3/32 (9%)	6/50 (12%)
Adjusted Rates (c)	14 7%		15 3%
Terminal Rates (d)	4/33 (12%)		4/36 (11%)
Day of First Observation	709		604
Life Table Test (e)			P=0 552
Logistic Regression Test (e)			P=0 497
Fisher Exact Test (e)			P=0 500
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	15/50 (30%)	(b) 11/32 (34%)	16/50 (32%)
Adjusted Rates (c)	38 3%		39 8%
Terminal Rates (d)	10/33 (30%)		12/36 (33%)
Day of First Observation	409		604
Life Table Test (e)			P=0 576N
Logistic Regression Test (e)			P=0 488
Fisher Exact Test (e)			P=0 500
Circulatory System: Hemangiosarcoma			
Overall Rates (f)	4/50 (8%)	(b,g) 2/50 (4%)	4/50 (8%)
Adjusted Rates (c)	11 0%	5 9%	10 2%
Terminal Rates (d)	2/33 (6%)	2/34 (6%)	2/36 (6%)
Day of First Observation	635	741	637
Life Table Tests (e)	P=0 540N	P=0 330N	P=0 602N
Logistic Regression Tests (e)	P=0 576	P=0 349N	P=0 640
Cochran Armitage Trend Test (e)	P=0 579		
Fisher Exact Test (e)		P=0 339N	P=0 643N

TABLE C3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	3 mg/m^3
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (f)	5/50 (10%)	(b,g) 2/50 (4%)	5/50 (10%)
Adjusted Rates (c)	13 1%	5 9%	12 8%
Terminal Rates (d)	2/33 (6%)	2/34 (6%)	3/36 (8%)
Day of First Observation	610	741	637
Life Table Tests (e)	P=0 534N	P=0 217N	P=0 588N
Logistic Regression Tests (e)	P=0 569	P=0 223N	P=0 627
Cochran-Armitage Trend Test (e)	P=0 573		
Fisher Exact Test (e)		P=0 218N	P=0 630N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (f)	8/50 (16%)	(b,g) 6/50 (12%)	5/50 (10%)
Adjusted Rates (c)	21 1%	16 4%	13 9%
Terminal Rates (d)	4/33 (12%)	4/34 (12%)	5/36 (14%)
Day of First Observation	573	654	741
Life Table Tests (e)	P=0 194N	P=0 388N	P=0 238N
Logistic Regression Tests (e)	P=0 226N	P=0 405N	P=0 276N
Cochran-Armitage Trend Test (e)	P=0 226N		
Fisher Exact Test (e)		P=0 387N	P=0 277N
All Sites: Benign Tumors			
Overall Rates (f)	20/50 (40%)	17/50 (34%)	19/50 (38%)
Adjusted Rates (c)	50 0%	46 6%	44 5%
Terminal Rates (d)	14/33 (42%)	15/34 (44%)	13/36 (36%)
Day of First Observation	409	456	381
Life Table Tests (e)	P=0 372N	P=0 320N	P=0 418N
Logistic Regression Tests (e)	P=0 469N	P=0 369N	P=0 497N
Cochran Armitage Trend Test (e)	P=0 459N		
Fisher Exact Test (e)		P=0 339N	P=0 500N
All Sites: Malignant Tumors			
Overall Rates (f)	25/50 (50%)	21/50 (42%)	20/50 (40%)
Adjusted Rates (c)	55 0%	47 6%	45 2%
Terminal Rates (d)	13/33 (39%)	11/34 (32%)	12/36 (33%)
Day of First Observation	551	465	510
Life Table Tests (e)	P=0 177N	P=0 316N	P=0 199N
Logistic Regression Tests (e)	P=0 184N	P=0 269N	P=0 210N
Cochran Armitage Trend Test (e)	P=0 182N		
Fisher Exact Test (e)		P=0 274N	P=0 211N
All Sites: All Tumors			
Overall Rates (f)	38/50 (76%)	33/50 (66%)	33/50 (66%)
Adjusted Rates (c)	79 0%	73 3%	70 1%
Terminal Rates (d)	23/33 (70%)	22/34 (65%)	22/36 (61%)
Day of First Observation	409	456	381
Life Table Tests (e)	P=0 157N	P=0 256N	P=0 182N
Logistic Regression Tests (e)	P=0 171N	P=0 207N	P=0 187N
Cochran Armitage Trend Test (e)	P=0 165N		
Fisher Exact Test (e)		P=0 189N	P=0 189N

(a) Number of tumor bearing animals/number of animals examined microscopically at the site
(b) Incomplete sampling of tissues
(c) Kaplan Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence in animals killed at the end of the study
(e) 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 logistic regression test regards these lesions as nonfatal The Cochran Armitage and Fisher exact tests compare directly the overall incidence rates A negative trend or lower incidence in a dosed group than in controls is indicated by (N)
(f) Number of tumor bearing animals/number of animals examined grossly at the site
(g) Twenty spleens, 20 lymph nodes, and 25 livers were examined microscopically

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m³	3 mg/m³
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, rectum	(50)	(15)	(50)
Inflammation, suppurative			1 (2%)
Intestine small	(50)	(18)	(50)
Peyer's patch, hyperplasia, lymphoid			1 (2%)
Intestine small, ileum	(50)	(17)	(49)
Amyloid deposition			1 (2%)
Hyperplasia, lymphoid		1 (6%)	
Intestine small, jejunum	(50)	(17)	(50)
Hyperplasia, lymphoid		1 (6%)	1 (2%)
Liver	(50)	(25)	(50)
Congestion	1 (2%)		
Focal cellular change	1 (2%)	1 (4%)	1 (2%)
Hemorrhage			1 (2%)
Infarct	1 (2%)	1 (4%)	3 (6%)
Inflammation, subacute		1 (4%)	1 (2%)
Necrosis	1 (2%)	2 (8%)	
Bile duct, cyst			1 (2%)
Serosa, fibrosis, chronic		1 (4%)	
Pancreas	(50)	(16)	(50)
Hemorrhage			1 (2%)
Duct, cyst	1 (2%)		
Stomach, forestomach	(47)	(16)	(50)
Hyperkeratosis		1 (6%)	2 (4%)
Inflammation, subacute	1 (2%)		1 (2%)
Ulcer			1 (2%)
Stomach, glandular	(49)	(15)	(50)
Hyperplasia	2 (4%)	1 (7%)	2 (4%)
Subserosa, cyst	1 (2%)		
Tooth	(2)		(1)
Inflammation, suppurative	2 (100%)		1 (100%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(16)	(50)
Artery, inflammation, subacute	1 (2%)		
Atrium, thrombus			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(32)	(48)
Hyperplasia		1 (3%)	3 (6%)
Hyperplasia, diffuse			2 (4%)
Hyperplasia, focal	2 (4%)	4 (13%)	1 (2%)
Hypertrophy		2 (6%)	3 (6%)
Hypertrophy, diffuse		1 (3%)	3 (6%)
Hypertrophy, focal	16 (32%)	12 (38%)	13 (27%)
Adrenal gland, medulla	(48)	(16)	(45)
Hyperplasia, focal	1 (2%)		
Pituitary gland	(50)	(16)	(48)
Cyst	1 (2%)		
GENERAL BODY SYSTEM			
None			

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	3 mg/m^3
GENITAL SYSTEM			
Penis		(2)	
Abscess		1 (50%)	
Inflammation, chronic		1 (50%)	
Preputial gland	(13)	(9)	(7)
Inflammation, chronic	1 (8%)	1 (11%)	
Inflammation, suppurative	5 (38%)	4 (44%)	4 (57%)
Duct, dilatation	6 (46%)	4 (44%)	1 (14%)
Duct, hyperplasia	1 (8%)		
Prostate	(48)	(13)	(49)
Inflammation, suppurative	2 (4%)	1 (8%)	1 (2%)
Seminal vesicle	(2)	(4)	(1)
Dilatation		1 (25%)	
Inflammation, chronic	1 (50%)		
Inflammation, suppurative	1 (50%)		
Testes	(50)	(15)	(50)
Atrophy	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(16)	(50)
Hyperplasia, neutrophil	1 (2%)	1 (6%)	
Lymph node	(49)	(20)	(50)
Mediastinal, hyperplasia, lymphoid		1 (5%)	
Mesenteric, hyperplasia, lymphoid	1 (2%)		
Mesenteric, sinus, dilatation		1 (5%)	
Renal, hyperplasia, lymphoid		1 (5%)	
Lymph node, bronchial	(43)	(13)	(49)
Hyperplasia, lymphoid		1 (8%)	1 (2%)
Lymph node, mandibular	(43)	(12)	(41)
Hyperplasia, lymphoid	3 (7%)		2 (5%)
Spleen	(50)	(20)	(50)
Atrophy		1 (5%)	
Hematopoietic cell proliferation	3 (6%)	2 (10%)	1 (2%)
Hyperplasia, lymphoid			2 (4%)
INTEGUMENTARY SYSTEM			
Skin	(48)	(21)	(49)
Alopecia	3 (6%)	4 (19%)	3 (6%)
Inflammation, necrotizing			1 (2%)
Inflammation, suppurative	2 (4%)	1 (5%)	1 (2%)
Subcutaneous tissue, inflammation, chronic	2 (4%)		
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(50)	(16)	(50)
Abscess		1 (6%)	
Infiltration cellular, lymphocytic			1 (2%)
Mineralization	30 (60%)	2 (13%)	31 (62%)
Meninges, hyperplasia, lymphoid			1 (2%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	3 mg/m^3
RESPIRATORY SYSTEM			
Lung	(50)	(32)	(50)
Congestion	2 (4%)		2 (4%)
Hemorrhage, acute		1 (3%)	
Hemorrhage, focal			4 (8%)
Infiltration cellular, histiocytic	2 (4%)	3 (9%)	
Inflammation, subacute	4 (8%)	1 (3%)	2 (4%)
Inflammation, suppurative		3 (9%)	1 (2%)
Leukocytosis			1 (2%)
Alveolar epithelium, hyperplasia	7 (14%)	6 (19%)	6 (12%)
Alveolar epithelium, hyperplasia, focal	1 (2%)		2 (4%)
Bronchiole, hyperplasia			2 (4%)
Bronchiole, hyperplasia, focal		5 (16%)	
Bronchus, ulcer, focal			1 (2%)
Pleura, inflammation, subacute	1 (2%)		
Nose	(50)	(50)	(50)
Hemorrhage, acute		1 (2%)	
Inflammation, suppurative	1 (2%)	4 (8%)	3 (6%)
Nasolacrimal duct, inflammation, suppurative		1 (2%)	
Olfactory epithelium, degeneration, hyaline	3 (6%)	17 (34%)	39 (78%)
Olfactory epithelium, degeneration, hyaline, focal			1 (2%)
Olfactory epithelium, metaplasia, focal	8 (16%)	11 (22%)	8 (16%)
Respiratory epithelium, degeneration, hyaline	5 (10%)	2 (4%)	2 (4%)
Respiratory epithelium, hyperplasia, focal	1 (2%)	2 (4%)	
SPECIAL SENSES SYSTEM			
None			
URINARY SYSTEM			
Kidney	(50)	(16)	(50)
Atrophy		1 (6%)	
Bacterium, acute	1 (2%)		
Developmental malformation		1 (6%)	
Fibrosis, focal	1 (2%)		
Hemorrhage, focal			1 (2%)
Infiltration cellular, lymphocytic	1 (2%)		
Inflammation, chronic, focal	1 (2%)		
Inflammation, suppurative		1 (6%)	1 (2%)
Metaplasia, osseous	1 (2%)		1 (2%)
Mineralization		1 (6%)	1 (2%)
Nephropathy	1 (2%)		1 (2%)
Pelvis, inflammation, chronic	2 (4%)	2 (13%)	2 (4%)
Pelvis, inflammation, suppurative		1 (6%)	1 (2%)
Renal tubule, casts			2 (4%)
Renal tubule, degeneration			2 (4%)
Renal tubule, dilatation			1 (2%)
Renal tubule, regeneration	3 (6%)		3 (6%)
Renal tubule, regeneration, focal	1 (2%)		1 (2%)
Urinary bladder	(50)	(16)	(50)
Concretion	1 (2%)		
Dilatation	1 (2%)	1 (6%)	
Hyperplasia		1 (6%)	
Inflammation, subacute	1 (2%)	1 (6%)	
Inflammation, suppurative	1 (2%)		

