NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 307

TOXICOLOGY AND CARCINOGENESIS STUDIES OF EPHEDRINE SULFATE (CAS NO. 134-72-5) IN F344/N RATS AND B6C3F$_1$ MICE (FEED STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF EPHEDRINE SULFATE

(CAS NO. 134-72-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

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

May 1986

NTP TR 307

NIH Publication No. 86-2563

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

NOTE TO THE READER

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

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

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

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

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

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

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

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

CONTENTS

PAGE

ABSTRACT 10

CONTRIBUTORS 12

PEER REVIEW PANEL 13

SUMMARY OF PEER REVIEW COMMENTS 14

I. INTRODUCTION 15

II. MATERIALS AND METHODS 21

PROCUREMENT AND CHARACTERIZATION OF EPHEDRINE SULFATE 22

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS 22

SINGLE-ADMINISTRATION STUDIES 22

FOURTEEN-DAY STUDIES 22

THIRTEEN-WEEK STUDIES 24

TWO-YEAR STUDIES 24

STUDY DESIGN 24

SOURCE AND SPECIFICATIONS OF ANIMALS 24

ANIMAL MAINTENANCE 28

CLINICAL EXAMINATIONS AND PATHOLOGY 28

STATISTICAL METHODS 29

III. RESULTS 31

RATS 32

SINGLE-ADMINISTRATION STUDIES 32

FOURTEEN-DAY STUDIES 32

THIRTEEN-WEEK STUDIES 34

TWO-YEAR STUDIES 36

BODY WEIGHTS AND CLINICAL SIGNS 36

SURVIVAL 39

PATHOLOGY AND STATISTICAL ANALYSES OF RESULTS 39

MICE 43

SINGLE-ADMINISTRATION STUDIES 43

FOURTEEN-DAY STUDIES 43

THIRTEEN-WEEK STUDIES 45

TWO-YEAR STUDIES 47

BODY WEIGHTS AND CLINICAL SIGNS 47

SURVIVAL 50

PATHOLOGY AND STATISTICAL ANALYSES OF RESULTS 50

CONTENTS (Continued)

PAGE

IV. DISCUSSION AND CONCLUSIONS 55

V. REFERENCES 59

TABLES

TABLE 1 THE EFFECT OF AMBIENT TEMPERATURE AND HOUSING CONDITIONS ON THE LD_{50} VALUES OF MICE INTRAPERITONEALLY ADMINISTERED EPHEDRINE SULFATE 18

TABLE 2 PREPARATION AND STORAGE OF FORMULATED DIETS AND DOSE MIXTURES IN THE STUDIES OF EPHEDRINE SULFATE 23

TABLE 3 RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 23

TABLE 4 EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE STUDIES OF EPHEDRINE SULFATE 25

TABLE 5 SURVIVAL OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF EPHEDRINE SULFATE 32

TABLE 6 SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF RATS IN THE FOURTEEN-DAY DRINKING WATER STUDIES OF EPHEDRINE SULFATE 33

TABLE 7 PACKED CELL VOLUME OF RATS IN THE FOURTEEN-DAY STUDIES OF EPHEDRINE SULFATE 33

TABLE 8 SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF EPHEDRINE SULFATE 34

TABLE 9 SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE 35

TABLE 10 PUPILLARY MEASUREMENTS OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE 35

TABLE 11 PACKED CELL VOLUME OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE 35

TABLE 12 ADRENAL GLAND AND HEART WEIGHTS OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE 36

TABLE 13 MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 37

TABLES (Continued)

PAGE

TABLE 14 SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 39

TABLE 15 ANALYSIS OF PITUTARY GLAND LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 41

TABLE 16 ANALYSIS OF MAMMARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 42

TABLE 17 SURVIVAL OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF EPHEDRINE SULFATE 43

TABLE 18 SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF MICE IN THE FOURTEEN-DAY DRINKING WATER STUDIES OF EPHEDRINE SULFATE 44

TABLE 19 PACKED CELL VOLUME OF MICE IN THE FOURTEEN-DAY STUDIES OF EPHEDRINE SULFATE 44

TABLE 20 SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF EPHEDRINE SULFATE 45

TABLE 21 SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE 46

TABLE 22 PUPILLARY MEASUREMENTS OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE 46

TABLE 23 PACKED CELL VOLUME OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE 46

TABLE 24 ADRENAL GLAND AND HEART WEIGHTS OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE 47

TABLE 25 MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 48

TABLE 26 SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 50

TABLE 27 ANALYSIS OF ADRENAL GLAND LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 53

FIGURES

PAGE

FIGURE 1 GROWTH CURVES FOR RATS FED DIETS CONTAINING EPHEDRINE SULFATE FOR TWO YEARS 38

FIGURE 2 KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING EPHEDRINE SULFATE FOR TWO YEARS 40

FIGURE 3 GROWTH CURVES FOR MICE FED DIETS CONTAINING EPHEDRINE SULFATE FOR TWO YEARS 49

FIGURE 4 KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING EPHEDRINE SULFATE FOR TWO YEARS 51

FIGURE 5 INFRARED ABSORPTION SPECTRUM OF EPHEDRINE SULFATE (LOT NO. 926EW) .. 151

FIGURE 6 NUCLEAR MAGNETIC RESONANCE SPECTRUM OF EPHEDRINE SULFATE (LOT NO. 926EW) 153

APPENDIXES

APPENDIX A SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 63

TABLE A1 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 64

TABLE A2 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 67

TABLE A3 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 70

TABLE A4 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 76

APPENDIX B SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 83

TABLE B1 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 84

TABLE B2 SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 87

TABLE B3 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 90

APPENDIXES (Continued)

PAGE

TABLE B4 INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 96

APPENDIX C SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 103

TABLE C1 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 104

TABLE C2 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 108

APPENDIX D SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 113

TABLE D1 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 114

TABLE D2 SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 120

APPENDIX E ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 127

TABLE E1 ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 128

TABLE E2 ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 131

TABLE E3 ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 134

TABLE E4 ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 137

APPENDIX F HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE RECEIVING NO TREATMENT 141

TABLE F1 HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT 142

TABLE F2 HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT 142

TABLE F3 HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL STROMAL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT 143

APPENDIXES (Continued)

PAGE

TABLE F4 HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT 143

TABLE F5 HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT 144

TABLE F6 HISTORICAL INCIDENCE OF OVARIAN TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT 144

APPENDIX G GENETIC TOXICOLOGY OF EPHEDRINE SULFATE 145

TABLE G1 MUTAGENICITY OF EPHEDRINE SULFATE IN *SALMONELLA TYPHIMURIUM* 146

TABLE G2 INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY EPHEDRINE SULFATE 147

TABLE G3 INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY EPHEDRINE SULFATE 147

APPENDIX H CHEMICAL CHARACTERIZATION OF EPHEDRINE SULFATE 149

APPENDIX I PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES AND AND FORMULATED DIETS 159

APPENDIX J METHODS OF ANALYSIS OF FORMULATED DIETS 165

APPENDIX K RESULTS OF ANALYSIS OF FORMULATED DIETS 169

TABLE K1 RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 170

TABLE K2 RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 170

APPENDIX L INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION 171

TABLE L1 INGREDIENTS OF NIH 07 RAT AND MOUSE RATION 172

TABLE L2 VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION 172

TABLE L3 NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION 173

TABLE L4 CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION 174

APPENDIX M SENTINEL ANIMAL PROGRAM 177

APPENDIX N FEED AND COMPOUND CONSUMPTION BY RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE 179

APPENDIXES (Continued)

PAGE

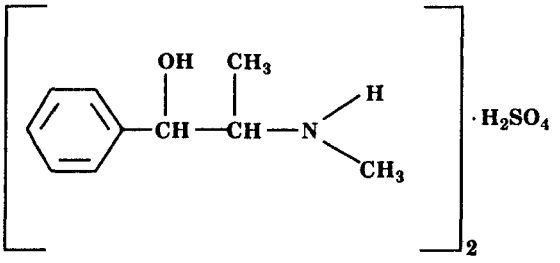
TABLE N1 FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 180

TABLE N2 FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 181

TABLE N3 FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 182

TABLE N4 FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE 183

APPENDIX O DATA AUDIT SUMMARY 185



EPHEDRINE SULFATE

$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$

Molecular weight 428.55

ABSTRACT

Ephedrine sulfate is a sympathomimetic amine that affects both the central and peripheral nervous systems. An effective bronchiodilator and weak vasoconstrictor, ephedrine sulfate is used extensively in nonprescription pharmaceutical preparations such as nose drops, cold tablets, cough syrups, and, in particular, asthma relief medicines. Ephedrine sulfate was nominated for carcinogenesis studies by the National Cancer Institute because of its widespread and long-term use for the relief of symptoms associated with asthma.

In 14-day repeated-exposure studies, F344/N rats of each sex received diets containing 0-1,500 ppm ephedrine sulfate or drinking water containing 0-1,200 ppm ephedrine sulfate; B6C3F$_1$ mice received diets or drinking water containing 0-5,000 ppm ephedrine sulfate. In the feed studies, the average feed consumption by dosed rats and mice was comparable to that of their respective controls. The average water consumption by rats and mice decreased with increasing concentration of ephedrine sulfate in the drinking water. Thus, subsequent studies used the feed route of administration.

Doses for the 2-year studies were selected on the basis of results from 13-week studies in which F344/N rats of each sex were given diets containing 0, 125, 250, 500, 1,000, or 2,000 ppm ephedrine sulfate and B6C3F$_1$ mice of each sex were given diets containing 0, 310, 630, 1,250, 2,500, or 5,000 ppm ephedrine sulfate. The major response that occurred during the 13-week studies was compound-associated reduction in weight gain. Toxicology and carcinogenesis studies of ephedrine sulfate were conducted by administering diets containing 0, 125, or 250 ppm ephedrine sulfate to groups of 50 F344/N rats and 50 B6C3F$_1$ mice of each sex for 103 weeks. The estimated average amount of ephedrine sulfate consumed per day during the 2-year study was 4 mg/kg and 9 mg/kg for low dose and high dose male rats, 5 mg/kg and 11 mg/kg for female rats, 14 mg/kg and 29 mg/kg for male mice, and 12 mg/kg and 25 mg/kg for female mice.

Survival of chemically exposed female rats during the 2-year study was greater than that of the controls (control, 27/50; low dose, 39/50; high dose, 39/50); survival of exposed male rats and male and female mice was comparable to that of controls. Throughout most of the 2-year studies, mean body weights of rats and mice of each sex receiving diets containing ephedrine sulfate were lower than those of controls.

Neoplasms that occurred in these studies were not considered to be related to administration of ephedrine sulfate. Two high dose female mice had ovarian granulosa cell tumors, and luteomas were

found in one low dose and one high dose female mouse. Because of the low incidence, these uncommon, benign tumors could not be clearly related to ephedrine sulfate administration.

Ephedrine sulfate was not mutagenic in four strains of *Salmonella typhimurium* (TA100, TA1535, TA97, or TA98) with or without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 activation. Ephedrine sulfate did not induce sister-chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells.

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

Under the conditions of these studies, there was *no evidence of carcinogenicity** for F344/N rats or B6C3F$_1$ mice of either sex receiving 125 or 250 ppm ephedrine sulfate in the diet for 2 years.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Ephedrine Sulfate is based on the 13-week studies that began in December 1979 and ended in March 1980 and on the 2-year studies that began in August 1980 and ended in August 1982 at Physiological Research Laboratories.

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

Richard Irwin, Ph.D., Chemical Manager

Gary A. Boorman, D.V.M., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
C.W. Jameson, Ph.D.
William Kluwe, Ph.D.
E.E. McConnell, D.V.M.
G.N. Rao, D.V.M., Ph.D.
M.A. Resnick, Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
Raymond W. Tennant, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report on 3/6/84)

Paul Hildebrandt, D.V.M. (Chair)
Tracor Jitco, Inc.
Scot Eustis, D.V.M., Ph.D. (NTP)
Carel Hollander, M.D., Ph.D.
TNO, The Netherlands
Henk Solleveld, D.V.M., Ph.D. (NTP)
John Toft, D.V.M., Ph.D.
Battelle Columbus Laboratories
Marilyn Wolfe, D.V.M., Ph.D. (NTP)

Principal Contributors at Physiological Research Laboratories
(Conducted Studies and Evaluated Tissues)

D. Elsberry, Ph.D.
Principal Investigator
M. Cowan, Ph.D.
Principal Investigator
A. Hall, D.V.M.
Principal Investigator
and Pathologist (for mice)
R. Pieper, B.S.
Chemist
G. Baskin, D.V.M.
Pathologist (for rats)

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

D. Banas, D.V.M

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

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

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on Ephedrine Sulfate on August 14, 1985, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

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

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

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

Ad Hoc Subcommittee Panel of Experts

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

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

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

Richard J. Kociba, D.V.M., Ph.D.
(Principal Reviewer)
Dow Chemical USA
Midland, Michigan

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

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

I.F.H. Purchase, Ph.D.
Central Toxicology Laboratory
Imperial Chemical Industries, PLC
Alderley Park, England

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

Steven R. Tannenbaum, Ph.D.*
Professor, Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts

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

*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF EPHEDRINE SULFATE

On August 14, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of ephedrine sulfate received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

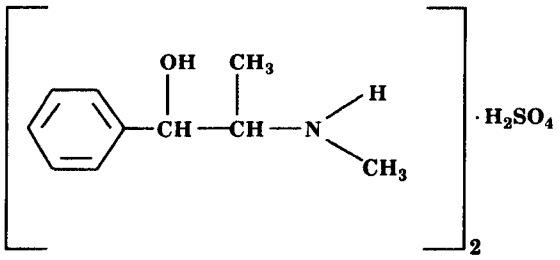
Dr. Kociba, a principal reviewer, said a more complete explanation needed to be given for not considering adrenal gland pheochromocytomas in rats to be chemically related. [See p. 56.] He considered the endometrial mucosal cyst gland formation to be compound related and as such it could be mentioned in the Discussion [see p. 57].

As a second principal reviewer, Dr. Perera agreed with the conclusions. She questioned, however, whether maximum tolerated doses had been achieved. She suggested that there be mention in the Abstract of prior studies of nitrosoephedrine, a potential reaction product of ephedrine and nitrite in the stomach, and of ephedrine administered with sodium nitrite. These studies were positive for carcinogenicity and indicate the need for further studies of ephedrine with nitrite because of relevance to human exposure. Dr. J. Huff, NIEHS, noted that according to policy previously endorsed by the Panel, only studies performed or supported by the NTP are mentioned in the Abstract, and other studies are cited more appropriately in the Introduction [see p. 19] or the Discussion.

Dr. Kociba moved that the Technical Report on the toxicology and carcinogenesis studies of ephedrine sulfate be accepted with modifications as discussed. Dr. Swenberg seconded the motion, and the Technical Report was approved unanimously by the Panel.

I. INTRODUCTION

I. INTRODUCTION



EPHEDRINE SULFATE

$(C_{10}H_{15}NO)_2 \cdot H_2SO_4$

Molecular weight 428.55

(R,S)(−) Ephedrine sulfate is an odorless, white, water-soluble, crystalline solid that melts with decomposition at 245° C and exhibits a specific rotation ($[\alpha]_D$ at 25° C) of −29.5° to −32.0°. The propanolamine side chain contains two chiral centers, and thus ephedrine may exist in four stereoisomeric configurations that consist of two pairs of enantiomers: (R,S)(−) and (S,R)(+) ephedrine, and (R,R)(−) and (S,S)(+) ephedrine. The latter pair of enantiomers has been given the trivial name pseudoephedrine.

Ephedrine is a sympathomimetic amine that affects both the peripheral and central nervous systems (Weiner, 1980), and both its sulfate and hydrochloride salts are orally efficacious. Ephedrine sulfate is an effective bronchiodilator and weak vasoconstrictor that is used extensively in nonprescription pharmaceutical preparations such as nose drops, cold tablets, time release capsules, and cough syrup as well as in various ointments and suppositories for relief of hemorrhoidal swelling (PDR for Non-Prescription Drugs, 1983). It is used for the management of urinary frequency and enuresis and for the treatment of asthma and other allergic conditions (Harvey, 1980; Wilson and McPhillips, 1978). It is also used in the treatment of narcolepsy because it produces mild central nervous system stimulation but has a much lower abuse potential than amphetamines (Harvey, 1980). Ephedrine sulfate produces cardiac stimulation, increased cardiac output, elevated blood pressure, increased cerebral and muscle blood flow, and decreased splanchnic and renal blood flow (Cohn, 1965; Zsoter, 1982). As a result of these hemodynamic actions, its use in combination with nitroprusside was evaluated in certain types of individuals with left ventricular failure (Franciosa and Cohn, 1979).

Pharmacologic Action

Many of the pharmacologic actions of ephedrine are thought to be mediated through its ability to cause the release of norepinephrine from adrenergic nerve terminals and therefore produce indirect stimulation of adrenoceptors (Weiner, 1980). This conclusion is based on the direct measurement of ephedrine-stimulated catecholamine release in isolated preparations (Kaul and Grewal, 1971; Schumann and Philippu, 1962) and on the observation that pretreatment of cats with reserpine markedly reduces the peripheral actions of ephedrine (Trendelenburg et al., 1962). In certain preparations from reserpinized animals, ephedrine is still capable of eliciting a response, and therefore it is also considered to have some direct agonistic effects on adrenoceptors.

More conclusive evidence for the direct interaction of ephedrine with adrenergic receptors was demonstrated in a study in which ephedrine inhibited the binding of iodohydroxybenzylpinadol to β-adrenergic receptors on membranes prepared from freshly isolated lymphocytes (Aarons et al., 1983).

In another study, propranolol or alprenolol antagonized the ephedrine-stimulated increase in respiration of brown adipocytes isolated from Wistar rats (Bukowiecki et al., 1982). Since propranolol and alprenolol are β-adrenergic

antagonists, these results suggest that ephedrine acts as a β-adrenergic agonist in the stimulation of brown adipocyte respiration. Phentolamine and phenoxybenzamine, α-adrenergic antagonists, produced only slight inhibitions. The ability of ephedrine to stimulate adipocyte respiration was also stereoselective, since the (R,S)(−) isomer produced significantly greater stimulation than did the other three isomers.

Pharmacokinetics

After oral administration, ephedrine is well absorbed from the gastrointestinal tract of humans and rodents and is rapidly excreted in the urine (Wilkinson and Beckett, 1968a,b; Marvola and Kivirinta, 1978). Direct measurement of ephedrine concentration in plasma shows that the peak blood level is reached within 5-6 minutes after oral administration of ephedrine hydrochloride to mice (time to maximum plasma concentration, 5.7 minutes; absorption half-life, 1.15 minutes). Elimination from plasma occurs monoexponentially with a half-life of 30.6 minutes (Marvola and Kivirinta, 1978). Pharmacokinetic studies in humans indicate that absorption of an orally administered dose of ephedrine is complete within 2-2.5 hours and occurs before the peak urinary excretion rate is reached (Wilkinson and Beckett, 1968a,b; Welling et al., 1971).

The major route for elimination of ephedrine in humans is urinary excretion. Within 24 hours after oral administration of ephedrine hydrochloride, 88% of the administered dose was excreted in the urine, and within 48 hours, 97% was excreted (Sever et al., 1975). Elimination occurs rapidly, and maximal rates of urinary excretion are generally reached within 3 hours of oral administration (Wilkinson and Beckett, 1968a; Welling et al., 1971).

Because of the presence of an ionizable group in the ephedrine molecule, differences in urinary pH could potentially affect renal reabsorption. In a study designed to answer this question, lower rates of excretion were observed with alkaline urine (pH 7-8) than with acidic urine (pH 5) (Wilkinson and Beckett, 1968a). However, in another study conducted without urinary pH control and in which the pH of individual urine samples varied from 5.32 to 7.28, no correlation was found between rate of excretion and pH (Welling et al., 1971). No systematic study has been conducted to compare the absorption of ephedrine with that of its diastereomer pseudoephedrine.

Metabolism

The metabolism of ephedrine in humans, dogs, and several species of rodents proceeds primarily by three reactions: aromatic hydroxylation, *N*-dealkylation, and oxidative deamination. However, the extent to which ephedrine is metabolized and the major metabolites produced vary with species (Williams et al., 1974).

In a study conducted without control of urinary pH, 53% to 74% of a dose of ephedrine hydrochloride orally administered to three humans was excreted unchanged (Sever et al., 1975). The major urinary metabolites were identified as norephedrine (8% to 20% of the administered dose), free and conjugated benzoic acid (3% to 6% of the administered dose), and 1-phenyl-1,2-propanediol (which was excreted in measurable concentrations by only one subject and represented 1.2% of the dose administered to that subject). In another study also conducted with three humans, only urinary excretion of norephedrine was evaluated (Wilkinson and Beckett, 1968a). When the urine was maintained acidic, 3.7% to 10.4% of orally administered ephedrine was recovered as norephedrine, and under conditions of alkaline urine, 10.9% to 24.4% of the dose was excreted as norephedrine. These studies indicate that in humans ephedrine sulfate undergoes either *N*-dealkylation to norephedrine or oxidative deamination to 1-phenyl-1,2-propanediol and further side-chain oxidation to benzoic acid; norephedrine appears to be metabolized little if at all in humans (Wilkinson and Beckett, 1968a; Sever et al., 1975).

Ephedrine is extensively metabolized by rabbits. Analysis of the radioactivity in urine collected for 24 hours after administration of ^{14}C-ephedrine revealed that the parent compound accounted for only 3.4% of the total radioactivity excreted by rabbits administered (S,R)(+) ephedrine and 0.7% of the radioactivity excreted by rabbits administered (R,S)(−) ephedrine

(Feller and Malspeis, 1977). The major urinary metabolites identified in this study were hippuric acid, benzoic acid, norephedrine, and 1-phenyl-1,2-propanediol. However, the amount of each metabolite excreted was different for the (S,R)(+) and (R,S)(−) isomers. In rabbits administered (R,S)(+) ephedrine, hippuric acid accounted for 16.3%, benzoic acid, 41.2%, norephedrine, 2.4%, and 1-phenyl-1,2-propanediol, 16% of the total radioactivity recovered in urine. In rabbits administered (R,S)(−) ephedrine, hippuric acid accounted for 29.7%, benzoic acid, 20.2%, norephedrine, 1.5%, and 1-phenyl-1,2-propanediol, 3.5% of the total radioactivity recovered in urine. In addition, radioactivity was excreted more rapidly from rabbits given the (S,R)(+) isomer than from rabbits given the (R,S)(−) isomer.

The biotransformation of ephedrine stereoisomers in vitro by rabbit liver microsomes was also examined (Feller et al., 1973). All four isomers were N-demethylated at approximately the same rate, and the rate of N-demethylation was observed to be faster than the rate of benzoic acid formation. However, (S,S)(+) ephedrine and (R,S)(−) ephedrine were converted to benzoic acid at a faster rate than were the (R,R)(−) or the (S,R)(+) isomers. In another comparison between enantiomers, (R,S)(−) ephedrine was metabolized more rapidly than was the (S,R)(+) isomer by rabbit liver microsomes and benzoic acid was formed from the (R,S)(−) isomer at a rate approximately three times faster than that observed for the (S,R)(+) isomer. Norephedrine and 1-phenyl-1,2,-propanediol, however, were formed in equivalent amounts from either isomer (Feller and Malspeis, 1977). These results suggest that the configuration of the methylamino group may be the major factor determining stereoselective metabolism; the results also are consistent with the observation from in vivo studies that the formation of benzoic acid does not necessarily occur from norephedrine (Feller et al., 1973).

Williams et al. (1974) assembled metabolic information on ephedrine and several amphetamine compounds, and their analysis indicates the following: The extent of aromatic hydroxylation of ephedrine is greatest in rats, followed in descending order by rabbits, guinea pigs, and dogs; no aromatic hydroxylation of ephedrine has been observed in human studies. *N*-dealkylation of ephedrine is greatest in rabbits, followed in descending order by dogs, guinea pigs, rats, and humans; deamination is greatest in rabbits, followed by humans and rats.

Toxicity

Information about the toxicity of ephedrine and its salts in rodents is limited. An oral LD_{50} value of 600 mg/kg in rats was reported (NIOSH, 1980). An acute toxicity study in Swiss-Webster male mice examined the effect of ambient temperature and housing (group or individual) on the LD_{50} values for intraperitoneally administered ephedrine sulfate (Table 1) (Peterson and Hardinge, 1967). Thirty degrees centigrade was determined to be the temperature at which

TABLE 1. THE EFFECT OF AMBIENT TEMPERATURE AND HOUSING CONDITIONS ON THE LD_{50} VALUES OF MICE INTRAPERITONEALLY ADMINISTERED EPHEDRINE SULFATE (a)

Temperature	LD_{50} Value (mg/kg)	
	Group Housed	Individually Housed
18° C	360	325
22° C	350	385
26° C	257	380
30° C	55	273
34° C	13.5	14

(a) Peterson and Hardinge, 1967; 10 animals per temperature point for individually housed animals and 10 animals per cage for group-housed animals.

group housing was first noted to have a significant effect on toxicity compared with individual housing; the effect of forced exercise on animals housed individually at this temperature was examined. When animals were forced to exercise, the LD_{50} values dropped from 273 mg/kg (observed for a sedentary individually housed animal) to 28 mg/kg. In another study conducted in mice, the LD_{50} values for (R,S)(−) and (S,R)(+) ephedrine were found to be essentially the same: the LD_{50} value for (R,S)(−) ephedrine was 244 mg/kg, and the LD_{50} value for (S,R)(+) ephedrine was 246 mg/kg (Fairchild and Aalles, 1967).

Dietary administration of ephedrine hydrochloride at nontoxic concentrations (1 g/kg feed) produced weight loss in normal (lean) mice, in rats and mice made obese through dietary manipulation, and in genetically obese mice (ob/ob) and rats (fa/fa) (Massoudi and Miller, 1977). The weight loss was associated with reduced carcass fat, increased oxygen consumption, and appetite suppression. However, reduced feed intake could not account for all of the observed loss.

Administration of ephedrine hydrochloride in the diet (0.1%) to genetically obese A^{vy}/a mice for 39 days resulted in significant weight loss during the first 2 weeks of dosing compared with controls fed normal diets or with diet-restricted controls fed the same quantity of feed consumed by the dosed animals (Yen et al., 1981). Although animals receiving feed containing ephedrine ate less than did the controls, reduced feed consumption was not due to poor palatability, since mice given an equivalent dose of ephedrine by subcutaneous injection but fed normal diets also ate less than controls and lost weight. The majority of weight loss was observed during the first 2 weeks of dosing, after which the mean body weight of the dosed animals remained constant. Increasing the dose of ephedrine produced additional weight loss after which mean body weights again reached a constant level. The mean rectal temperature of dosed mice was significantly higher than that of control animals, suggesting that part of the observed weight loss associated with ephedrine administration may be due to thermogenesis. Analysis of the liver and carcass of dosed and control mice indicated that weight loss in the dosed animals was associated with a significant decrease in triacylglycerol content but with no loss of hepatic protein.

Carcinogenesis

No long-term carcinogenicity studies of ephedrine or any of its salts were found in the literature. The carcinogenicity of nitrosoephedrine, a potential product of the reaction of ephedrine and nitrite in the acidic environment of the stomach, was examined (Wogan et al., 1975). Male and female C57BL/6J × C3HeB/FeJ F_1 mice were given intraperitoneal injections of nitrosoephedrine in trioctanoin on days 1, 4, and 7 after birth and then maintained for 78 weeks, after which a necropsy was performed and the collected tissues examined histopathologically. In animals surviving 50 or more weeks, hepatocellular carcinomas were observed in 15/15 males and 13/15 females and metastasis to the lung was found in 1 male and 8 females. Male vehicle controls developed liver cell hyperplasia (2/14) but no hepatocellular carcinomas, and female vehicle controls developed one hepatocellular carcinoma (1/12).