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m³	3 mg/m³
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine small, duodenum	(50)	*(50)	(50)
Adenocarcinoma	1 (2%)		
Intestine small, jejunum	(49)	*(50)	(50)
Lymphoma malignant mixed		3 (6%)	
Lymphoma malignant undifferentiated cell type		1 (2%)	
Liver	(50)	*(50)	(50)
Hemangiosarcoma	1 (2%)		
Hemangiosarcoma, metastatic	1 (2%)		
Hepatocellular carcinoma	1 (2%)	1 (2%)	2 (4%)
Hepatocellular adenoma	2 (4%)	1 (2%)	4 (8%)
Hepatocholangiocarcinoma		1 (2%)	
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant histiocytic		1 (2%)	
Lymphoma malignant lymphocytic			3 (6%)
Lymphoma malignant mixed	9 (18%)	5 (10%)	4 (8%)
Lymphoma malignant undifferentiated cell type		1 (2%)	
Sarcoma		1 (2%)	
Pancreas	(50)	*(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Lymphoma malignant mixed			2 (4%)
Salivary glands	(49)	*(50)	(49)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed		1 (2%)	
Stomach, forestomach	(50)	*(50)	(49)
Papilloma squamous		1 (2%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	*(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic lung			1 (2%)
Hemangiosarcoma, metastatic, spleen			1 (2%)
Hepatocholangiocarcinoma, metastatic liver		1 (2%)	
Lymphoma malignant mixed	1 (2%)		
ENDOCRINE SYSTEM			
Adrenal gland	(50)	*(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Capsule, adenoma			1 (2%)
Capsule, lymphoma malignant lymphocytic			1 (2%)
Capsule, lymphoma malignant mixed			1 (2%)
Adrenal gland, cortex	(50)	*(50)	(49)
Lymphoma malignant lymphocytic		1 (2%)	2 (4%)
Lymphoma malignant mixed	1 (2%)	2 (4%)	1 (2%)
Pituitary gland	(49)	(46)	(49)
Adenoma	7 (14%)	11 (24%)	12 (24%)
Pars intermedia, adenoma		1 (2%)	
Thyroid gland	(49)	*(50)	(48)
Lymphoma malignant mixed		1 (2%)	
Bilateral, follicular cell adenoma		1 (2%)	
Follicular cell, adenocarcinoma			1 (2%)
Follicular cell, adenoma	3 (6%)	1 (2%)	1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m³	3 mg/m³
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(50)	*(50)	(50)
Adenocarcinoma		1 (2%)	
Adenoma		1 (2%)	
Cystadenoma	3 (6%)		1 (2%)
Hemangioma		1 (2%)	
Lymphoma malignant lymphocytic		1 (2%)	4 (8%)
Lymphoma malignant mixed	2 (4%)	2 (4%)	1 (2%)
Teratoma	1 (2%)		
Uterus	(50)	*(50)	(50)
Adenocarcinoma		1 (2%)	2 (4%)
Adenoma	1 (2%)	1 (2%)	
Fibrous histiocytoma	1 (2%)		
Hemangiosarcoma	1 (2%)		
Histiocytic sarcoma	1 (2%)		
Leiomyoma		1 (2%)	
Lymphoma malignant lymphocytic		1 (2%)	2 (4%)
Lymphoma malignant mixed	1 (2%)		
Sarcoma stromal			1 (2%)
Endometrium, polyp stromal		1 (2%)	3 (6%)
Vagina	*(50)	*(50)	*(50)
Sarcoma stromal, metastatic, uterus			1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	*(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)		
Lymph node	(50)	*(50)	(49)
Axillary, lymphoma malignant mixed	1 (2%)	1 (2%)	
Iliac, lymphoma malignant mixed	2 (4%)	1 (2%)	1 (2%)
Inguinal, lymphoma malignant mixed		1 (2%)	1 (2%)
Mediastinal, lymphoma malignant lymphocytic			2 (4%)
Mediastinal, lymphoma malignant mixed	4 (8%)	2 (4%)	3 (6%)
Mediastinal, lymphoma malignant undifferentiated cell type		1 (2%)	
Mesenteric, lymphoma malignant lymphocytic		1 (2%)	
Mesenteric, lymphoma malignant mixed	4 (8%)	9 (18%)	3 (6%)
Mesenteric, lymphoma malignant undifferentiated cell type		1 (2%)	
Pancreatic, lymphoma malignant mixed	2 (4%)	1 (2%)	2 (4%)
Popliteal, lymphoma malignant mixed		1 (2%)	
Renal, lymphoma malignant lymphocytic		1 (2%)	
Renal, lymphoma malignant mixed	5 (10%)	6 (12%)	5 (10%)
Lymph node, bronchial	(45)	*(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (2%)
Lymphoma malignant histiocytic		1 (2%)	
Lymphoma malignant lymphocytic		1 (2%)	1 (2%)
Lymphoma malignant mixed	8 (18%)	6 (12%)	4 (8%)
Lymph node, mandibular	(49)	*(50)	(45)
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	9 (18%)	6 (12%)	6 (13%)
Lymphoma malignant undifferentiated cell type		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m³	3 mg/m³
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(50)	*(50)	(50)
Hemangioma	1 (2%)		
Hemangiosarcoma			1 (2%)
Hemangiosarcoma, metastatic, skin		1 (2%)	
Hemangiosarcoma, metastatic, skeletal muscle			1 (2%)
Lymphoma malignant histiocytic		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)	2 (4%)	4 (8%)
Lymphoma malignant mixed	14 (28%)	9 (18%)	6 (12%)
Lymphoma malignant undifferentiated cell type		1 (2%)	1 (2%)
Thymus	(46)	*(50)	(45)
Lymphoma malignant mixed	2 (4%)	2 (4%)	
INTEGUMENTARY SYSTEM			
Mammary gland	(44)	*(50)	(45)
Adenoacanthoma			1 (2%)
Adenocarcinoma	1 (2%)		2 (4%)
Skin	(49)	*(50)	(49)
Lymphoma malignant lymphocytic		1 (2%)	
Subcutaneous tissue, hemangiosarcoma		2 (4%)	
Subcutaneous tissue, lymphoma malignant lymphocytic			1 (2%)
Subcutaneous tissue, lymphoma malignant mixed	1 (2%)		
Subcutaneous tissue, mast cell tumor malignant		1 (2%)	
Vulva, papilloma			1 (2%)
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Hemangiosarcoma			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)
RESPIRATORY SYSTEM			
Larynx	(50)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)
Lung	(50)	*(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	5 (10%)	
Alveolar/bronchiolar adenoma, multiple			1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)		
Hemangiosarcoma, metastatic	1 (2%)		
Hepatocholangiocarcinoma, metastatic liver		1 (2%)	
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant histiocytic		1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	2 (4%)
Lymphoma malignant mixed	7 (14%)	6 (12%)	1 (2%)
Lymphoma malignant undifferentiated cell type			1 (2%)
Osteosarcoma, metastatic, uncertain primary site		1 (2%)	
Sarcoma, metastatic, liver		1 (2%)	
Nose	(50)	*(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)
Turbinate, hemangioma	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	3 mg/m^3
SPECIAL SENSES SYSTEM			
Harderian gland	*(50)	*(50)	*(50)
Adenocarcinoma	1 (2%)		
Adenoma	1 (2%)		
URINARY SYSTEM			
Kidney	(50)	*(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)	
Lymphoma malignant lymphocytic			1 (2%)
Lymphoma malignant mixed	4 (8%)	1 (2%)	3 (6%)
Renal tubule, adenoma			1 (2%)
Urinary bladder	(50)	*(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant mixed	15 (30%)	15 (30%)	7 (14%)
Lymphoma malignant lymphocytic	1 (2%)	2 (4%)	7 (14%)
Histiocytic sarcoma	1 (2%)		
Lymphoma malignant histiocytic		1 (2%)	
Lymphoma malignant undifferentiated cell		1 (2%)	1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Dead	11	7	9
Moribund	7	8	8
Terminal sacrifice	32	35	33
TUMOR SUMMARY			
Total animals with primary neoplasms **	36	35	30
Total primary neoplasms	49	53	52
Total animals with benign neoplasms	19	19	19
Total benign neoplasms	23	26	25
Total animals with malignant neoplasms	25	26	23
Total malignant neoplasms	26	27	27
Total animals with secondary neoplasms ***	1	4	4
Total secondary neoplasms	2	8	5
Total animals with malignant neoplasms		1	

* Number of animals receiving complete necropsy examination, all gross lesions including masses examined microscopically
** Primary tumors all tumors except secondary tumors
*** Secondary tumors metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: CHAMBER CONTROL

WEEKS ON STUDY	0 3 3	0 4 7	0 7 2	0 8 0	0 8 1	0 8 8	0 9 6	0 9 7	0 9 8	0 9 9	1 0 1	1 0 2	1 0 2	1 0 2	1 0 3	1 0 4	1 0 5	1 0 5	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6	1 0 6
CARCASS ID	0 5 3 1	0 8 4 1	0 6 5 1	0 7 2 1	0 5 2 1	0 8 2 1	0 5 1 1	0 9 7 1	0 9 9 1	0 8 9 1	0 7 3 1	0 9 0 1	0 6 3 1	0 7 4 1	0 5 6 1	0 7 8 1	0 7 0 1	0 6 7 1	0 5 4 1	0 5 5 1	0 5 7 1	0 5 8 1	0 5 9 1	0 6 0 1	0 6 1 1
ALIMENTARY SYSTEM																									
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Intestine small, ileum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Hemangiosarcoma, metastatic						X																			
Hepatocellular carcinoma							X																		
Hepatocellular adenoma																			X						
Histiocytic sarcoma												X													
Lymphoma malignant mixed			X	X									X	X	X		X						X		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth								+																	
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed														X											
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed											X														
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	M	+	M	M	M	+	M	M	M	+	+	+	+	M	+	M	M	M	+	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X													X		X				
Thyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																		X	X						
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Lymphoma malignant mixed				X							X														
Teratoma		X																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Fibrous histiocytoma																									
Hemangiosarcoma						X																			
Histiocytic sarcoma												X													
Lymphoma malignant mixed				X																					

\+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A Autolysis precludes examination
X Incidence of listed morphology

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL TISSUES TUMORS
CARCASS ID	06221	06411	06661	06881	06991	07111	07515	07661	07711	07791	08001	08111	08331	08551	08661	08711	08811	09111	09221	09331	09441	09551	09661	09881	10101	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																									X	1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hemangiosarcoma, metastatic																										1
Hepatocellular carcinoma																										1
Hepatocellular adenoma																								X		2
Histiocytic sarcoma																										1
Lymphoma malignant mixed																		X		X						9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	M	M	M	M	M	M	M	M	+	M	+	+	+	+	M	M	+	+	M	M	M	M	M	M	18
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Adenoma		X					X						X			X										7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																						X				3
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma	X													X	X											3
Lymphoma malignant mixed																										2
Teratoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Fibrous histiocytoma										X																1
Hemangiosarcoma																										1
Histiocytic sarcoma																										1
Lymphoma malignant mixed																										1

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

WEEKS ON STUDY	033	047	072	080	081	088	096	097	098	099	101	102	102	102	103	104	105	105	106	106	106	106	106	106	106
CARCASS ID	05311	08411	06511	07211	05211	08211	05111	09711	09911	08911	07311	09011	06311	07411	05611	07811	07011	06711	05411	05511	05711	05811	05911	06011	06111
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, lymphoma malignant mixed														X											
Iliac, lymphoma malignant mixed																		X				X			
Mediastinal, lymphoma malignant mixed											X			X			X								
Mesenteric, lymphoma malignant mixed														X				X	X				X		
Pancreatic, lymphoma malignant mixed																		X					X		
Renal, lymphoma malignant mixed														X				X	X			X	X		
Lymph node, bronchial	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed				X							X			X			X		X			X	X		
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Lymphoma malignant mixed			X	X									X	X	X			X	X			X	X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed			X	X									X	X	X		X	X	X			X	X		
Thymus	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																			X						
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+
Adenocarcinoma																				X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, lymphoma malignant mixed														X											
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Alveolar/bronchiolar carcinoma				X																					
Alveolar/bronchiolar carcinoma, multiple										X															
Hemangiosarcoma, metastatic						X																			
Histiocytic sarcoma												X													
Lymphoma malignant lymphocytic																									
Lymphoma malignant mixed			X	X							X		X	X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Turbinate, hemangioma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland																									
Adenocarcinoma																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed														X								X	X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									

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

WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TOTAL.
CARCASS ID	06221	06641	06661	06681	06691	07111	07551	07661	07771	07791	08001	08111	08331	08551	08661	08671	08881	09111	09221	09331	09411	09511	09611	09811	10101	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic		X																								1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, lymphoma malignant mixed																										1
Iliac, lymphoma malignant mixed																										2
Mediastinal, lymphoma malig mixed																				X						4
Mesenteric, lymphoma malignant mixed																										4
Pancreatic, lymphoma malignant mixed																										2
Renal, lymphoma malignant mixed																										5
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant mixed																				X						8
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																										9
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																				X						1
Lymphoma malignant lymphocytic		X																								1
Lymphoma malignant mixed							X								X			X		X						14
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymphoma malignant mixed															X											2
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Subcutaneous tissue, lymphoma malignant mixed																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																					X	3
Alveolar/bronchiolar carcinoma																										1
Alveolar/bronchiolar carcinoma, multiple																										1
Hemangiosarcoma, metastatic																										1
Histiocytic sarcoma																										1
Lymphoma malignant lymphocytic		X																								1
Lymphoma malignant mixed															X					X						7
Nose	+	+	+	+	+	+	+	+	+	·	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Turbinate, hemangioma																X										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland			+		+																					2
Adenocarcinoma					X																					1
Adenoma			X																							1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																		X								4
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic		X																								1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: 1.5 mg/m³

WEEKS ON STUDY	0 5 5	0 6 7	0 7 2	0 7 7	0 8 3	0 8 7	0 8 8	0 9 2	0 9 4	0 9 5	0 9 9	0 9 9	0 9 9	0 9 9	1 0 3	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7
CARCASS ID	1 9 6 1	1 5 3 1	1 6 0 1	1 6 6 1	1 7 8 1	1 8 6 1	1 9 2 1	1 7 4 1	1 6 5 1	1 8 5 1	1 7 7 1	1 5 5 1	1 9 4 1	2 0 0 1	1 7 1 1	1 5 1 1	1 5 2 1	1 5 4 1	1 5 6 1	1 5 7 1	1 5 8 1	1 5 9 1	1 6 1 1	1 6 2 1	1 6 3 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Intestine large, cecum		+		+	+	+	+	+	+	+	+	+	+	+	+										
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+			
Intestine small, duodenum	+		+	+	+	+	+	+	+	+	+	+	+	+	+										
Intestine small, ileum	+		+	+	+	+	+	+	+	+	+	+	+	+	+										
Intestine small, jejunum	+		+	+	+	+	+	+	+	+	+	+	+	+	+							+			
Lymphoma malignant mixed																						X			
Lymphoma malignant undifferentiated cell type																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+		
Hepatocellular carcinoma																									
Hepatocellular adenoma																							X		
Hepatocholangiocarcinoma				X																					
Lymphoma malignant histiocytic			X																						
Lymphoma malignant mixed					X								X		X								X		
Lymphoma malignant undifferentiated cell type																									
Sarcoma	X																								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Hepatocholangiocarcinoma, metastatic, liver				X																					
Salivary glands		+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Lymphoma malignant mixed					X																				
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+				
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+					+				
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Hepatocholangiocarcinoma, metastatic, liver				X																					
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Hepatocholangiocarcinoma, metastatic, liver				X																					
Adrenal gland, cortex	+	+	+		+	+	+	+	+	+	+	+	+	+	+										
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed										X			X												
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Parathyroid gland	M	+	+	+	+	M	+	M	+	+	M	M	M	M	+								+		
Pituitary gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Adenoma										X											X		X		
Pars intermedia, adenoma																									X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+		
Lymphoma malignant mixed																							X		
Bilateral, follicular cell, adenoma																							X		
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+		+	+				+			+
Adenocarcinoma																									X
Adenoma						X																			
Hemangioma																									
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed										X			X												
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+						+				
Adenocarcinoma																									
Adenoma																									
Leiomyoma																									
Lymphoma malignant lymphocytic									X																
Endometrium polyp stromal																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TOTAL
CARCASS ID	16411	16711	16811	16911	17011	17211	17311	17511	17611	17911	18011	18111	18211	18311	18411	18711	18811	18911	19011	19111	19311	19511	19711	19811	19911		TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus																											15
Gallbladder																											15
Intestine large																											15
Intestine large, cecum																											13
Intestine large, colon																											15
Intestine large, rectum																											15
Intestine small		+	+													+											19
Intestine small, duodenum																											14
Intestine small, ileum																											14
Intestine small, jejunum		+	+													+											18
Lymphoma malignant mixed			X													X											3
Lymphoma malignant undifferentiated cell type		X																									1
Liver		+	+		+														+								20
Hepatocellular carcinoma					X																						1
Hepatocellular adenoma																											1
Hepatocholangiocarcinoma																											1
Lymphoma malignant histiocytic																											1
Lymphoma malignant mixed			X																								5
Lymphoma malignant undifferentiated cell type		X																									1
Sarcoma																											1
Pancreas																+											16
Hepatocholangiocarcinoma, metastatic, liver																											1
Salivary glands																											14
Lymphoma malignant mixed																											1
Stomach																+			+								19
Stomach, forestomach																+			+								19
Papilloma squamous																			X								1
Stomach, glandular																											15
CARDIOVASCULAR SYSTEM																											
Heart																											15
Hepatocholangiocarcinoma, metastatic, liver																											1
ENDOCRINE SYSTEM																											
Adrenal gland												+														+	17
Hepatocholangiocarcinoma, metastatic, liver																											1
Adrenal gland, cortex												+															15
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed																											2
Adrenal gland, medulla																										+	16
Islets, pancreatic																											15
Parathyroid gland																											9
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Adenoma			X	X					X				X			X			X				X		X		11
Pars intermedia, adenoma																											1
Thyroid gland									+														+				18
Lymphoma malignant mixed																											1
Bilateral, follicular cell, adenoma																											1
Follicular cell, adenoma									X																		1
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Ovary				+						+	+			+	+				+	+		+					26
Adenocarcinoma																											1
Adenoma																											1
Hemangioma																				X							1
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed																											2
Uterus										+		+											+				19
Adenocarcinoma										X																	1
Adenoma												X															1
Leiomyoma												X															1
Lymphoma malignant lymphocytic																											1
Endometrium, polyp stromal										X																	1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	055	067	072	077	083	087	088	092	094	095	099	099	099	099	103	107	107	107	107	107	107	107	107	107	107
CARCASS ID	19611	15311	16011	16611	17811	18611	19211	17411	16511	18511	17711	15511	19411	20011	17111	15111	15211	15411	15611	15711	15811	15911	16111	16211	16311
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Lymph node	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+		+	+		
Axillary, lymphoma malignant mixed					X																				
Iliac, lymphoma malignant mixed																									
Inguinal, lymphoma malignant mixed													X												
Mediastinal, lymphoma malignant mixed										X															
Mediastinal, lymphoma malignant undifferentiated cell type																									
Mesenteric, lymphoma malignant lymphocytic									X																
Mesenteric, lymphoma malignant mixed					X								X							X		X	X		
Mesenteric, lymphoma malignant undifferentiated cell type																									
Pancreatic, lymphoma malignant mixed																									
Popliteal, lymphoma malignant mixed					X																				
Renal, lymphoma malignant lymphocytic									X																
Renal, lymphoma malignant mixed					X								X										X		
Lymph node, bronchial	M	+	+	+	+	+	+	+	+		+	+	+	+	+	+				+					
Lymphoma malignant histiocytic			X																						
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed					X							X	X							X					
Lymph node, mandibular	M	+	+	+	+	+	+	+	+		+	+	+	+	M								+		
Lymphoma malignant mixed					X							X	X										X		
Lymphoma malignant undifferentiated cell type																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							+		+
Hemangiosarcoma, metastatic, skin							X																		
Lymphoma malignant histiocytic			X																						
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed					X							X	X		X								X		
Lymphoma malignant undifferentiated cell type																									
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+										
Lymphoma malignant mixed					X								X												
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+				+	+		+			
Lymphoma malignant lymphocytic									X																
Subcutaneous tissue, hemangiosarcoma							X																		
Subcutaneous tissue, mast cell tumor malignant																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
RESPIRATORY SYSTEM																									
Larynx	+	+		+	+	+	+	+	+	+	+	+	+	+	+										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+	+	
Alveolar/bronchiolar adenoma												X												X	
Hepatocholangiocarcinoma, metastatic, liver				X																					
Lymphoma malignant histiocytic			X																						
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed										X			X		X								X		
Osteosarcoma, metastatic, uncertain primary site		X																							
Sarcoma, metastatic, liver	X																								
Nose	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
SPECIAL SENSES SYSTEM																									
None																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								+		
Hepatocholangiocarcinoma, metastatic, liver				X																					
Lymphoma malignant mixed																							X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										
Lymphoma malignant lymphocytic									X																