In a study designed to examine the effect of coadministration of sodium nitrite and amine-containing drugs, 26 hooded rats received ephedrine (80 mg/kg) and sodium nitrite (50 mg/kg) by gavage once a week for 2 weeks and then were maintained without further dosing for 6 months, while another group of 5 animals was given only ephedrine and also maintained for 6 months (Schneider et al., 1977). A third group of 30 rats was given feed containing ephedrine (0.5%) and sodium nitrite (0.2%), while a fourth group of 10 rats was given only ephedrine (0.5%) in feed. Malignant neoplasms, mostly paracecal reticulum cell sarcomas, were found in 21% of the animals administered the mixture by gavage and in 43% of the animals administered the mixture in feed. No malignancies were found in animals receiving ephedrine alone.

No data on the genetic toxicology of ephedrine were found in the literature. In studies conducted by the National Toxicology Program, ephedrine sulfate was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA97, or TA98 in the presence or absence of S9

from Aroclor 1254-induced male Sprague-Dawley rat livers (Appendix G, Table G1). Results of tests to detect an increased frequency of sister-chromatid exchanges (SCE's) in Chinese hamster ovary (CHO) cells in culture were considered equivocal, since a positive response was observed only at a dose at which slight toxicity of ephedrine sulfate was indicated by the necessity for delayed harvest before evaluation of cells. The slight, consistent elevation in SCE's at all doses in the presence of S9 was not statistically significant. Results of tests to detect an increased frequency of chromosomal aberrations in CHO cells were also considered equivocal. No significant responses were observed in the absence of metabolic activation; the two significantly elevated responses in the presence of S9 from Aroclor 1254-induced Sprague-Dawley rat livers occurred in the mid-range of a series of extremely high doses (5,600-8,000 μg/ml).

Exposure

Humans have long been exposed to ephedrine. Ephedrine occurs naturally in certain plants from the genus ephedra, which are distributed throughout temperate and subtropical regions of Europe, Asia, and America. The best known of these plants is the herb Ma Huang, which contains approximately 1% ephedrine (dry weight) and whose medicinal use has been recorded in Chinese history for over 5,000 years. Following its purification from Ma Huang extracts in 1887, ephedrine became a popular pharmaceutical in Japan and China. However, it was not introduced to western cultures until the mid-1920's (Chen and Schmidt, 1924). In 1926, 12.5 pounds of pure ephedrine were imported into the United States from China. In 1980, U.S. imports of ephedrine sulfate were approximately 110,000 pounds. No information is available on current production levels of ephedrine sulfate alone; however, in 1983, 1,151,000 pounds of autonomic agents were produced in the United States (USITC, 1984). Its presence in preparations used for the relief of the symptoms of asthma and in such popular nonprescription pharmaceuticals as cold tablets, nighttime cold remedies, and nose drops suggests that most citizens of the United States have been or will be exposed at some time during childhood and may continue to be exposed periodically throughout their lifetime.

Study Rationale: Because of extensive human exposure and the absence of adequate carcinogenesis studies, ephedrine sulfate was nominated to the NTP by the National Cancer Institute for toxicology and carcinogenesis studies.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF EPHEDRINE SULFATE

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

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

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF EPHEDRINE SULFATE

U.S.P.-grade *l*-ephedrine sulfate was obtained in one lot (lot no. 926EW) from The Upjohn Company (Kalamazoo, Michigan). The manufacturer provided documentation that this lot of *l*-ephedrine sulfate conformed to USP specifications and that it was 99.4% pure. Purity and identity analyses were conducted at Midwest Research Institute (Appendix H). The identity of the study material was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectroscopic data were consistent with the structure of ephedrine sulfate.

The purity of the ephedrine sulfate was determined to be greater than 99% by elemental analysis, weight loss on drying, titration of the amine group, thin-layer chromatography, and high-performance liquid chromatography. Results of elemental analyses agreed with the theoretical values. Weight loss on drying was 0.14%. Lot no. 926EW was 99.3% pure by nonaqueous titration of the amine group. Three impurities with a total peak area of 0.36% that of the major peak were detected by high-performance liquid chromatography. No attempt was made to identify these impurities.

Ephedrine sulfate was stable in storage for 2 weeks at 60° C (Appendix H). Ephedrine sulfate was stored at the study laboratory in the dark at 25° C. Periodic characterization by infrared spectroscopy and high-performance liquid chromatography or titration of the amine group detected no deterioration of the ephedrine sulfate over the course of the studies.

PREPARATION AND CHARACTERIZATION OF FORMULATED DIETS

The homogeneity of a formulated diet mixture was evaluated and found to be satisfactory (Appendix I). Further studies showed that ephedrine sulfate was stable in feed when stored for 2 weeks at temperatures equal to or less than 25° C. The formulated diets were prepared by adding a dry premix of feed and ephedrine sulfate to the amount of feed necessary to achieve the designated final concentration (Table 2). Formulated diets were stored at room temperature for no longer than 14 days. Periodic analyses for ephedrine sulfate in feed mixtures were performed by the study and analytical chemistry laboratories to determine if the formulated diets contained the correct concentrations of ephedrine sulfate (Appendix J). Because 48/51 samples analyzed were within ± 10% of the target concentration, the data can be extrapolated to indicate that the mixes were formulated according to specifications approximately 94% of the time (Table 3; Appendix K, Table K1).

SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 16 days before the studies began.

Groups of five rats of each sex were administered a single dose of ephedrine sulfate in water by gavage at doses of 75, 150, 300, 600, or 1,200 mg/kg. Groups of five mice of each sex were administered 125, 250, 500, 1,000, or 2,000 mg/kg. The volume of solution administered was 10 ml/kg body weight for both rats and mice. Rats were fasted 4 hours and mice 18 hours before dosing; controls were not used.

Animals were observed two times per day for 14 days. Body weights were taken 2 days before dosing; final body weights were not recorded. A necropsy was performed on animals dying during the study, but no histopathologic evaluation was conducted.

FOURTEEN-DAY STUDIES

Two 14-day studies were conducted: one in which ephedrine sulfate was administered in drinking water and one in feed. Five- to six-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and held for approximately 3 weeks in quarantine before the study began.

TABLE 2. PREPARATION AND STORAGE OF FORMULATED DIETS AND DOSE MIXTURES IN THE STUDIES OF EPHEDRINE SULFATE

Single-Administration Studies	Fourteen-Day Drinking Water Studies	Fourteen-Day Feed Studies	Thirteen-Week Studies	Two-Year Studies
Preparation				
Stock solutions prepared 24 h before dosing by diluting chemical with water in 50-ml flasks. Two h before dosing, dose mixtures prepared by dilution of stock solution with water in volumetric flasks.	Data not available	Premix mixed with feed in an 8-qt Patterson-Kelly® twin-shell blender for 5 min with intensifier bar and then 10 min without intensifier bar	Same as 14-d feed studies	Premix prepared by thoroughly mixing weighed amount of feed with weighed chemical with a spatula in a tared beaker; premix mixed with weighed feed in Patterson-Kelly® 1-ft^3 twin-shell blender with intensifier bar on for 5 min and off for 10 min
Maximum Storage Time				
24 h	14 d	14 d	14 d	14 d
Storage Conditions				
4° C	4° C	Room temperature	Room temperature	Room temperature

TABLE 3. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

	Determined Concentration for Target Concentration of			
	125 ppm	250 ppm	125 ppm	250 ppm
	Rats		Mice	
Mean (ppm)	123	261	126	251
Standard deviation	7.7	28.5	7.0	9.9
Coefficent of variation (percent)	6.3	10.9	5.6	3.9
Range (ppm)	113-137	231-347	112-137	237-266
Number of samples	13	13	13	12

Drinking Water Studies: Groups of five rats of each sex were given drinking water containing 0, 75, 150, 300, 600, or 1,200 ppm ephedrine sulfate. Groups of five mice of each sex were given drinking water containing 0, 312.5, 625, 1,250, 2,500, or 5,000 ppm.

Feed Studies: Groups of five rats of each sex were fed diets containing 0, 90, 190, 380, 750, or 1,500 ppm ephedrine sulfate. Groups of five mice of each sex were fed diets containing 0, 300, 600, 1,250, 2,500, or 5,000 ppm.

Animals were approximately 8 weeks old when placed on study. Rats and mice were observed twice per day and were weighed on days 1, 7 (drinking water study only), and 15. The period of chemical exposure was 14 consecutive days followed by 1 day of observation before the scheduled necropsy. Blood for the determination of packed cell volume was taken from the external jugular vein at the scheduled kill. Further details on animal maintenance are given in Table 4.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of ephedrine sulfate and to determine the concentrations to be used in the 2-year studies.

Four- to five-week old male and female F344/N rats and $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 20 days, distributed to weight classes, and then assigned to cages according to a table of random numbers. Cages were assigned to dosed and control groups according to a table of random numbers.

Groups of 10 rats of each sex were given diets containing 0, 125, 250, 500, 1,000, or 2,000 ppm ephedrine sulfate for 13 weeks. Groups of 10 mice of each sex were given diets containing 0, 310, 630, 1,250, 2,500 or 5,000 ppm. Control diets consisted of NIH 07 Rat and Mouse Ration (Appendix L). Formulated diets, control diets, and water were available ad libitum. Further experimental details are summarized in Table 4. Animals were checked two times per day; moribund animals were killed. Feed consumption was measured weekly by cage. Individual animal weights were recorded once per week.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 4. Adrenal gland weight, heart weight, and packed cell volume were measured for controls, for the 2,000-ppm groups of rats, and for the 5,000-ppm groups of mice. A bilateral measurement of pupil diameter was conducted on all animals at the end of the studies. Pupils of both eyes were photographed, and diameters were measured from the photographs.

TWO-YEAR STUDIES

Study Design

Diets containing 0, 125, or 250 ppm ephedrine sulfate were fed to groups of 50 rats and mice of each sex for 103 weeks.

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female, × C3H/HeN MTV^-, male) mice used in this study were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age, 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 rats were placed on study at 7-8 weeks of age and mice at 8-9 weeks of age. The health of the animals was monitored during

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE STUDIES OF EPHEDRINE SULFATE

Single-Administration Studies	Fourteen-Day Drinking Water Studies	Fourteen-Day Feed Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Size of Study Groups				
5 males and 5 females of each species	Same as single-admistration studies	Same as single-admistration studies	10 males and 10 females of each species	50 males and 50 females of each species
Doses				
Rats--75, 150, 300, 600, or 1,200 ppm ephedrine sulfate in water by gavage; mice--125, 250, 500, 1,000, or 2,000 ppm ephedrine sulfate in water by gavage; dose vol: 10 ml/kg	Rats--0, 75, 150, 300, 600, or 1,200 ppm ephedrine sulfate in drinking water; mice--0, 312.5, 625, 1,250, 2,500, or 5,000 ppm ephedrine sulfate in drinking water	Rats--0, 90, 190, 380, 750, or 1,500 ppm ephedrine sulfate in feed; mice--0, 300, 600, 1,250, 2,500, or 5,000 ppm ephedrine sulfate in feed	Rats--0, 125, 250, 500, 1,000, or 2,000 ppm ephedrine sulfate in feed; mice--0, 310, 630, 1,250, 2,500, or 5,000 ppm ephedrine sulfate in feed	0, 125, or 250 ppm ephedrine sulfate in feed
Date of First Dose				
3/22/79	6/4/79	5/28/79	12/31/79	Rats--8/26/80; mice--8/18/80
Date of Last Dose				
N/A	6/17/79	6/10/79	3/29/80	Rats--8/18/82; mice--8/08/82
Duration of Dosing				
Single administration	14 consecutive d	Same as 14-d drinking water studies	13 wk	103 wk
Type and Frequency of Observation				
Observed 2 × d	Observed 2 × d; weighed on d 1, 7, and 15; water consumption measured 1 × wk	Observed 2 × d; weighed on d 1 and 15 and feed consumption measured 1 × wk	Observed 2 × d; individual animal weights determined 1 × wk; feed consumption measured 1 × wk	Observed 2 × d; individual animal weights determined 1 × wk for 13 wk, then 1 × mo; feed consumption measured 1 × mo
Necropsy and Histologic Examination				
Necropsy performed on animals that died before the end of the studies	Necropsy performed on all animals; 10% of animals examined histologically; packed cell volume determined on blood taken at terminal kill	Same as 14-d drinking water studies	Necropsy and histologic exam performed on all animals; tissues examined: tissue masses, regional lymph node, blood smear, skin, mandibular lymph node, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach duodenum, jejunum, ileum, colon, rectum, mesenteric lymph node, liver, gallbladder, pancreas, spleen, kidneys,	Necropsy and histologic examination performed on all animals; the following tissues were examined: gross lesions, skin, mandibular lymph node, mammary gland, salivary gland, thigh muscle, sciatic nerve, sternebrae, vertebrae or femur including marrow, costochondral junction (rib), oral cavity, thymus, larynx and pharynx, trachea, lungs and bronchi, heart and aorta, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, tongue, gallbladder (mice), regional lymph nodes, ileum, colon, cecum, rectum, mesenteric lymph node, liver,

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE STUDIES OF EPHEDRINE SULFATE (Continued)

Single-Administration Studies	Fourteen-Day Drinking Water Studies	Fourteen-Day Feed Studies	Thirteen-Week Studies	Two-Year Studies
Necropsy and Histologic Examination (Continued)				
			adrenal glands, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary gland, eyes, external and middle ear, and spinal cord; adrenal gland and heart weight measured for control and highest dose groups; pupil diameter measured.	pancreas, spleen, kidneys, adrenal glands, seminal vesicles/prostate/testes/ epididymis or ovaries/ uterus, nasal cavity and nasal turbinates, brain, pituitary gland, spinal cord, eyes, and preputial or clitoral gland.
ANIMALS AND ANIMAL MAINTENANCE				
Strain and Species				
F344/N rats; $B6C3F_1$ mice	Same as single-admistration studies	Same as single-admistration studies	Same as single-admistration studies	Same as single-admistration studies
Animal Source				
Charles River Breeding Laboratories (Portage, MI)	Harlan Industries (Indianapolis, IN)	Same as 14-d drinking water studies	Charles River Breeding Laboratories (rats--Portage, MI; mice--Kingston, NY)	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory				
Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories	Physiological Research Laboratories
Method of Animal Identification				
Marked on tail with indelible ink	Rats--tail marking; mice--ear punch	Same as 14-d drinking water studies	Rats--ear tag; mice--toe clip	Toe clip and ear clip
Time Held Before Study				
16 d	18-19 d	18-19 d	20 d	20 d
Age When Placed on Study				
Not available	8 wk	8 wk	7-8 wk	Rats--7-8 wk; mice--8-9 wk
Age When Killed				
Not available	10 wk	10 wk	20-22 wk	Rats--111-112 wk; mice--113-114 wk
Necropsy Dates				
4/5/79	6/19/79-6/21/79	6/12/84-6/14/84	3/31/80-4/4/80	Rats--8/23/82-8/26/82; mice--8/16/82-8/19/82
Method of Animal Distribution				
Assigned to weight distribution classes and then to dosed groups according to a table of random numbers	Same as single-admistration studies	Same as single-admistration studies	Same as single-admistration studies	Assigned to groups according to a table of random numbers

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE STUDIES OF EPHEDRINE SULFATE (Continued)

Single-Administration Studies	Fourteen-Day Drinking Water Studies	Fourteen-Day Feed Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)				
Feed				
Rodent Laboratory Chow 5001 (Ralston Purina Co., St. Louis, MO); provided ad libitum	Same as single-admistration studies	Same as single-admistration studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners,PA); available ad libitum	Same as 13-wk studies
Bedding				
Kiln-dried pine shavings (Minnesota Sawdust & Shavings Co., Anoka, MN)	Aspen wood chips (Minnesota Sawdust & Shavings Co., Anoka, MN)	Same as 14-d drinking water studies	Aspen wood chips	Aspen wood chips (Minnesota Sawdust & Shavings Co., Anoka, MN)
Water				
City water provided ad libitum in glass bottles with stainless steel sipper tubes	Available ad libitum in water bottles	Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 14-d feed studies	Well water from public supply softened to <1 grain per gallon hardness by passage through sodium zeolite and filter; automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum
Cages				
Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Polycarbonate (Laboratory Products, Inc.)	Same as 14-d drinking water studies	Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)	Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD)
Cage Filters				
Reemay Spun-bonded polyester filters (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage				
5	5	5	5	Rats--5; male mice--1; female mice--5
Other Chemicals on Study in the Same Room				
None	None	None	None	None
Animal Room Environment				
Temp--22.2°-24.4° C; rel hum--35%-45%; 120 room air changes/h	Temp--20°-28° C; hum--40%-46%; 120 room air changes/h; light 12 h/d	Same as 14-d drinking water studies	Temp--20.0°-26.6° C; rel hum--20%-48%; 120 room air changes/h; light 12 h/d	Temp--21.1°-26.7° C (a); rel hum--32%-74%; 15 room air changes/h; fluorescent light 12 h/d

(a) Excursion to >26.6° C on 4/15/82; excursions to >26° C on 3/28/81 for 6 h and on 10/29/80, 10/30/80, and 10/6/80.

the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix M).

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

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

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

Animal Maintenance

Rats and female mice were housed five per cage. Male mice were housed individually. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 4.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week for the first 13 weeks and monthly thereafter during the 1st year of the study. During the 2nd year of the study, clinical signs were recorded weekly. Body weights by cage were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the study. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 4.

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent evaluations, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Nonneoplastic lesions are not examined routinely by the quality assurance pathologist or PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and PWG if they are considered part of the toxic

response to a chemical or if they are deemed of special interest.

Statistical Methods

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

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

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

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

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

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

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions

were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

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

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

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SINGLE-ADMINISTRATION STUDIES

Single-administration range-finding studies were conducted to determine the lethality of ephedrine sulfate administered orally to F344/N rats. Deaths occurred in all dose groups (Table 5). All but one death occurred on day 1. Rats that died exhibited hyperkinesia that progressed to convulsive seizures, ataxia, and lethargy.

TABLE 5. SURVIVAL OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF EPHEDRINE SULFATE

Dose (mg/kg)	Survival (a)
MALE	
75	4/5
150	3/5
300	0/5
600	0/5
1,200	0/5
FEMALE	
75	3/5
150	1/5
300	0/5
600	0/5
1,200	0/5

(a) Number surviving/number initially in group. All deaths occurred on day 1 except for one female in the 600 mg/kg group that died on day 2.

Epistaxis occurred at the 300, 600, and 1,200 mg/kg doses. Mild portal-hepatic congestion, mild pulmonary congestion, and epistaxis were found in animals that died before the end of the studies. No histopathologic evaluation was conducted.

FOURTEEN-DAY STUDIES

Drinking Water Studies: None of the rats died before the end of the studies (Table 6). The final mean body weights were not significantly affected by ephedrine sulfate. Average water consumption decreased with increasing dose. Water consumption by male rats that received 1,200 ppm was 50% that of the controls. Water consumption by female rats that received 1,200 ppm was 25% that of the controls. Hyperexcitability was observed for animals that received the three highest doses, and dehydration was observed for rats that received 600 or 1,200 ppm. The mean packed cell volume of female rats that received 1,200 ppm was 8% lower than that of the controls (Table 7). No compound-related effects were observed at necropsy.

Feed Studies: None of the rats died before the end of the studies (Table 8). Final mean body weights of males that received 1,500 ppm were 10% lower than that of the controls. Final mean body weights of dosed females were not affected by ephedrine sulfate. Feed consumption by rats that were given diets containing 1,500 ppm ephedrine sulfate was 76% that of the controls for males and 87% for females. Hyperexcitability and rough hair coats were observed in rats that received 380, 750, or 1,500 ppm. The mean packed cell volume was not affected by ephedrine sulfate (Table 7). No clear compound-related effects were observed at necropsy.

TABLE 6. SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF RATS IN THE FOURTEEN-DAY DRINKING WATER STUDIES OF EPHEDRINE SULFATE

Conc. (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Mean Water Consumption (d) Week 1	Week 2
MALE							
0	5/5	83 ± 4	154 ± 8	+71 ± 5	--	28.9	25.5
75	5/5	93 ± 4	172 ± 7	+79 ± 4	112	26.0	23.0
150	5/5	85 ± 2	162 ± 3	+77 ± 1	105	22.0	20.0
300	5/5	87 ± 3	151 ± 4	+64 ± 2	98	19.6	19.4
600	5/5	95 ± 5	158 ± 5	+63 ± 6	103	14.4	17.9
1,200	5/5	91 ± 4	148 ± 8	+57 ± 4	96	10.5	13.1
FEMALE							
0	5/5	77 ± 5	122 ± 8	+45 ± 3	--	20.0	16.2
75	5/5	76 ± 3	131 ± 3	+55 ± 2	107	18.8	15.0
150	5/5	80 ± 4	131 ± 6	+51 ± 3	107	16.7	14.2
300	5/5	81 ± 3	128 ± 6	+47 ± 4	105	11.5	10.8
600	5/5	79 ± 3	123 ± 5	+44 ± 3	101	7.9	10.9
1,200	5/5	82 ± 5	119 ± 5	+37 ± 4	98	8.9	4.4

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

TABLE 7. PACKED CELL VOLUME OF RATS IN THE FOURTEEN-DAY STUDIES OF EPHEDRINE SULFATE (a)

Concentration (ppm)	Male	Female
Drinking Water		
0	48.4 ± 6.0	49.0 ± 2.7
75	46.8 ± 1.6	45.4 ± 3.2
150	53.6 ± 7.2	47.0 ± 3.5
300	49.8 ± 1.5	47.6 ± 1.5
600	47.2 ± 1.1	47.2 ± 1.6
1,200	46.0 ± 2.4	(b) 45.2 ± 0.5
Feed		
0	48.6 ± 3.1	48.6 ± 1.5
90	49.6 ± 2.1	48.6 ± 2.4
190	48.0 ± 3.1	46.2 ± 3.0
380	46.4 ± 2.5	48.0 ± 1.2
750	45.4 ± 3.3	46.8 ± 1.1
1,500	47.0 ± 4.1	45.0 ± 1.9

(a) Mean (percent) ± standard deviation for five animals
(b) $P<0.05$ vs the controls by Dunnett's test

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

Conc. (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption Week 2 (d)
MALE						
0	5/5	124 ± 4	181 ± 7	+57 ± 3	--	17
90	5/5	113 ± 8	172 ± 9	+59 ± 2	95	15
190	5/5	112 ± 5	169 ± 6	+57 ± 4	93	14
380	5/5	121 ± 7	185 ± 8	+64 ± 3	102	15
750	5/5	119 ± 6	178 ± 9	+59 ± 3	98	14
1,500	5/5	119 ± 2	162 ± 6	+43 ± 5	90	13
FEMALE						
0	5/5	101 ± 2	123 ± 4	+22 ± 2	--	15
90	5/5	103 ± 2	126 ± 4	+23 ± 3	102	15
190	5/5	102 ± 4	125 ± 5	+23 ± 2	102	15
380	5/5	99 ± 1	122 ± 3	+23 ± 3	99	15
750	5/5	96 ± 2	120 ± 3	+24 ± 1	98	14
1,500	5/5	105 ± 2	131 ± 3	+26 ± 1	107	13

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

THIRTEEN-WEEK STUDIES

None of the rats died before the end of the studies (Table 9). Final mean body weights of rats that received 1,000 or 2,000 ppm were 20% and 23% lower than those of the controls for males and 10% and 17% lower for females. Feed consumption by dosed and control groups was generally comparable. Rats that received 2,000 ppm were hyperexcitable and had rough coats. No compound-related histopathologic effects were observed. The mean pupil diameters for dosed and control animals were comparable (Table 10). The mean packed cell volume of male rats that received 2,000 ppm was 6% greater than that of the controls (Table 11). The relative adrenal gland weight of male rats that received 2,000 ppm was significantly greater than that of the controls, and the adrenal gland weight and heart weight of female rats that received 2,000 ppm were significantly lower than those of the controls (Table 12).

Dose Selection Rationale: Concentrations selected for rats for the 2-year studies were 125 and 250 ppm ephedrine sulfate in feed. The reduced weight gain that occurred at higher concentrations was felt to be potentially life threatening over the duration of a 2-year study.

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

Conc. (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 6	Week 12
MALE							
0	10/10	141 ± 3	359 ± 5	+218 ± 5	--	15.1	14.8
125	10/10	158 ± 5	347 ± 6	+189 ± 5	97	14.2	12.9
250	10/10	140 ± 6	339 ± 5	+199 ± 4	94	14.4	13.0
500	10/10	129 ± 4	315 ± 2	+186 ± 2	88	15.4	14.0
1,000	10/10	140 ± 2	286 ± 8	+146 ± 7	80	14.1	12.4
2,000	10/10	135 ± 3	277 ± 4	+142 ± 5	77	12.7	12.1
FEMALE							
0	10/10	111 ± 2	201 ± 3	+90 ± 4	--	9.7	12.7
125	10/10	109 ± 3	189 ± 5	+80 ± 3	94	9.3	12.2
250	10/10	110 ± 2	184 ± 3	+74 ± 4	92	8.6	12.2
500	10/10	111 ± 1	184 ± 3	+73 ± 3	92	8.9	13.1
1,000	10/10	112 ± 3	180 ± 4	+68 ± 2	90	8.8	12.1
2,000	10/10	115 ± 2	167 ± 2	+52 ± 2	83	8.5	12.1

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

TABLE 10. PUPILLARY MEASUREMENTS OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE (a)

Concentration (ppm)	Male Left	Right	Combined	Female Left	Right	Combined
0	1.55 ± 0.31	1.36 ± 0.25	1.46 ± 0.29	1.06 ± 0.21	1.01 ± 0.15	1.04 ± 0.18
125	1.66 ± 0.34	1.25 ± 0.26	1.46 ± 0.36	1.41 ± 0.39	1.26 ± 0.38	(b) 1.34 ± 0.38
250	1.37 ± 0.61	1.21 ± 0.44	1.29 ± 0.53	1.13 ± 0.19	0.89 ± 0.12	1.01 ± 0.20
500	1.40 ± 0.37	1.12 ± 0.20	1.26 ± 0.33	0.94 ± 0.20	0.78 ± 0.16	0.86 ± 0.19
1,000	1.15 ± 0.30	0.97 ± 0.25	1.06 ± 0.29	1.12 ± 0.64	0.90 ± 0.19	1.01 ± 0.48
2,000	1.63 ± 1.20	1.35 ± 0.87	1.49 ± 1.03	0.95 ± 0.15	0.99 ± 0.68	0.97 ± 0.48

(a) Mean (millimeters) ± standard deviation for 10 animals
(b) $P<0.05$ vs the controls by Dunnett's test

TABLE 11. PACKED CELL VOLUME OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE (a)

Concentration (ppm)	Male	Female
0	47.1 ± 1.66	46.2 ± 2.15
2,000	(b) 49.7 ± 1.83	46.6 ± 1.84

(a) Mean (percent) ± standard deviation for 10 animals
(b) $P=0.004$ vs the controls by *t*-test

TABLE 12. ADRENAL GLAND AND HEART WEIGHTS OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE (a)

Conc. (ppm)	Final Body Weight (grams)	Adrenal Gland Weight (milligrams)	Adrenal Gland Weight/Body Weight ($\times 10^4$)	Heart Weight (grams)	Heart Weight/ Body Weight ($\times 10^3$)
MALE					
0	359.0 ± 16.1	39.9 ± 5.6	1.11 ± 0.16	0.828 ± 0.271	2.30 ± 0.76
2,000	276.7 ± 14.1	37.9 ± 6.5	(b) 1.37 ± 0.22	0.772 ± 0.069	2.79 ± 0.27
FEMALE					
0	201.0 ± 10.4	51.3 ± 8.9	2.55 ± 0.44	0.660 ± 0.199	3.27 ± 0.92
2,000	167.3 ± 5.9	(b) 37.1 ± 5.4	2.27 ± 0.41	(b) 0.451 ± 0.041	2.69 ± 0.21

(a) Mean ± standard deviation for 10 animals; the relative organ weights were calculated with the final rather than the necropsy body weight.
(b) $P<0.01$ vs the controls by *t*-test

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were 5%-9% lower than those of the controls after week 11 (Table 13 and Figure 1). Mean body weights of low dose male rats were 5%-7% lower than those of the controls after week 34. Mean body weights of high dose female rats were 5% lower than those of the controls by week 8, 10% lower by week 34, and 10%-20% lower for the remainder of the study. Mean body weights of low dose female rats were 6%-13% lower than those of the controls after week 18. The average daily feed consumption was 94% and 92% that of the controls for low dose and high dose males and 92% and 89% for females (Appendix N, Tables N1 and N2). The average amount of ephedrine sulfate consumed per day was estimated to be 4 mg/kg and 9 mg/kg for low dose and high dose male rats and 5 mg/kg and 11 mg/kg for low dose and high dose female rats.

TABLE 13. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

Weeks on Study	Control		125 ppm			250 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
1	212	50	210	99	50	208	98	50
2	236	50	235	100	50	233	99	50
3	261	50	257	98	50	255	98	50
4	281	50	274	98	50	272	97	50
5	299	50	292	98	50	290	97	50
6	310	50	301	97	50	300	97	50
7	324	50	315	97	50	313	97	50
8	336	50	325	97	50	323	96	50
9	344	50	332	97	50	330	96	50
10	351	50	338	96	50	336	96	50
11	365	50	352	96	50	350	96	50
12	373	50	357	96	50	355	95	50
13	379	50	363	96	50	360	95	50
18	400	50	379	95	50	376	94	50
21	416	50	395	95	50	390	94	50
27	428	50	409	96	50	399	93	50
29	442	50	421	95	50	411	93	50
34	450	49	424	94	50	415	92	50
39	457	49	431	94	50	423	93	50
43	460	48	432	94	50	420	91	50
47	467	48	438	94	50	427	91	50
51	472	48	445	94	50	430	91	50
56	472	48	444	94	50	432	92	50
60	479	48	450	94	50	441	92	50
65	475	48	447	94	50	438	92	50
68	480	47	453	94	49	443	92	50
73	471	46	444	94	49	437	93	50
76	462	46	438	95	49	428	93	50
81	462	42	431	93	48	421	91	50
85	450	39	429	95	46	421	94	49
89	450	37	436	97	43	427	95	48
94	441	37	416	94	41	408	93	48
98	437	35	410	94	34	407	93	44
102	425	31	398	94	27	400	94	39
FEMALE								
1	145	50	143	99	50	144	99	50
2	154	50	152	99	50	152	99	50
3	166	50	162	98	50	161	97	50
4	174	50	170	98	50	169	97	50
5	184	50	179	97	50	178	97	50
6	187	50	182	97	50	179	96	50
7	194	50	188	97	50	186	96	50
8	197	50	190	96	50	187	95	50
9	201	50	192	96	50	190	95	50
10	202	50	194	96	50	192	95	50
11	210	50	201	96	50	198	94	50
12	212	50	203	96	50	200	94	50
13	211	50	203	96	50	199	94	50
18	219	50	206	94	50	203	93	50
21	228	50	214	94	50	211	93	50
27	235	50	220	94	50	215	91	50
29	237	50	223	94	50	218	92	50
34	242	50	224	93	50	218	90	50
39	249	50	230	92	50	225	90	50
43	255	50	234	92	50	226	89	50
47	264	50	237	90	50	229	87	50
51	272	50	242	89	50	234	86	50
56	279	50	249	89	50	238	85	50
60	296	49	260	88	50	245	83	50
65	301	48	266	88	50	248	82	50
68	311	48	271	87	50	252	81	50
73	319	45	278	87	50	255	80	49
76	317	43	278	88	49	254	80	49
81	313	42	287	92	49	263	84	47
85	330	39	294	89	49	267	81	46
89	332	38	299	90	47	270	81	45
94	332	37	299	90	45	272	82	41
98	332	34	293	88	43	271	82	39
102	331	30	295	89	40	275	83	39

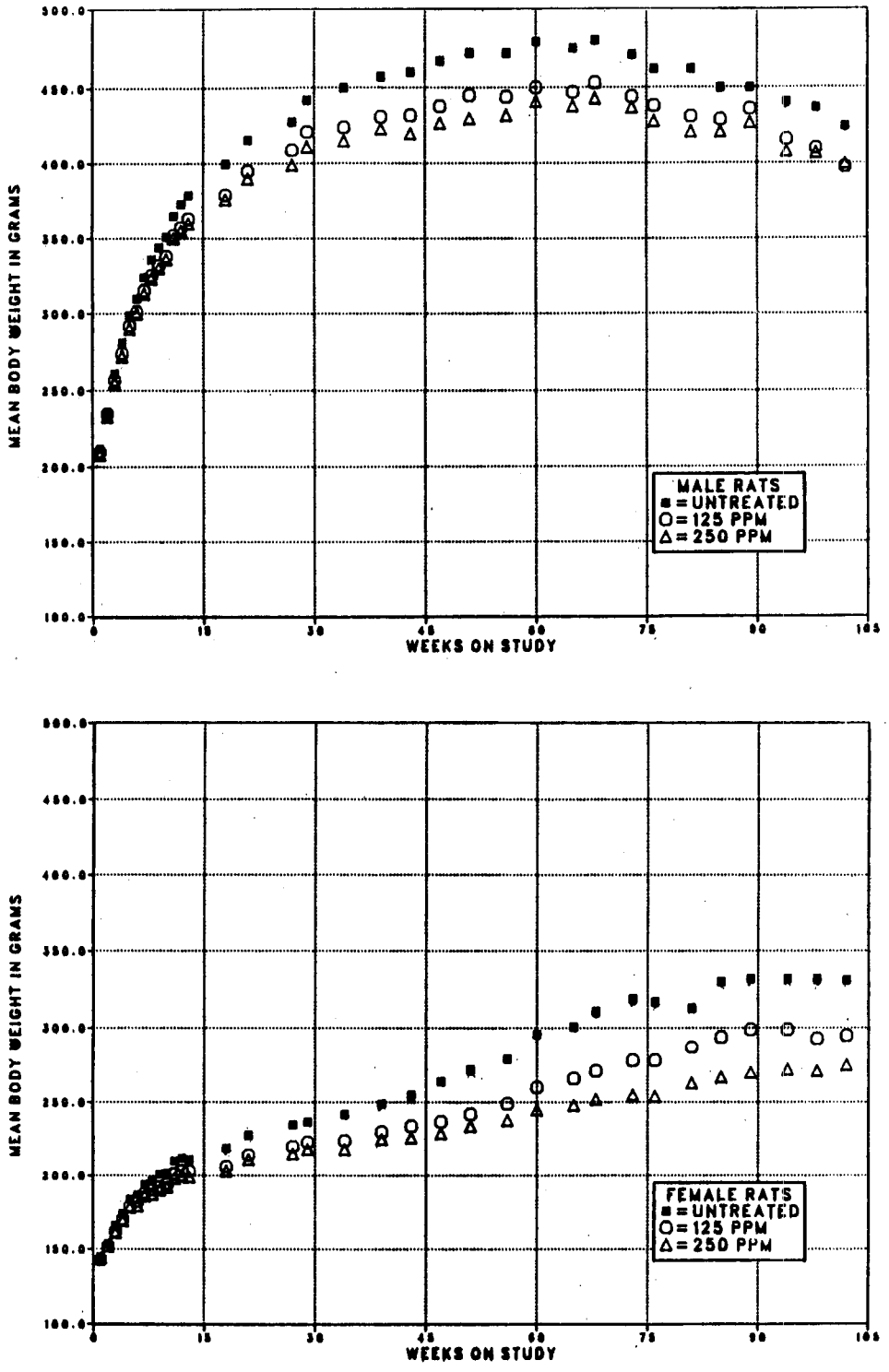


FIGURE 1. GROWTH CURVES FOR RATS FED DIETS CONTAINING EPHEDRINE SULFATE FOR TWO YEARS

Survival

Estimates of the probabilities of the survival for male and female rats fed diets containing ephedrine sulfate at the concentrations used in these studies and for the controls are shown in the Kaplan and Meier curves in Figure 2. The survival of the control group of female rats was significantly lower than that of the low dose group after week 97 and of the high dose group after week 102 (Table 14).

Pathology and Statistical Analyses of Results

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

TABLE 14. SURVIVAL OF RATS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

	Control	125 ppm	250 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	21	23	15
Killed at termination	29	27	35
Survival P values (c)	0.118	0.925	0.149
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	23	11	11
Killed at termination	27	39	39
Survival P values (c)	0.011	0.013	0.022

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

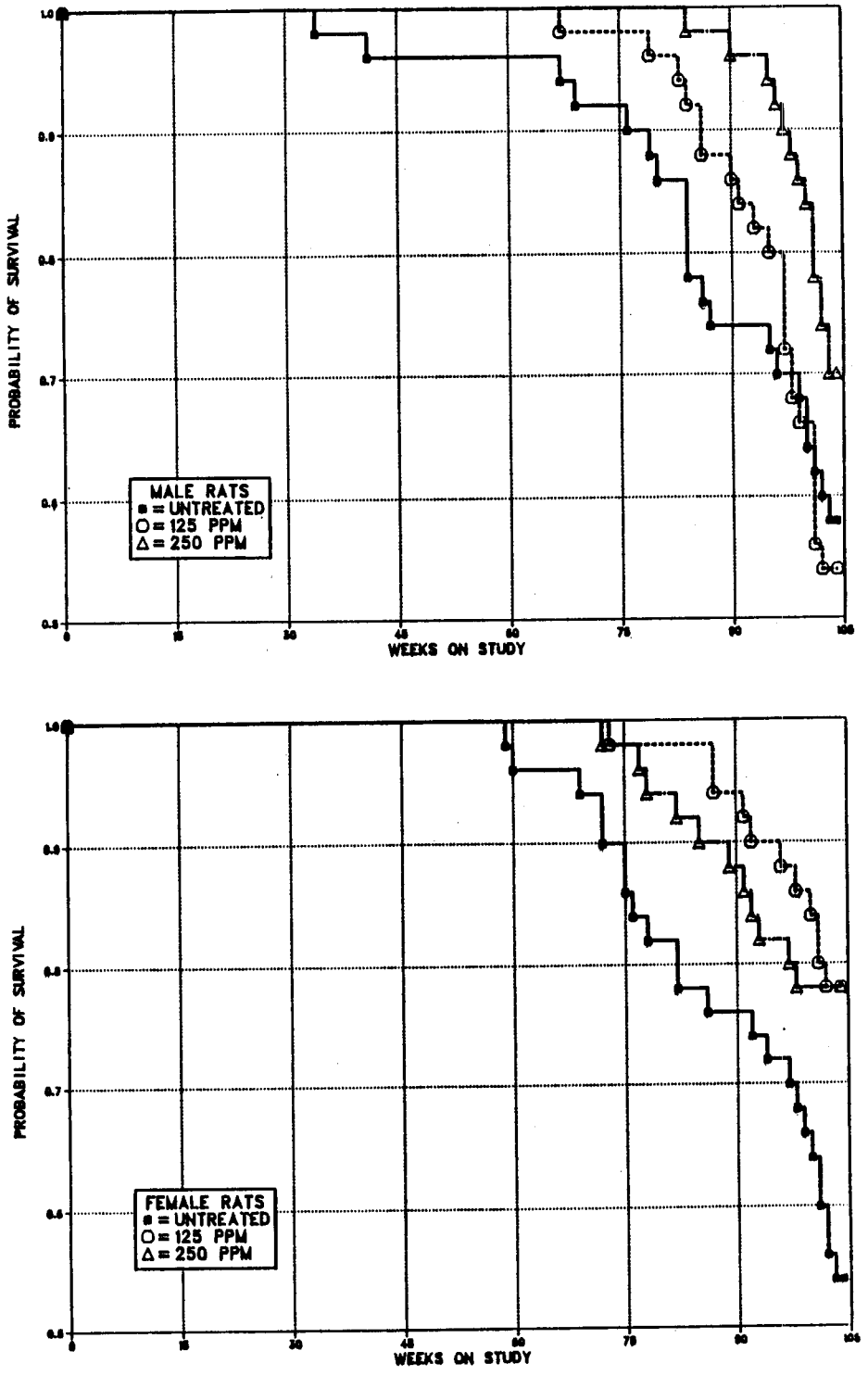


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS FED DIETS CONTAINING EPHEDRINE SULFATE FOR TWO YEARS

Pituitary Gland: Adenomas in male rats occurred with a positive trend, and the incidences in the low and high dose groups were significantly greater than that in the controls (Table 15). The incidence of hyperplasia or adenomas (combined) in dosed male rats was not significantly different from that of the controls. Since it is difficult to distinguish between adenoma and hyperplasia in the pituitary gland and the lesion is considered to be progressive, it is appropriate to combine them for the purpose of analyzing compound-related effects. The following incidences of adenomas were observed in female rats: control, 18/49 (37%); low dose, 24/50 (48%); high dose, 23/49 (47%).

Adrenal Gland: Angiectasis of the adrenal cortex was observed at an increased incidence in high dose male rats (male: control, 11/50, 22%; low dose, 13/50, 26%; high dose, 22/49, 45%; female: control, 33/49, 67%; low dose, 36/50, 72%; high dose, 35/49, 71%). The incidence of pheochromocytomas in low dose male rats was significantly greater than that in the controls by the life table test (P = 0.038; control, 10/50, 20%; low dose, 19/50, 38%; high dose, 11/49, 22%). The following incidences of pheochromocytomas were observed in female rats: control, 1/49 (2%); low dose, 4/50 (8%); high dose, 2/49 (4%).

Uterus: Endometrial gland cysts were observed at increased incidences in dosed female rats (control, 6/49, 12%; low dose, 13/50, 26%; high dose, 15/50, 30%). The incidence of endometrial stromal polyps in dosed groups was not significantly different from that in the controls.

TABLE 15. ANALYSIS OF PITUITARY GLAND LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (a)

	Control	125 ppm (b)	250 ppm (b)
Hyperplasia			
Overall Rates	14/49 (29%)	15/49 (31%)	12/48 (25%)
Adenoma			
Overall Rates	4/49 (8%)	13/49 (27%)	13/48 (27%)
Adjusted Rates	13.2%	34.5%	34.3%
Terminal Rates	3/29 (10%)	5/27 (19%)	9/33 (27%)
Week of First Observation	102	79	97
Life Table Tests	P=0.059	P=0.021	P=0.041
Incidental Tumor Tests	P=0.046	P=0.047	P=0.059
Adenoma or Hyperplasia			
Overall Rates	17/49 (35%)	26/49 (53%)	23/48 (48%)
Adjusted Rates	46.4%	63.5%	55.0%
Terminal Rates	10/29 (34%)	13/27 (48%)	15/33 (45%)
Week of First Observation	69	79	95
Life Table Tests	P=0.393	P=0.074	P=0.378
Incidental Tumor Tests	P=0.301	P=0.146	P=0.404
Carcinoma			
Overall Rates	1/49 (2%)	0/49 (0%)	1/48 (2%)
Adenoma or Carcinoma (c)			
Overall Rates	5/49 (10%)	13/49 (27%)	13/48 (27%)
Adjusted Rates	16.6%	34.5%	34.3%
Terminal Rates	4/29 (14%)	5/27 (19%)	9/33 (27%)
Week of First Observation	102	79	97
Life Table Tests	P=0.097	P=0.040	P=0.077
Incidental Tumor Tests	P=0.081	P=0.085	P=0.106

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) The estimated dose in milligrams per kilogram per day is given in Chapter III (Body Weights and Clinical Signs) and in Appendix N.
(c) Historical incidence in NTP studies (mean ± SD): 363/1,614 (22% ± 11%)

Small Intestine: A leiomyoma was observed in 1/46 high dose female rats, and a leiomyosarcoma was observed in another high dose female rat.

Mammary Gland: Fibroadenomas in female rats occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that in the controls (Table 16).

Testis: Testicular atrophy was initially observed at increased incidences in dosed male rats (control, 19/50, 38%; low dose, 34/50, 68%; high dose, 33/50, 66%). An independent blind review of all available sections of testis from male rats, conducted under the direction of the NTP Chemical Pathology Branch, resulted in the observation of the following incidences of testicular atrophy: control, 42/50 (84%); low dose, 44/50 (88%); high dose, 45/50 (90%). The presence of testicular atrophy was associated with the presence of testicular interstitial cell tumors which occurred with the following incidences: control, 45/50; low dose, 47/50; high dose, 46/50.

Circulatory System: Lymphangiectasis was observed at increased incidences in dosed female rats (control, 7/41, 17%; low dose, 19/43, 44%; 14/46, 30%).

TABLE 16. ANALYSIS OF MAMMARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	Control	125 ppm	250 ppm
Cystic Hyperplasia			
Overall Rates	32/49 (65%)	29/50 (58%)	18/50 (36%)
Fibroadenoma (a)			
Overall Rates	10/49 (20%)	7/50 (14%)	(b) 3/50 (6%)
Adjusted Rates	28.9%	17.3%	7.7%
Terminal Rates	5/27 (19%)	6/39 (15%)	3/39 (8%)
Week of First Observation	69	98	104
Life Table Tests	P=0.006N	P=0.118N	P=0.012N
Incidental Tumor Tests	P=0.030N	P=0.310N	P=0.044N

(a) Historical incidence in NTP studies (mean ± SD): 70/1,772 (27% ± 11%)
(b) An adenoma was also present in one of these animals.

SINGLE-ADMINISTRATION STUDIES

Single-administration range-finding studies were conducted to determine the toxicity of ephedrine sulfate administered orally to $B6C3F_1$ mice. All the mice that received 2,000 mg/kg and 4/5 males and 2/5 females that received 1,000 mg/kg were dead by day 2 (Table 17).

TABLE 17. SURVIVAL OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF EPHEDRINE SULFATE

Dose (mg/kg)	Survival (a)
MALE (b)	
125	5/5
250	5/5
500	5/5
1,000	(c) 1/5
2,000	(d) 0/5
FEMALE (e)	
125	5/5
250	5/5
500	5/5
1,000	(d) 3/5
2,000	(d) 0/5

(a) Number surviving/number initially in group
(b) LD_{50} value by Spearman-Karber method: 812 mg/kg with a 95% confidence interval of 619-1,066 mg/kg
(c) Day of death: 1,1,2,2
(d) Day of death: all 1
(e) LD_{50} value by Spearman-Karber method: 1,072 mg/kg with a 95% confidence interval of 768-1,495 mg/kg

Hyperkinesis that progessed to convulsive seizures, ataxia, and lethargy occurred in mice that died. Epistaxis was observed in mice that received 1,000 or 2,000 mg/kg. Mild portal-hepatic congestion, mild pulmonary congestion, and epistaxis were found in animals that died.

FOURTEEN-DAY STUDIES

Drinking Water Studies: None of mice died before the end of the studies (Table 18). Final mean body weights of mice that received 5,000 ppm were 12% lower than those of the controls for males and 5% lower for females. Mean water consumption was lower than that of the controls for all but the lowest dose group of males and for all dosed groups of females. Compound-related clinical signs observed in chemically exposed animals were hyperexcitability, arched backs, rough hair coats, and dehydration. Cachexia was observed at 5,000 ppm. No compound-related gross lesions were observed at necropsy. Mean packed cell volumes of males and females that received 5,000 ppm were 22% and 16% lower than those of the controls (Table 19).

Feed Studies: One male and one female that received 2,500 ppm died before the end of the studies (Table 20). Final mean body weights of mice that received 5,000 ppm were 11% lower than those of the controls for males and 10% lower for females. Feed consumption was not adversely affected by ephedrine sulfate. Hyperactivity, rough hair coats, dehydration, and arched backs were observed in both sexes at the three highest doses. No compound-related clinical signs were observed at 300 or 600 ppm. No compound-related effects were observed at necropsy. Mean packed cell volume was not notably affected by administration of ephedrine sulfate (Table 19).

TABLE 18. SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF MICE IN THE FOURTEEN-DAY DRINKING WATER STUDIES OF EPHEDRINE SULFATE

Conc. (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Mean Water Consumption (d) Week 1	Week 2
MALE							
0	5/5	19.0 ± 0.6	23.2 ± 0.4	+4.2 ± 0.3	--	4.8	4.0
312.5	5/5	19.4 ± 0.3	22.6 ± 0.7	+3.2 ± 1.0	97.4	5.7	6.3
625	5/5	19.9 ± 0.7	22.4 ± 0.4	+2.5 ± 0.7	96.6	3.0	3.3
1,250	5/5	20.0 ± 0.9	22.2 ± 0.4	+2.2 ± 0.8	95.7	2.5	2.6
2,500	5/5	19.9 ± 0.5	23.2 ± 0.4	+3.3 ± 0.2	100.0	2.1	2.1
5,000	5/5	18.6 ± 0.5	(e) 20.3 ± 0.6	+1.7 ± 0.6	87.5	1.3	1.6
FEMALE							
0	5/5	16.3 ± 0.7	19.6 ± 0.5	+3.3 ± 0.4	--	4.8	4.9
312.5	5/5	17.0 ± 0.6	19.6 ± 0.4	+2.6 ± 0.7	100.0	3.6	3.7
625	5/5	16.3 ± 0.4	18.6 ± 0.2	+2.3 ± 0.5	94.9	3.2	3.1
1,250	5/5	17.1 ± 0.9	19.0 ± 0.8	+1.9 ± 0.4	96.9	2.0	2.3
2,500	5/5	17.6 ± 0.8	19.0 ± 0.4	+1.4 ± 0.7	96.9	1.4	1.3
5,000	5/5	17.2 ± 0.4	18.6 ± 0.5	+1.4 ± 0.3	94.9	1.3	1.4

(a) Number surviving/number initially in the group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Milliliters of water consumed per animal per day
(e) Only four final body weights were recorded for this group. Final weight, weight change, and relative weight values are based on these four animals.

TABLE 19. PACKED CELL VOLUME OF MICE IN THE FOURTEEN-DAY STUDIES OF EPHEDRINE SULFATE (a)

Concentration (ppm)	Male	Female
Drinking Water		
0	50.8 ± 0.8	(b) 52.6 ± 2.0
312.5	(c) 50.0 ± 0.7	(d) 48.8 ± 0.8
625	49.4 ± 1.5	(d) 48.8 ± 0.8
1,250	50.2 ± 1.9	(d) 48.6 ± 1.1
2,500	46.6 ± 3.0	(d) 45.6 ± 0.9
5,000	(d,e) 39.8 ± 5.9	(d) 44.2 ± 1.3
Feed		
0	45.2 ± 3.0	47.0 ± 2.5
312.5	(f) 50.6 ± 1.8	46.6 ± 0.9
625	49.2 ± 0.5	48.0 ± 2.6
1,250	47.8 ± 1.3	46.4 ± 2.5
2,500	45.8 ± 5.1	44.3 ± 2.2
5,000	47.6 ± 4.0	45.0 ± 2.1

(a) Mean (percent) ± standard deviation for five animals except as noted
(b) One sample slightly hemolyzed
(c) Two samples hemolyzed
(d) $P<0.01$ vs the controls by Dunnett's test
(e) Four animals; one of the four was icteric.
(f) $P<0.05$ vs the controls by Dunnett's test

TABLE 20. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF EPHEDRINE SULFATE

Conc. (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption Week 2 (d)
MALE						
0	5/5	16.0 ± 0.4	25.2 ± 0.5	+9.2 ± 0.4	--	4.0
300	5/5	17.0 ± 0.9	22.4 ± 0.7	+5.4 ± 1.1	88.9	3.7
600	5/5	19.5 ± 2.0	24.0 ± 0.6	+4.5 ± 1.6	95.2	3.2
1,250	5/5	20.3 ± 1.7	23.2 ± 0.5	+2.9 ± 1.3	92.1	3.7
2,500	(e) 4/5	18.4 ± 1.4	26.5 ± 1.0	+8.0 ± 1.7	105.2	4.4
5,000	5/5	18.9 ± 1.9	22.4 ± 0.6	+3.5 ± 1.6	88.9	4.0
FEMALE						
0	5/5	14.8 ± 1.3	19.6 ± 0.2	+4.8 ± 1.3	--	2.7
300	5/5	14.4 ± 0.9	19.2 ± 0.4	+4.8 ± 1.1	98.0	3.2
600	5/5	16.7 ± 1.6	18.4 ± 0.5	+1.7 ± 1.6	93.9	3.0
1,250	5/5	15.1 ± 1.2	18.6 ± 0.5	+3.5 ± 1.2	94.9	3.4
2,500	(f) 4/5	14.2 ± 1.4	19.8 ± 0.3	+4.9 ± 1.5	101.0	3.9
5,000	5/5	14.2 ± 0.9	17.6 ± 0.4	+3.4 ± 1.0	89.8	3.0

(a) Number surviving/number in group
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Grams of feed consumed per animal per day
(e) Day of death: 3
(f) Day of death: 2

THIRTEEN-WEEK STUDIES

The deaths that occurred in male mice receiving 1,250, 2,500, or 5,000 ppm were the result of fighting. All female mice survived to the end of the studies (Table 21). Final mean body weights of males that received 1,250, 2,500, or 5,000 ppm were 14%, 17%, and 12% lower than those of the controls. Final mean body weights of chemically exposed female mice were more than 13% lower than that of the controls. Estimated feed consumption by dosed groups was greater than that of the controls.

Rough coats, hyperexcitability, and fighting among males were compound related. No compound-related histopathologic effects were observed. Mean pupil diameter was not affected by ephedrine sulfate (Table 22). The mean packed cell volume of male mice that received 5,000 ppm was 9% lower than that of the controls (Table 23). The relative heart weight and adrenal gland weight of mice receiving 5,000 ppm were comparable to those of the controls (Table 24).

Dose Selection Rationale: The high dose selected for the 2-year studies was 250 ppm ephedrine sulfate in feed and the low dose, 125 ppm. The reduced weight gain observed at 310 ppm in female mice and at 620 ppm and higher concentrations in both sexes was felt to be potentially life threatening over the duration of a 2-year study.

TABLE 21. SURVIVAL, MEAN BODY WEIGHTS, AND FEED CONSUMPTION OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE

Conc. (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Feed Consumption (d) Week 6	Week 12
MALE							
0	10/10	25.4 ± 0.6	35.1 ± 0.8	+9.7 ± 0.9	--	3.8	2.8
310	10/10	26.0 ± 0.3	33.4 ± 0.5	+7.4 ± 0.3	95.2	3.6	3.0
620	10/10	26.1 ± 0.8	31.8 ± 0.7	+5.7 ± 0.2	90.6	3.8	3.5
1,250	8/10	24.8 ± 0.5	30.3 ± 0.7	+5.6 ± 0.5	86.3	3.4	2.9
2,500	5/10	25.6 ± 0.6	29.2 ± 0.8	+3.6 ± 0.8	83.2	4.1	4.0
5,000	9/10	26.3 ± 0.4	30.8 ± 0.7	+4.6 ± 0.7	87.7	4.1	4.1
FEMALE							
0	10/10	20.2 ± 0.3	29.1 ± 0.8	+8.9 ± 0.7	--	3.2	2.8
310	10/10	19.0 ± 0.2	25.4 ± 0.3	+6.4 ± 0.2	87.3	3.2	2.8
620	10/10	18.8 ± 0.2	24.3 ± 0.3	+5.5 ± 0.2	83.5	3.2	3.0
1,250	10/10	19.1 ± 0.2	23.0 ± 0.7	+3.9 ± 0.7	79.0	3.2	3.3
2,500	10/10	20.3 ± 0.3	25.2 ± 0.5	+4.9 ± 0.2	86.6	3.7	4.0
5,000	10/10	20.6 ± 0.3	24.4 ± 0.4	+3.8 ± 0.2	83.8	3.7	4.4

(a) Number surviving/number in group. All deaths were the result of fighting.
(b) Initial mean group body weight ± standard error of the mean
(c) Mean body weight change of the survivors of the group ± standard error of the mean
(d) Estimated grams of feed consumed per animal per day

TABLE 22. PUPILLARY MEASUREMENTS OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE (a)

Concentration (ppm)	Male Left	Right	Combined	Female Left	Right	Combined
0	1.26 ± 0.45	1.10 ± 0.17	1.18 ± 0.34	1.39 ± 0.79	(b) 1.17 ± 0.17	1.28 ± 0.58
310	1.19 ± 0.16	(b) 1.18 ± 0.18	1.18 ± 0.16	1.55 ± 0.76	(b) 1.90 ± 1.21	1.72 ± 0.99
620	(b) 1.13 ± 0.11	1.15 ± 0.14	1.14 ± 0.13	1.53 ± 0.69	1.42 ± 0.61	1.48 ± 0.63
(c) 1,250	1.15 ± 0.19	1.13 ± 0.18	1.14 ± 0.18	(b) 1.14 ± 0.20	1.26 ± 0.28	1.21 ± 0.25
(d) 2,500	1.34 ± 0.39	1.24 ± 0.22	1.29 ± 0.30	1.27 ± 0.37	1.58 ± 1.04	1.43 ± 0.78
(e) 5,000	1.13 ± 0.18	1.21 ± 0.33	1.17 ± 0.26	1.13 ± 0.16	1.37 ± 0.86	1.25 ± 0.62

(a) Mean (millimeters) ± standard deviation for 10 animals except as noted
(b) Nine animals
(c) Eight male animals
(d) Five male animals
(e) Nine male animals

TABLE 23. PACKED CELL VOLUME OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE (a)

Concentration (ppm)	Male	Female
0	39.8 ± 3.74	40.7 ± 3.09
5,000	(b) 36.2 ± 3.19	41.7 ± 1.25

(a) Mean (percent) ± standard deviation for 10 animals except as noted
(b) Nine animals. P=0.038 vs the controls by *t*-test.