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 1.5 mg/m³ (Continued)

WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TOTAL.
CARCASS ID	1641	1671	1681	1691	1701	1721	1731	1751	1761	1791	1801	1811	1821	1831	1841	1871	1881	1891	1901	1911	1931	1951	1971	1981	1991		TISSUES TUMORS
HEMATOPOIETIC SYSTEM																											
Bone marrow																											15
Lymph node		+	+	+		+		+		+	+	+				+				+			+				29
Axillary, lymphoma malignant mixed																											1
Iliac, lymphoma malignant mixed								X																			1
Inguinal, lymphoma malignant mixed																											1
Mediastinal, lymphoma malig mixed								X																			2
Mediastinal, lymphoma malignant undifferentiated cell type		X																									1
Mesenteric, lymphoma malignant lymphocytic																											1
Mesenteric, lymphoma malignant mixed			X			X		X				X															9
Mesenteric, lymphoma malignant undifferentiated cell type		X																									1
Pancreatic, lymphoma malignant mixed								X																			1
Popliteal, lymphoma malignant mixed																											1
Renal, lymphoma malig lymphocytic																											1
Renal, lymphoma malignant mixed			X			X		X																			6
Lymph node, bronchial			+			+				+										+			+				20
Lymphoma malignant histiocytic																											1
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed			X			X																					6
Lymph node, mandibular		+	+							+	+					+							+				19
Lymphoma malignant mixed			X								X																6
Lymphoma malignant undifferentiated cell type		X																									1
Spleen		+	+			+		+					+			+											25
Hemangiosarcoma, metastatic, skin																											1
Lymphoma malignant histiocytic																											1
Lymphoma malignant lymphocytic													X														2
Lymphoma malignant mixed			X			X		X		X																	9
Lymphoma malignant undifferentiated cell type		X																									1
Thymus																											14
Lymphoma malignant mixed																											2
INTEGUMENTARY SYSTEM																											
Mammary gland																											14
Skin									+			+						+		+				+			23
Lymphoma malignant lymphocytic																											1
Subcutaneous tissue, hemangiosarcoma									X																		2
Subcutaneous tissue, mast cell tumor malignant																		X									1
MUSCULOSKELETAL SYSTEM																											
Bone																											15
NERVOUS SYSTEM																											
Brain																											15
RESPIRATORY SYSTEM																											
Larynx																											14
Lung			+	+		+				+	+		+		+		+	+					+		+		27
Alveolar/bronchiolar adenoma				X									X				X										5
Hepatocholangiocarcinoma, metastatic, liver																											1
Lymphoma malignant histiocytic																											1
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed			X							X																	6
Osteosarcoma, metastatic, uncertain primary site																											1
Sarcoma, metastatic, liver																											1
Nose	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Trachea																											15
SPECIAL SENSES SYSTEM																											
None																											
URINARY SYSTEM																											
Kidney						+						+						+									19
Hepatocholangiocarcinoma, metastatic, liver																											1
Lymphoma malignant mixed																											1
Urinary bladder																											15
Lymphoma malignant lymphocytic																											1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE: 3 mg/m³

WEEKS ON STUDY	0 3 9	0 4 9	0 6 1	0 6 1	0 8 7	0 9 5	0 9 6	0 9 8	0 9 8	0 9 9	0 9 9	0 9 9	1 0 1	1 0 4	1 0 5	1 0 5	1 0 6	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7
CARCASS ID	2 7 8 1	3 0 0 1	2 7 5 1	2 7 4 1	2 7 0 1	2 6 6 1	2 7 9 1	2 9 3 1	2 9 8 1	2 8 4 1	2 7 6 1	2 9 1 1	2 5 1 1	2 8 5 1	2 9 0 1	2 6 5 1	2 6 9 1	2 5 2 1	2 5 3 1	2 5 4 1	2 5 5 1	2 5 6 1	2 5 7 1	2 5 8 1	2 5 9 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma												X													
Hepatocellular adenoma													X												
Lymphoma malignant lymphocytic			X		X		X																		
Lymphoma malignant mixed								X			X														X
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed								X																	
Salivary glands	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																								+	
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung									X																
Hemangiosarcoma, metastatic, spleen																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																		X							
Capsule, lymphoma malignant lymphocytic			X																						
Capsule, lymphoma malignant mixed											X														
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic						X	X																		
Lymphoma malignant mixed								X																	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	M	M	+	M	M	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X	X														X		X
Thyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenocarcinoma																									
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Lymphoma malignant lymphocytic			X		X	X					X														
Lymphoma malignant mixed								X																	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																				X					
Lymphoma malignant lymphocytic			X		X																				
Sarcoma stromal																X									
Endometrium, polyp stromal															X					X					
Vagina																+									
Sarcoma stromal, metastatic, uterus																X									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 3 mg/m³
(Continued)

WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TOTAL
CARCASS ID	26011	26111	26211	26311	26411	26711	26811	27111	27211	27311	27711	28011	28111	28211	28311	28611	28711	28811	28911	29211	29411	29511	29611	29711	29911	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																	X									2
Hepatocellular adenoma	X														X			X								4
Lymphoma malignant lymphocytic																										3
Lymphoma malignant mixed																X										4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																X										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic								X																		1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth					+						+															3
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hemangiosarcoma, metastatic, spleen											X															1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																										1
Capsule, lymphoma malignant lymphocytic																										1
Capsule, lymphoma malignant mixed																										1
Adrenal gland, cortex	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	M	M	+	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	M	M	29
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Adenoma	X			X	X		X	X							X							X	X			12
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenocarcinoma															X											1
Follicular cell, adenoma								X																		1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma																X										1
Lymphoma malignant lymphocytic																										4
Lymphoma malignant mixed																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma											X															2
Lymphoma malignant lymphocytic																										2
Sarcoma stromal																										1
Endometrium, polyp stromal											X															3
Vagina																										1
Sarcoma stromal, metastatic, uterus																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 3 mg/m³ (Continued)

WEEKS ON STUDY	039	049	061	061	087	095	096	098	098	099	099	099	101	104	105	105	106	107	107	107	107	107	107	107	107
CARCASS ID	27811	30101	27511	27411	27701	26611	27911	29311	29811	28411	27611	29111	25111	28511	29011	26511	26911	25211	25311	25411	25511	25611	25711	25811	25911
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Iliac, lymphoma malignant mixed																									X
Inguinal, lymphoma malignant mixed																							X		
Mediastinal, lymphoma malignant lymphocytic					X	X																			
Mediastinal, lymphoma malignant mixed													X												X
Mesenteric, lymphoma malignant mixed												X											X		
Pancreatic, lymphoma malignant mixed																							X		X
Renal, lymphoma malignant mixed								X			X	X											X		X
Lymph node, bronchial	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, *metastatic, lung*									X																
Lymphoma malignant lymphocytic						X																			
Lymphoma malignant mixed								X			X													X	X
Lymph node, mandibular	M	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed								X			X		X											X	X
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hemangiosarcoma, metastatic, skeletal muscle																									
Lymphoma malignant lymphocytic			X		X		X															X			
Lymphoma malignant mixed											X	X	X											X	X
Lymphoma malignant undifferentiated cell type																									
Thymus	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenoacanthoma																									
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, lymphoma malignant lymphocytic					X																				
Vulva, papilloma																		X							
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Hemangiosarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic			X																						
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma, multiple															X										
Alveolar/bronchiolar carcinoma									X																
Lymphoma malignant lymphocytic			X																				X		
Lymphoma malignant mixed													X												
Lymphoma malignant undifferentiated cell type																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic							X																		
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
None																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				
Lymphoma malignant mixed											X		X												X
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic					X																				

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 3 mg/m³ (Continued)

WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TOTAL:
CARCASS ID	26001	26111	26221	26331	26441	26671	26811	27111	27211	27311	27711	28011	28111	28211	28311	28611	28711	28811	28911	29211	29411	29511	29611	29711	29911		TISSUES TUMORS
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Iliac, lymphoma malignant mixed																											1
Inguinal, lymphoma malignant mixed																											1
Mediastinal, lymphoma malignant lymphocytic																											2
Mediastinal, lymphoma malig. mixed																X										3
Mesenteric, lymphoma malignant mixed																X										3
Pancreatic, lymphoma malignant mixed																											2
Renal, lymphoma malignant mixed																											5
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed																											4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M		45
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed																X											6
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma											X																1
Hemangiosarcoma, metastatic, skeletal muscle																								X			1
Lymphoma malignant lymphocytic																											4
Lymphoma malignant mixed																X											6
Lymphoma malignant undifferentiated cell type						X																					1
Thymus	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M		45
INTEGUMENTARY SYSTEM																											
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
Adenoacanthoma								X																			1
Adenocarcinoma	X								X																		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M		49
Subcutaneous tissue, lymphoma malignant lymphocytic																											1
Vulva, papilloma																											1
MUSCULOSKELETAL SYSTEM																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Skeletal muscle																								+			1
Hemangiosarcoma																								X			1
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant lymphocytic																											1
RESPIRATORY SYSTEM																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant lymphocytic																											1
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma, multiple																											1
Alveolar/bronchiolar carcinoma																											1
Lymphoma malignant lymphocytic																											2
Lymphoma malignant mixed																											1
Lymphoma malignant undifferentiated cell type						X																					1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant lymphocytic																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
SPECIAL SENSES SYSTEM																											
None																											
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant lymphocytic																											1
Lymphoma malignant mixed																											3
Renal tubule, adenoma									X																		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant lymphocytic																											1

TABLE D3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m^3	3 mg/m^3
Liver: Hepatocellular Adenoma			
Overall Rates (a)	2/50 (4%)	(b) 1/20 (5%)	4/50 (8%)
Adjusted Rates (c)	6.3%		11.2%
Terminal Rates (d)	2/32 (6%)		3/34 (9%)
Day of First Observation	742		704
Life Table Test (e)			P=0.357
Logistic Regression Test (e)			P=0.342
Fisher Exact Test (e)			P=0.339
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	(b) 2/20 (10%)	6/50 (12%)
Adjusted Rates (c)	8.4%		16.2%
Terminal Rates (d)	2/32 (6%)		4/34 (12%)
Day of First Observation	667		693
Life Table Test (e)			P=0.264
Logistic Regression Test (e)			P=0.242
Fisher Exact Test (e)			P=0.243
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	(b) 5/27 (19%)	1/50 (2%)
Adjusted Rates (c)	9.4%		2.8%
Terminal Rates (d)	3/32 (9%)		0/34 (0%)
Day of First Observation	742		730
Life Table Test (e)			P=0.286N
Logistic Regression Test (e)			P=0.296N
Fisher Exact Test (e)			P=0.309N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	(b) 5/27 (19%)	2/50 (4%)
Adjusted Rates (c)	13.5%		5.1%
Terminal Rates (d)	3/32 (9%)		0/34 (0%)
Day of First Observation	558		685
Life Table Test (e)			P=0.210N
Logistic Regression Test (e)			P=0.216N
Fisher Exact Test (e)			P=0.218N
Ovary: Cystadenoma			
Overall Rates (a)	3/50 (6%)	(b) 0/26 (0%)	1/50 (2%)
Adjusted Rates (c)	9.4%		2.9%
Terminal Rates (d)	3/32 (9%)		1/34 (3%)
Day of First Observation	742		742
Life Table Test (e)			P=0.283N
Logistic Regression Test (e)			P=0.283N
Fisher Exact Test (e)			P=0.309N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	7/49 (14%)	11/46 (24%)	12/49 (24%)
Adjusted Rates (c)	21.1%	32.9%	33.5%
Terminal Rates (d)	6/31 (19%)	10/32 (31%)	10/33 (30%)
Day of First Observation	615	661	680
Life Table Tests (e)	P=0.159	P=0.229	P=0.186
Logistic Regression Tests (e)	P=0.131	P=0.163	P=0.152
Cochran-Armitage Trend Test (e)	P=0.132		
Fisher Exact Test (e)		P=0.175	P=0.153

TABLE D3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	3 mg/m^3
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	3/49 (6%)	(b) 2/18 (11%)	1/48 (2%)
Adjusted Rates (c)	9.1%		2.9%
Terminal Rates (d)	2/32 (6%)		1/34 (3%)
Day of First Observation	732		742
Life Table Test (e)			P=0.288N
Logistic Regression Test (e)			P=0.295N
Fisher Exact Test (e)			P=0.316N
Thyroid Gland: Follicular Cell Adenoma or Adenocarcinoma			
Overall Rates (a)	3/49 (6%)	(b) 2/18 (11%)	2/48 (4%)
Adjusted Rates (c)	9.1%		5.9%
Terminal Rates (d)	2/32 (6%)		2/34 (6%)
Day of First Observation	732		742
Life Table Test (e)			P=0.475N
Logistic Regression Test (e)			P=0.487N
Fisher Exact Test (e)			P=0.510N
Uterus/Endometrium: Stromal Polyp			
Overall Rates (f)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (c)	0.0%	2.9%	8.5%
Terminal Rates (d)	0/32 (0%)	1/35 (3%)	2/34 (6%)
Day of First Observation		742	730
Life Table Tests (e)	P=0.066	P=0.518	P=0.134
Logistic Regression Tests (e)	P=0.062	P=0.518	P=0.123
Cochran-Armitage Trend Test (e)	P=0.060		
Fisher Exact Test (e)		P=0.500	P=0.121
Uterus/Endometrium: Stromal Polyp or Sarcoma			
Overall Rates (f)	0/50 (0%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (c)	0.0%	2.9%	11.1%
Terminal Rates (d)	0/32 (0%)	1/35 (3%)	2/34 (6%)
Day of First Observation		742	730
Life Table Tests (e)	P=0.029	P=0.518	P=0.073
Logistic Regression Tests (e)	P=0.027	P=0.518	P=0.064
Cochran-Armitage Trend Test (e)	P=0.026		
Fisher Exact Test (e)		P=0.500	P=0.059
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (f)	4/50 (8%)	(b,g) 3/50 (6%)	2/50 (4%)
Adjusted Rates (c)	10.5%	7.9%	5.9%
Terminal Rates (d)	2/32 (6%)	2/35 (6%)	2/34 (6%)
Day of First Observation	615	616	742
Life Table Tests (e)	P=0.249N	P=0.478N	P=0.321N
Logistic Regression Tests (e)	P=0.264N	P=0.501N	P=0.337N
Cochran-Armitage Trend Test (e)	P=0.264N		
Fisher Exact Test (e)		P=0.500N	P=0.339N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (f)	16/50 (32%)	(b,g) 19/50 (38%)	14/50 (28%)
Adjusted Rates (c)	39.3%	44.7%	31.9%
Terminal Rates (d)	8/32 (25%)	12/35 (34%)	6/34 (18%)
Day of First Observation	503	504	421
Life Table Tests (e)	P=0.352N	P=0.408	P=0.395N
Logistic Regression Tests (e)	P=0.375N	P=0.339	P=0.413N
Cochran-Armitage Trend Test (e)	P=0.375N		
Fisher Exact Test (e)		P=0.338	P=0.414N

TABLE D3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	3 mg/m^3
All Sites: Benign Tumors			
Overall Rates (f)	19/50 (38%)	19/50 (38%)	19/50 (38%)
Adjusted Rates (c)	53.6%	49.5%	49.6%
Terminal Rates (d)	16/32 (50%)	16/35 (46%)	15/34 (44%)
Day of First Observation	324	607	680
Life Table Tests (e)	P=0.461N	P=0.466N	P=0.502N
Logistic Regression Tests (e)	P=0.542N	P=0.576	P=0.582
Cochran-Armitage Trend Test (e)	P=0.541		
Fisher Exact Test (e)		P=0.582N	P=0.582N
All Sites: Malignant Tumors			
Overall Rates (f)	25/50 (50%)	27/50 (54%)	23/50 (46%)
Adjusted Rates (c)	55.1%	58.1%	51.6%
Terminal Rates (d)	12/32 (38%)	16/35 (46%)	13/34 (38%)
Day of First Observation	503	384	421
Life Table Tests (e)	P=0.356N	P=0.500	P=0.391N
Logistic Regression Tests (e)	P=0.381N	P=0.418	P=0.422N
Cochran-Armitage Trend Test (e)	P=0.382N		
Fisher Exact Test (e)		P=0.421	P=0.421N
All Sites: All Tumors			
Overall Rates (f)	36/50 (72%)	36/50 (72%)	30/50 (60%)
Adjusted Rates (c)	78.0%	76.3%	66.4%
Terminal Rates (d)	22/32 (69%)	24/35 (69%)	19/34 (56%)
Day of First Observation	324	384	421
Life Table Tests (e)	P=0.141N	P=0.449N	P=0.164N
Logistic Regression Tests (e)	P=0.119N	P=0.587	P=0.145N
Cochran-Armitage Trend Test (e)	P=0.119N		
Fisher Exact Test (e)		P=0.588N	P=0.146N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence in animals killed at the end of the study
(e) 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 logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in controls is indicated by (N).
(f) Number of tumor-bearing animals/number of animals examined grossly at the site
(g) Twenty-five spleens, 29 lymph nodes, and 20 livers were examined microscopically.

TABLE D4. HISTORICAL INCIDENCE OF UTERINE STROMAL NEOPLASMS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Polyp	Sarcoma	Polyp or Sarcoma
Historical Incidence for Chamber Controls at Battelle Pacific Northwest Laboratories			
1,2-Propylene oxide	2/48	0/48	2/48
Methyl methacrylate	1/48	0/48	1/48
Propylene	0/47	0/47	0/47
1,2-Epoxybutane	0/50	0/50	0/50
Dichloromethane	1/50	0/50	1/50
Ethylene oxide	1/49	0/49	1/49
Bromoethane	2/50	0/50	2/50
Tetrachloroethylene	1/43	0/43	1/43
TOTAL	8/385 (2.1%)	0/385 (0.0%)	8/385 (2.1%)
SD (b)	1.55%	0.00%	1.55%
Range (c)			
High	2/48	0/50	2/48
Low	0/50	0/50	0/50
Overall Historical Incidence for Untreated Controls in NTP Studies			
TOTAL	34/1,675 (2.0%)	6/1,675 (0.4%)	39/1,675 (2.3%)
SD (b)	2.37%	0.93%	2.44%
Range (c)			
High	4/50	2/50	4/50
Low	0/50	0/50	0/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE

	Chamber Control	1.5 mg/m^3	3 mg/m^3
Animals initially in study	50	50	50
Animals removed	50	50	50
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(47)	(15)	(48)
Dilatation		1 (7%)	
Intestine large	(50)	(15)	(50)
Inflammation, chronic		1 (7%)	
Intestine large, rectum	(50)	(15)	(50)
Prolapse		1 (7%)	
Intestine small, ileum	(49)	(14)	(50)
Amyloid deposition	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
Intestine small, jejunum	(49)	(18)	(50)
Inflammation, suppurative		1 (6%)	
Liver	(50)	(20)	(50)
Cyst	2 (4%)		
Cytologic alterations		1 (5%)	
Focal cellular change		1 (5%)	2 (4%)
Hemorrhage	1 (2%)		
Infarct	1 (2%)		
Infiltration cellular, lymphocytic	1 (2%)		1 (2%)
Inflammation, subacute	2 (4%)		3 (6%)
Necrosis	3 (6%)		1 (2%)
Pancreas	(50)	(16)	(50)
Inflammation, subacute	1 (2%)		
Acinus, hypoplasia			1 (2%)
Duct, cyst			1 (2%)
Salivary glands	(49)	(14)	(49)
Hemorrhage		1 (7%)	
Stomach, forestomach	(50)	(19)	(49)
Hyperkeratosis	6 (12%)	1 (5%)	3 (6%)
Hyperplasia, lymphoid		1 (5%)	
Inflammation, subacute			1 (2%)
Inflammation, suppurative			1 (2%)
Ulcer		1 (5%)	1 (2%)
Epithelium, hyperplasia		1 (5%)	
Stomach, glandular	(50)	(15)	(50)
Hyperplasia	3 (6%)		
Inflammation, subacute	1 (2%)		
Mineralization	1 (2%)		1 (2%)
Pigmentation	1 (2%)		
Tooth	(1)		(3)
Abscess	1 (100%)		
Developmental malformation			3 (100%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(15)	(50)
Atrium, thrombus	1 (2%)		1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(17)	(50)
Hyperplasia, focal			1 (2%)
Adrenal gland, cortex	(50)	(15)	(49)
Hyperplasia			1 (2%)
Hyperplasia, focal	1 (2%)		
Hypertrophy, focal	2 (4%)	1 (7%)	1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m³	3 mg/m³
ENDOCRINE SYSTEM (Continued)			
Adrenal gland, medulla	(50)	(16)	(50)
Hyperplasia	1 (2%)	1 (6%)	2 (4%)
Pituitary gland	(49)	(46)	(49)
Congestion	4 (8%)	1 (2%)	1 (2%)
Hyperplasia	18 (37%)	17 (37%)	22 (45%)
Pigmentation		1 (2%)	
Pars distalis, hyperplasia		1 (2%)	
Pars intermedia, hyperplasia	1 (2%)		
Thyroid gland	(49)	(18)	(48)
Infiltration cellular, lymphocytic	1 (2%)		
Inflammation, chronic		1 (6%)	
Follicular cell, cyst		1 (6%)	
Follicular cell, hyperplasia	4 (8%)		6 (13%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(50)	(26)	(50)
Corpora amylacea	1 (2%)		
Cyst	18 (36%)	12 (46%)	11 (22%)
Cyst, multiple		1 (4%)	
Hemorrhage			1 (2%)
Mineralization		2 (8%)	
Pigmentation		1 (4%)	
Germinal epithelium, hyperplasia		1 (4%)	
Rete ovarii, hyperplasia			1 (2%)
Uterus	(50)	(19)	(50)
Angiectasis			1 (2%)
Dilatation	1 (2%)	1 (5%)	
Hyperplasia, cystic	1 (2%)		
Hyperplasia, lymphoid			1 (2%)
Prolapse			1 (2%)
Thrombus			1 (2%)
Artery, thrombus			1 (2%)
Endometrium, degeneration, hyaline	1 (2%)		
Endometrium, hyperplasia	8 (16%)	1 (5%)	8 (16%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(15)	(50)
Myelofibrosis	2 (4%)		1 (2%)
Lymph node	(50)	(29)	(49)
Iliac, hyperplasia, lymphoid		1 (3%)	1 (2%)
Mediastinal, hyperplasia, lymphoid			1 (2%)
Mesenteric, congestion	1 (2%)	1 (3%)	
Mesenteric, hyperplasia, lymphoid	2 (4%)		
Renal, hyperplasia, lymphoid			2 (4%)
Lymph node, bronchial	(45)	(20)	(49)
Hyperplasia, lymphoid		3 (15%)	1 (2%)
Lymph node, mandibular	(49)	(19)	(45)
Atrophy			1 (2%)
Hyperplasia, lymphoid		3 (16%)	7 (16%)
Pigmentation	1 (2%)		1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	3 mg/m^3
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(50)	(25)	(50)
Atrophy			2 (4%)
Hematopoietic cell proliferation	4 (8%)	2 (8%)	
Hyperplasia, histiocyte	1 (2%)		
Hyperplasia, lymphoid	4 (8%)	3 (12%)	5 (10%)
Inflammation, granulomatous			1 (2%)
Inflammation, suppurative		1 (4%)	
INTEGUMENTARY SYSTEM			
Mammary gland	(44)	(14)	(45)
Duct, dilatation, multifocal			1 (2%)
Skin	(49)	(23)	(49)
Alopecia	5 (10%)	6 (26%)	6 (12%)
Edema		1 (4%)	2 (4%)
Inflammation, chronic		1 (4%)	1 (2%)
Inflammation, necrotizing		1 (4%)	1 (2%)
Ulcer			1 (2%)
Sebaceous gland, hyperplasia		1 (4%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(15)	(50)
Costochondral junction, degeneration			1 (2%)
NERVOUS SYSTEM			
Brain	(50)	(15)	(50)
Hemorrhage, acute, multifocal		1 (7%)	
Inflammation, subacute	1 (2%)		
Mineralization	9 (18%)	3 (20%)	16 (32%)
RESPIRATORY SYSTEM			
Lung	(50)	(27)	(50)
Congestion			1 (2%)
Hyperplasia, lymphoid			1 (2%)
Infiltration cellular, lymphocytic	2 (4%)	1 (4%)	1 (2%)
Infiltration cellular, histiocytic			1 (2%)
Inflammation, granulomatous	5 (10%)	2 (7%)	3 (6%)
Inflammation, subacute	2 (4%)	1 (4%)	1 (2%)
Thrombus		2 (7%)	
Alveolar epithelium, hyperplasia	2 (4%)	2 (7%)	1 (2%)
Interstitium, fibrosis	1 (2%)		
Nose	(50)	(48)	(50)
Inflammation, suppurative	1 (2%)	7 (15%)	8 (16%)
Olfactory epithelium, degeneration, hyaline	44 (88%)	43 (90%)	47 (94%)
Olfactory epithelium, metaplasia	1 (2%)		
Olfactory epithelium, metaplasia, focal	10 (20%)	21 (44%)	12 (24%)
Respiratory epithelium, degeneration	1 (2%)		
Respiratory epithelium, degeneration, hyaline	7 (14%)	28 (58%)	19 (38%)
Respiratory epithelium, metaplasia, squamous			1 (2%)
Respiratory epithelium, necrosis			1 (2%)
SPECIAL SENSES SYSTEM			
None			

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF *l*-EPINEPHRINE HYDROCHLORIDE (Continued)

	Chamber Control	1.5 mg/m^3	3 mg/m^3
URINARY SYSTEM			
Kidney	(50)	(19)	(50)
Cyst	1 (2%)		1 (2%)
Hemorrhage, acute		1 (5%)	
Hydronephrosis	1 (2%)	1 (5%)	
Inflammation, subacute	1 (2%)		2 (4%)
Metaplasia, osseous	1 (2%)		
Glomerulus, amyloid deposition	1 (2%)		
Renal tubule, degeneration, hyaline		1 (5%)	
Urinary bladder	(50)	(15)	(50)
Infiltration cellular, lymphocytic			1 (2%)

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. SENTINEL ANIMAL PROGRAM

Methods

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

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Sera from four moribund mice on study were collected at 21-22 months and from eight moribund rats on study at 21-22 months. Data from animals surviving 24 months were collected from 5/50 randomly selected control animals of each sex and species. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) **IFA** EDIM (epizootic diarrhea of infant mice) (24 mo)	MHV (mouse hepatitis virus) GDVII (21-22,24 mo) Reo 3 (24 mo) PVM (24 mo) Sendai (24 mo) Ectro (24 mo) M. Ad. (24 mo) *M. pul. (Mycoplasma pulmonis)* (24 mo) *M. arth. (Mycoplasma arthritidis)* (24 mo)

		Complement Fixation	
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus) (6 mo)	RCV/SDA (RCV/sialodacryoadenitis) PVM (24 mo) Sendai (24 mo) RCV (24 mo) *M. pul.* (24 mo) *M. arth.* (24 mo)

Results

Results are presented in Table E1.

TABLE E1. MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	10/10	PVM
	8/10	*M. pul.* (b)
	6/10	RCV/SDA
12	10/10	PVM
	10/10	RCV/SDA
18	8/10	PVM
	6/10	RCV/SDA
21-22	6/8	PVM
	5/8	RCV/SDA
24	10/10	PVM
	9/10	RCV/SDA
MICE		
6	7/10	PVM
12	5/7	PVM
18	3/10	PVM
21-22	(c)	None positive
24	10/10	PVM

(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 determination of antibody titers.
(b) Further evaluation of this assay indicated that it was not specific for *M. pulmonis*, and these results were considered to be false positive.
(c) None of the samples of sera from four moribund mice was positive.