TABLE 24. ADRENAL GLAND AND HEART WEIGHTS OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF EPHEDRINE SULFATE (a)

Concentration (ppm)	Final Body Weight (grams)	Adrenal Gland Weight (milligrams)	Adrenal Gland Weight/Body Weight ($\times 10^4$)	Heart Weight (grams)	Heart Weight/ Body Weight ($\times 10^3$)
MALE					
0	35.1 ± 2.65	6.30 ± 1.66	1.79 ± 0.47	0.151 ± 0.013	4.32 ± 0.40
(b) 5,000	(c) 30.8 ± 2.19	5.42 ± 1.95	1.76 ± 0.62	(c) 0.130 ± 0.014	4.22 ± 0.46
FEMALE					
0	29.1 ± 2.56	7.78 ± 2.22	2.66 ± 0.66	0.120 ± 0.010	4.14 ± 0.36
5,000	(c) 24.4 ± 1.20	(d) 5.87 ± 1.82	2.40 ± 0.72	(c) 0.102 ± 0.130	4.16 ± 0.45

(a) Mean ± standard deviation for 10 animals except as noted; the relative organ weights were calculated with the final rather than the necropsy body weight.
(b) Nine animals
(c) $P<0.01$ vs the controls by *t*-test
(d) $P<0.05$ vs the controls by *t*-test

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were 9%-18% lower than those of the controls after week 9, and those of low dose male mice were 5%-9% lower than those of the controls after week 10 (Table 25 and Figure 3). Mean body weights of high dose female mice were 10%-23% lower than those of the controls after week 11, and those of low dose female mice were 13%-16% lower than those of the controls after week 22.

The average daily feed consumption by both dosed male mouse groups was 100% that of the controls and by low dose and high dose female mice, 97% and 94% that of the controls (Appendix N, Tables N3 and N4). The average amount of ephedrine sulfate consumed per day was estimated to be 14 mg/kg and 29 mg/kg for low dose and high dose male mice and 12 mg/kg and 25 mg/kg for low dose and high dose female mice.

TABLE 25. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

Weeks on Study	Control		125 ppm			250 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
1	25.5	50	25.1	98	49	24.6	96	50
2	25.6	50	24.5	96	49	24.7	96	50
3	26.0	50	26.1	100	48	25.2	97	50
4	26.8	50	27.0	101	47	25.4	95	50
5	27.5	50	27.2	99	47	26.2	95	50
6	27.9	50	27.6	99	47	26.5	95	50
7	28.7	50	27.9	97	47	27.0	94	50
8	29.3	50	28.5	97	47	27.2	93	50
9	30.2	50	29.0	96	47	27.5	91	50
10	31.0	50	28.9	93	47	28.1	91	50
11	31.1	50	29.5	95	47	28.6	92	50
12	31.9	50	29.9	94	47	28.8	90	50
13	32.9	50	30.1	91	47	29.4	89	50
17	34.5	50	31.8	92	47	29.9	87	50
19	34.5	50	31.8	92	47	29.9	87	50
22	37.2	50	33.9	91	47	32.0	86	50
28	37.9	50	35.7	94	47	33.5	88	50
30	39.6	50	36.7	93	47	34.4	87	50
35	42.1	50	39.6	94	47	37.0	88	50
40	41.1	50	38.8	94	47	35.5	86	50
44	40.9	50	38.7	95	47	35.4	87	50
48	41.9	50	39.6	95	47	36.3	87	49
52	40.7	49	38.5	95	47	35.1	86	49
57	42.8	49	40.9	96	47	36.9	86	48
61	41.8	49	39.9	95	46	36.3	87	48
66	43.0	49	40.2	93	46	37.0	86	48
70	41.5	49	39.9	96	46	36.6	88	48
74	42.4	48	39.5	93	46	36.2	85	48
77	41.3	48	38.4	93	46	35.5	86	48
81	41.5	46	38.1	92	45	34.8	84	47
86	39.4	45	38.2	97	44	34.2	87	46
90	41.8	44	38.2	91	44	34.2	82	43
95	40.4	44	36.7	91	43	33.5	83	43
99	39.5	43	36.3	92	42	33.4	85	41
103	39.2	41	35.5	91	42	33.2	85	39
FEMALE								
1	20.3	50	20.5	101	50	20.2	100	50
2	20.4	50	20.4	100	50	20.0	98	50
3	21.6	50	21.7	100	50	21.7	100	50
4	21.8	50	21.4	98	50	21.6	99	50
5	22.8	50	22.5	99	50	22.6	99	50
6	23.6	50	22.8	97	50	22.7	96	50
7	24.0	50	23.0	96	50	23.1	96	50
8	24.7	50	23.5	95	50	23.5	95	50
9	25.4	50	24.2	95	50	24.0	94	50
10	26.3	50	24.8	94	50	24.5	93	50
11	26.8	50	24.7	92	50	24.4	91	50
12	27.6	50	25.6	93	50	24.9	90	50
13	28.1	50	25.7	91	50	25.3	90	50
17	29.0	50	26.5	91	50	25.8	89	50
19	29.0	50	26.5	91	50	25.8	89	50
22	32.7	49	29.2	89	50	28.1	86	50
28	36.3	48	31.9	88	49	29.9	82	50
30	36.1	48	31.3	87	49	30.6	85	50
35	40.4	48	35.3	87	49	32.9	81	50
40	40.6	48	35.0	86	49	32.8	81	50
44	40.2	48	35.1	87	49	32.7	81	50
48	41.3	48	36.5	88	48	34.1	83	50
52	41.7	48	36.9	88	48	34.2	82	50
57	43.8	48	38.0	87	48	35.1	80	49
61	43.4	48	37.7	87	48	35.3	81	49
66	44.1	48	38.5	87	48	36.1	82	49
70	44.8	48	38.8	87	48	36.0	80	49
74	44.3	48	38.3	86	47	35.1	79	48
77	41.6	48	36.7	88	47	33.9	81	48
81	42.2	48	36.8	87	45	33.9	80	47
86	42.4	48	36.3	86	44	33.3	79	46
90	43.6	47	37.0	85	42	33.6	77	45
95	43.2	44	36.7	85	41	33.1	77	42
99	42.5	41	36.4	86	39	32.9	77	38
103	42.4	40	35.7	84	35	32.8	77	36

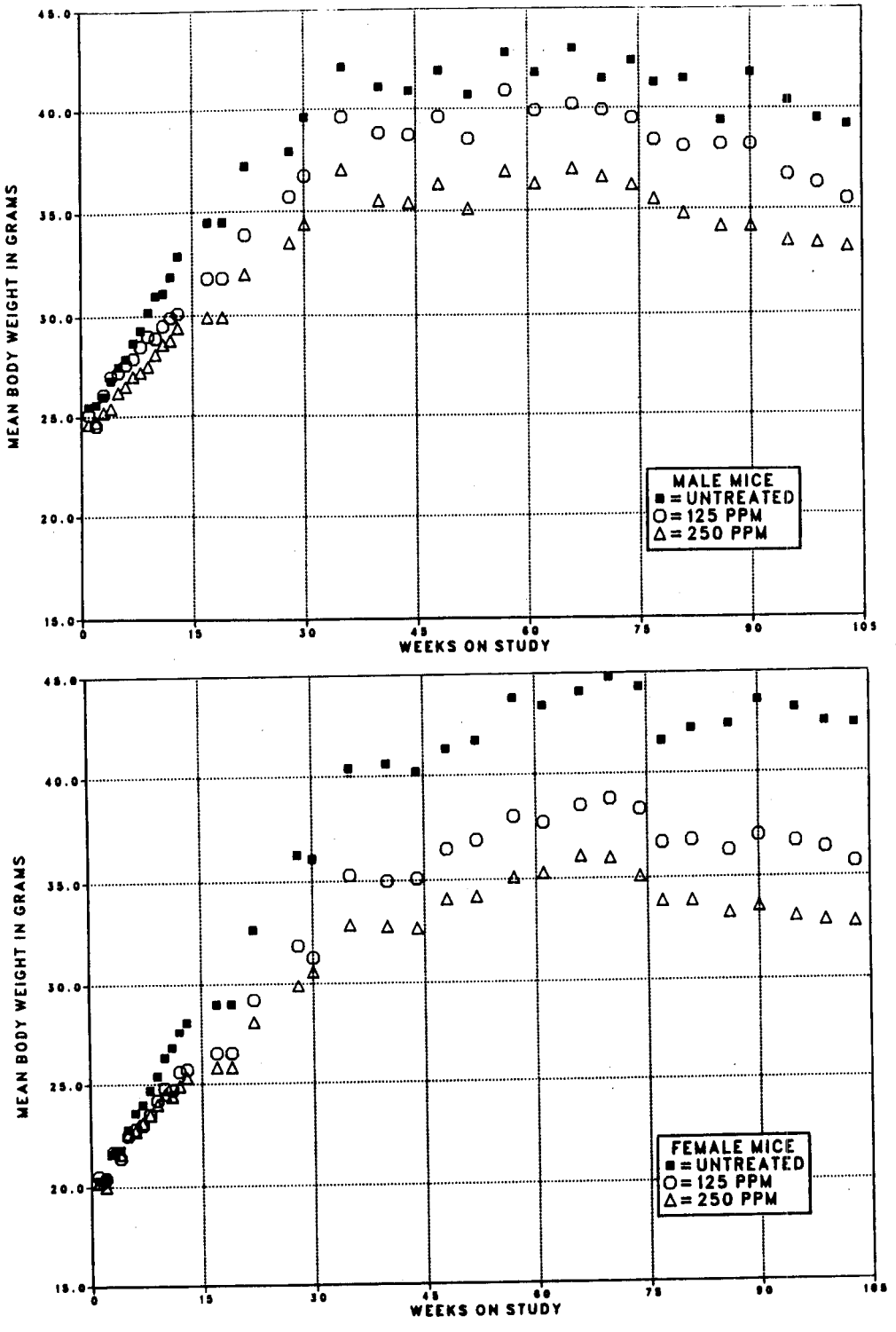


FIGURE 3. GROWTH CURVES FOR MICE FED DIETS CONTAINING EPHEDRINE SULFATE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing ephedrine sulfate at the concentrations used in these studies and for the controls are shown in the Kaplan and Meier curves in Figure 4. There were no significant differences in survival between any groups of either sex (Table 26).

Pathology and Statistical Analyses of Results

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

TABLE 26. SURVIVAL OF MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

	Control	125 ppm	250 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	10	8	11
Accidentally killed	0	1	1
Killed at termination	40	41	38
Survival P values (c)	0.885	0.853	0.974
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	10	15	14
Killed at termination	40	35	36
Survival P values (c)	0.433	0.349	0.476

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

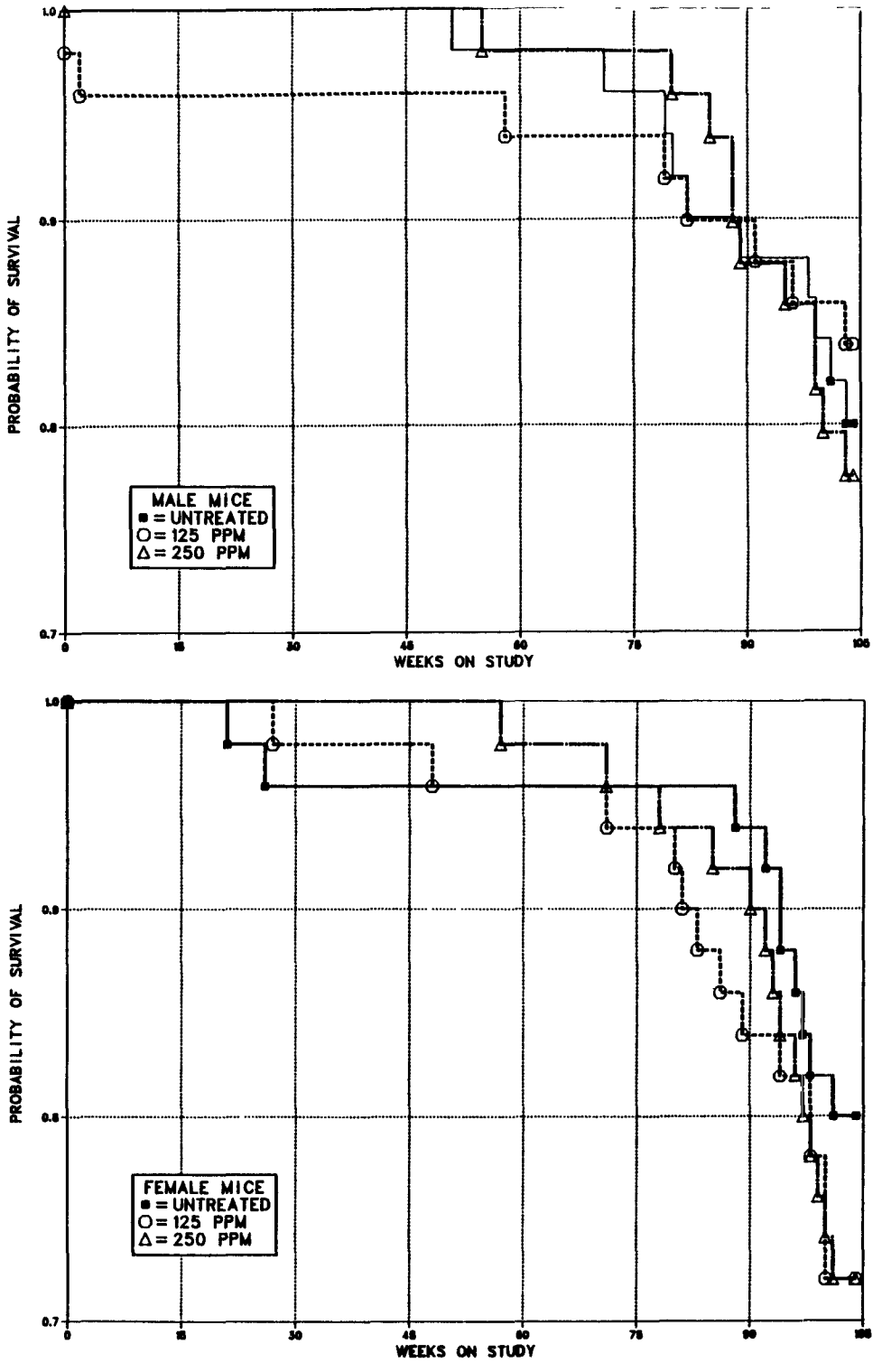


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE FED DIETS CONTAINING EPHEDRINE SULFATE FOR TWO YEARS

Ovary: Granulosa cell tumors were found in 2/43 high dose female mice. In one animal, the neoplasm was small and contained numerous mitotic figures. Cells within this mass were not arranged in any particular pattern or structure. In the other animal, the neoplasm was significantly larger and exhibited distinct patterns of cellular organization. In some areas of the tumor, neoplastic cells were clumped into angular islands edged by rows of nuclei and separated by a thin, fibrous stroma. In other areas, adenoid structures resembling follicles were present, and some of these structures contained fluid-filled spaces. Cells lining these structures were perpendicularly arranged with indistinct cytoplasmic boundaries.

Luteomas were found in 1/42 low dose and 1/43 high dose female mice. These tumors were composed of a uniform population of large polyhedral cells with eosinophilic vacuolated cytoplasm, round to ovoid vesicular nuclei, and prominent nucleoli. Lipid-laden stromal cells were also present.

Teratomas were observed in 1/41 control and 1/42 low dose female mice. The tumor in the control animal was composed of glands lined by ciliated columnar epithelial cells. Multiple layers containing solid squamous epithelial nests were present throughout the mass. Areas of cartilage and neovasculature were also present. This tumor had undergone extensive necrosis. The tumor in the low dose animal contained multiple cysts lined by stratified squamous epithelium, which commonly showed cornification.

Areas with cartilage, blood vessels, fat, and gland formation lined by cuboidal epithelium cells were also present. This mass had also undergone extensive necrosis.

Adrenal Gland: Cortical adenomas in male mice occurred with a negative trend, and the incidence in the high dose group was significantly lower than that in the controls (Table 27). One low dose and one high dose male mouse had adenomas that appeared to arise from the subscapular cells. Stromal hyperplasia of the subscapular cells occurred at the following incidences: control, 34/50 (68%); low dose, 33/50 (66%); high dose, 35/48 (73%). The incidences of adenomas or cortical adenomas (combined) in female mice were as follows: control, 1/48 (2%); low dose, 0/49; high dose, 2/49 (4%).

Thyroid Gland: Hyperplasia of the thyroid follicle was observed at increased incidence in dosed female mice (control, 6/48, 13%; low dose, 13/49, 27%; high dose, 14/49, 29%). The following incidences of follicular cell adenomas were observed in female mice: control, 2/48; low dose, 1/49; high dose, 0/49.

TABLE 27. ANALYSIS OF ADRENAL GLAND LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (a)

	Control	125 ppm	250 ppm
Cortical Hyperplasia			
Overall Rates	6/50 (12%)	5/50 (10%)	2/48 (4%)
Cortical Hypertrophy			
Overall Rates	3/50 (6%)	0/50 (0%)	2/48 (4%)
Cortical Adenoma			
Overall Rates	7/50 (14%)	3/50 (6%)	1/48 (2%)
Adjusted Rates	16.8%	7.3%	2.7%
Terminal Rates	6/40 (15%)	3/41 (7%)	1/37 (3%)
Week of First Observation	79	104	104
Life Table Tests	P=0.021N	P=0.153N	P=0.042N
Incidental Tumor Tests	P=0.020N	P=0.162N	P=0.038N
Adenoma or Cortical Adenoma (b)			
Overall Rates	7/50 (14%)	4/50 (8%)	2/48 (4%)
Adjusted Rates	16.8%	9.8%	5.4%
Terminal Rates	6/40 (15%)	4/41 (10%)	2/37 (5%)
Week of First Observation	79	104	104
Life Table Tests	P=0.066N	P=0.252N	P=0.100N
Incidental Tumor Tests	P=0.063N	P=0.264N	P=0.093N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence in NTP studies (mean ± SD): 43/1,716 (3% ± 3%)

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Fourteen-day and 13-week toxicity studies of ephedrine sulfate provided a basis for the selection of doses for the 2-year studies and for determining the most appropriate route of administration. During the 14-day studies, comparable toxicity occurred at similar concentrations of ephedrine sulfate administered in feed or in drinking water. During the 14-day feed studies, there was no difference in feed consumption between animals receiving control diets and those receiving diets containing ephedrine sulfate. However, during the 14-day drinking water studies, mean water consumption by animals receiving ephedrine sulfate at 6,000 ppm or above was significantly reduced. Since reduced water consumption would limit the amount of chemical ingested and could lead to dehydration, administration of ephedrine sulfate in drinking water was not considered suitable for long-term studies. Therefore dietary administration was selected for the 13-week and 2-year studies.

No deaths attributable to compound-related toxicity occurred during the 14-day or 13-week studies. Hyperactivity and excitability were the most frequent clinical observations and were observed with the greatest incidence in animals receiving ephedrine sulfate at concentrations of 1,000 ppm or higher. Compound-related reduced weight gain was observed in each sex of both species during the 14-day and 13-week studies. Feed consumption by dosed and control animals was comparable in both the 14-day and 13-week studies, suggesting that the reduced weight gain that occurred in chemically exposed animals was associated with ingestion of ephedrine sulfate.

Weight loss associated with administration of ephedrine or its hydrochloride or sulfate salts has been observed in other strains of rats and mice (Massoudi and Miller, 1977). In some animals, the weight loss was accompanied by reduced feed consumption; however, studies with diet-restricted controls have demonstrated that reduced feed consumption alone cannot account for all of the weight loss (Yen et al., 1981). Reduced carcass fat, increased oxygen consumption (Massoudi and Miller, 1977), and elevated rectal temperature (Yen et al., 1981) were consistently observed in animals receiving ephedrine compared with untreated controls that consumed the same quantity of feed.

The weight loss that occurred during the 13-week studies of ephedrine sulfate at concentrations of 500 ppm or higher was considered to be potentially life threatening over the course of a 2-year study. For this reason, the doses selected for the 2-year studies were 125 and 250 ppm ephedrine sulfate in feed.

Throughout most of the 2-year studies, mean body weights of each sex of both species were lower than those of controls (see Figures 1 and 3). This result is consistent with the results of the 13-week studies and indicates that the ingestion of ephedrine sulfate was associated with reduced weight gain over the entire period of the 2-year studies. Survival of chemically exposed female rats was greater than survival of controls (control, 27/50; low dose, 39/50; high dose, 39/50); survival of chemically exposed male rats and chemically exposed mice was comparable to survival of controls. Therefore, the concentrations of ephedrine sulfate used in this study produced a mild weight gain depression without affecting survival.

The incidence of pituitary gland adenomas in male rats occurred with a positive trend, and the incidences in the low and high dose groups were greater than that of the controls (see Table 15). Since adenoma and hyperplasia in the pituitary gland represent different stages of progression of the same lesion and the histologic distinction between adenoma and hyperplasia is somewhat arbitrary, it is appropriate to combine these lesions when compound-related effects are analyzed. The incidences of hyperplasia or adenomas (combined) in dosed and control male rats did not differ significantly. The overall control rate of 10% in this study is somewhat low relative to the historical control rate for pituitary gland adenomas in male rats (20%, range--5%-52%; Appendix F, Table F1).

The incidence of adrenal gland pheochromocytomas in low dose male rats was significantly greater than the incidence in controls by the life table test but not by the incidental tumor test. The incidence in high dose males was similar to the control incidence and comparable to the mean historical control incidence of 20% (Table F2). Nonmalignant pheochromocytoma is generally not a lethal tumor in rats and in the

present study was not associated with any early deaths. Because this increased incidence was observed only in low dose male rats and because this marginal increase was not significant by the more appropriate incidental tumor test, it was not considered to be compound related.

The incidence of mammary gland fibroadenomas in female rats occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that in controls. In previous feed studies conducted by the National Toxicology Program, a decreased incidence of mammary gland fibroadenomas in chemically exposed female rats has been found to be associated with reduced weight gain (Haseman, 1983). This association is also seen in the present study, in which a decreased incidence of mammary gland fibroadenomas parallels a reduction in weight gain in both groups of chemically exposed female rats.

The incidences of endometrial gland cysts were greater in chemically exposed female rats than in control animals, but the incidence of endometrial stromal polyps was not significantly different from the control incidence.

Follicular cell hyperplasia of the thyroid gland occurred at increased incidences in chemically exposed female mice (control, 6/48; low dose, 13/49; high dose, 14/49); however, the incidence of follicular cell adenomas was marginally lower in chemically exposed animals than in control animals (control, 2/48; low dose, 1/49; high dose, 0/49). Hyperplasia and adenoma of the thyroid gland follicle are generally considered to be different stages of progression of the same lesion, and the lack of correlation between the increase in the incidence of hyperplasia and the incidence of adenomas indicates that these lesions are probably not compound related in the present study.

Granulosa cell tumors were found in two high dose female mice, and a luteoma was found in one low dose and one high dose female mouse. Although ovarian tumors are rare in female $B6C3F_1$ mice (mean historical control rate, 0.4%), the low incidence of these tumors in the present study, the marked histologic differences among individual tumors, and their benign status make it unlikely that their presence is associated with exposure to ephedrine sulfate.

Conclusion: Under the conditions of these studies, there was *no evidence of carcinogenicity** for F344/N rats or $B6C3F_1$ mice of either sex receiving 125 or 250 ppm ephedrine sulfate in the diet for 2 years.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

V. REFERENCES

V. REFERENCES

1. Aarons, R.; Nies, A.; Gerber, J.; Molinoff, P. (1983) Decreased *beta*-adrenergic receptor density on human lymphocytes after chronic treatment with agonists. J. Pharm. Exp. Res. 244:1-6.

2. Aldrich Chemical Company, Inc. (1974) The Aldrich Library of NMR Spectra, Vol. 5, p. 160.

3. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons, Inc., pp. 362-365.

4. Berenblum, I., Ed. (1969) Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2. Geneva: International Union Against Cancer.

5. Boorman, G.; Montgomery, C., Jr.; Hardisty, J.; Eustis, S.; Wolfe, M.; McConnell, E. (1985) Quality assurance in pathology for rodent toxicology and carcinogenicity tests. Milman, H.; Weisburger, E., Eds.: Handbook of Carcinogen Testing. Park Ridge, NJ: Noyes Publications, pp. 345-357.

6. Bukowiecki, L.; Jahjah, L.; Follea, N. (1982) Ephedrine, a potential slimming drug, directly stimulates thermogenesis in brown adipocytes via β-adrenoreceptors. Int. J. Obesity 6:343-350.

7. Chen, K.; Schmidt, C. (1924) The action of ephedrine, an alkaloid from Ma Huang. Proc. Soc. Exp. Biol. Med. 21:351.

8. Cohn, J. (1965) Comparative cardiovascular effects of tyramine, ephedrine, and norephedrine in man. Circ. Res. 16:174-182.

9. Cox, D. (1972) Regression models and life tables. J. R. Stat. Soc. B34:187-220.

10. Fairchild, M.; Aalles, G. (1967) The central locomotor stimulatory activity and acute toxicity of the ephedrine and norephedrine isomers in mice. J. Pharm. Exp. Therap. 158:135-139.

11. Feller, D.; Malspeis, L. (1977) Biotransformation of D(−)-ephedrine and L(+)-ephedrine in the rabbit, in vivo and in vitro. Drug Metab. Dispos. 5:37-46.

12. Feller, D.; Basu, P.; Mellon, W.; Curott, J.; Malspeis, L. (1973) Metabolism of ephedrine isomers in rabbit liver. Arch. Int. Pharmacodyn. Ther. 203:187.

13. Franciosa, J.; Cohn, J. (1979) Hemodynamic effects of oral ephedrine given alone or combined with nitroprusside infusion in patients with severe left ventricular failure. Am. J. Cardiol. 43:79-85.

14. Galloway, S.; Bloom, A.; Resnick, M.; Margolin, B.; Nakamura, F.; Archer, P.; Zeiger, E. (1985) Development of a standard protocol for in vitro cytogenetic testing with Chinese hamster ovary cells: Comparison of results for 22 compounds in two laboratories. Environ. Mutagen. 7:1-51.

15. Gart, J.; Chu, K.; Tarone, R. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62(4):957-974.

16. Harvey, S. (1980) Sympathomimetic drugs. Osal, A.; Chase, G.; Gennaro, A.; Gibson, M.; Granberg, C.; Harvey, S.; King, R.; Martin, A.; Swinyard, E.; Zink, G., Eds.: Remington's Pharmaceutical Sciences. Easton, PA: Mach Publishing Co.

17. Haseman, J. (1983) Patterns of tumor incidence in 2-year cancer bioassay feeding studies in Fischer 344 rats. Fundam. Appl. Toxicol. 3:1-9.

18. Haseman, J. (1984) Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environ. Health Perspect. 58:385-392.

19. Haseman, J.; Huff, J.; Boorman, G. (1984) Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol. 12:126-135.

20. Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W.; Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. (Suppl. 1) 5:3-142.