APPENDIX F

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

Pellet Diet: July 1982 to August 1984

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

TABLE F1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE F2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE F3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.16 ± 1.22	21.3-26.3	18
Crude fat (percent by weight)	5.29 ± 0.49	4.4-6.5	18
Crude fiber (percent by weight)	3.42 ± 0.60	2.8-5.6	18
Ash (percent by weight)	6.50 ± 0.36	5.7-7.2	18
Amino Acids (percent of total diet)			
Arginine	1.320 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.050	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.830-2.520	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	12,572 ± 3,892	8,600-24,000	18
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	17.72 ± 3.32	13.0-24.0	18
Riboflavin (ppm)	7.6 ± 0.85	6.10-8.20	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.80	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.70	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.27 ± 0.12	1.11-1.54	18
Phosphorus (percent)	0.96 ± 0.05	0.90-1.10	18
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.70-99.40	5
Zinc (ppm)	52.78 ± 4.94	46.10-58.20	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.52 ± 0.15	0.17-0.74	18
Cadmium (ppm) (a)	<0.10		18
Lead (ppm)	0.81 ± 0.72	0.33-3.37	18
Mercury (ppm) (a)	<0.05		18
Selenium (ppm)	0.31 ± 0.07	0.13-0.42	18
Aflatoxins (ppb) (a)	<5.0		18
Nitrate nitrogen (ppm) (b)	8.12 ± 3.71	0.10-15.0	18
Nitrite nitrogen (ppm) (b)	1.41 ± 1.80	0.10-7.20	18
BHA (ppm) (c)	4.89 ± 5.43	2.00-17.0	18
BHT (ppm) (c)	3.22 ± 2.90	1.00-12.0	18
Aerobic plate count (CFU/g) (d)	40,117 ± 34,754	6,600-130,000	18
Coliform (MPN/g) (e,f)	12.47 ± 15.27	<3.0-43.0	17
Coliform (MPN/g) (g)	37.33 ± 107	<3.00-460.0	18
E. coli (MPN/g)	<3.00		18
Total nitrosamines (ppb) (h)	6.35 ± 6.69	1.80-30.90	18
N-Nitrosodimethylamine (ppb) (h)	5.28 ± 6.70	0.80-30.00	18
N-Nitrosopyrrolidine (ppb) (h)	1.07 ± 0.27	0.81-1.70	18
Pesticides (ppm)			
α-BHC (a,i)	<0.01		18
β-BHC (a)	<0.02		18
γ-BHC (a)	<0.01		18
δ-BHC (a)	<0.01		18
Heptachlor (a)	<0.01		18
Aldrin (a)	<0.01		18
Heptachlor epoxide (a)	<0.01		18
DDE (a)	<0.01		18
DDD (a)	<0.01		18
DDT (a)	<0.01		18
HCB (a)	<0.01		18
Mirex (a)	<0.01		18
Methoxychlor (a)	<0.05		18
Dieldrin (a)	<0.01		18
Endrin (a)	<0.01		18
Telodrin (a)	<0.01		18
Chlordane (a)	<0.05		18
Toxaphene (a)	<0.10		18
Estimated PCBs (a)	<0.20		18
Ronnel (a)	<0.01		18
Ethion (a)	<0.02		18
Trithion (a)	<0.05		18
Diazinon (a)	<0.10		18
Methyl parathion (a)	<0.02		18
Ethyl parathion (a)	<0.02		18
Malathion (j)	0.09 ± 0.06	0.05-0.25	18
Endosulfan I (a)	<0.01		18
Endosulfan II (a)	<0.01		18
Endosulfan sulfate (a)	<0.03		18

(a) All values were less than the detection limit, given in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source of contamination: soy oil and fish meal
(d) CFU = colony-forming unit
(e) MPN = most probable number
(f) Mean, standard deviation, and range exclude one high value of 460 MPN/g obtained from the batch milled on September 23, 1982.
(g) Mean, standard deviation, and range include high value noted in (f).
(h) All values were corrected for percent recovery.
(i) BHC = hexachlorocyclohexane or benzene hexachloride
(j) Ten lots contained more than 0.05 ppm.

APPENDIX G

ORGAN WEIGHT DATA FOR RATS AND MICE IN THE FIFTEEN-MONTH INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

TABLE G1. ORGAN WEIGHTS OF RATS IN THE FIFTEEN-MONTH INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE (a)

Organ	Control	1.5 mg/m^3	5 mg/m^3
MALE			
Body weight (grams)	435 ± 5.9	442 ± 5.9	436 ± 7.0
Brain			
Absolute	1,950 ± 36	1,988 ± 20	2,017 ± 17
Relative	4.5 ± 0.10	4.5 ± 0.06	4.6 ± 0.07
Right kidney			
Absolute	1,299 ± 27	1,317 ± 40	1,310 ± 41
Relative	3.0 ± 0.04	3.0 ± 0.07	3.0 ± 0.06
Liver			
Absolute	14,230 ± 380	13,910 ± 510	*12,730 ± 390
Relative	32.7 ± 0.66	31.4 ± 0.90	**29.1 ± 0.45
FEMALE			
Body weight (grams)	285 ± 5.3	282 ± 9.5	276 ± 7.5
Brain			
Absolute	1,836 ± 10	1,825 ± 27	1,819 ± 20
Relative	6.5 ± 0.12	6.5 ± 0.17	6.6 ± 0.16
Right kidney			
Absolute	881 ± 13	874 ± 25	856 ± 24
Relative	3.1 ± 0.06	3.1 ± 0.06	3.1 ± 0.10
Liver			
Absolute	8,790 ± 169	8,724 ± 397	*7,975 ± 169
Relative	30.8 ± 0.20	30.9 ± 1.05	**29.0 ± 0.46

(a) Mean ± standard error in milligrams (absolute) or milligrams per gram (relative) unless otherwise specified for groups of 10 animals; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
*P<0.05
**P<0.01

TABLE G2. ORGAN WEIGHTS OF MICE IN THE FIFTEEN-MONTH INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE (a)

	Control	1.5 mg/m^3	3 mg/m^3
MALE			
Number weighed	10	9	9
Body weight (grams)	38.1 ± 0.94	*34.8 ± 1.01	36.5 ± 0.68
Brain			
Absolute	467 ± 5.8	470 ± 4.4	467 ± 6.2
Relative	12.3 ± 0.29	*13.6 ± 0.33	12.8 ± 0.16
Right kidney			
Absolute	440 ± 14.7	*392 ± 10.5	**372 ± 10.1
Relative	11.6 ± 0.43	11.3 ± 0.29	*10.2 ± 0.23
Liver			
Absolute	2,130 ± 82	**1,763 ± 64	**1,848 ± 53
Relative	56.1 ± 2.47	50.9 ± 1.91	50.6 ± 1.25
FEMALE			
Number weighed	10	8	10
Body weight (grams)	34.3 ± 1.05	31.9 ± 1.06	**29.6 ± 1.35
Brain			
Absolute	498 ± 5.1	494 ± 9.0	*478 ± 6.1
Relative	14.6 ± 0.46	15.6 ± 0.50	*16.4 ± 0.57
Right kidney			
Absolute	252 ± 6.5	245 ± 9.5	*220 ± 7.2
Relative	7.4 ± 0.25	7.7 ± 0.29	7.5 ± 0.17
Liver			
Absolute	1,659 ± 36	1,546 ± 53	**1,365 ± 72
Relative	48.7 ± 1.76	48.6 ± 1.63	46.1 ± 0.98

(a) Mean ± standard error in milligrams (absolute) or milligrams per gram (relative) unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
*P<0.05
**P<0.01

APPENDIX H

HEMATOLOGIC ANALYSES FOR RATS AND MICE IN THE FIFTEEN-MONTH INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

TABLE H1. HEMATOLOGIC DATA FOR RATS IN THE FIFTEEN-MONTH INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

	Control	1.5 mg/m^3	5 mg/m^3
MALE			
Leukocytes (1,000/μl)	3.5 ± 0.39	3.8 ± 0.30	*4.2 ± 0.23
Lymphocytes (1,000/μl)	2.2 ± 0.30	1.9 ± 0.14	2.4 ± 0.16
Segmented neutrophils (1,000/μl)	1.2 ± 0.09	*1.8 ± 0.23	*1.6 ± 0.13
Monocytes (1,000/μl)	0.08 ± 0.022	0.08 ± 0.011	0.08 ± 0.012
Eosinophils (1,000/μl)	0.07 ± 0.012	0.04 ± 0.011	0.04 ± 0.006
Hemoglobin (g/dl)	14.9 ± 0.18	15.3 ± 0.23	15.2 ± 0.23
Hematocrit (percent)	39.5 ± 0.39	40.3 ± 0.53	40.2 ± 0.53
Nucleated erythrocytes (percent of leukocytes)	0.004 ± 0.002	0.012 ± 0.008	0.011 ± 0.007
Mean corpuscular hemoglobin (pg)	18.4 ± 0.05	18.5 ± 0.19	18.4 ± 0.18
Mean corpuscular hemoglobin concentration (g/dl)	37.8 ± 0.17	38.1 ± 0.15	37.9 ± 0.15
Mean cell volume (μ^3)	48.9 ± 0.31	48.9 ± 0.41	49.2 ± 0.65
Erythrocytes (10^6/μl)	8.1 ± 0.11	8.3 ± 0.10	8.3 ± 0.17
FEMALE			
Leukocytes (1,000/μl)	2.4 ± 0.10	3.0 ± 0.30	2.8 ± 0.18
Lymphocytes (1,000/μl)	1.3 ± 0.06	*1.7 ± 0.13	*1.7 ± 0.12
Segmented neutrophils (1,000/μl)	1.0 ± 0.08	1.2 ± 0.19	1.0 ± 0.07
Monocytes (1,000/μl)	0.05 ± 0.011	0.06 ± 0.012	0.04 ± 0.008
Eosinophils (1,000/μl)	0.03 ± 0.005	0.04 ± 0.011	0.04 ± 0.010
Hemoglobin (g/dl)	15.2 ± 0.06	15.3 ± 0.30	15.5 ± 0.14
Hematocrit (percent)	40.8 ± 0.31	41.0 ± 0.69	41.0 ± 0.27
Nucleated erythrocytes (percent of leukocytes)	0.021 ± 0.006	0.008 ± 0.004	0.006 ± 0.003
Mean corpuscular hemoglobin (pg)	20.1 ± 0.11	20.1 ± 0.08	20.3 ± 0.09
Mean corpuscular hemoglobin concentration (g/dl)	37.4 ± 0.17	37.5 ± 0.15	37.8 ± 0.15
Mean cell volume (μ^3)	54.1 ± 0.50	54.0 ± 0.21	54.1 ± 0.31
Erythrocytes (10^6/μl)	7.6 ± 0.04	7.6 ± 0.14	7.6 ± 0.07

(a) Mean ± standard error for groups of 10 animals; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
*P<0.05

TABLE H2. HEMATOLOGIC DATA FOR MICE IN THE FIFTEEN-MONTH INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE (a)

	Control	1.5 mg/m^3	3 mg/m^3
MALE			
Number examined	10	9	9
Leukocytes (1,000/µl)	8.1 ± 0.75	6.7 ± 0.44	6.9 ± 0.71
Lymphocytes (1,000/µl)	3.4 ± 0.43	*1.9 ± 0.17	**1.5 ± 0.18
Segmented neutrophils (1,000/µl)	4.6 ± 0.53	4.5 ± 0.44	5.3 ± 0.69
Monocytes (1,000/µl)	0.07 ± 0.029	**0.21 ± 0.057	*0.14 ± 0.036
Eosinophils (1,000/µl)	0.06 ± 0.015	**0.000 ± 0.000	**0.000 ± 0.000
Hemoglobin (g/dl)	15.3 ± 0.45	15.4 ± 0.18	15.4 ± 0.14
Hematocrit (percent)	42.2 ± 1.59	42.0 ± 0.45	42.1 ± 0.44
Mean corpuscular hemoglobin (pg)	16.7 ± 0.11	16.9 ± 0.09	17.0 ± 0.06
Mean corpuscular hemoglobin concentration (g/dl)	36.3 ± 0.31	36.8 ± 0.14	36.6 ± 0.21
Mean cell volume (µ^3)	46.6 ± 0.27	46.0 ± 0.24	46.8 ± 0.36
Erythrocytes (10^6/µl)	9.2 ± 0.33	9.2 ± 0.09	9.1 ± 0.10
FEMALE			
Number examined	10	8	10
Leukocytes (1,000/µl)	4.9 ± 0.54	3.6 ± 0.35	4.5 ± 0.33
Lymphocytes (1,000/µl)	2.6 ± 0.27	2.4 ± 0.14	2.8 ± 0.15
Segmented neutrophils (1,000/µl)	2.2 ± 0.60	1.1 ± 0.22	1.6 ± 0.34
Monocytes (1,000/µl)	0.06 ± 0.013	0.06 ± 0.015	0.08 ± 0.019
Eosinophils (1,000/µl)	0.06 ± 0.022	0.04 ± 0.014	0.05 ± 0.011
Hemoglobin (g/dl)	15.1 ± 0.45	16.1 ± 0.19	16.0 ± 0.34
Hematocrit (percent)	41.3 ± 1.10	44.1 ± 0.72	44.9 ± 1.24
Mean corpuscular hemoglobin (pg)	16.9 ± 0.12	16.9 ± 0.06	16.6 ± 0.17
Mean corpuscular hemoglobin concentration (g/dl)	36.7 ± 0.27	36.6 ± 0.30	35.7 ± 0.41
Mean cell volume (µ^3)	46.6 ± 0.27	46.5 ± 0.27	46.8 ± 0.20
Erythrocytes (10^6/µl)	9.0 ± 0.23	9.6 ± 0.11	9.7 ± 0.25

(a) Mean ± standard error; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
*P<0.05
**P<0.01

APPENDIX I

CHEMICAL CHARACTERIZATION, GENERATION, AND MONITORING OF CHAMBER CONCENTRATIONS OF *l*-EPINEPHRINE HYDROCHLORIDE FOR THE TOXICOLOGY STUDIES

APPENDIX I. CHEMICAL CHARACTERIZATION

PROCUREMENT OF *l*-EPINEPHRINE, PREPARATION OF *l*-EPINEPHRINE HYDROCHLORIDE, AND CHARACTERIZATION OF *l*-EPINEPHRINE AND *l*-EPINEPHRINE HYDROCHLORIDE

l-Epinephrine was obtained from Henley and Co., Inc. (New York, NY) in four lots as a white, microcrystalline powder (Table I1), labeled USP Grade. Purity and identity analyses of all lots were conducted on representative samples at Midwest Research Insitute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the *l*-epinephrine hydrochloride studies are on file at the National Institute of Environmental Health Sciences.

All lots of the study chemical were identified as *l*-epinephrine by spectroscopic analyses. The infrared and nuclear magnetic resonance spectra were consistent with those expected for the structure and with the literature spectra (Sadtler Standard Spectra) (representative infrared and nuclear magnetic resonance spectra presented in Figures I1 and I2). The ultraviolet/visible spectrum was consistent with that expected for the structure and the literature spectrum (Florey, 1978), having no maximum in the visible region (800-350 nm) but a gradual increase in absorbance toward 350 nm (10 mg/ml in 1 N hydrochloric acid).

The purity of *l*-epinephrine was determined by elemental analysis, Karl Fischer water analysis, titration in glacial acetic acid of the amino group with 0.1 N perchloric acid, thin-layer chromatography, and high-performance liquid chromatography. Thin-layer chromatography was performed on 0.25-mm silica gel plates, with two solvent systems, *n*-butanol:water:acetic acid (60:25:15) (system 1) and chloroform:methanol:water:acetic acid (40:40:10:10) (system 2), and visualization with visible and ultraviolet light and a spray of 0.5% (w/v) ninhydrin in *n*-butanol. High-performance liquid chromatography was performed with ultraviolet detection at 280 nm, a Waters μBondapak C_{18} column, and the solvent system, which was 5% acetic acid in aqueous 0.01 M sodium lauryl sulfate:5% acetic acid in methanolic 0.01 M sodium lauryl sulfate (55:45).

Results of elemental analysis of lot no. 859 were slightly low for carbon and were in agreement with the theoretical values for hydrogen and nitrogen. Lot no. 859 contained 0.56% water. Titration of the amino group indicated a purity of 98.4%. The specific optical rotation was −50.95°. Thin-layer chromatography indicated one trace impurity with each system. High-performance liquid chromatography, with a solvent system of aqueous 0.01 M sodium lauryl sulfate containing 5% (v/v) glacial acetic acid:0.01 M sodium lauryl sulfate in methanol containing 5% glacial acetic acid (v/v) (60:40), indicated a single impurity eluting before the major peak, with a relative area 1.1% that of the major peak. A comparison of the major peak of lot no. 859 with that of a USP reference standard by high-performance liquid chromatography indicated a purity of 99.0%. An ultraviolet spectrophotometric assay of lot no. 859 vs. a USP standard indicated a purity of 99.3%.

TABLE I1. IDENTITY AND SOURCE OF *l*-EPINEPHRINE

Fourteen-Day Studies	Thirteen-Week Studies	Fifteen-Month and Two-Year Studies
Lot Numbers		
859	866	872; 887
Date of Initial Use		
6/6/81	11/4/81	872--9/29/82; 887--9/11/84
Supplier		
Henley and Co., Inc. (New York, NY)	Henley and Co., Inc. (New York, NY)	Henley and Co., Inc. (New York, NY)

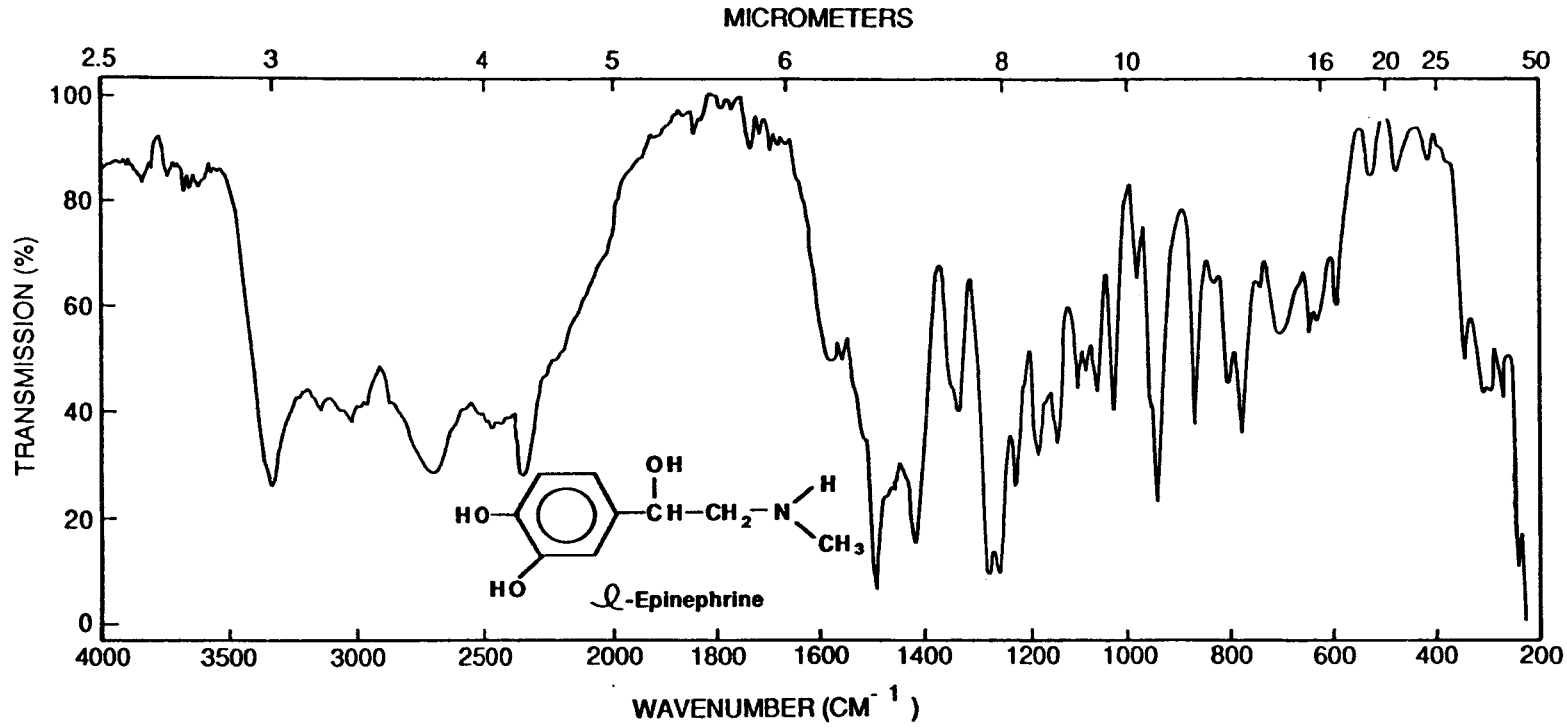

FIGURE 11. INFRARED ABSORPTION SPECTRUM OF *l*-EPINEPHRINE (LOT NO. 887)

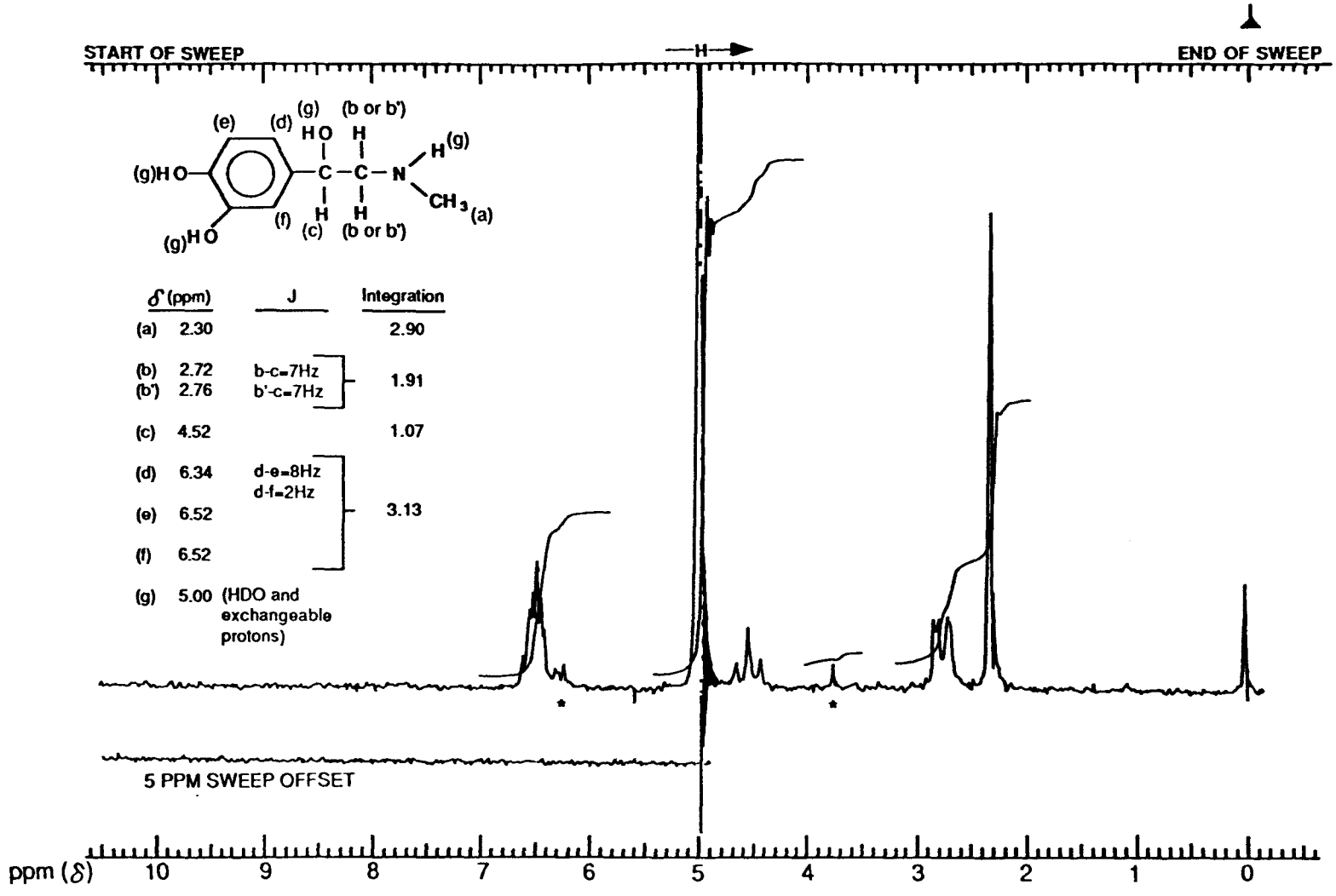

FIGURE 12. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF *l*-EPINEPHRINE (LOT NO. 887)

Results of elemental analysis of lot no. 866 were low for carbon and were in agreement with the theoretical values for hydrogen and nitrogen. Lot no. 866 contained 1.07% water. Titration of the amino group indicated a purity of 97.8%. The specific optical rotation was −50.77°. Thin-layer chromatography indicated one trace impurity with each system. High-performance liquid chromatography, with the same solvent system as for lot no. 859 but with a ratio of 53:47, indicated one impurity with an area 1.3% that of the major peak. A comparison of the major peak of lot no. 866 with that of the USP *l*-epinephrine reference standard by high-performance liquid chromatography (solvent ratio 60:40) indicated a purity of 97.5%. An ultraviolet spectrophotometric assay at 280 nm indicated a purity of 98.0% relative to a USP reference standard of *l*-epinephrine bitartrate.

Results of elemental analysis of lot no. 872 were in agreement with the theoretical values for carbon, hydrogen, and nitrogen. Lot no. 872 contained 0.81% water. Titration of the amino group indicated a purity of 98.8%. The specific optical rotation, calculated on a dried basis, was −50.2°. Thin-layer chromatography indicated one trace impurity with each system. High-performance liquid chromatography indicated three impurities, with the largest impurity estimated at 0.9% and the other two with areas that were each 0.1% of the major peak area. A comparison of lot no. 872 with a USP reference standard by high-performance liquid chromatography indicated that the area of the major peak of lot no. 872 was 99.1% that of the USP standard. An ultraviolet spectrophotometric assay at 280 nm indicated a purity of 101.2% relative to a USP standard.

Results of elemental analysis of lot no. 887 were low for carbon and in agreement with the theoretical values for hydrogen and nitrogen. Lot no. 887 contained 0.70% water. The specific optical rotation was −51.0°. Titration of the amino group indicated a purity of 97.7%. Thin-layer chromatography indicated one trace impurity with each system. High-performance liquid chromatography (same solvent system as for lot no. 859 but with a ratio of 54:46) indicated one impurity, with a relative area 1.1% that of the major peak. A comparison of the major peak of lot no. 887 with that of a USP reference standard by high-performance liquid chromatography (solvent ratio 55:45) indicated that the area of the major peak for lot no. 887 was 98.1% that of the USP standard.

Lot no. 887 was subjected to the complete battery of USP tests, including color developed upon addition of iodine in phthalate buffer and sodium thiosulfate to an acid solution of study compound, specific rotation, weight loss on drying, residue on ignition, a spectrophotometric assay for adrenalone, limit of levarterenol (norepinephrine), and titration in glacial acetic acid with 0.1 N perchloric acid using both potentiometric and colorimetric monitoring. Lot no. 887 met all requirements for USP-grade *l*-epinephrine as given in the 20th revision of the U.S. Pharmacopeia.

The stability of the bulk chemical was determined by high-performance liquid chromatographic analysis on samples stored under nitrogen and protected from light for 2 weeks at temperatures of −20°, 5°, 25°, and 60° C. No degradation was observed. Periodic analysis of the bulk chemical stored at −20° C at the toxicology laboratory with nonaqueous titration and high-performance liquid chromatographic methods demonstrated no degradation throughout the studies.

The hydrochloric salt of *l*-epinephrine was prepared by titration of the free base in water with 3 N hydrogen chloride to a pH of 2.8. Subsequently, the solutions were diluted to a concentration of 2.0 mg/ml for use in the generation system. The solutions were stored at 3°-4° C for a maximum of 3 weeks. Stability studies of aqueous solutions of *l*-epinephrine hydrochloride prepared in a similar fashion to that described above were conducted by MRI. Results from a 21-day stability study by polarimetry of a 10 mg/ml solution prepared at pH 2.8 (pH 4.7 after final dilution) did not indicate any racemization after storage at 5° C in the dark. Solutions were also stable after storage at room temperature for 6 hours. In another study at pH 1.3, solutions exhibited a 1% racemization after storage at 5° C for 14 days and 3% racemization after storage for 21 days. After storage at 25° C, the pH 1.3 solutions showed a significantly greater extent of racemization at 6%, 10%, and 16% after 7, 14, and 21 days, respectively.

APPENDIX I. CHEMICAL CHARACTERIZATION

During the toxicology studies, fresh solutions of *l*-epinephrine hydrochloride were prepared every 3 weeks and stored at 5° C. The specific optical rotations were within USP specifications for all preparations except for one, which was slightly low.

GENERATION AND MEASUREMENT OF CHAMBER CONCENTRATIONS

Aerosol Generation System

An aqueous aerosol of *l*-epinephrine hydrochloride was produced by one generator for each chamber (Hazleton 2000®, Lab Products, Inc.). The generator was operated as follows. A solution of 2.0 mg/ml epinephrine hydrochloride in water was contained in a polyethylene plastic reservoir. The configuration of this reservoir supplied the liquid at a constant level to one to four modifed Model 7301 Retec nebulizers (Cavitron, Englewood Cliffs, NJ) through a Tygon® distribution manifold (Norton Performance Plastics, Worcester, MA). Air pressure to operate the nebulizers was supplied from the house-pressurized air system through an emergency shutoff valve, which shut off all generators in the event of a critical alarm situation. Operating air pressure was regulated by a manually controlled pressure regulator. The air then passed through an on/off valve for each nebulizer in the generator. Output from each nebulizer was collected in a 1.5-inch diameter, polyvinyl chloride aerosol collection manifold, which was connected to the chamber inlet tube through a tee. Dilution air was pulled through the polyvinyl chloride aerosol delivery tube to sweep the aerosol into the chamber. The quantity of this airflow was controlled by manually adjusting the dilution airflow control caps on each end of the polyvinyl chloride aerosol collection manifold.

The generator system was capable of delivering greater than 1 g/min of water aerosol when four nebulizers were operated at 25-30 psi (170-200 kPa). The output of the generator was roughly linear with respect to operating pressure and with respect to the number of nebulizers in operation. Each nebulizer was modified by the addition of a baffle that effectively eliminated the large mode (or "population") of aerosol particles produced by the nebulizers. The particles were deionized by krypton-85 radioactive charge neutralizers placed in the aerosol collection manifolds. All nebulizers produced approximately the same aerosol particle size distribution when operated in the range of 100-200 kPa and when operated under the above conditions and yielded an aerosol that was almost totally in the respirable size range (as defined by the American Conference of Governmental Industrial Hygienists). The standard method for maintaining the desired aerosol concentration in the chambers was to make minor adjustments in the dilution airflow through the chamber.

Aerosol generation systems used during the various studies are described in Table I2. A schematic diagram of the aerosol generator system is shown in Figure I3.