21. Kaplan, E.; Meier, P. (1958) Nonparametric estimation of incomplete observations. J. Am. Stat. Assoc. 53:457-481.

22. Kaul, C.; Grewal, R. (1971) Release of catecholamine from the cat heart by some directly and indirectly acting sympathomimetic amines. Biochem. Pharmacol. 20:1787-1795.

23. Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J. (1974) Carcinogenesis bioassay data system. Comp. Biomed. Res. 7:230-248.

24. Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

25. Maronpot, R.; Boorman, G. (1982) Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. Toxicol. Pathol. 10:71-80.

26. Marvola, M.; Kivirinta R. (1978) Pharmacokinetics and locomotor activity increasing effect of ephedrine in mice. Acta Pharmacol. Toxicol. 43:381-386.

27. Massoudi, M.; Miller, D. (1977) Proc. Nutr. Soc. 36:135A.

28. McConnell, E.; Solleveld, H.; Swenberg, J.; Boorman, G. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. (in press).

29. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Carcinogenesis Technical Report Series No. 1. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health.

30. National Institute for Occupational Safety and Health (NIOSH) (1980) Registry of Toxic Effects.

31. National Institutes of Health (NIH) (1978) NIH Specification, NIH-11-133f, November 1.

32. PDR for Non-Prescription Drugs (1983) 4th ed. Oradell, NJ: Medical Economics Co.

33. Peterson, D.; Hardinge, M. (1967) The effect of various environmental factors on cocaine and ephedrine toxicity. J. Pharm. Pharmacol. 19:810-814.

34. Sammul, O.; et al. (1964) Infrared spectra of some compounds of pharmaceutical interest. J. Assoc. Off. Anal. Chem. 47(5):948.

35. Schneider, J.; Worzok, R.; Schwary, N. (1977) Endogene Bildung kanzerogener N-Nitrosoverbindungen nach Gabe von Pharmaka und Nitrit an Ratten. Exp. Pathol. 13:32-43.

36. Schumann, H.; Philippu, A. (1962) Release of catechol amines from isolated medullary granules by sympathomimetic amines. Nature 193:890- 891.

37. Sever, P.; Dring, L.; Williams, R. (1975) The metabolism of (−)-ephedrine in man. Eur. J. Clin. Pharmacol. 9:193-198.

38. Tarone, R. (1975) Tests for trend in life table analysis. Biometrika 62:679-682.

39. Trendelenburg, U.; Muskus, A.; Fleming, W.; de la Sierra, B. (1962) Modification by reserpine of the action of sympathomimetic amines in spinal cats; a classification of sympathomimetic amines. J. Pharmacol. 138:170-180.

40. United States Pharmacopeia (1975) XIX, pp. 167-168.

41. U.S. International Trade Commission (USITC) (1984) Synthetic Organic Chemicals, United States Production and Sales 1983. USITC Publication No. 1588, Washington, DC: Government Printing Office.

42. Weiner, N. (1980) Norephedrine, ephedrine, and the sympathomimetic amines. Gilman, A.G.; Goodman, L.; Gilman A., Eds.: The Pharmacological Basis of Therapeutics, 6th ed. New York: MacMillan.

43. Welling, P.; Lee, K.; Patel, J.; Walker, J.; Wagner, J. (1971) Urinary excretion of ephedrine in man without pH control following oral administration of three commercial ephedrine sulfate preparations. J. Pharm. Sci. 60:1629-1634.

V. REFERENCES

44. Wilkinson, G.; Beckett, A. (1968a) Absorption, metabolism and excretion of the ephedrines in man. I. The influence of urinary pH and urine volume output. J. Pharmacol. Exp. Ther. 162:139-147.

45. Wilkinson, G.; Beckett, A. (1968b) Absorption, metabolism and excretion of the ephedrines in man. II. Pharmacokinetics. J. Pharm. Sci. 57:1933-1938.

46. Williams, R.; Caldwell, J.; Dring, L. (1974) Comparative metabolism of some amphetamines in various species. Usdin, E.; Snyder, S., Eds.: Frontiers in Catecholamine Research. New York: Pergamon Press, pp. 765-770.

47. Wilson, A.; McPhillips, J. (1978) Pharmacological control of asthma. Ann. Rev. Pharmacol. Toxicol. 18:541-561.

48. Wogan, G.; Paglialunga, S.; Archer, M.; Tannenbaum, S. (1975) Carcinogenicity of nitrosation products of ephedrine, sarcosine, folic acid, and creatinine. Cancer Res. 35:1981-1984.

49. Yen, T.; McKee, M.; Bemis, K. (1981) Ephedrine reduces weight of viable yellow obese mice. Life Sci. 28:119-128.

50. Zsoter, T. (1982) Clinical pharmacology of bronchodilators: A review. J. Med. 13:138-144.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	1 (2%)		
Basal cell tumor	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	4 (8%)	1 (2%)	1 (2%)
Fibrosarcoma	1 (2%)		
Lipoma		1 (2%)	
Neurofibrosarcoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma			1 (2%)
C-cell carcinoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undiffer type			1 (2%)
Eosinophilic leukemia		1 (2%)	
Leukemia, mononuclear cell	25 (50%)	29 (58%)	30 (60%)
#Spleen	(50)	(50)	(50)
Fibroma			1 (2%)
Leukemia, mononuclear cell		2 (4%)	2 (4%)
#Thymus	(42)	(37)	(36)
Thymoma, benign	1 (2%)		
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Neoplastic nodule	1 (2%)	5 (10%)	5 (10%)
Hepatocellular carcinoma	2 (4%)	1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Lipoma	1 (2%)		
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(49)	(48)
Adenoma, NOS	1 (2%)		1 (2%)
#Anterior pituitary	(49)	(49)	(48)
Carcinoma, NOS	1 (2%)		1 (2%)
Adenoma, NOS	4 (8%)	13 (27%)	13 (27%)
#Adrenal	(50)	(50)	(49)
Cortical adenoma		1 (2%)	
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	10 (20%)	19 (38%)	11 (22%)
Neuroblastoma	1 (2%)		

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma	1 (2%)		1 (2%)
Follicular cell carcinoma	1 (2%)		1 (2%)
C-cell adenoma	4 (8%)	2 (4%)	3 (6%)
C-cell carcinoma	4 (8%)	3 (6%)	3 (6%)
#Parathyroid	(38)	(32)	(30)
Adenoma, NOS	1 (3%)		
#Pancreatic islets	(50)	(49)	(50)
Islet cell adenoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma		1 (2%)	1 (2%)
*Preputial gland	(50)	(50)	(50)
Adenoma, NOS	2 (4%)	3 (6%)	1 (2%)
#Testis	(50)	(50)	(50)
Interstitial cell tumor	45 (90%)	47 (94%)	46 (92%)
#Tunica albuginea	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
NERVOUS SYSTEM			
#Cerebellum	(50)	(50)	(50)
Medulloblastoma	1 (2%)		
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3	1	
Moribund sacrifice	18	22	15
Terminal sacrifice	29	27	35

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

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	49	50	50
Total primary tumors	117	129	124
Total animals with benign tumors	45	50	49
Total benign tumors	77	88	80
Total animals with malignant tumors	30	32	36
Total malignant tumors	36	36	39
Total animals with secondary tumors##	1		
Total secondary tumors	1		
Total animals with tumors uncertain-- *benign or malignant*	4	5	5
Total uncertain tumors	4	5	5

* Number of animals necropsied
** Primary tumors: all tumors except secondary tumor
# Number of animals with tissue examined microscopically
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(49)	(50)	(50)
Neurofibrosarcoma	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#Lung	(49)	(50)	(49)
C-cell carcinoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Malignant lymphoma, lymphocytic type	1 (2%)		
Leukemia, mononuclear cell	12 (24%)	16 (32%)	12 (24%)
#Spleen	(48)	(50)	(50)
Leukemia, mononuclear cell	1 (2%)		6 (12%)
#Thymus	(42)	(41)	(47)
Thymoma, benign			1 (2%)
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Tongue	(49)	(50)	(50)
Squamous cell papilloma		1 (2%)	
#Liver	(49)	(50)	(50)
Neoplastic nodule	2 (4%)	2 (4%)	
#Small intestine	(48)	(48)	(46)
Leiomyoma			1 (2%)
Leiomyosarcoma			1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(50)	(49)
Carcinoma, NOS	2 (4%)	1 (2%)	
Adenoma, NOS	18 (37%)	24 (48%)	23 (47%)
#Adrenal	(49)	(50)	(49)
Cortical adenoma	3 (6%)	1 (2%)	2 (4%)
#Adrenal medulla	(49)	(50)	(49)
Pheochromocytoma	1 (2%)	4 (8%)	2 (4%)
Ganglioneuroma		1 (2%)	
#Thyroid	(48)	(50)	(49)
Follicular cell adenoma	1 (2%)		
C-cell adenoma	5 (10%)	4 (8%)	4 (8%)
C-cell carcinoma	2 (4%)	1 (2%)	2 (4%)
#Pancreatic islets	(47)	(50)	(49)
Islet cell adenoma	1 (2%)		

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Adenoma, NOS			1 (2%)
Adenocarcinoma, NOS	1 (2%)		
Papillary adenocarcinoma		1 (2%)	1 (2%)
Fibroadenoma	10 (20%)	7 (14%)	3 (6%)
*Clitoral gland	(49)	(50)	(50)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	5 (10%)	2 (4%)	1 (2%)
#Uterus	(49)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)		
Leiomyoma		1 (2%)	
Leiomyosarcoma	1 (2%)		
Endometrial stromal polyp	11 (22%)	14 (28%)	17 (34%)
#Ovary	(49)	(50)	(50)
Granulosa cell tumor		1 (2%)	
NERVOUS SYSTEM			
#Brain	(49)	(50)	(50)
Oligodendroglioma		1 (2%)	
#Cerebral cortex	(49)	(50)	(50)
Astrocytoma	1 (2%)		
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Mesothelioma, malignant	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	3		4
Moribund sacrifice	20	11	7
Terminal sacrifice	27	39	39

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	45	43	45
Total primary tumors	82	82	78
Total animals with benign tumors	35	40	37
Total benign tumors	55	59	55
Total animals with malignant tumors	25	19	21
Total malignant tumors	25	20	23
Total animals with secondary tumors##	1		
Total secondary tumors	1		
Total animals with tumors uncertain-- benign or malignant	2	2	
Total uncertain tumors	2	3	

* Number of animals necropsied
** Primary tumors: all tumors except secondary tumors
# Number of animals with tissue examined microscopically
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: UNTREATED CONTROL

ANIMAL NUMBER	11133	11177	10133	13137	12020	12525	13030	12222	13434	13636	13939	13838	13535	10606	11212	11818	14040	14545	14949	12626	14242	10101	10202	10404	10505
WEEKS ON STUDY	03434	04141	06067	06969	07676	07979	08080	08484	08484	08484	08486	08487	08795	09096	09599	09900	10000	10101	10202	10303	10404	10404	10404	10404	10404
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Basal cell tumor																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									X
Fibrosarcoma			X																						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Thymus	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																			X						
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & commo1duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																									
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																				X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma														X					X						
Neuroblastoma							X																		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
C-cell adenoma																						X			
C-cell carcinoma																					X				
Parathyroid	–	–	–	+	–	+	+	–	+	+	+	–	–	+	–	+	+	+	+	+	–	+	–	+	+
Adenoma, NOS																									X
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X		X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X
Mesothelioma, NOS																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS						X				X															
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Medulloblastoma		X																							
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS													X												
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS							X																		
Leukemia, mononuclear cell				X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

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

ANIMAL NUMBER	107	108	109	110	111	114	115	116	119	121	123	124	127	128	129	131	132	133	141	143	144	146	147	148	150	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma										X																1
Basal cell tumor																	X									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma									X										X	X						4
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, metastatic											X															1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	–	+	+	+	–	+	–	+	–	+	+	+	+	+	+	–	+	+	+	44
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	–	+	–	42
Thymoma, benign																			X							1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Hepatocellular carcinoma			X																						X	2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																						X				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS				X																						1
Adenoma, NOS	X										X					X							X			5
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma			X				X	X			X					X	X			X		X				10
Neuroblastoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma			X																							1
Follicular cell carcinoma																		X								1
C-cell adenoma						X									X									X		4
C-cell carcinoma				X						X	X															4
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	38
Adenoma, NOS																										1
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma	X																									1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	45
Mesothelioma, NOS																			X							1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Medulloblastoma																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																										1
Leukemia, mononuclear cell			X		X					X				X				X		X				X		25

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: LOW DOSE

ANIMAL NUMBER	00091	00113	00118	00116	00101	00334	00222	00443	00033	00233	00202	00117	00228	00445	00151	00441	00446	00129	00238	00448	00501	00220	00404	00005
WEEKS ON STUDY	06771	07979	08833	08844	08866	08866	09900	09911	09933	09955	09977	09977	09977	09977	09988	09981	09991	10111	10011	10111	10111	10111	10224	10404
INTEGUMENTARY SYSTEM																								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								
Lipoma																X								
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																								
Lymph nodes	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Thymus	+	+	+	–	+	+	+	–	–	–	+	+	+	–	+	–	+	+	+	+	–	+	–	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule						X																		
Hepatocellular carcinoma						X																		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Esophagus	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X	X						X						X	X		X			X	X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma				X																				
Pheochromocytoma					X						X	X	X			X		X	X					X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma														X										
C-cell carcinoma																						X		
Parathyroid	+	+	+	+	–	–	+	–	+	–	+	–	+	–	+	–	–	+	–	–	+	+	–	+	+
REPRODUCTIVE SYSTEM																								
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Fibroadenoma																X								
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor	X			X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS					X															X				
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Eosinophilic leukemia																		X						
Leukemia, mononuclear cell	X	X				X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X		

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

ANIMAL NUMBER	00 06	00 07	00 08	01 10	01 11	01 14	01 19	02 21	02 24	02 25	02 26	02 27	03 30	03 31	03 32	03 33	03 35	03 36	03 37	03 39	04 40	04 42	04 44	04 47	04 49	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma										X																1
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, mononuclear cell	X									X																2
Lymph nodes	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+°	46
Thymus	+	–	+	–	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	37
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule						X	X				X									X						5
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS															X		X					X	X			13
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma		X	X	X	X								X		X			X	X	X		X	X			19
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma													X													2
C-cell carcinoma																		X		X						3
Parathyroid	–	–	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	–	–	+	+	+		32
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	47
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																						X				3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Eosinophilic leukemia																										1
Leukemia, mononuclear cell		X		X		X	X		X			X	X	X			X	X					X			29

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: HIGH DOSE

ANIMAL NUMBER	08 66	05 51	05 54	07 78	07 72	09 99	07 99	09 91	06 11	07 77	09 95	05 53	05 57	06 60	08 33	05 11	05 52	05 56	05 58	05 59	06 62	06 63	06 64	06 65	06 66
WEEKS ON STUDY	08 84	09 90	09 95	09 96	09 97	09 98	09 99	10 00	10 01	10 01	10 01	10 02	10 02	10 03	10 03	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma														X											
Leukemia, mononuclear cell										X															
Lymph nodes	+	+	–	+	+	+	+	–	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+
Thymus	–	+	–	+	–	+	–	+	+	+	+	–	+	–	–	+	+	+	+	–	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																	X			X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS					X							X	X		X	X					X		X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma			X				X	X	X	X		X								X					X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																			X						
C-cell adenoma																		X							
C-cell carcinoma												X													
Parathyroid	–	+	+	+	+	–	–	+	+	–	–	+	–	+	+	+	+	+	+	–	–	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma												X													
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prostate	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, undiffer type			X																						
Leukemia, mononuclear cell	X	X		X	X	X	X	X	X		X	X	X	X	X					X					X

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

ANIMAL NUMBER	0067	0068	0069	0070	0071	0073	0074	0075	0076	0080	0081	0082	0084	0085	0087	0088	0089	0090	0092	0093	0094	0096	0097	0098	0100	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																				X						1
Neurofibrosarcoma									X																	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma																										1
Leukemia, mononuclear cell							X																			2
Lymph nodes	+	–	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Thymus	+	–	–	+	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	36
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																		X				X		X		5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																				X						1
Adenoma, NOS				X		X					X					X				X		X				14
Adrenal	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma				X														X							X	11
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																	X									1
Follicular cell carcinoma																										1
C-cell adenoma							X				X															3
C-cell carcinoma						X													X							3
Parathyroid	–	–	+	–	–	+	+	+	+	+	+	–	–	+	+	+	–	+	–	–	–	+	+	–	–	30
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Fibroadenoma																										1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	46
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS			X																							1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, undiffer type																										1
Leukemia, mononuclear cell	X	X	X		X			X	X		X	X		X				X		X	X	X	X		X	30

*Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: UNTREATED CONTROL

ANIMAL NUMBER	12091	10061	10139	13940	14041	10411	14112	13134	12258	12828	13336	12247	14478	13664	14418	11861	14611	12231	13838	14491	10051	10021	10033
WEEKS ON STUDY	05 9	06 0	06 9	07 2	07 2	07 5	07 6	07 8	08 2	08 2	08 6	09 2	09 4	09 7	09 8	09 9	10 0	10 1	10 1	10 2	10 2	10 3	10 4	10 4
INTEGUMENTARY SYSTEM																								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Neurofibrosarcoma																								
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic									X															
Trachea	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																								
Lymph nodes	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	A	+	+	–	+	+	–	+	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Neoplastic nodule																								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Carcinoma, NOS		X																						
Adenoma, NOS			X					X		X	X		X		X				X				X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Cortical adenoma																					X			
Pheochromocytoma																								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Follicular cell adenoma																								
C-cell adenoma																	X			X				
C-cell carcinoma									X															
Parathyroid	+	+	+	+	+	+	–	+	–	+	–	–	–	+	+	A	–	+	+	+	+	+	–	+
Pancreatic islets	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	A	+	+	+	+	+	+	+	+
Islet cell adenoma																								
REPRODUCTIVE SYSTEM																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS											X													
Fibroadenoma			X					X				X					X		X					
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N
Carcinoma, NOS	X																							
Adenoma, NOS													X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS								X																
Leiomyosarcoma																								
Endometrial stromal polyp		X		X			X		X			X	X		X								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Astrocytoma						X																		
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	A	N	N	N	N	N	N	N	N
Mesothelioma, malignant																		X						
Malig. lymphoma, lymphocytic type															X									
Leukemia, mononuclear cell							X					X		X					X		X	X		

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: : No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

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

ANIMAL NUMBER	107	108	109	110	113	114	115	116	117	119	120	121	122	126	127	130	131	132	135	137	142	143	145	148	150	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Neurofibrosarcoma										X																1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia, mononuclear cell							X																			1
Lymph nodes	+	–	–	+	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	41
Thymus	–	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule						X														X						2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																		X								2
Adenoma, NOS				X			X			X	X	X		X	X		X	X						X		18
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma		X			X																					3
Pheochromocytoma							X																			1
Thyroid	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma							X																			1
C-cell adenoma															X						X	X				5
C-cell carcinoma														X												2
Parathyroid	+	+	+	–	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Islet cell adenoma		X																								1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Adenocarcinoma, NOS																										1
Fibroadenoma						X				X	X	X					X									10
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Carcinoma, NOS																										1
Adenoma, NOS								X			X			X					X							5
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS																										1
Leiomyosarcoma				X																						1
Endometrial stromal polyp			X									X						X								11
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Astrocytoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Mesothelioma, malignant																										1
Malig. lymphoma, lymphocytic type																										1
Leukemia, mononuclear cell	X														X	X			X	X					X	12

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: LOW DOSE

ANIMAL NUMBER	02 07	00 04	02 03	04 02	03 03	04 00	03 01	03 02	00 03	00 07	02 02	00 01	00 02	00 05	00 06	00 08	00 09	01 00	01 11	01 12	01 13	01 14	01 15	01 16	01 17
WEEKS ON STUDY	07 73	08 77	08 77	09 91	09 92	09 96	09 98	10 00	10 01	10 01	10 02	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+
Thymus	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma															X										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS	X					X	X			X			X	X	X		X				X	X	X		X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma					X			X		X															
Ganglioneuroma								X																	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma												X				X									
C-cell carcinoma																									
Parathyroid	–	+	–	–	–	–	+	–	–	–	–	+	–	+	+	+	+	–	+	–	+	+	–	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenocarcinoma																									
Fibroadenoma							X											X						X	
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma		X																							
Endometrial stromal polyp			X	X				X	X	X	X						X			X					X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma				X																					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X	X		X	X	X	X	X		X		X		X					X					

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

ANIMAL NUMBER	018	019	020	021	024	025	026	028	029	030	034	035	036	037	038	039	041	043	044	045	046	047	048	049	050	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+		49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph nodes	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+	43
Thymus	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma																										1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule					X						X															2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS												X														1
Adenoma, NOS		X	X	X				X	X	X	X			X	X			X						X		24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma									X																	1
Pheochromocytoma																		X								4
Ganglioneuroma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma																		X	X							4
C-cell carcinoma															X											1
Parathyroid	+	–	+	+	–	–	+	–	+	+	–	+	+	+	–	+	+	+	–	–	+	+	–	+	+	28
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papillary adenocarcinoma									X																	1
Fibroadenoma												X	X				X								X	7
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS													X					X								2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Endometrial stromal polyp		X		X																	X		X		X	14
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor											X															1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Oligodendroglioma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X				X				X										X				X			16

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: HIGH DOSE

ANIMAL NUMBER	07771	06595	09898	06622	08866	07711	05577	07733	09933	09944	06677	05511	05522	05533	05544	05555	05566	05588	05599	06600	06611	06633	06644	06666	06688
WEEKS ON STUDY	07722	07778	07882	08822	08855	08899	09911	09922	09933	09977	09988	10044	10044	10044	10044	10044	10444	10444	10444	10444	10444	10444	10444	10444	10444
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibrosarcoma																	X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell														X	X										
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	
Thymoma, benign																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–
Stomach	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma							X																		
Leiomyosarcoma																									
Large intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS								X				X		X	X				X		X	X	X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																							X		
Pheochromocytoma																X									
Thyroid	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma												X													
C-cell carcinoma																									
Parathyroid	+	+	–	–	+	–	+	–	–	+	–	+	–	–	+	+	+	+	+	–	–	+	–	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Papillary adenocarcinoma																									
Fibroadenoma															X										
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp				X					X		X				X		X	X	X	X	X				X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell	X	X		X	X	X			X	X	X		X						X						

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

ANIMAL NUMBER	0069	0070	0072	0074	0075	0076	0078	0079	0080	0081	0082	0083	0084	0085	0087	0088	0089	0090	0091	0092	0095	0096	0097	0099	0100	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia, *mononuclear cell*		X													X	X					X					6
Lymph nodes	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	46
Thymus	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymoma, benign								X																		1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leiomyoma																										1
Leiomyosarcoma												X														1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X					X	X		X	X	X		X		X	X	X			X		X		X	23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma					X																					2
Pheochromocytoma																							X			2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma											X								X		X					4
C-cell carcinoma	X															X										2
Parathyroid	+	+	+	–	+	–	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	35
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																									X	1
Papillary adenocarcinoma																		X								1
Fibroadenoma					X																				X	3
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																				X						1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp			X	X							X	X	X				X								X	17
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X												X													12

*Animals Necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Fibrous histiocytoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic	1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar adenoma	4 (8%)	6 (12%)	3 (6%)
Alveolar/bronchiolar carcinoma	5 (10%)	5 (10%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	2 (4%)	1 (2%)	
Malignant lymphoma, undiffer type	1 (2%)		
Malignant lymphoma, lymphocytic type	2 (4%)		
Malignant lymphoma, histiocytic type	1 (2%)		1 (2%)
Malignant lymphoma, mixed type		1 (2%)	2 (4%)
#Spleen	(50)	(50)	(49)
Malignant lymphoma, NOS	2 (4%)	1 (2%)	2 (4%)
Malignant lymphoma, mixed type		1 (2%)	1 (2%)
#Mandibular lymph node	(35)	(31)	(33)
Carcinoma, NOS, metastatic			1 (3%)
#Mesenteric lymph node	(35)	(31)	(33)
Malignant lymphoma, undiffer type			1 (3%)
*Mesentery	(50)	(50)	(50)
Malignant lymphoma, mixed type			1 (2%)
#Duodenum	(49)	(46)	(49)
Malignant lymphoma, NOS			1 (2%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
#Spleen	(50)	(50)	(49)
Hemangiosarcoma	2 (4%)		1 (2%)
#Liver	(50)	(50)	(49)
Hemangiosarcoma		1 (2%)	
Hemangiosarcoma, metastatic	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(49)
Hepatocellular adenoma	10 (20%)	9 (18%)	14 (29%)
Hepatocellular carcinoma	13 (26%)	11 (22%)	13 (27%)
#Forestomach	(50)	(50)	(49)
Squamous cell carcinoma			1 (2%)
#Small intestine	(49)	(46)	(49)
Carcinoma, NOS	1 (2%)		1 (2%)
Adenomatous polyp, NOS			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(48)
Adenoma, NOS	1 (2%)		1 (2%)
#Adrenal	(50)	(50)	(48)
Cortical adenoma	7 (14%)	3 (6%)	1 (2%)
#Adrenal/capsule	(50)	(50)	(48)
Adenoma, NOS		1 (2%)	1 (2%)
#Adrenal medulla	(50)	(50)	(48)
Pheochromocytoma		2 (4%)	
#Thyroid	(50)	(50)	(50)
Follicular cell adenoma	1 (2%)	1 (2%)	
#Pancreatic islets	(49)	(50)	(49)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
None			
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)
Adenoma, NOS	3 (6%)	1 (2%)	3 (6%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	1	4	1
Moribund sacrifice	9	4	10
Terminal sacrifice	40	41	38
Accidentally killed, nda		1	
Accidentally killed, NOS			1

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	38	31	36
Total primary tumors	55	47	52
Total animals with benign tumors	18	19	22
Total benign tumors	26	26	24
Total animals with malignant tumors	27	18	24
Total malignant tumors	29	21	28
Total animals with secondary tumors##	2	1	2
Total secondary tumors	2	1	2

* Number of animals necropsied
** Primary tumors: all tumors except secondary tumors
# Number of animals with tissue examined microscopically
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(49)
Sarcoma, NOS			1 (2%)
Fibrosarcoma	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(49)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(49)
Malignant lymphoma, undiffer type		2 (4%)	1 (2%)
Malignant lymphoma, lymphocytic type	7 (14%)	6 (12%)	8 (16%)
Malignant lymphoma, histiocytic type	4 (8%)	5 (10%)	4 (8%)
Malignant lymphoma, mixed type	23 (46%)	23 (46%)	19 (39%)
Lymphocytic leukemia		1 (2%)	
Granulocytic leukemia	1 (2%)		
#Spleen	(48)	(50)	(49)
Malignant lymphoma, histiocytic type		1 (2%)	
Malignant lymphoma, mixed type	2 (4%)	1 (2%)	1 (2%)
#Mandibular lymph node	(39)	(45)	(41)
Malignant lymphoma, lymphocytic type		1 (2%)	
#Thymus	(40)	(37)	(39)
Malignant lymphoma, mixed type	1 (3%)		
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(49)
Hemangiosarcoma			1 (2%)
#Spleen	(48)	(50)	(49)
Hemangioma	1 (2%)		
Hemangiosarcoma		1 (2%)	
*Adipose tissue	(50)	(50)	(49)
Hemangiosarcoma	1 (2%)		
#Liver	(50)	(50)	(49)
Hemangioma		1 (2%)	
#Uterus	(50)	(50)	(49)
Hemangioma	3 (6%)	1 (2%)	1 (2%)
Hemangiosarcoma	1 (2%)		
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(49)
Hepatocellular adenoma	6 (12%)	2 (4%)	3 (6%)
Hepatocellular carcinoma	3 (6%)	1 (2%)	
#Pancreas	(48)	(50)	(48)
Acinar cell adenoma			1 (2%)
URINARY SYSTEM			
None			