Aerosol Concentration Monitoring

Online measurement of chamber concentration was accomplished with a RAM-1 Real-Time Aerosol Monitor (GCA Corporation, Bedford, MA), which is a forward light-scattering photometer. The RAM-1 was moved manually from chamber to chamber so that all exposure chambers were sampled approximately once per hour during the exposure period. This device was calibrated by comparing the filter samples taken from each chamber by the following procedure. The RAM-1 probe was inserted into the chamber; three stable readings from the RAM-1 were then recorded. The RAM-1 probe was removed and replaced by the filter probe. After the completion of the filter sample, the probe was again inserted and three more readings were recorded. If the mean of the second three readings was more than 10% different than the mean of the first three readings, the procedure was repeated. Filter samples were taken once per week from each chamber by pulling a known volume of the chamber atmosphere through a Gelman type A/E 25-mm diameter, glass fiber filter. The deposited epinephrine hydrochloride was extracted from these inline filters with a known volume of

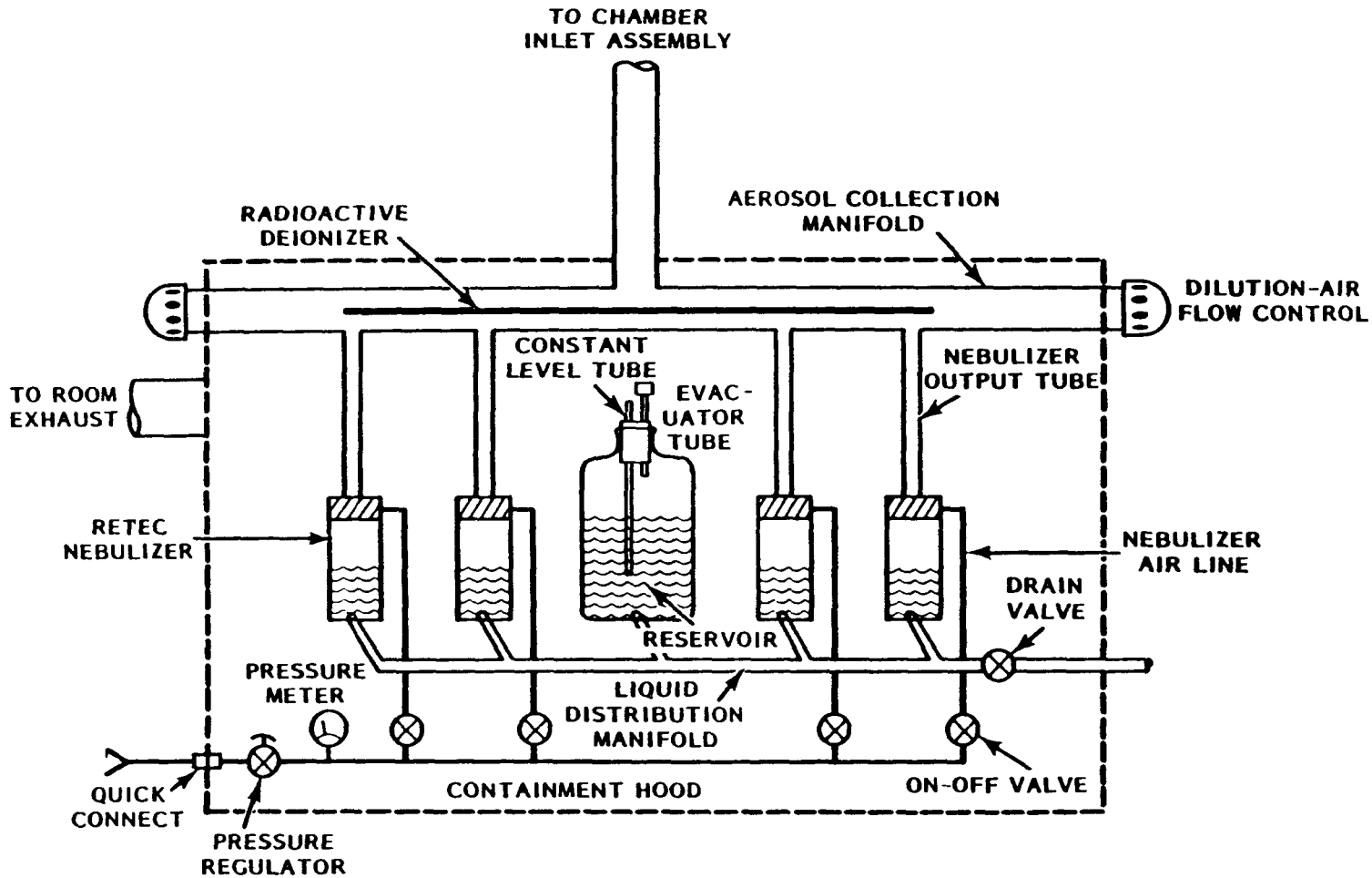

FIGURE I3. *l*-EPINEPHRINE HYDROCHLORIDE AEROSOL GENERATION SYSTEM

TABLE I2. AEROSOL GENERATION SYSTEMS IN THE INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLORIDE

Fourteen-Day Studies	Thirteen-Week Studies	Fifteen-Month and Two-Year Studies
Preparation		
A 25% solution of *l* epinephrine hydrochloride (w/v) contained in a polycarbonate plastic reservoir was passed through one to four modified Retec nebulizers through a Tygon® distribution manifold. The aerosol was collected in a polyvinyl chloride pipe that was connected to the chamber inlet tube. Dilution air swept the aerosol into the chamber	Similar to 14-d studies	Similar to 14-d studies, nebulizers were modified by baffles. Particles were deionized by krypton-85 radioactive charge neutralizers placed in the aerosol collection manifolds.
Maximum Storage Time of Solution		
3 wk	3 wk	3 wk
Storage Conditions		
3°-4° C in foil-wrapped containers under nitrogen headspace	Refrigerated	3°-4° C in amber glass bottles under nitrogen headspace

0.1 N hydrogen chloride and analyzed by measuring the absorbance of the solution at 278 nm on a Varian Cary 219 spectrophotometer (Varian Instruments, Sunnyville, CA). From these data, the concentration of epinephrine hydrochloride in the chamber was calculated Weekly mean exposure concentrations for the 2-year studies are presented in Figures I4 through I7. A summary of the chamber concentrations is presented in Table I3; Table I4 summarizes the distribution of mean daily concentrations

TABLE 13. SUMMARY OF CHAMBER CONCENTRATIONS IN THE TWO-YEAR INHALATION STUDIES OF *l*-EPINEPHRINE HYDROCHLOR DE

Target Concentration (mg/m^3)	Total Number of Readings	Average Concentration (a) (mg/m^3)
Rat Chambers		
1.5	3,357	1.5 ±0 10
5	3,359	5.02 ± 0 33
Mouse Chambers		
1 5	3,425	1.51 ± 0.09
3	3,425	3.03 ± 0.18

(a) Mean ± standard deviation

TABLE 14. DISTRIBUTION OF MEAN DAILY CONCENTRATIONS OF J-EPINEPHRINE HYDROCHLORIDE DURING THE TWO-YEAR INHALATION STUDIES (a)

Range of Concentration (percent of target)	Number of Days Mean Within Range		
	1.5 mg/m^3	3 mg/m^3	5 mg/m^3
Rat Chambers			
110-120	0		1
100-110	248		283
90-100	244		209
80-90	2		1
Mouse Chambers			
110-120	0	0	
100-110	295	325	
90-100	207	176	
80-90	0	1	

(a) Number of days mean within specified range

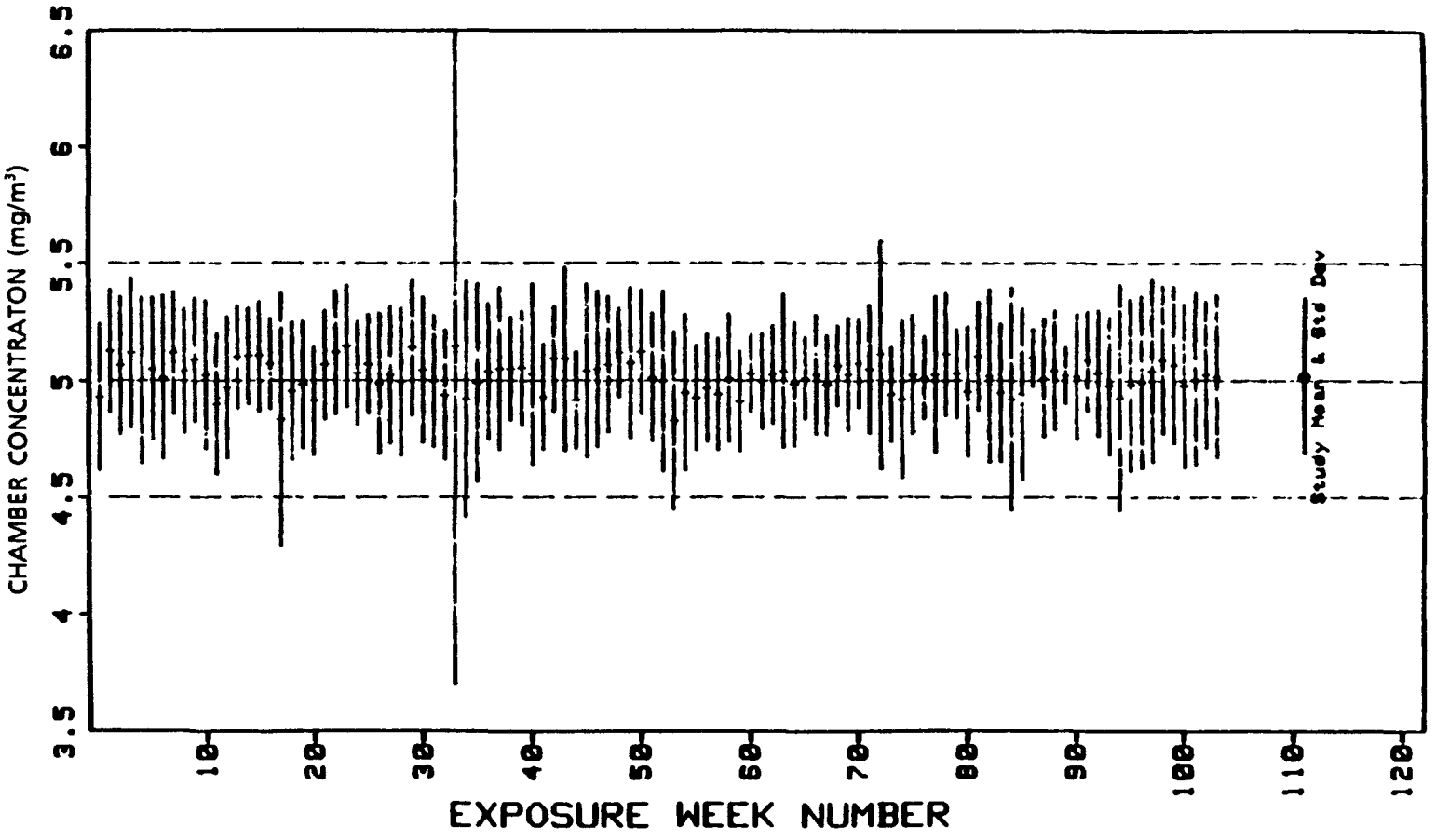

FIGURE I5. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN THE 5 mg/m³ *l*-EPINEPHRINE HYDROCHLORIDE RAT EXPOSURE CHAMBER FOR THE ENTIRE 103-WEEK STUDIES

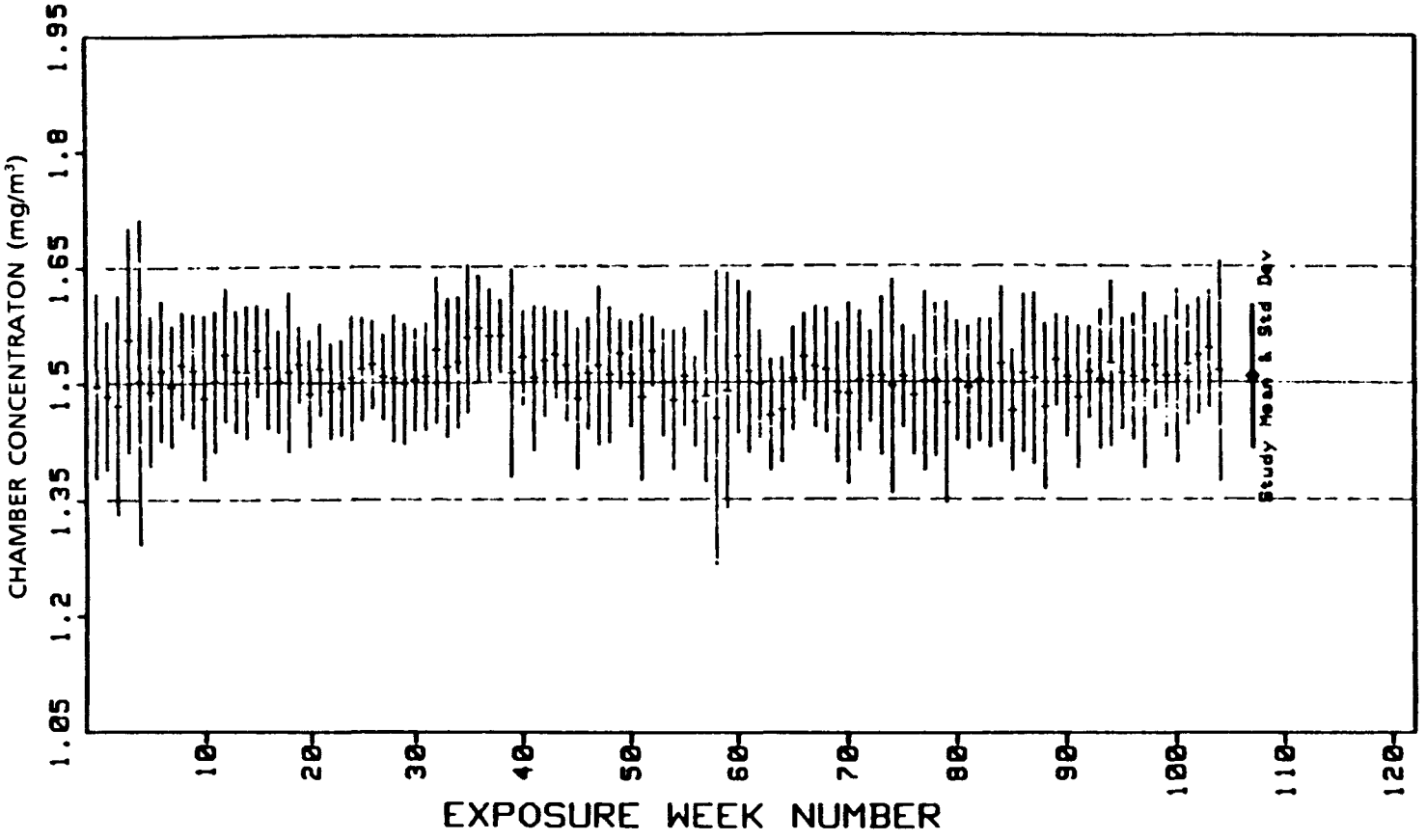

FIGURE I6. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN THE 1.5 mg/m³ *l*-EPINEPHRINE HYDROCHLORIDE MOUSE EXPOSURE CHAMBER FOR THE ENTIRE 104-WEEK STUDIES

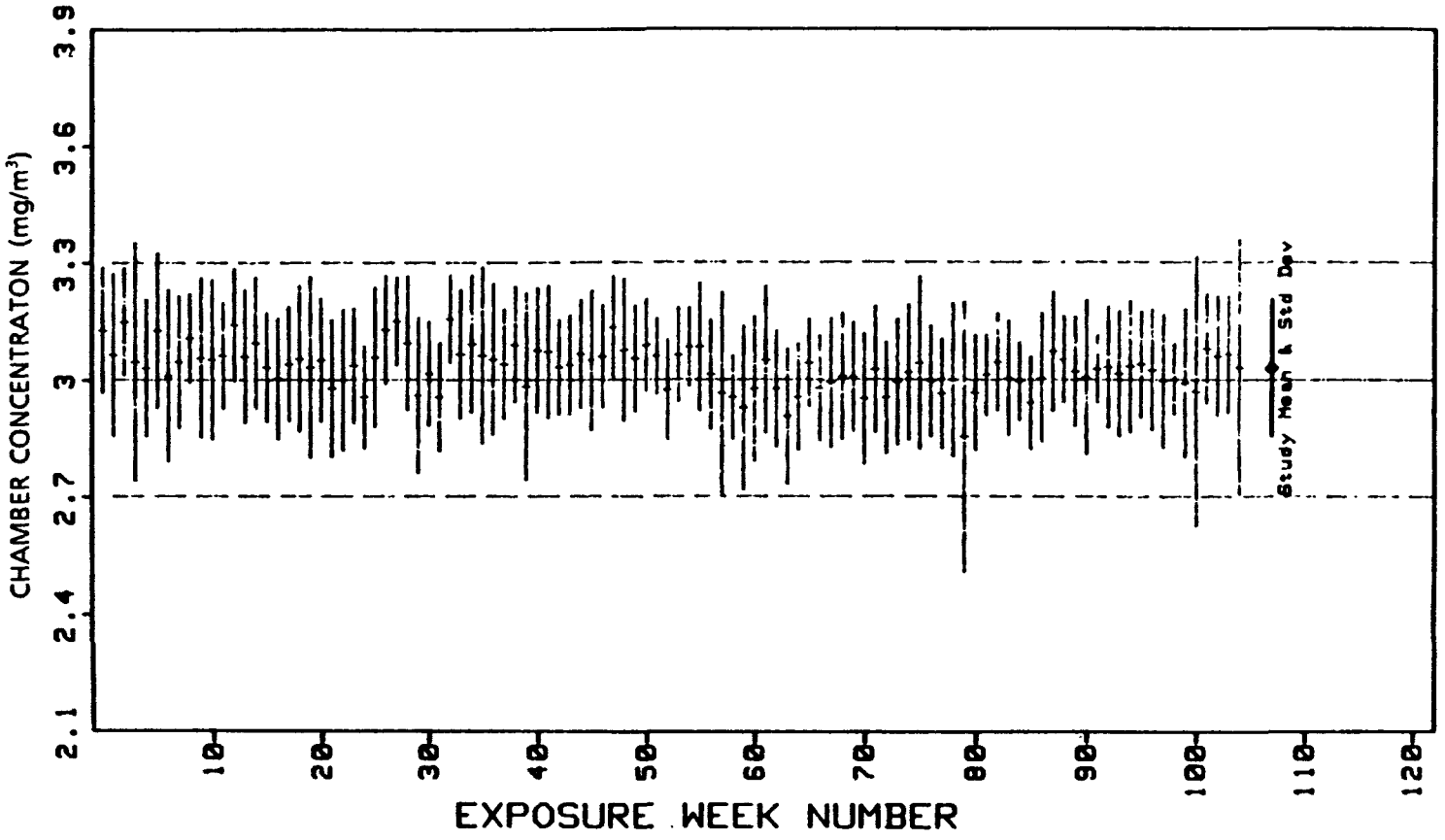

FIGURE I7. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN THE 3 mg/m³ *l*-EPINEPHRINE HYDROCHLORIDE MOUSE EXPOSURE CHAMBER FOR THE ENTIRE 104-WEEK STUDIES

APPENDIX J

GENETIC TOXICOLOGY

OF *l*-EPINEPHRINE

APPENDIX J. GENETIC TOXICOLOGY

METHODS

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Zeiger et al. (1987) and Mortelmans et al. (1986). Chemicals were sent to the laboratory as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

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

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

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985, 1987) and is described briefly below. Chemicals were sent to the laboratory as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 10 µg/ml.

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

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

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the chromosomal

aberration test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 200 first-division metaphase cells were scored at each dose for the chromosomal aberration test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P < 0.003$) trend test or a significantly increased dose point ($P < 0.05$) was sufficient to indicate a chemical effect.

RESULTS

l-Epinephrine was considered to give an equivocal response when tested for mutation induction in *S. typhimurium* strain TA100 in the absence of exogenous metabolic activation; no mutagenic activity was observed in TA100 in the presence of Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9, or in strains TA98, TA1535, or TA1537 with or without S9 (Table J1; Zeiger et al., 1987). In cytogenetic tests with CHO cells, epinephrine gave an equivocal response in the test for SCE induction without S9 activation: the first trial was considered negative because the response at the highest dose tested (10 µg/ml) was not statistically significant, but in trial 2, the response produced at this same concentration of epinephrine was significant, and the trial was called weakly positive. Epinephrine was negative for SCE induction in the presence of Aroclor 1254-induced male Sprague Dawley rat S9 (Table J2). Epinephrine did not induce chromosomal aberrations in CHO cells with or without S9 (Table J3).

TABLE J1. MUTAGENICITY OF *l*-EPINEPHRINE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
		−S9			+10% S9 (hamster)		
		Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3
TA100	0	113 ± 6.1	156 ± 9.9	83 ± 5.2	124 ± 1.9	152 ± 7.4	95 ± 5.1
	100	125 ± 9.6			137 ± 0.6		
	333	123 ± 13.2	136 ± 22.4	116 ± 8.8	144 ± 4.4	159 ± 7.7	119 ± 7.7
	1,000	128 ± 9.3	133 ± 27.4	116 ± 9.2	154 ± 4.6	182 ± 3.5	115 ± 10.8
	3,333	156 ± 14.0	162 ± 8.4	138 ± 4.8	177 ± 2.3	141 ± 4.5	124 ± 4.1
	6,666		108 ± 13.4	124 ± 4.7		168 ± 4.7	123 ± 6.3
	10,000	181 ± 11.2	85 ± 5.2	135 ± 3.2	205 ± 15.1	93 ± 2.0	120 ± 2.0
Trial summary		Weakly positive	Negative	Equivocal	Weakly positive	Negative	Negative
Positive control (c)		338 ± 1.2	451 ± 15.6	192 ± 9.0	1,737 ± 87.4	2,020 ± 24.6	584 ± 16.5
		+10% S9 (rat)					
		Trial 1	Trial 2	Trial 3			
TA100	0	134 ± 2.8	150 ± 6.9	108 ± 3.2			
	100	132 ± 12.5					
	333	139 ± 7.1	156 ± 24.8	114 ± 13.1			
	1,000	155 ± 3.5	168 ± 4.0	127 ± 9.5			
	3,333	165 ± 1.7	133 ± 8.8	120 ± 5.4			
	6,666		164 ± 15.9	112 ± 8.2			
	10,000	188 ± 12.3	92 ± 6.0	123 ± 5.2			
Trial summary		Equivocal	Negative	Negative			
Positive control (c)		650 ± 30.6	972 ± 38.6	350 ± 4.8			

		−S9		+10% S9 (hamster)		+10% S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA1535	0	15 ± 1.5	10 ± 2.4	11 ± 2.6	11 ± 2.6	6 ± 0.9	8 ± 0.6
	100	16 ± 5.5		9 ± 1.5		7 ± 0.6	
	333	10 ± 1.9	11 ± 1.2	13 ± 1.0	10 ± 1.8	7 ± 0.7	5 ± 1.5
	1,000	9 ± 2.6	6 ± 1.2	7 ± 1.0	8 ± 2.8	5 ± 0.6	8 ± 2.3
	3,333	12 ± 1.9	9 ± 2.6	8 ± 2.7	7 ± 2.7	3 ± 0.7	7 ± 1.0
	6,666		13 ± 0.9		3 ± 1.2		3 ± 1.0
	10,000	2 ± 0.0	6 ± 1.2	6 ± 1.7	7 ± 0.9	6 ± 0.9	6 ± 0.7
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		265 ± 21.7	218 ± 4.6	244 ± 5.9	196 ± 4.0	117 ± 22.4	91 ± 14.1
TA1537	0	4 ± 0.3	2 ± 1.0	10 ± 2.8	9 ± 3.7	5 ± 1.2	4 ± 0.0
	100	5 ± 1.7		7 ± 0.3		6 ± 1.8	
	333	8 ± 2.7	8 ± 2.7	7 ± 2.7	5 ± 0.9	9 ± 2.3	5 ± 1.3
	1,000	8 ± 2.7	6 ± 0.9	10 ± 1.7	7 ± 0.9	8 ± 1.2	8 ± 2.5
	3,333	5 ± 0.0	7 ± 0.7	10 ± 0.9	6 ± 0.9	7 ± 0.6	6 ± 1.2
	6,666		6 ± 2.0		6 ± 1.7		6 ± 0.7
	10,000	2 ± 0.7	4 ± 0.7	4 ± 0.7	5 ± 1.7	10 ± 0.3	8 ± 2.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		136 ± 6.2	56 ± 9.2	408 ± 25.3	258 ± 3.7	132 ± 10.6	129 ± 8.4
TA98	0	20 ± 2.9	14 ± 1.2	24 ± 3.0	22 ± 2.0	23 ± 2.7	15 ± 1.2
	100	19 ± 1.2		31 ± 1.5		31 ± 2.3	
	333	17 ± 2.0	18 ± 3.3	39 ± 3.2	20 ± 2.0	25 ± 2.7	26 ± 0.9
	1,000	17 ± 4.0	17 ± 2.2	32 ± 4.3	19 ± 3.3	35 ± 3.7	23 ± 2.5
	3,333	21 ± 3.0	22 ± 2.3	30 ± 1.2	22 ± 3.7	27 ± 3.5	20 ± 2.6
	6,666		17 ± 3.6		21 ± 3.5		28 ± 3.0
	10,000	21 ± 2.5	17 ± 1.2	23 ± 1.8	20 ± 1.2	21 ± 0.6	21 ± 1.5
Trial summary		Negative	Negative	Equivocal	Negative	Negative	Negative
Positive control (c)		723 ± 41.2	527 ± 51.0	1,242 ± 32.7	271 ± 20.5	451 ± 21.7	160 ± 7.3

TABLE J1. MUTAGENICITY OF *l*-EPINEPHRINE IN *SALMONELLA TYPHIMURIUM* (Continued)

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

TABLE J2. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY *l*-EPINEPHRINE (a)

Compound	Dose (μg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)								
Trial 1--Summary: Negative								
Dimethyl sulfoxide		50	1,037	438	0.42	8.8	26.0	
l-Epinephrine	0.5	50	1,048	477	0.45	9.5	26.0	7.76
	1.6	50	1,050	446	0.42	8.9	26.0	0.57
	5	50	1,046	447	0.42	8.9	26.0	1.18
	10	50	1,050	528	0.50	10.6	26.0	19.05
Mitomycin C	0.0007	50	1,048	537	0.51	10.7	26.0	21.32
	0.005	10	210	273	1.30	27.3	26.0	207.79
Trend test: P = 0.033								
Trial 2--Summary: Weakly positive								
Dimethyl sulfoxide		50	1,051	399	0.37	8.0	26.0	
l-Epinephrine	3	50	1,049	419	0.39	8.4	26.0	5.21
	5	50	1,050	435	0.41	8.7	26.0	9.13
	7.5	50	1,050	413	0.39	8.3	26.0	3.61
	10	50	1,050	480	0.45	9.6	26.0	**20.42
Mitomycin C	0.0005	50	1,043	503	0.48	10.1	26.0	27.03
	0.005	10	210	265	1.26	26.5	26.0	232.40
Trend test: P = 0.012								
+S9 (d) Summary: Negative								
Dimethyl sulfoxide		50	1,048	454	0.43	9.1	26.0	
l-Epinephrine	0.5	50	1,045	457	0.43	9.1	26.0	0.95
	1.6	50	1,042	462	0.44	9.2	26.0	2.35
	5	50	1,045	481	0.46	9.6	26.0	6.25
	10	50	1,050	431	0.41	8.6	26.0	−5.25
Cyclophosphamide	0.1	50	1,050	592	0.56	11.8	26.0	30.15
	0.6	10	210	244	1.16	24.4	26.0	168.21
Trend test: P = 0.586								

(a) Study performed at Environmental Health Research and Testing, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as described in (c) and (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
**P<0.01

TABLE J3. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY *l*-EPINEPHRINE (a)

Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
−S9 (b)				
Harvest time: 12 hours				
Dimethyl sulfoxide				
	200	2	0.01	1.0
l-Epinephrine				
1.6	200	2	0.01	1.0
5	200	0	0.00	0.0
10	200	3	0.02	1.5
Summary: Negative				
Mitomycin C				
0.125	200	38	0.19	17.5
0.25	50	19	0.38	32.0
Trend test: P = 0.490				
+S9 (c)				
Harvest time: 13 hours				
Dimethyl sulfoxide				
	200	0	0	0.0
l-Epinephrine				
1.6	200	1	0.01	0.5
5	200	2	0.01	1.0
10	200	1	0.01	0.5
Summary: Negative				
Cyclophosphamide				
5	200	32	0.16	15.5
7.5	50	20	0.40	36.0
Trend test: P = 0.164				

(a) Study performed at Environmental Health Research and Testing, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985, 1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

APPENDIX K

AUDIT SUMMARY

APPENDIX K. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft Technical Report for the 2-year studies of *l*-epinephrine hydrochloride in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by quality assurance support contractors. The audit included review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to the start of dosing.
(2) All inlife records including protocol, correspondence, animal identification, animal husbandry, environmental conditions, dosing, external masses, mortality, and serology.
(3) Body weight and clinical observation data; all data were scanned before individual data for a random 10% sample of animals in each study group were reviewed in detail.
(4) All study chemical records.
(5) All postmortem records for individual animals concerning date of death, disposition code, condition code, tissue accountability, correlation of masses or clinical signs recorded at or near the last inlife observation with gross observations and microscopic diagnoses, consistency of data entry or necropsy record forms, and correlation between gross observations and microscopic diagnoses.
(6) Inventory for wet tissue bags from all animals and residual wet tissues from a random 20% sample of animals in each study group, plus other relevant cases, to evaluate the integrity of individual animal identity and the thoroughness of necropsy and trimming procedure performance.
(7) Blocks and slides of tissues from a random 20% sample of animals from each study group, plus animals with less than complete or correct identification, to examine for proper inventory, labeling, matching of tissue sections, and preservation.
(8) All microscopic diagnoses for a random 10% sample of animals, plus 100% of the changes in diagnoses made to preliminary pathology tables, to verify their incorporation into the final pathology tables.
(9) The extent of correlation between the data, factual information, and procedures for the 2-year studies as presented in the draft Technical Report and the study records available at the NTP Archives.

Procedures and events for the exposure phase of the studies were documented adequately by records at the Archives. Review of the archival records indicated that protocol-specified procedures for animal care were followed adequately. Records that documented the generation, analysis, distribution, and delivery of doses to animals were complete and adequate. Review of body weight records for rats and mice showed that 48/48 recalculated mean values were correct.

Data entries on necropsy forms were made appropriately for rats and mice. The external masses recorded at the last inlife observation period correlated well with observations made at necropsy (62/64 in rats and 22/24 in mice correlated). The date of death recorded at necropsy for each unscheduled-death animal had matching entries among the inlife records for 113/117 rats and 96/100 mice; the differences in date of death entries for 1 rat and 1 mouse were 5 and 4 months, respectively, whereas the remaining six differences involved 1 day. The reason for animal removal recorded in the inlife records was in agreement with the disposition code recorded at necropsy for 297/300 rats and 298/300 mice; the five mode-of-death discrepancies involved either moribund-kill or natural-death animals that had no effect on overall survival values. The condition code for each animal was consistent with the disposition code and gross observations assigned at necropsy.

An individual animal identifier (ear tag) was present and correct in the residual tissue bag for 47/49 rats and 63/63 mice examined. Review of the entire data trail for the two rats with less than complete and correct identifiers indicated that the integrity of their individual-animal identity had been maintained throughout the studies. A total of two untrimmed potential lesions were found in the wet

tissues of 49 rats, and none was found in those of 53 mice examined. Intestinal segments were opened incompletely for 6/49 rats and 5/63 mice examined, and ceca were not opened for 12/49 rats and 1/63 mice examined; however, no untrimmed potential lesions were evident by external examination, and all other organs had been opened or incised properly. Each gross observation made at necropsy had a corresponding microscopic diagnosis for all but 21 in rats and 14 in mice. Blocks and slides were present, and corresponding tissue sections matched each other properly. All post-Pathology Working Group changes in diagnoses had been incorporated into the final pathology tables. The P values and incidences of neoplasms given in the Technical Report were the same as those in the final pathology tables at the Archives, except for some obvious discrepancies in P values associated with logistic regression and Fischer exact tests applied to the analysis of primary neoplasms in male rats for the categories of all benign neoplasms combined for all sites and of all neoplasms combined for all sites.

This summary describes general audit findings and the extent to which the data and factual information presented in the Technical Report are supported by records at the NTP Archives. Full details are presented in the audit reports that are on file at the NIEHS.

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