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(50)	(48)
Adenoma, NOS			1 (2%)
#Anterior pituitary	(48)	(50)	(48)
Carcinoma, NOS	2 (4%)		2 (4%)
Adenoma, NOS	8 (17%)	10 (20%)	9 (19%)
#Adrenal	(48)	(49)	(49)
Cortical adenoma			1 (2%)
#Adrenal/capsule	(48)	(49)	(49)
Adenoma, NOS	1 (2%)		1 (2%)
#Adrenal medulla	(48)	(49)	(49)
Pheochromocytoma	2 (4%)	1 (2%)	
#Thyroid	(48)	(49)	(49)
Follicular cell adenoma	2 (4%)	1 (2%)	
#Pancreatic islets	(48)	(50)	(48)
Islet cell adenoma	1 (2%)	1 (2%)	1 (2%)
Islet cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(49)
Adenocarcinoma, NOS			1 (2%)
Adenosquamous carcinoma		1 (2%)	
Fibroadenoma		1 (2%)	
#Uterus	(50)	(50)	(49)
Endometrial stromal polyp	1 (2%)	1 (2%)	1 (2%)
#Ovary	(41)	(42)	(43)
Luteoma		1 (2%)	1 (2%)
Granulosa cell tumor			2 (5%)
Teratoma, NOS	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
#Brain	(50)	(50)	(49)
Fibrosarcoma, metastatic			1 (2%)
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(49)
Adenoma, NOS	1 (2%)		1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
Tail			
Osteosarcoma		1	
Toe			
Squamous cell papilloma			1

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	4	2
Moribund sacrifice	6	11	12
Terminal sacrifice	40	35	36
TUMOR SUMMARY			
Total animals with primary tumors**	43	45	41
Total primary tumors	75	66	65
Total animals with benign tumors	22	17	16
Total benign tumors	27	21	24
Total animals with malignant tumors	41	40	35
Total malignant tumors	47	44	39
Total animals with secondary tumors##			1
Total secondary tumors			1
Total animals with tumors uncertain-- benign or malignant	1	1	2
Total uncertain tumors	1	1	2

* Number of animals necropsied
** Primary tumors: all tumors except secondary tumors
# Number of animals with tissue examined microscopically
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: UNTREATED CONTROL

ANIMAL NUMBER	1 0 5	1 1 1	1 1 8	1 1 0	1 2 4	1 2 7	1 3 3	1 4 4	1 4 6	1 1 2	1 0 1	1 0 2	1 0 3	1 0 4	1 0 6	1 0 7	1 0 8	1 0 9	1 1 3	1 1 4	1 1 5	1 1 6	1 1 7	1 1 9	1 2 0
WEEKS ON STUDY	0 5 1	0 7 1	0 7 9	0 8 0	0 8 2	0 8 9	0 9 8	0 9 9	1 0 1	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metas										X															
Alveolar/bronchiolar adenoma															X				X						
Alveolar/bronchiolar carcinoma											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma		X														X									
Malignant lymphoma, NOS																									
Lymph nodes	–	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	–	+	+	–	+	+	–
Thymus	+	–	+	–	+	+	+	+	–	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma			X									X				X	X						X		
Hepatocellular carcinoma			X		X	X			X	X		X					X			X				X	
Hemangiosarcoma, metastatic		X																							
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma			X									X						X			X				
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	+	+	+	+	–	+	–	–	–	+	+	+	+	–	–	–	+	–	+	–	–	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS															X			X							
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS														X											
Malig. lymphoma, undiffer type				X																					
Malig. lymphoma, lymphocytic type																									
Malig. lymphoma, histiocytic type																				X					

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: : No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

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

ANIMAL NUMBER	12 21	12 22	12 23	12 25	12 26	12 28	12 29	13 30	13 31	13 32	13 34	13 35	13 36	13 37	13 38	13 39	14 40	14 41	14 42	14 43	14 45	14 47	14 48	14 49	15 50	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metas																										1
Alveolar/bronchiolar adenoma							X	X																		4
Alveolar/bronchiolar carcinoma											X							X	X				X			5
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										2
Malignant lymphoma, NOS																					X	X				2
Lymph nodes	–	–	–	+	–	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	–	–	35
Thymus	–	–	+	+	+	–	+	+	+	+	–	–	+	+	+	–	–	–	–	+	+	+	+	–	–	33
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X				X	X				X	X												10
Hepatocellular carcinoma			X	X													X								X	13
Hemangiosarcoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																								X		1
Large intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																							X			1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma			X		X																		X			7
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma			X																							1
Parathyroid	+	+	+	–	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	–	+	–	+	35
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS			X																							3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																							X			2
Malig. lymphoma, undiffer type																										1
Malig. lymphoma, lymphocytic type		X								X																2
Malig. lymphoma, histiocytic type																										1

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: LOW DOSE

ANIMAL NUMBER	0 3 2	0 4 1	0 0 3	0 0 2	0 5 0	0 0 8	0 4 6	0 1 1	0 0 5	0 0 1	0 0 4	0 0 6	0 0 7	0 0 9	1 1 0	1 1 2	1 1 3	1 1 4	1 1 5	1 1 6	1 1 7	1 1 8	1 1 9	1 2 0	0 2 1
WEEKS ON STUDY	0 0 0	0 0 2	0 0 4	0 5 8	0 7 9	0 8 2	0 9 1	0 9 6	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma																			X						
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metas																									
Alveolar/bronchiolar adenoma												X							X						
Alveolar/bronchiolar carcinoma														X							X				X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Malignant lymphoma, mixed type																									
Lymph nodes	–	+	+	+	–	+	+	–	+	+	+	+	+	+	–	–	–	+	–	–	+	+	+	+	–
Thymus	+	+	+	+	–	+	–	+	+	–	+	+	–	+	+	+	+	–	+	+	+	+	+	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma													X					X	X		X	X			
Hepatocellular carcinoma				X		X	X	X	X		X							X							
Hemangiosarcoma													X												
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	+	+	N	+	+	+	+	+	N	+	+	+	+	N	+	N	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	–	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	–	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	–	–	–	+	–	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma					X																				
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS												X													
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	0222	0223	0224	0225	0226	0227	0228	0229	0301	0311	0333	0334	0335	0336	0337	0338	0339	0400	0402	0403	0404	0405	0407	0408	0409	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrous histiocytoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metas				X																						1
Alveolar/bronchiolar adenoma		X	X									X									X					6
Alveolar/bronchiolar carcinoma														X			X									5
Trachea	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, NOS				X																						1
Malignant lymphoma, mixed type																	X									1
Lymph nodes	–	+	–	–	+	–	–	+	–	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	–	31
Thymus	+	+	+	+	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	–	+	+	–	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X				X									X				X					9
Hepatocellular carcinoma	X			X												X								X		11
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	N	N	+	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS															X											1
Cortical adenoma									X								X	X								3
Pheochromocytoma												X				X										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																									X	1
Parathyroid	–	–	–	+	+	–	+	–	–	+	–	–	+	+	+	+	–	+	+	+	+	–	–	+	+	30
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS												X														1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										1
Malignant lymphoma, mixed type																							X			1

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: HIGH DOSE

ANIMAL NUMBER	09754	05499	09991	09165	06879	07993	09899	08559	07090	08787	09981	05151	05252	05353	05555	05656	05757	05858	06060	06161	06262	06363	06464	06666
WEEKS ON STUDY	04885	05508	08805	08858	08888	08899	09595	09999	09900	10003	10044	10044	10044	10044	10044	10044	10044	10044	10044	10044	10044	10044	10044	10044
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metas																								
Alveolar/bronchiolar adenoma																					X			
Alveolar/bronchiolar carcinoma																				X				
Trachea	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Malignant lymphoma, NOS																								
Malignant lymphoma, mixed type															X									
Lymph nodes	−	−	−	+	+	+	+	+	−	−	+	+	+	+	−	+	−	+	+	+	−	+	+	+
Carcinoma, NOS, metastatic																								
Malig. lymphoma, undiffer type																		X						
Thymus	+	−	+	−	−	−	+	−	+	+	−	+	+	+	−	+	−	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma	X				X		X		X			X					X			X		X		
Hepatocellular carcinoma					X	X	X						X							X	X			
Bile duct	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma										X														
Small intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																								
Adenomatous polyp, NOS																						X		
Malignant lymphoma, NOS																								
Large intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																		X						
Adrenal	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Adenoma, NOS																								
Cortical adenoma																						X		
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	−	−	+	+	−	+	+	+	+	−	−	−	+	−	−	+	−	+	−	−	−	+	−	+
REPRODUCTIVE SYSTEM																								
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																								
Adenoma, NOS					X			X																
BODY CAVITIES																								
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, mixed type																							X	
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma								X																
Malig. lymphoma, histiocytic type												X												
Malignant lymphoma, mixed type											X													

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

ANIMAL NUMBER	0067	0068	0069	0071	0072	0073	0074	0075	0076	0077	0078	0080	0081	0082	0083	0084	0085	0086	0088	0090	0092	0094	0095	0096	0100	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metas								X																		1
Alveolar/bronchiolar adenoma												X													X	3
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																									X	1
Malignant lymphoma, NOS				X																			X			2
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	–	+	–	+	–	–	+	–	+	+	+	+	+	–	+	+	–	+	–	–	33
Carcinoma, NOS, metastatic				X																						1
Malig. lymphoma, undiffer type																										1
Thymus	+	+	+	–	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	38
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma	X				X			X	X	X											X					14
Hepatocellular carcinoma	X	X						X		X	X				X									X		13
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS								X																		1
Adenomatous polyp, NOS																										1
Malignant lymphoma, NOS							X																			1
Large intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS													X													1
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	34
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS				X																						1
Adenoma, NOS																X										3
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, mixed type																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma																										1
Malig. lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																						X				2

*Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: UNTREATED CONTROL

ANIMAL NUMBER	12201	11101	14409	12505	10909	13005	14501	14401	14404	14808	10101	10204	10304	10404	10505	10606	10707	10808	11001	11202	11303	11404	11505	11606	11707
WEEKS ON STUDY	02101	02606	08808	09202	09404	09404	09606	09707	09808	10104	10104	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404	10404
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma										X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma									X																
Malignant lymphoma, mixed type																					X			X	
Lymph nodes	+	–	+	+	+	+	+	+	+	–	–	+	+	–	+	+	+	+	+	+	+	+	+	–	+
Thymus	+	+	–	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type							X																		
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X				X											X	
Hepatocellular carcinoma											X														
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS														X					X						X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																					X				
Pheochromocytoma						X																			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	A	–	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	–	+	–	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																							X		
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp											X														
Hemangioma							X																		
Hemangiosarcoma								X																	
Ovary	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Teratoma, NOS		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																X									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type														X			X						X		
Malig. lymphoma, histiocytic type																									X
Malignant lymphoma, mixed type				X	X	X			X		X		X		X	X		X		X			X		
Granulocytic leukemia			X																						
Adipose tissue																									
Hemangiosarcoma																									

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: : No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

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

ANIMAL NUMBER	1 1 8	1 1 9	1 2 0	1 2 1	1 2 3	1 2 4	1 2 6	1 2 7	1 2 8	1 2 9	1 3 1	1 3 2	1 3 3	1 3 4	1 3 5	1 3 6	1 3 7	1 3 8	1 3 9	1 4 0	1 4 2	1 4 3	1 4 6	1 4 7	1 5 0	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X							1
Trachea	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	48
Hemangioma																										1
Malignant lymphoma, mixed type																										2
Lymph nodes	+	+	+	+	–	+	–	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	+	–	+	39
Thymus	+	–	+	+	–	+	+	–	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	40
Malignant lymphoma, mixed type																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X													X				X						6
Hepatocellular carcinoma				X																				X		3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS								X																	X	2
Adenoma, NOS	X		X							X						X					X					8
Adrenal	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS																										1
Pheochromocytoma											X															2
Thyroid	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma								X		X																2
Parathyroid	+	+	+	+	–	+	+	+	–	–	+	+	–	+	+	+	–	–	+	+	+	–	+	–	+	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Islet cell adenoma																										1
Islet cell carcinoma																X										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp																										1
Hemangioma		X																		X						3
Hemangiosarcoma																										1
Ovary	+	+	+	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	41
Teratoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, lymphocytic type								X			X					X				X						7
Malig. lymphoma, histiocytic type	X														X										X	4
Malignant lymphoma, mixed type		X	X	X			X		X	X		X	X					X	X		X	X				23
Granulocytic leukemia																										1
Adipose tissue																										
Hemangiosarcoma																X										1

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: LOW DOSE

ANIMAL NUMBER	0 2 4	0 0 2	0 3 6	0 2 3	0 3 4	0 2 7	0 4 8	0 1 5	0 2 9	0 1 4	0 4 1	0 0 8	0 1 7	0 2 1	0 1 1	0 0 1	0 0 3	0 0 4	0 0 5	0 0 6	0 0 7	0 0 9	0 1 0	0 1 2	0 1 3
WEEKS ON STUDY	0 2 7	0 4 8	0 7 1	0 8 0	0 8 1	0 8 3	0 8 6	0 8 9	0 9 4	0 9 8	0 9 8	1 0 0	1 0 0	1 0 0	1 0 1	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Malig. lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–
Malig. lymphoma, lymphocytic type																									
Thymus	+	+	+	+	–	–	+	+	–	+	+	–	–	+	–	+	+	+	+	+	+	+	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																					X	X			
Hepatocellular carcinoma																									
Hemangioma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Small intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS												X				X				X			X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	–	–	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Adenosquamous carcinoma							X																		
Fibroadenoma																					X				
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp												X													
Hemangioma																									
Ovary	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	–	+	+
Luteoma																			X						
Teratoma, NOS		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, undiffer type			X																						
Malig. lymphoma, lymphocytic type										X															
Malig. lymphoma, histiocytic type				X		X	X						X												
Malignant lymphoma, mixed type									X			X		X	X		X	X		X	X	X	X	X	X
Lymphocytic leukemia					X																				
Tail																									
Osteosarcoma																									

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

ANIMAL NUMBER	0116	0118	0119	0220	0225	0226	0228	0230	0231	0232	0233	0235	0237	0238	0239	0240	0242	0243	0244	0245	0246	0247	0249	0250	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																				1
Malig. lymphoma, histiocytic type																								X	1
Malignant lymphoma, mixed type							X																		1
Lymph nodes	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	45
Malig. lymphoma, lymphocytic type						X																			1
Thymus	+	+	+	–	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	–	+	+	–	+	37
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																									2
Hepatocellular carcinoma						X																			1
Hemangioma						X																			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS					X						X				X		X						X	X	10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Pheochromocytoma										X															1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma															X										1
Parathyroid	+	+	+	+	+	+	+	–	+	–	–	+	+	+	+	–	+	+	–	+	+	–	+	–	+	37
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma			X																						1
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Adenosquamous carcinoma																									1
Fibroadenoma																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp																									1
Hemangioma			X																						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	+	+	–	42
Luteoma																									1
Teratoma, NOS																									1
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, undiffer type												X													2
Malig. lymphoma, lymphocytic type				X	X								X					X					X		6
Malig. lymphoma, histiocytic type																			X						5
Malignant lymphoma, mixed type	X	X							X	X	X			X	X	X			X		X		X		23
Lymphocytic leukemia																									1
Tail																									
Osteosarcoma																			X						1

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE: HIGH DOSE

ANIMAL NUMBER	0959	0887	0998	0778	0770	0990	0797	0808	0666	0733	0833	0766	0556	0599	0511	0522	0533	0544	0555	0577	0588	0600	0611	0622	0633
WEEKS ON STUDY	057	071	078	085	090	092	093	094	096	097	098	099	100	101	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibrosarcoma					X																				
RESPIRATORY SYSTEM																									
Lungs and bronchi	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X				
Trachea	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	A	+	+	–	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+
Thymus	A	+	–	–	–	+	+	+	–	–	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																X		X					X		
Bile duct	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	A	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																									
Esophagus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	A	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	A	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS						X						X				X	X					X	X	X	
Adrenal	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS														X											
Cortical adenoma																									
Thyroid	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	A	+	+	+	+	+	–	+	+	–	+	+	+	+	–	–	+	+	–	+	+	+	+	+	+
Pancreatic islets	A	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																								X	
REPRODUCTIVE SYSTEM																									
Mammary gland	A	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Uterus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																			X						
Hemangioma																									
Ovary	A	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+
Luteoma																			X						
Granulosa cell tumor					X																				
NERVOUS SYSTEM																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic					X																				
SPECIAL SENSE ORGANS																									
Harderian gland	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	A	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma														X											
Malig. lymphoma, undiffer type			X																						
Malig. lymphoma, lymphocytic type				X	X												X			X				
Malig. lymphoma, histiocytic type							X				X												X		
Malignant lymphoma, mixed type									X	X		X	X			X		X	X		X				X
Toe, NOS	A																								
Squamous cell papilloma																									X

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

ANIMAL NUMBER	064	065	067	068	069	071	072	074	075	079	081	082	084	085	086	088	089	091	092	093	094	096	097	099	100	TOTAL:
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	TISSUES / TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Sarcoma, NOS															X											1
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma												X														2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type						X																				1
Lymph nodes	+	+	+	+	+	+	–	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	41
Thymus	+	+	+	+	–	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma																										3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinar cell adenoma														X												1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	44
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Carcinoma, NOS					X															X						2
Adenoma, NOS	X			X																X						10
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS																										1
Cortical adenoma	X																									1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid	+	–	+	+	–	+	–	+	–	–	+	+	+	+	+	–	+	–	+	–	–	+	–	+	–	33
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	*49
Adenocarcinoma, NOS																X										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp																										1
Hemangioma																				X						1
Ovary	+	+	+	+	–	+	+	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	43
Luteoma																										1
Granulosa cell tumor				X																						2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, metastatic																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Adenoma, NOS														X												1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Hemangiosarcoma																										1
Malig. lymphoma, undiffer type																										1
Malig. lymphoma, lymphocytic type													X						X			X	X			8
Malig. lymphoma, histiocytic type								X																		4
Malignant lymphoma, mixed type		X							X		X			X	X	X				X	X			X	X	19
Toe, NOS																										
Squamous cell papilloma																										1

* Animals Necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Mineralization	1 (2%)		
Epidermal inclusion cyst		1 (2%)	
Ulcer, NOS	1 (2%)		
Inflammation, necrotizing	1 (2%)		
Fibrosis	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Epidermal inclusion cyst	5 (10%)	4 (8%)	1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Congestion, NOS	2 (4%)		
Hemorrhage	1 (2%)		
Pneumonia, interstitial chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		
Perivascular cuffing	5 (10%)	7 (14%)	7 (14%)
Necrosis, NOS		1 (2%)	
Hemosiderosis			1 (2%)
Hyperplasia, alveolar epithelium	3 (6%)	1 (2%)	2 (4%)
#Lung/alveoli	(50)	(50)	(50)
Distention	1 (2%)		1 (2%)
Edema, NOS	4 (8%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)		
Inflammation, chronic focal		1 (2%)	
Fibrosis, focal			1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(50)
Hyperplasia, NOS	28 (56%)	29 (58%)	25 (50%)
Myelofibrosis	3 (6%)		1 (2%)
#Spleen	(50)	(50)	(50)
Ectopia		1 (2%)	1 (2%)
Fibrosis	4 (8%)	5 (10%)	7 (14%)
Necrosis, focal		1 (2%)	
Hemosiderosis	2 (4%)	1 (2%)	4 (8%)
Hyperplasia, stromal		1 (2%)	
Hyperplasia, lymphoid			1 (2%)
Hematopoiesis	4 (8%)	3 (6%)	
#Splenic capsule	(50)	(50)	(50)
Fibrosis	2 (4%)	1 (2%)	
#Mandibular lymph node	(44)	(46)	(42)
Hemorrhage	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
#Thymus	(42)	(37)	(36)
Cyst, NOS		1 (3%)	3 (8%)
Hemorrhage	3 (7%)	2 (5%)	1 (3%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Thrombus, fibrin		1 (2%)	
#Mandibular lymph node	(44)	(46)	(42)
Lymphangiectasis	6 (14%)	6 (13%)	4 (10%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
#Myocardium	(50)	(50)	(50)
Mineralization	12 (24%)	6 (12%)	4 (8%)
Inflammation, chronic	11 (22%)	9 (18%)	3 (6%)
Fibrosis	44 (88%)	45 (90%)	46 (92%)
Degeneration, NOS	11 (22%)	3 (6%)	7 (14%)
#Mitral valve	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
*Artery	(50)	(50)	(50)
Inflammation, active chronic			1 (2%)
*Pulmonary artery	(50)	(50)	(50)
Mineralization	4 (8%)	1 (2%)	3 (6%)
*Splenic artery	(50)	(50)	(50)
Hypertrophy, NOS		1 (2%)	
*Testicular artery	(50)	(50)	(50)
Inflammation, fibrinoid		1 (2%)	
*Portal vein	(50)	(50)	(50)
Thrombus, organized	1 (2%)		
#Pancreas	(50)	(49)	(50)
Lymphangiectasis	1 (2%)		
DIGESTIVE SYSTEM			
#Submaxillary duct	(50)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
#Liver	(50)	(50)	(50)
Inflammation, acute focal	1 (2%)		
Granuloma, NOS	2 (4%)	1 (2%)	
Necrosis, NOS			1 (2%)
Necrosis, coagulative	3 (6%)	4 (8%)	2 (4%)
Metamorphosis, fatty	3 (6%)	4 (8%)	5 (10%)
Hemosiderosis			1 (2%)
Cytoplasmic change, NOS	3 (6%)	2 (4%)	4 (8%)
Basophilic cyto change	23 (46%)	18 (36%)	18 (36%)
Ground glass cyto change	3 (6%)	3 (6%)	1 (2%)
Focal cellular change		1 (2%)	1 (2%)
Eosinophilic cyto change	1 (2%)		
Clear cell change	12 (24%)	13 (26%)	13 (26%)
Hyperplasia, focal	3 (6%)	2 (4%)	3 (6%)
Angiectasis	14 (28%)	16 (32%)	18 (36%)
#Hepatic capsule	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
#Portal tract	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Periportal bile duct	(50)	(50)	(50)
Hyperplasia, NOS	47 (94%)	48 (96%)	49 (98%)
#Liver/centrilobular	(50)	(50)	(50)
Metamorphosis, fatty	1 (2%)		
#Liver/periportal	(50)	(50)	(50)
Inflammation, active chronic	1 (2%)		
Inflammation, chronic			1 (2%)
#Liver/hepatocytes	(50)	(50)	(50)
Cytoplasmic vacuolization	6 (12%)	1 (2%)	5 (10%)
#Pancreas	(50)	(49)	(50)
Cystic ducts			1 (2%)
Inflammation, acute diffuse	1 (2%)		
Inflammation, chronic	1 (2%)		
#Pancreatic acinus	(50)	(49)	(50)
Atrophy, NOS	18 (36%)	20 (41%)	23 (46%)
Hyperplasia, NOS			1 (2%)
#Peripancreatic tissue	(50)	(49)	(50)
Necrosis, fat		1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Esophagus	(48)	(47)	(49)
Hyperplasia, epithelial			1 (2%)
#Glandular stomach	(50)	(50)	(50)
Multiple cysts	23 (46%)	30 (60%)	31 (62%)
#Forestomach	(50)	(50)	(50)
Edema, NOS		2 (4%)	
Ulcer, NOS		1 (2%)	
Inflammation, active chronic		2 (4%)	
Inflammation, chronic		2 (4%)	
Hyperplasia, epithelial	1 (2%)	5 (10%)	2 (4%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Hydronephrosis	1 (2%)		1 (2%)
Scar		1 (2%)	
Perivascular cuffing			1 (2%)
Nephropathy	49 (98%)	48 (96%)	49 (98%)
Nephrosis, NOS			1 (2%)
Pigmentation, NOS	2 (4%)	1 (2%)	
#Convoluted tubules	(50)	(50)	(50)
Metamorphosis, fatty		1 (2%)	
#Urinary bladder	(48)	(49)	(49)
Hemorrhage			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(49)	(48)
Cyst, NOS	3 (6%)		1 (2%)
Angiectasis	2 (4%)	6 (12%)	3 (6%)
#Anterior pituitary	(49)	(49)	(48)
Cyst, NOS	2 (4%)	1 (2%)	3 (6%)
Degeneration, NOS		1 (2%)	
Necrosis, focal		1 (2%)	
Hyperplasia, atypical	1 (2%)		
Hyperplasia, focal	14 (29%)	15 (31%)	12 (25%)
Angiectasis	1 (2%)	3 (6%)	2 (4%)
#Pituitary posterior	(49)	(49)	(48)
Multiple cysts			1 (2%)
#Adrenal cortex	(50)	(50)	(49)
Cyst, NOS	1 (2%)		
Degeneration, ballooning	1 (2%)		
Necrosis, focal	1 (2%)		
Metamorphosis, fatty	5 (10%)	4 (8%)	4 (8%)
Hyperplasia, focal	25 (50%)	24 (48%)	23 (47%)
Angiectasis	11 (22%)	13 (26%)	22 (45%)
#Adrenal medulla	(50)	(50)	(49)
Hyperplasia, focal	2 (4%)	2 (4%)	1 (2%)
Angiectasis	1 (2%)		
#Thyroid	(50)	(50)	(50)
Cyst, NOS			1 (2%)
Follicular cyst, NOS	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, C-cell	8 (16%)	12 (24%)	12 (24%)
#Thyroid follicle	(50)	(50)	(50)
Degeneration, NOS			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Hyperplasia, NOS	3 (6%)		
Hyperplasia, cystic	4 (8%)	4 (8%)	2 (4%)
*Preputial gland	(50)	(50)	(50)
Inflammation, necrotizing	2 (4%)		
Inflammation, active chronic	1 (2%)		
#Prostate	(49)	(50)	(48)
Mineralization			1 (2%)
Distention	1 (2%)	1 (2%)	
Inflammation, active chronic	29 (59%)	25 (50%)	25 (52%)
Hyperplasia, epithelial		3 (6%)	
#Testis	(50)	(50)	(50)
Necrosis, diffuse		1 (2%)	
Atrophy, NOS	19 (38%)	34 (68%)	33 (66%)
Hyperplasia, interstitial cell	39 (78%)	47 (94%)	45 (90%)
#Testis/tubule	(50)	(50)	(50)
Distention			1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Hemorrhage		1 (2%)	
#Brain stem	(50)	(50)	(50)
Hemorrhage			1 (2%)
#Cerebellum	(50)	(50)	(50)
Hemorrhage		2 (4%)	
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(50)
Inflammation, acute			1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	2 (4%)	5 (10%)	
*Eye/lens, cortex	(50)	(50)	(50)
Mineralization		4 (8%)	1 (2%)
Cataract		1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Epicardium	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
ALL OTHER SYSTEMS			
Adipose tissue			
Eosinophilic leukocytic infiltrate			1
Inflammation, chronic			1
Necrosis, fat	2	4	8
SPECIAL MORPHOLOGY SUMMARY			
None			

Number of animals with tissue examined microscopically
* Number of animals necropsied

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	49	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Subcutaneous tissue	(49)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
#Trachea	(48)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Lung	(49)	(50)	(49)
Congestion, NOS	1 (2%)		1 (2%)
Edema, NOS	1 (2%)	1 (2%)	
Pneumonia, interstitial chronic		2 (4%)	
Perivascular cuffing	2 (4%)	2 (4%)	1 (2%)
Hyperplasia, alveolar epithelium	2 (4%)		
#Lung/alveoli	(49)	(50)	(49)
Edema, NOS		1 (2%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(49)	(50)
Hyperplasia, NOS	17 (35%)	12 (24%)	12 (24%)
Myelofibrosis	4 (8%)	1 (2%)	2 (4%)
#Spleen	(48)	(50)	(50)
Ectopia	1 (2%)		
Fibrosis	1 (2%)	1 (2%)	
Necrosis, NOS		1 (2%)	
Hemosiderosis	18 (38%)	22 (44%)	18 (36%)
Hyperplasia, lymphoid	1 (2%)		
Hematopoiesis	9 (19%)	3 (6%)	1 (2%)
#Splenic capsule	(48)	(50)	(50)
Fibrosis		1 (2%)	
#Thymus	(42)	(41)	(47)
Cyst, NOS	3 (7%)	1 (2%)	
Hemorrhage	1 (2%)	4 (10%)	3 (6%)
CIRCULATORY SYSTEM			
#Lymph node	(41)	(43)	(46)
Lymphangiectasis		1 (2%)	
#Mandibular lymph node	(41)	(43)	(46)
Lymphangiectasis	7 (17%)	18 (42%)	14 (30%)
#Myocardium	(49)	(50)	(50)
Inflammation, chronic	8 (16%)		1 (2%)
Fibrosis	29 (59%)	32 (64%)	36 (72%)
Degeneration, NOS	6 (12%)	4 (8%)	3 (6%)
#Mitral valve	(49)	(50)	(50)
Inflammation, chronic	1 (2%)		
*Pulmonary artery	(49)	(50)	(50)
Mineralization			2 (4%)
DIGESTIVE SYSTEM			
#Salivary gland	(48)	(50)	(50)
Inflammation, active chronic	1 (2%)		
Atrophy, NOS	3 (6%)	2 (4%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Liver	(49)	(50)	(50)
Granuloma, NOS	15 (31%)	21 (42%)	19 (38%)
Necrosis, NOS	1 (2%)		
Necrosis, focal			2 (4%)
Necrosis, coagulative	1 (2%)	2 (4%)	1 (2%)
Metamorphosis, fatty	6 (12%)	4 (8%)	2 (4%)
Hemosiderosis	1 (2%)		
Nuclear alteration		1 (2%)	
Basophilic cyto change	42 (86%)	43 (86%)	42 (84%)
Ground glass cyto change		1 (2%)	
Focal cellular change	1 (2%)	2 (4%)	1 (2%)
Eosinophilic cyto change	1 (2%)	1 (2%)	
Clear cell change	2 (4%)	2 (4%)	1 (2%)
Hyperplasia, focal		1 (2%)	
Angiectasis	3 (6%)	4 (8%)	1 (2%)
#Periportal bile duct	(49)	(50)	(50)
Hyperplasia, NOS	18 (37%)	26 (52%)	20 (40%)
#Liver/centrilobular	(49)	(50)	(50)
Necrosis, NOS	1 (2%)		
#Liver/hepatocytes	(49)	(50)	(50)
Cytoplasmic vacuolization	1 (2%)	1 (2%)	3 (6%)
#Pancreas	(47)	(50)	(49)
Edema, NOS		1 (2%)	
#Pancreatic acinus	(47)	(50)	(49)
Atrophy, NOS	13 (28%)	16 (32%)	12 (24%)
Hypertrophy, NOS		3 (6%)	
#Pancreas/interstitium	(47)	(50)	(49)
Inflammation, chronic	1 (2%)		
#Glandular stomach	(49)	(50)	(49)
Multiple cysts	35 (71%)	42 (84%)	33 (67%)
#Forestomach	(49)	(50)	(49)
Ulcer, NOS	1 (2%)	1 (2%)	
Hyperplasia, epithelial		2 (4%)	
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Mineralization			1 (2%)
Cyst, NOS	1 (2%)		
Nephropathy	43 (88%)	45 (90%)	38 (76%)
Pigmentation, NOS	1 (2%)		1 (2%)
#Convoluted tubules	(49)	(50)	(50)
Metamorphosis, fatty		1 (2%)	
#Urinary bladder	(48)	(49)	(50)
Inflammation, acute		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(50)	(49)
Cyst, NOS	1 (2%)		
Angiectasis	4 (8%)	1 (2%)	5 (10%)
#Anterior pituitary	(49)	(50)	(49)
Cyst, NOS	3 (6%)	1 (2%)	4 (8%)
Hypertrophy, focal	1 (2%)		
Hyperplasia, focal	12 (24%)	7 (14%)	6 (12%)
Angiectasis	29 (59%)	27 (54%)	21 (43%)
#Adrenal cortex	(49)	(50)	(49)
Degeneration, NOS			1 (2%)
Degeneration, cystic		1 (2%)	
Degeneration, ballooning			1 (2%)
Degeneration, lipoid			1 (2%)
Metamorphosis, fatty	3 (6%)	3 (6%)	1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Adrenal cortex (Continued)	(49)	(50)	(49)
Hyperplasia, atypical			1 (2%)
Hyperplasia, focal	25 (51%)	24 (48%)	20 (41%)
Angiectasis	33 (67%)	36 (72%)	35 (71%)
#Adrenal medulla	(49)	(50)	(49)
Hyperplasia, focal	1 (2%)		1 (2%)
#Thyroid	(48)	(50)	(49)
Follicular cyst, NOS		1 (2%)	1 (2%)
Hyperplasia, C-cell	14 (29%)	16 (32%)	13 (27%)
#Parathyroid	(36)	(28)	(35)
Hyperplasia, focal		1 (4%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(49)	(50)	(50)
Galactocele	1 (2%)		
Hyperplasia, cystic	32 (65%)	29 (58%)	18 (36%)
*Clitoral gland	(49)	(50)	(50)
Inflammation, active chronic	1 (2%)		
#Uterus	(49)	(50)	(50)
Prolapse	1 (2%)		
Hydrometra		1 (2%)	
Inflammation, acute hemorrhagic	1 (2%)		
Inflammation, active chronic	1 (2%)		
Adenomyosis			1 (2%)
#Endometrial gland	(49)	(50)	(50)
Cyst, NOS	6 (12%)	13 (26%)	15 (30%)
#Ovary	(49)	(50)	(50)
Cyst, NOS	3 (6%)	1 (2%)	2 (4%)
NERVOUS SYSTEM			
#Brain	(49)	(50)	(50)
Hydrocephalus, NOS	2 (4%)	1 (2%)	1 (2%)
Hemorrhage	2 (4%)		
SPECIAL SENSE ORGANS			
*Eye/retina	(49)	(50)	(50)
Atrophy, NOS	3 (6%)	3 (6%)	
*Eye/lens, cortex	(49)	(50)	(50)
Mineralization	3 (6%)	1 (2%)	
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
Adipose tissue			
Necrosis, fat	6	2	3

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
Autolysis/no necropsy	1		

Number of animals with tissue examined microscopically
* Number of animals necropsied

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Hyperplasia, cystic			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Necrosis, fat		1 (2%)	
RESPIRATORY SYSTEM			
#Tracheal gland	(50)	(47)	(47)
Cyst, NOS		1 (2%)	
#Lung	(50)	(50)	(50)
Multiple cysts		1 (2%)	
Atelectasis	1 (2%)		
Congestion, NOS		1 (2%)	1 (2%)
Hemorrhage		2 (4%)	2 (4%)
Lymphocytic inflammatory infiltrate	1 (2%)		1 (2%)
Inflammation, chronic			1 (2%)
Fibrosis, focal		1 (2%)	
Perivascular cuffing	4 (8%)	10 (20%)	5 (10%)
Alveolar macrophages	4 (8%)	1 (2%)	1 (2%)
Hyperplasia, adenomatous			1 (2%)
Hyperplasia, alveolar epithelium		2 (4%)	1 (2%)
#Lung/alveoli	(50)	(50)	(50)
Hemorrhage	1 (2%)	4 (8%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid			1 (2%)
*Blood	(50)	(50)	(50)
Leukocytosis, neutrophilic			1 (2%)
#Bone marrow	(50)	(50)	(48)
Fibrosis			2 (4%)
Atrophy, NOS		1 (2%)	
Hyperplasia, NOS	1 (2%)		
Angiectasis	1 (2%)	4 (8%)	5 (10%)
Hyperplasia, hematopoietic	1 (2%)		2 (4%)
Hyperplasia, granulocytic	1 (2%)	1 (2%)	1 (2%)
#Spleen	(50)	(50)	(49)
Ectopia		1 (2%)	
Fibrosis	2 (4%)		1 (2%)
Fibrosis, focal	1 (2%)		
Angiectasis	1 (2%)		
Hyperplasia, lymphoid	14 (28%)	19 (38%)	15 (31%)
Hematopoiesis	7 (14%)	7 (14%)	11 (22%)
#Splenic follicles	(50)	(50)	(49)
Atrophy, NOS		1 (2%)	
#Mandibular lymph node	(35)	(31)	(33)
Hemorrhage		2 (6%)	
Hyperplasia, reticulum cell		1 (3%)	
Hyperplasia, lymphoid	2 (6%)	1 (3%)	
#Pancreatic lymph node	(35)	(31)	(33)
Depletion, lymphoid		1 (3%)	
Angiectasis		1 (3%)	
#Mesenteric lymph node	(35)	(31)	(33)
Hemorrhage		1 (3%)	1 (3%)
Angiectasis			1 (3%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Renal lymph node	(35)	(31)	(33)
Erythrophagocytosis			1 (3%)
Hyperplasia, lymphoid	1 (3%)		
#Lung	(50)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)		
*Pulmonary vein	(50)	(50)	(50)
Leukocytosis, NOS			1 (2%)
#Liver	(50)	(50)	(49)
Hematopoiesis			1 (2%)
#Peyers patch	(49)	(46)	(49)
Hyperplasia, lymphoid		1 (2%)	1 (2%)
#Kidney	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)	2 (4%)	1 (2%)
#Thymus	(33)	(39)	(38)
Cyst, NOS	4 (12%)	5 (13%)	5 (13%)
Multiple cysts	6 (18%)	7 (18%)	6 (16%)
Hemorrhage		1 (3%)	
Amyloidosis	1 (3%)		
Atrophy, NOS	2 (6%)	1 (3%)	2 (5%)
Hyperplasia, epithelial		1 (3%)	1 (3%)
Hyperplasia, lymphoid	1 (3%)		
CIRCULATORY SYSTEM			
#Lung	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
#Heart	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, chronic focal		1 (2%)	1 (2%)
Perivasculitis	1 (2%)	1 (2%)	
#Myocardium	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal			1 (2%)
Degeneration, NOS		1 (2%)	
Calcification, NOS	1 (2%)		
*Pulmonary vein	(50)	(50)	(50)
Mineralization		1 (2%)	
#Stomach	(50)	(50)	(49)
Perivasculitis		1 (2%)	
#Prostate	(49)	(50)	(50)
Perivasculitis	1 (2%)		
#Thyroid	(50)	(50)	(50)
Perivasculitis	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(50)
Mineralization		1 (2%)	
Hemorrhage		1 (2%)	
Perivascular cuffing	25 (50%)	21 (42%)	21 (42%)
#Liver	(50)	(50)	(49)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, necrotizing		1 (2%)	1 (2%)
Inflammation, chronic focal	1 (2%)	2 (4%)	1 (2%)
Cholangiofibrosis	1 (2%)		
Perivascular cuffing			1 (2%)
Degeneration, NOS	1 (2%)		
Necrosis, NOS	2 (4%)		1 (2%)
Necrosis, focal	6 (12%)	1 (2%)	1 (2%)
Metamorphosis, fatty	2 (4%)		
Cytoplasmic vacuolization		1 (2%)	
Basophilic cytoplasmic change		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Liver (Continued)	(50)	(50)	(49)
Focal cellular change	9 (18%)	3 (6%)	7 (14%)
Eosinophilic cytoplasmic change			1 (2%)
Clear cell change	1 (2%)		
Hepatocytomegaly		2 (4%)	
Angiectasis	1 (2%)		
#Liver/centrilobular	(50)	(50)	(49)
Degeneration, NOS	1 (2%)		
Metamorphosis, fatty	1 (2%)		
#Liver/hepatocytes	(50)	(50)	(49)
Metamorphosis, fatty	1 (2%)		
Cytoplasmic vacuolization		1 (2%)	
*Gallbladder	(50)	(50)	(50)
Multiple cysts			1 (2%)
Perivascular cuffing			2 (4%)
Hyperplasia, epithelial	1 (2%)		
Hyperplasia, papillary		1 (2%)	
#Pancreas	(49)	(50)	(49)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic focal			1 (2%)
Perivascular cuffing			1 (2%)
Atrophy, focal			1 (2%)
#Pancreatic acinus	(49)	(50)	(49)
Degeneration, NOS		1 (2%)	
Cytoplasmic vacuolization		2 (4%)	4 (8%)
Hypertrophy, NOS			1 (2%)
#Esophagus	(48)	(48)	(49)
Perivascular cuffing		1 (2%)	
#Stomach	(50)	(50)	(49)
Lymphocytic inflammatory infiltrate			1 (2%)
#Gastric mucosa	(50)	(50)	(49)
Hyperkeratosis			1 (2%)
#Glandular stomach	(50)	(50)	(49)
Mineralization	1 (2%)		
Cyst, NOS			2 (4%)
Multiple cysts		2 (4%)	1 (2%)
Inflammation, acute/chronic	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		1 (2%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, adenomatous	1 (2%)		
#Gastric submucosa	(50)	(50)	(49)
Inflammation, acute	1 (2%)		
#Gastric serosa	(50)	(50)	(49)
Inflammation, chronic focal	1 (2%)		
#Forestomach	(50)	(50)	(49)
Cyst, NOS			2 (4%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Mineralization	23 (46%)	17 (34%)	17 (34%)
Cyst, NOS	1 (2%)		
Multiple cysts	2 (4%)		
Lymphocytic inflammatory infiltrate	3 (6%)	2 (4%)	
Inflammation, chronic focal	4 (8%)		
Perivascular cuffing	5 (10%)	7 (14%)	4 (8%)
Nephropathy	36 (72%)	25 (50%)	23 (46%)
Nephrosis, NOS	1 (2%)		2 (4%)
Calcification, NOS	2 (4%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney (Continued)	(50)	(50)	(50)
Hyperplasia, tubular cell	1 (2%)	7 (14%)	
Metaplasia, osseous	1 (2%)	1 (2%)	
#Kidney/cortex	(50)	(50)	(50)
Cyst, NOS		2 (4%)	
Multiple cysts			1 (2%)
Hyperplasia, epithelial			1 (2%)
#Perirenal tissue	(50)	(50)	(50)
Perivascular cuffing	1 (2%)		
#Kidney/tubule	(50)	(50)	(50)
Multiple cysts		1 (2%)	
#Convoluted tubules	(50)	(50)	(50)
Metamorphosis, fatty	1 (2%)		1 (2%)
#Urinary bladder	(48)	(49)	(47)
Congestion, NOS		2 (4%)	
Perivascular cuffing	11 (23%)	7 (14%)	7 (15%)
Hyperplasia, epithelial			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary intermedia	(50)	(49)	(48)
Focal cellular change		1 (2%)	
#Anterior pituitary	(50)	(49)	(48)
Cyst, NOS	3 (6%)	2 (4%)	3 (6%)
Multiple cysts	1 (2%)		1 (2%)
Focal cellular change	2 (4%)		
Hyperplasia, focal	1 (2%)		
#Adrenal/capsule	(50)	(50)	(48)
Hyperplasia, stromal	34 (68%)	33 (66%)	35 (73%)
#Adrenal cortex	(50)	(50)	(48)
Ectopia	1 (2%)		2 (4%)
Cyst, NOS		1 (2%)	
Multiple cysts			1 (2%)
Degeneration, lipoid		1 (2%)	
Focal cellular change	24 (48%)	23 (46%)	25 (52%)
Cytomegaly			1 (2%)
Hypertrophy, focal	3 (6%)		2 (4%)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal	5 (10%)	5 (10%)	2 (4%)
#Adrenal medulla	(50)	(50)	(48)
Degeneration, NOS	1 (2%)		
Hyperplasia, focal			1 (2%)
Metaplasia, osseous			1 (2%)
#Thyroid	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Follicular cyst, NOS	3 (6%)		
Inflammation, chronic focal		1 (2%)	
Hyperplasia, follicular cell	1 (2%)	1 (2%)	1 (2%)
#Thyroid follicle	(50)	(50)	(50)
Multiple cysts	1 (2%)		1 (2%)
Crystals, NOS		1 (2%)	
Hyperplasia, cystic		1 (2%)	
#Thyroid colloid	(50)	(50)	(50)
Degeneration, NOS	1 (2%)		1 (2%)
Crystals, NOS			1 (2%)
#Parathyroid	(35)	(30)	(34)
Ectopia	1 (3%)		
Cyst, NOS			1 (3%)
#Pancreatic islets	(49)	(50)	(49)
Hyperplasia, NOS	9 (18%)	13 (26%)	9 (18%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS	32 (64%)	30 (60%)	33 (66%)
Cyst, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Abscess, NOS	1 (2%)		
Inflammation, acute/chronic	4 (8%)		1 (2%)
Inflammation, chronic	4 (8%)	2 (4%)	4 (8%)
Necrosis, NOS		1 (2%)	
Hyperkeratosis	3 (6%)	1 (2%)	
Metaplasia, squamous	7 (14%)	3 (6%)	6 (12%)
#Prostate	(49)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute			1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)	
Inflammation, chronic focal	1 (2%)		
Perivascular cuffing	8 (16%)	14 (28%)	3 (6%)
Hyperplasia, focal			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
Necrosis, NOS			1 (2%)
#Testis	(50)	(50)	(50)
Degeneration, NOS			1 (2%)
Atrophy, NOS		3 (6%)	
Atrophy, focal	2 (4%)		
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Mineralization	1 (2%)		
Hemorrhage	1 (2%)		
Perivascular cuffing		1 (2%)	
#Brain/thalamus	(50)	(50)	(50)
Mineralization	1 (2%)	1 (2%)	1 (2%)
Hemorrhage		1 (2%)	
Calcification, NOS	34 (68%)	28 (56%)	27 (54%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage			1 (2%)
*Eye/cornea	(50)	(50)	(50)
Vascularization	1 (2%)		
*Eye/lens, cortex	(50)	(50)	(50)
Cataract	1 (2%)		
*Eye/lacrimal gland	(50)	(50)	(50)
Hyperplasia, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Enostosis	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Steatitis			1 (2%)
*Pericardium	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
*Mesentery	(50)	(50)	(50)
Steatitis	1 (2%)		
Perivascular cuffing	1 (2%)	1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Perivascular cuffing	1 (2%)	1 (2%)	2 (4%)
Adipose tissue			
Necrosis, fat	1	2	2
SPECIAL MORPHOLOGY SUMMARY			
None			

Number of animals with tissue examined microscopically
* Number of animals necropsied

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
None			
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(49)
Cyst, NOS		1 (2%)	
Congestion, NOS	1 (2%)	1 (2%)	
Hemorrhage	6 (12%)	2 (4%)	1 (2%)
Inflammation, chronic	1 (2%)		
Perivascular cuffing	5 (10%)	1 (2%)	2 (4%)
Alveolar macrophages		1 (2%)	
Hyperplasia, adenomatous		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(49)
Leukemoid reaction		1 (2%)	
Hyperplasia, lymphoid	2 (4%)	2 (4%)	7 (14%)
*Mediastinum	(50)	(50)	(49)
Hyperplasia, lymphoid	1 (2%)		
#Bone marrow	(50)	(50)	(49)
Fibrosis	4 (8%)	10 (20%)	6 (12%)
Hyperplasia, NOS		1 (2%)	1 (2%)
Angiectasis	2 (4%)	1 (2%)	
Hyperplasia, erythroid	1 (2%)		1 (2%)
Hyperplasia, granulocytic	5 (10%)	7 (14%)	6 (12%)
#Spleen	(48)	(50)	(49)
Angiectasis		1 (2%)	
Hyperplasia, plasma cell		1 (2%)	
Hyperplasia, reticulum cell	1 (2%)	1 (2%)	
Hyperplasia, lymphoid	10 (21%)	9 (18%)	6 (12%)
Hematopoiesis	7 (15%)	10 (20%)	5 (10%)
Erythropoiesis			1 (2%)
#Mandibular lymph node	(39)	(45)	(41)
Hemorrhage		1 (2%)	
Hyperplasia, plasma cell			1 (2%)
#Mesenteric lymph node	(39)	(45)	(41)
Infarct, NOS		1 (2%)	
#Lung	(50)	(50)	(49)
Hyperplasia, lymphoid		1 (2%)	2 (4%)
#Liver	(50)	(50)	(49)
Hyperplasia, lymphoid			1 (2%)
Hematopoiesis			1 (2%)
#Thymus	(40)	(37)	(39)
Cyst, NOS	4 (10%)	1 (3%)	2 (5%)
Multiple cysts	2 (5%)		
Inflammation, acute/chronic		1 (3%)	
Atrophy, NOS			1 (3%)
Angiectasis	1 (3%)		
Hyperplasia, lymphoid	2 (5%)		1 (3%)
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(49)
Perivasculitis	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
#Heart	(50)	(50)	(49)
Thrombosis, NOS			1 (2%)
Perivascular cuffing	1 (2%)		
#Myocardium	(50)	(50)	(49)
Mineralization		1 (2%)	
Fibrosis, focal	1 (2%)		
Degeneration, NOS		1 (2%)	
Calcification, NOS	1 (2%)		
Cytomegaly			1 (2%)
*Pulmonary vein	(50)	(50)	(49)
Thrombosis, NOS	1 (2%)		
#Kidney	(50)	(50)	(49)
Perivasculitis	1 (2%)		
#Thymus	(40)	(37)	(39)
Lymphangiectasis			1 (3%)
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(49)	(47)
Perivascular cuffing	3 (6%)		2 (4%)
Degeneration, NOS			1 (2%)
Atrophy, NOS			1 (2%)
#Liver	(50)	(50)	(49)
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Fibrosis	1 (2%)		
Perivascular cuffing	1 (2%)		
Degeneration, NOS	1 (2%)		1 (2%)
Necrosis, NOS	1 (2%)	2 (4%)	1 (2%)
Necrosis, focal	8 (16%)	6 (12%)	4 (8%)
Metamorphosis, fatty		1 (2%)	
Lipoidosis	1 (2%)		
Pigmentation, NOS			1 (2%)
Cytoplasmic vacuolization		1 (2%)	
Focal cellular change	2 (4%)	1 (2%)	1 (2%)
Hyperplasia, nodular	1 (2%)		
Angiectasis	1 (2%)		
#Liver/hepatocytes	(50)	(50)	(49)
Cytoplasmic vacuolization	3 (6%)		
#Pancreas	(48)	(50)	(48)
Cyst, NOS	1 (2%)		1 (2%)
Inflammation, chronic focal			1 (2%)
Atrophy, NOS		1 (2%)	2 (4%)
#Pancreatic acinus	(48)	(50)	(48)
Cytoplasmic vacuolization		2 (4%)	
Focal cellular change	1 (2%)	1 (2%)	
Atrophy, NOS		1 (2%)	
#Esophagus	(48)	(49)	(49)
Inflammation, chronic focal			1 (2%)
#Stomach	(49)	(49)	(49)
Inflammation, chronic focal	1 (2%)		1 (2%)
#Glandular stomach	(49)	(49)	(49)
Cyst, NOS	2 (4%)	1 (2%)	
Multiple cysts		1 (2%)	2 (4%)
Inflammation, acute/chronic	1 (2%)	3 (6%)	2 (4%)
Inflammation, chronic focal		2 (4%)	1 (2%)
Degeneration, hyaline	1 (2%)		1 (2%)
Calcification, NOS		1 (2%)	
#Gastric serosa	(49)	(49)	(49)
Inflammation, chronic focal			1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(49)	(49)	(49)
Ulcer, NOS			1 (2%)
Inflammation, acute/chronic	1 (2%)		1 (2%)
Inflammation, chronic focal	1 (2%)		
Hyperkeratosis	1 (2%)		
#Duodenum	(48)	(49)	(48)
Ectopia			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Hydronephrosis	1 (2%)		
Cyst, NOS			1 (2%)
Glomerulonephritis, subacute	2 (4%)	2 (4%)	
Glomerulonephritis, chronic		1 (2%)	
Perivascular cuffing			2 (4%)
Nephropathy	7 (14%)	3 (6%)	2 (4%)
Degeneration, NOS			2 (4%)
Hypoplasia, NOS	1 (2%)		
Atrophy, NOS	1 (2%)		
Hyperplasia, tubular cell		1 (2%)	
Metaplasia, osseous	1 (2%)	1 (2%)	
#Kidney/capsule	(50)	(50)	(49)
Scar		1 (2%)	
#Perirenal tissue	(50)	(50)	(49)
Perivascular cuffing	1 (2%)		
#Kidney/glomerulus	(50)	(50)	(49)
Amyloidosis		1 (2%)	1 (2%)
Hypertrophy, NOS	1 (2%)		
#Kidney/tubule	(50)	(50)	(49)
Multiple cysts			1 (2%)
#Convoluted tubules	(50)	(50)	(49)
Degeneration, NOS	1 (2%)	1 (2%)	2 (4%)
Degeneration, hyaline	1 (2%)	4 (8%)	
#Kidney/pelvis	(50)	(50)	(49)
Mineralization	1 (2%)		
#Urinary bladder	(46)	(47)	(44)
Inflammation, chronic focal	1 (2%)		
Perivascular cuffing	3 (7%)	4 (9%)	4 (9%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(50)	(48)
Cyst, NOS	2 (4%)	1 (2%)	1 (2%)
Multiple cysts		1 (2%)	1 (2%)
Hemorrhagic cyst	1 (2%)		
Focal cellular change	6 (13%)	3 (6%)	5 (10%)
Cytomegaly		1 (2%)	
Hyperplasia, NOS		2 (4%)	
Hyperplasia, focal	5 (10%)	8 (16%)	5 (10%)
Angiectasis		1 (2%)	
#Adrenal	(48)	(49)	(49)
Cyst, NOS		1 (2%)	
Hypoplasia, NOS	1 (2%)		
#Adrenal/capsule	(48)	(49)	(49)
Hyperplasia, stromal	45 (94%)	48 (98%)	48 (98%)
#Adrenal cortex	(48)	(49)	(49)
Ectopia	3 (6%)		5 (10%)
Mineralization		1 (2%)	
Cyst, NOS	1 (2%)		1 (2%)
Multiple cysts			1 (2%)
Degeneration, lipoid	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Adrenal cortex (Continued)	(48)	(49)	(49)
Pigmentation, NOS		1 (2%)	
Focal cellular change	7 (15%)	5 (10%)	3 (6%)
Hypertrophy, focal		1 (2%)	
Hyperplasia, focal	1 (2%)		2 (4%)
Angiectasis		1 (2%)	2 (4%)
#Adrenal medulla	(48)	(49)	(49)
Hypertrophy, NOS			1 (2%)
Hyperplasia, focal			2 (4%)
#Thyroid	(48)	(49)	(49)
Cyst, NOS			1 (2%)
Follicular cyst, NOS		2 (4%)	
Inflammation, focal		1 (2%)	
Inflammation, acute focal			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	1 (2%)	1 (2%)	3 (6%)
Inflammation, granulomatous			1 (2%)
Hyperplasia, follicular cell	6 (13%)	13 (27%)	14 (29%)
#Thyroid follicle	(48)	(49)	(49)
Dilatation, NOS		1 (2%)	
#Parathyroid	(36)	(37)	(33)
Cyst, NOS			1 (3%)
Multiple cysts		1 (3%)	
Hyperplasia, NOS	1 (3%)		
#Pancreatic islets	(48)	(50)	(48)
Hyperplasia, NOS	15 (31%)	15 (30%)	9 (19%)
Angiectasis	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(49)
Multiple cysts	4 (8%)	1 (2%)	3 (6%)
Corpora amylacea		1 (2%)	
Hyperplasia, cystic		1 (2%)	
#Uterus	(50)	(50)	(49)
Dilatation, NOS	9 (18%)	6 (12%)	11 (22%)
Distention			1 (2%)
Cyst, NOS			1 (2%)
Multiple cysts			1 (2%)
Hemosiderosis			1 (2%)
Angiectasis	1 (2%)		1 (2%)
#Uterus/endometrium	(50)	(50)	(49)
Cyst, NOS		1 (2%)	
Multiple cysts	28 (56%)	32 (64%)	24 (49%)
Inflammation, suppurative		1 (2%)	
Inflammation, acute	3 (6%)	5 (10%)	5 (10%)
Hyperplasia, cystic	12 (24%)	11 (22%)	15 (31%)
Angiectasis	2 (4%)		1 (2%)
#Endometrial stroma	(50)	(50)	(49)
Degeneration, hyaline		1 (2%)	1 (2%)
#Ovary	(41)	(42)	(43)
Cyst, NOS	10 (24%)	11 (26%)	15 (35%)
Multiple cysts	4 (10%)	3 (7%)	3 (7%)
Hematoma, organized	1 (2%)		
Hemorrhagic cyst	10 (24%)	4 (10%)	5 (12%)
Abscess, NOS		1 (2%)	
Inflammation, chronic			2 (5%)
Necrosis, focal	1 (2%)		
Calcification, NOS		1 (2%)	2 (5%)
Angiectasis	1 (2%)	1 (2%)	1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Mesovarium	(41)	(42)	(43)
Perivascular cuffing	2 (5%)	1 (2%)	
NERVOUS SYSTEM			
#Lateral ventricle	(50)	(50)	(49)
Distention		1 (2%)	
#Brain	(50)	(50)	(49)
Hemorrhage			1 (2%)
Perivascular cuffing		1 (2%)	
#Cerebral cortex	(50)	(50)	(49)
Epidermal inclusion cyst			1 (2%)
Gliosis	1 (2%)		
Cholesterol deposit	1 (2%)		1 (2%)
#Hippocampus	(50)	(50)	(49)
Inflammation, acute/chronic	1 (2%)		
Perivascular cuffing		1 (2%)	
Degeneration, NOS		1 (2%)	
Malacia		1 (2%)	
#Corpus callosum	(50)	(50)	(49)
Malacia	1 (2%)		
#Brain/thalamus	(50)	(50)	(49)
Malacia		1 (2%)	
Calcification, NOS	26 (52%)	21 (42%)	18 (37%)
#Cerebellum	(50)	(50)	(49)
Hemorrhage		1 (2%)	
SPECIAL SENSE ORGANS			
*Eye/crystalline lens	(50)	(50)	(49)
Cataract	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(49)
Osteosclerosis	3 (6%)	1 (2%)	2 (4%)
Hyperplasia, NOS	3 (6%)	6 (12%)	2 (4%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(49)
Inflammation, chronic focal		1 (2%)	
*Epicardium	(50)	(50)	(49)
Inflammation, granulomatous	1 (2%)		
*Mesentery	(50)	(50)	(49)
Multiple cysts	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute/chronic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(49)
Perivascular cuffing	1 (2%)	1 (2%)	1 (2%)
Adipose tissue			
Congestion, NOS	1		
Hemorrhage	1		
Necrosis, fat	10	2	3

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	CONTROL (UNTR)	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
Auto/necropsy/histo performed	1		
Autolysis/no necropsy			1

Number of animals with tissue examined microscopically
* Number of animals necropsied

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	Control	125 ppm	250 ppm
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	13.8%	3.7%	2.9%
Terminal Rates (c)	4/29 (14%)	1/27 (4%)	1/35 (3%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.073N	P=0.199N	P=0.126N
Incidental Tumor Tests (d)	P=0.073N	P=0.199N	P=0.126N
Cochran-Armitage Trend Test (d)	P=0.101N		
Fisher Exact Test (d)		P=0.181N	P=0.181N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	5/50 (10%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	15.6%	3.7%	2.9%
Terminal Rates (c)	4/29 (14%)	1/27 (4%)	1/35 (3%)
Week of First Observation	67	104	104
Life Table Tests (d)	P=0.035N	P=0.116N	P=0.071N
Incidental Tumor Tests (d)	P=0.061N	P=0.158N	P=0.126N
Cochran-Armitage Trend Test (d)	P=0.049N		
Fisher Exact Test (d)		P=0.102N	P=0.102N
Subcutaneous Tissue: Fibroma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	5/50 (10%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	15.6%	3.7%	5.7%
Terminal Rates (c)	4/29 (14%)	1/27 (4%)	2/35 (6%)
Week of First Observation	67	104	104
Life Table Tests (d)	P=0.097N	P=0.116N	P=0.155N
Incidental Tumor Tests (d)	P=0.155N	P=0.158N	P=0.252N
Cochran-Armitage Trend Test (d)	P=0.133N		
Fisher Exact Test (d)		P=0.102N	P=0.218N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	25/50 (50%)	31/50 (62%)	32/50 (64%)
Adjusted Rates (b)	55.4%	68.1%	65.3%
Terminal Rates (c)	9/29 (31%)	13/27 (48%)	18/35 (51%)
Week of First Observation	69	67	84
Life Table Tests (d)	P=0.490	P=0.245	P=0.487
Incidental Tumor Tests (d)	P=0.095	P=0.362	P=0.096
Cochran-Armitage Trend Test (d)	P=0.093		
Fisher Exact Test (d)		P=0.157	P=0.113
Liver: Neoplastic Nodule			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (b)	3.1%	16.7%	14.3%
Terminal Rates (c)	0/29 (0%)	4/27 (15%)	5/35 (14%)
Week of First Observation	101	86	104
Life Table Tests (d)	P=0.151	P=0.102	P=0.156
Incidental Tumor Tests (d)	P=0.115	P=0.111	P=0.166
Cochran-Armitage Trend Test (d)	P=0.090		
Fisher Exact Test (d)		P=0.102	P=0.102
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (b)	9.8%	16.7%	14.3%
Terminal Rates (c)	2/29 (7%)	4/27 (15%)	5/35 (14%)
Week of First Observation	101	86	104
Life Table Tests (d)	P=0.416	P=0.341	P=0.469
Incidental Tumor Tests (d)	P=0.362	P=0.359	P=0.484
Cochran-Armitage Trend Test (d)	P=0.297		
Fisher Exact Test (d)		P=0.357	P=0.357

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	Control	125 ppm	250 ppm
Pituitary: Adenoma			
Overall Rates (a)	4/49 (8%)	13/49 (27%)	13/48 (27%)
Adjusted Rates (b)	13.2%	34.5%	34.3%
Terminal Rates (c)	3/29 (10%)	5/27 (19%)	9/33 (27%)
Week of First Observation	102	79	97
Life Table Tests (d)	P=0.059	P=0.021	P=0.041
Incidental Tumor Tests (d)	P=0.046	P=0.047	P=0.059
Cochran-Armitage Trend Test (d)	P=0.014		
Fisher Exact Test (d)		P=0.015	P=0.014
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	13/49 (27%)	13/48 (27%)
Adjusted Rates (b)	16.6%	34.5%	34.3%
Terminal Rates (c)	4/29 (14%)	5/27 (19%)	9/33 (27%)
Week of First Observation	102	79	97
Life Table Tests (d)	P=0.097	P=0.040	P=0.077
Incidental Tumor Tests (d)	P=0.081	P=0.085	P=0.106
Cochran-Armitage Trend Test (d)	P=0.028		
Fisher Exact Test (d)		P=0.033	P=0.029
Adrenal: Pheochromocytoma			
Overall Rates (a)	10/50 (20%)	19/50 (38%)	11/49 (22%)
Adjusted Rates (b)	31.7%	54.1%	26.0%
Terminal Rates (c)	8/29 (28%)	12/27 (44%)	5/34 (15%)
Week of First Observation	95	86	95
Life Table Tests (d)	P=0.400N	P=0.038	P=0.496N
Incidental Tumor Tests (d)	P=0.364N	P=0.073	P=0.405N
Cochran-Armitage Trend Test (d)	P=0.431		
Fisher Exact Test (d)		P=0.038	P=0.479
Thyroid: C-Cell Adenoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	13.8%	6.1%	8.6%
Terminal Rates (c)	4/29 (14%)	1/27 (4%)	3/35 (9%)
Week of First Observation	104	97	104
Life Table Tests (d)	P=0.321N	P=0.354N	P=0.397N
Incidental Tumor Tests (d)	P=0.313N	P=0.316N	P=0.397N
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.339N	P=0.500N
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	13.3%	10.7%	8.1%
Terminal Rates (c)	3/29 (10%)	2/27 (7%)	2/35 (6%)
Week of First Observation	103	102	102
Life Table Tests (d)	P=0.321N	P=0.544N	P=0.395N
Incidental Tumor Tests (d)	P=0.289N	P=0.432N	P=0.355N
Cochran-Armitage Trend Test (d)	P=0.421N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	8/50 (16%)	5/50 (10%)	6/50 (12%)
Adjusted Rates (b)	26.7%	16.4%	16.5%
Terminal Rates (c)	7/29 (24%)	3/27 (11%)	5/35 (14%)
Week of First Observation	103	97	102
Life Table Tests (d)	P=0.204N	P=0.317N	P=0.247N
Incidental Tumor Tests (d)	P=0.178N	P=0.219N	P=0.223N
Cochran-Armitage Trend Test (d)	P=0.326N		
Fisher Exact Test (d)		P=0.277N	P=0.387N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	Control	125 ppm	250 ppm
Testis: Interstitial Cell Tumor			
Overall Rates (a)	45/50 (90%)	47/50 (94%)	46/50 (92%)
Adjusted Rates (b)	97.8%	100.0%	95.8%
Terminal Rates (c)	28/29 (97%)	27/27 (100%)	33/35 (94%)
Week of First Observation	67	67	90
Life Table Tests (d)	P=0.084N	P=0.389	P=0.111N
Incidental Tumor Tests (d)	P=0.225N	P=0.658N	P=0.357N
Cochran-Armitage Trend Test (d)	P=0.427		
Fisher Exact Test (d)		P=0.357	P=0.500
Preputial Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	4.5%	8.7%	2.9%
Terminal Rates (c)	0/29 (0%)	1/27 (4%)	1/35 (3%)
Week of First Observation	79	86	104
Life Table Tests (d)	P=0.330N	P=0.527	P=0.449N
Incidental Tumor Tests (d)	P=0.564N	P=0.513	P=0.730
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.500	P=0.500N
All Sites: Mesothelioma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	8.1%	0.0%	0.0%
Terminal Rates (c)	1/29 (3%)	0/27 (0%)	0/35 (0%)
Week of First Observation	80		
Life Table Tests (d)	P=0.029N	P=0.113N	P=0.094N
Incidental Tumor Tests (d)	P=0.069N	P=0.139N	P=0.270N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.122N	P=0.122N

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

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	Control	125 ppm	250 ppm
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	13/49 (27%)	16/50 (32%)	18/50 (36%)
Adjusted Rates (b)	38.1%	33.7%	37.9%
Terminal Rates (c)	7/27 (26%)	8/39 (21%)	10/39 (26%)
Week of First Observation	75	87	72
Life Table Tests (d)	P=0.459	P=0.469N	P=0.515
Incidental Tumor Tests (d)	P=0.065	P=0.328	P=0.106
Cochran-Armitage Trend Test (d)	P=0.183		
Fisher Exact Test (d)		P=0.353	P=0.212
Pituitary: Adenoma			
Overall Rates (a)	18/49 (37%)	24/50 (48%)	23/49 (47%)
Adjusted Rates (b)	50.8%	55.5%	57.4%
Terminal Rates (c)	11/27 (41%)	20/39 (51%)	22/39 (56%)
Week of First Observation	69	73	92
Life Table Tests (d)	P=0.413N	P=0.523N	P=0.457N
Incidental Tumor Tests (d)	P=0.349	P=0.266	P=0.457
Cochran-Armitage Trend Test (d)	P=0.180		
Fisher Exact Test (d)		P=0.176	P=0.206
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	19/49 (39%)	25/50 (50%)	23/49 (47%)
Adjusted Rates (b)	51.8%	57.8%	57.4%
Terminal Rates (c)	11/27 (41%)	21/39 (54%)	22/39 (56%)
Week of First Observation	60	73	92
Life Table Tests (d)	P=0.329N	P=0.508N	P=0.379N
Incidental Tumor Tests (d)	P=0.402	P=0.225	P=0.500
Cochran-Armitage Trend Test (d)	P=0.239		
Fisher Exact Test (d)		P=0.178	P=0.270
Adrenal: Cortical Adenoma			
Overall Rates (a)	3/49 (6%)	1/50 (2%)	2/49 (4%)
Adjusted Rates (b)	10.7%	2.6%	5.1%
Terminal Rates (c)	2/27 (7%)	1/39 (3%)	2/39 (5%)
Week of First Observation	103	104	104
Life Table Tests (d)	P=0.267N	P=0.190N	P=0.340N
Incidental Tumor Tests (d)	P=0.361N	P=0.244N	P=0.482N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.301N	P=0.500N
Adrenal: Pheochromocytoma			
Overall Rates (a)	1/49 (2%)	4/50 (8%)	2/49 (4%)
Adjusted Rates (b)	3.7%	9.1%	5.1%
Terminal Rates (c)	1/27 (4%)	1/39 (3%)	2/39 (5%)
Week of First Observation	104	92	104
Life Table Tests (d)	P=0.521	P=0.282	P=0.628
Incidental Tumor Tests (d)	P=0.346	P=0.173	P=0.628
Cochran-Armitage Trend Test (d)	P=0.406		
Fisher Exact Test (d)		P=0.187	P=0.500
Thyroid: C-Cell Adenoma			
Overall Rates (a)	5/48 (10%)	4/50 (8%)	4/49 (8%)
Adjusted Rates (b)	17.1%	10.3%	10.3%
Terminal Rates (c)	3/26 (12%)	4/39 (10%)	4/39 (10%)
Week of First Observation	100	104	104
Life Table Tests (d)	P=0.229N	P=0.278N	P=0.285N
Incidental Tumor Tests (d)	P=0.345N	P=0.361N	P=0.481N
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.474N	P=0.487N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	Control	125 ppm	250 ppm
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	7/48 (15%)	5/50 (10%)	6/49 (12%)
Adjusted Rates (b)	22.6%	12.8%	15.4%
Terminal Rates (c)	4/26 (15%)	5/39 (13%)	6/39 (15%)
Week of First Observation	82	104	104
Life Table Tests (d)	P=0.207N	P=0.165N	P=0.248N
Incidental Tumor Tests (d)	P=0.298N	P=0.228N	P=0.397N
Cochran-Armitage Trend Test (d)	P=0.424N		
Fisher Exact Test (d)		P=0.351N	P=0.484N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	10/49 (20%)	7/50 (14%)	(e) 3/50 (6%)
Adjusted Rates (b)	28.9%	17.3%	7.7%
Terminal Rates (c)	5/27 (19%)	6/39 (15%)	3/39 (8%)
Week of First Observation	69	98	104
Life Table Tests (d)	P=0.006N	P=0.118N	P=0.012N
Incidental Tumor Tests (d)	P=0.030N	P=0.310N	P=0.044N
Cochran-Armitage Trend Test (d)	P=0.025N		
Fisher Exact Test (d)		P=0.282N	P=0.033N
Mammary Gland: Fibroadenoma, Adenocarcinoma, or Papillary Adenocarcinoma			
Overall Rates (a)	11/49 (22%)	8/50 (16%)	(e) 4/50 (8%)
Adjusted Rates (b)	30.7%	19.8%	10.3%
Terminal Rates (c)	5/27 (19%)	7/39 (18%)	4/39 (10%)
Week of First Observation	69	98	104
Life Table Tests (d)	P=0.008N	P=0.115N	P=0.014N
Incidental Tumor Tests (d)	P=0.032N	P=0.301N	P=0.046N
Cochran-Armitage Trend Test (d)	P=0.032N		
Fisher Exact Test (d)		P=0.288N	P=0.041N
Clitoral Gland: Adenoma			
Overall Rates (a)	5/49 (10%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	17.1%	5.1%	2.6%
Terminal Rates (c)	4/27 (15%)	2/39 (5%)	1/39 (3%)
Week of First Observation	94	104	104
Life Table Tests (d)	P=0.023N	P=0.103N	P=0.046N
Incidental Tumor Tests (d)	P=0.032N	P=0.125N	P=0.069N
Cochran-Armitage Trend Test (d)	P=0.057N		
Fisher Exact Test (d)		P=0.210N	P=0.098N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	6/49 (12%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	18.8%	5.1%	2.6%
Terminal Rates (c)	4/27 (15%)	2/39 (5%)	1/39 (3%)
Week of First Observation	59	104	104
Life Table Tests (d)	P=0.011N	P=0.061N	P=0.026N
Incidental Tumor Tests (d)	P=0.025N	P=0.116N	P=0.056N
Cochran-Armitage Trend Test (d)	P=0.027N		
Fisher Exact Test (d)		P=0.128N	P=0.053N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	11/49 (22%)	14/50 (28%)	17/50 (34%)
Adjusted Rates (b)	28.1%	30.9%	40.3%
Terminal Rates (c)	4/27 (15%)	8/39 (21%)	14/39 (36%)
Week of First Observation	60	87	82
Life Table Tests (d)	P=0.350	P=0.548N	P=0.402
Incidental Tumor Tests (d)	P=0.074	P=0.160	P=0.131
Cochran-Armitage Trend Test (d)	P=0.122		
Fisher Exact Test (d)		P=0.343	P=0.146

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

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

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	Control	125 ppm	250 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	10.0%	14.6%	7.9%
Terminal Rates (c)	4/40 (10%)	6/41 (15%)	3/38 (8%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.459N	P=0.384	P=0.528N
Incidental Tumor Tests (d)	P=0.459N	P=0.384	P=0.528N
Cochran-Armitage Trend Test (d)	P=0.429N		
Fisher Exact Test (d)		P=0.370	P=0.500N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	12.5%	12.2%	2.6%
Terminal Rates (c)	5/40 (13%)	5/41 (12%)	1/38 (3%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.098N	P=0.616N	P=0.115N
Incidental Tumor Tests (d)	P=0.098N	P=0.616N	P=0.115N
Cochran-Armitage Trend Test (d)	P=0.090N		
Fisher Exact Test (d)		P=0.630	P=0.102N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	11/50 (22%)	4/50 (8%)
Adjusted Rates (b)	22.5%	26.8%	10.5%
Terminal Rates (c)	9/40 (23%)	11/41 (27%)	4/38 (11%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.125N	P=0.424	P=0.134N
Incidental Tumor Tests (d)	P=0.125N	P=0.424	P=0.134N
Cochran-Armitage Trend Test (d)	P=0.110N		
Fisher Exact Test (d)		P=0.402	P=0.117N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	0.0%	4.9%	10.2%
Terminal Rates (c)	0/40 (0%)	2/41 (5%)	3/38 (8%)
Week of First Observation		104	100
Life Table Tests (d)	P=0.033	P=0.244	P=0.059
Incidental Tumor Tests (d)	P=0.040	P=0.244	P=0.067
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		P=0.247	P=0.059
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	8/50 (16%)	4/50 (8%)	9/50 (18%)
Adjusted Rates (b)	19.3%	9.8%	22.5%
Terminal Rates (c)	7/40 (18%)	4/41 (10%)	7/38 (18%)
Week of First Observation	80	104	100
Life Table Tests (d)	P=0.406	P=0.170N	P=0.459
Incidental Tumor Tests (d)	P=0.439	P=0.179N	P=0.497
Cochran-Armitage Trend Test (d)	P=0.443		
Fisher Exact Test (d)		P=0.179N	P=0.500
Liver: Hepatocellular Adenoma			
Overall Rates (a)	10/50 (20%)	9/50 (18%)	14/49 (29%)
Adjusted Rates (b)	24.1%	22.0%	32.0%
Terminal Rates (c)	9/40 (23%)	9/41 (22%)	9/38 (24%)
Week of First Observation	79	104	48
Life Table Tests (d)	P=0.173	P=0.479N	P=0.217
Incidental Tumor Tests (d)	P=0.200	P=0.492N	P=0.252
Cochran-Armitage Trend Test (d)	P=0.184		
Fisher Exact Test (d)		P=0.500N	P=0.224

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	Control	125 ppm	250 ppm
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	13/50 (26%)	11/50 (22%)	13/49 (27%)
Adjusted Rates (b)	28.6%	23.9%	31.1%
Terminal Rates (c)	8/40 (20%)	6/41 (15%)	10/38 (26%)
Week of First Observation	79	58	88
Life Table Tests (d)	P=0.502	P=0.406N	P=0.541
Incidental Tumor Tests (d)	P=0.536N	P=0.587N	P=0.554N
Cochran-Armitage Trend Test (d)	P=0.523		
Fisher Exact Test (d)		P=0.408N	P=0.567
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	19/50 (38%)	18/50 (36%)	21/49 (43%)
Adjusted Rates (b)	42.0%	39.1%	47.3%
Terminal Rates (c)	14/40 (35%)	13/41 (32%)	15/38 (39%)
Week of First Observation	79	58	48
Life Table Tests (d)	P=0.333	P=0.480N	P=0.368
Incidental Tumor Tests (d)	P=0.378	P=0.524	P=0.449
Cochran-Armitage Trend Test (d)	P=0.348		
Fisher Exact Test (d)		P=0.500N	P=0.387
Adrenal: Cortical Adenoma			
Overall Rates (a)	7/50 (14%)	3/50 (6%)	1/48 (2%)
Adjusted Rates (b)	16.8%	7.3%	2.7%
Terminal Rates (c)	6/40 (15%)	3/41 (7%)	1/37 (3%)
Week of First Observation	79	104	104
Life Table Tests (d)	P=0.021N	P=0.153N	P=0.042N
Incidental Tumor Tests (d)	P=0.020N	P=0.162N	P=0.038N
Cochran-Armitage Trend Test (d)	P=0.020N		
Fisher Exact Test (d)		P=0.159N	P=0.034N
Adrenal: Adenoma or Cortical Adenoma			
Overall Rates (a)	7/50 (14%)	4/50 (8%)	2/48 (4%)
Adjusted Rates (b)	16.8%	9.8%	5.4%
Terminal Rates (c)	6/40 (15%)	4/41 (10%)	2/37 (5%)
Week of First Observation	79	104	104
Life Table Tests (d)	P=0.066N	P=0.252N	P=0.100N
Incidental Tumor Tests (d)	P=0.063N	P=0.264N	P=0.093N
Cochran-Armitage Trend Test (d)	P=0.061N		
Fisher Exact Test (d)		P=0.262N	P=0.090N
Harderian Gland: Adenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	7.5%	2.4%	7.0%
Terminal Rates (c)	3/40 (7%)	1/41 (2%)	1/38 (3%)
Week of First Observation	104	104	88
Life Table Tests (d)	P=0.578	P=0.296N	P=0.645
Incidental Tumor Tests (d)	P=0.575N	P=0.296N	P=0.642N
Cochran-Armitage Trend Test (d)	P=0.594		
Fisher Exact Test (d)		P=0.309N	P=0.661
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	7.5%	2.4%	9.5%
Terminal Rates (c)	3/40 (7%)	1/41 (2%)	2/38 (5%)
Week of First Observation	104	104	88
Life Table Tests (d)	P=0.395	P=0.296N	P=0.480
Incidental Tumor Tests (d)	P=0.427	P=0.296N	P=0.514
Cochran-Armitage Trend Test (d)	P=0.412		
Fisher Exact Test (d)		P=0.309N	P=0.500

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

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

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	Control	125 ppm	250 ppm
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	7/50 (14%)	7/50 (14%)	8/49 (16%)
Adjusted Rates (b)	17.5%	19.2%	20.2%
Terminal Rates (c)	7/40 (18%)	6/35 (17%)	6/36 (17%)
Week of First Observation	104	98	85
Life Table Tests (d)	P=0.368	P=0.514	P=0.422
Incidental Tumor Tests (d)	P=0.400	P=0.524	P=0.468
Cochran-Armitage Trend Test (d)	P=0.427		
Fisher Exact Test (d)		P=0.613N	P=0.483
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	4/49 (8%)
Adjusted Rates (b)	10.0%	14.1%	10.0%
Terminal Rates (c)	4/40 (10%)	2/35 (6%)	2/36 (6%)
Week of First Observation	104	80	93
Life Table Tests (d)	P=0.517	P=0.313	P=0.592
Incidental Tumor Tests (d)	P=0.528N	P=0.495	P=0.639
Cochran-Armitage Trend Test (d)	P=0.556		
Fisher Exact Test (d)		P=0.370	P=0.631
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	26/50 (52%)	24/50 (48%)	20/49 (41%)
Adjusted Rates (b)	57.6%	61.4%	49.8%
Terminal Rates (c)	21/40 (53%)	20/35 (57%)	16/36 (44%)
Week of First Observation	92	94	96
Life Table Tests (d)	P=0.274N	P=0.493	P=0.298N
Incidental Tumor Tests (d)	P=0.165N	P=0.557N	P=0.184N
Cochran-Armitage Trend Test (d)	P=0.156N		
Fisher Exact Test (d)		P=0.421N	P=0.181N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	37/50 (74%)	39/50 (78%)	33/49 (67%)
Adjusted Rates (b)	82.1%	86.6%	73.1%
Terminal Rates (c)	32/40 (80%)	29/35 (83%)	24/36 (67%)
Week of First Observation	92	71	78
Life Table Tests (d)	P=0.496N	P=0.140	P=0.519N
Incidental Tumor Tests (d)	P=0.179N	P=0.344	P=0.242N
Cochran-Armitage Trend Test (d)	P=0.265N		
Fisher Exact Test (d)		P=0.407	P=0.307N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	38/50 (76%)	40/50 (80%)	33/49 (67%)
Adjusted Rates (b)	82.5%	86.9%	73.1%
Terminal Rates (c)	32/40 (80%)	29/35 (83%)	24/36 (67%)
Week of First Observation	88	71	78
Life Table Tests (d)	P=0.427N	P=0.145	P=0.448N
Incidental Tumor Tests (d)	P=0.111N	P=0.425	P=0.162N
Cochran-Armitage Trend Test (d)	P=0.193N		
Fisher Exact Test (d)		P=0.405	P=0.232N
Circulatory System: Hemangioma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	1/49 (2%)
Adjusted Rates (b)	9.4%	5.7%	2.8%
Terminal Rates (c)	2/40 (5%)	2/35 (6%)	1/36 (3%)
Week of First Observation	96	104	104
Life Table Tests (d)	P=0.144N	P=0.388N	P=0.209N
Incidental Tumor Tests (d)	P=0.119N	P=0.354N	P=0.164N
Cochran-Armitage Trend Test (d)	P=0.122N		
Fisher Exact Test (d)		P=0.339N	P=0.188N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

	Control	125 ppm	250 ppm
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	6/50 (12%)	3/50 (6%)	2/49 (4%)
Adjusted Rates (b)	13.8%	8.6%	5.4%
Terminal Rates (c)	3/40 (7%)	3/35 (9%)	1/36 (3%)
Week of First Observation	96	104	101
Life Table Tests (d)	P=0.119N	P=0.301N	P=0.170N
Incidental Tumor Tests (d)	P=0.081N	P=0.259N	P=0.099N
Cochran-Armitage Trend Test (d)	P=0.094N		
Fisher Exact Test (d)		P=0.244N	P=0.141N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	6/50 (12%)	2/50 (4%)	3/49 (6%)
Adjusted Rates (b)	14.6%	5.7%	8.3%
Terminal Rates (c)	5/40 (13%)	2/35 (6%)	3/36 (8%)
Week of First Observation	98	104	104
Life Table Tests (d)	P=0.210N	P=0.177N	P=0.294N
Incidental Tumor Tests (d)	P=0.198N	P=0.169N	P=0.274N
Cochran-Armitage Trend Test (d)	P=0.176N		
Fisher Exact Test (d)		P=0.135N	P=0.254N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/49 (0%)
Adjusted Rates (b)	7.5%	2.9%	0.0%
Terminal Rates (c)	3/40 (7%)	1/35 (3%)	0/36 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.074N	P=0.354N	P=0.140N
Incidental Tumor Tests (d)	P=0.074N	P=0.354N	P=0.140N
Cochran-Armitage Trend Test (d)	P=0.062N		
Fisher Exact Test (d)		P=0.309N	P=0.125N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	9/50 (18%)	3/50 (6%)	3/49 (6%)
Adjusted Rates (b)	21.9%	8.6%	8.3%
Terminal Rates (c)	8/40 (20%)	3/35 (9%)	3/36 (8%)
Week of First Observation	98	104	104
Life Table Tests (d)	P=0.049N	P=0.094N	P=0.087N
Incidental Tumor Tests (d)	P=0.046N	P=0.090N	P=0.079N
Cochran-Armitage Trend Test (d)	P=0.036N		
Fisher Exact Test (d)		P=0.061N	P=0.065N
Pituitary: Adenoma			
Overall Rates (a)	8/48 (17%)	10/50 (20%)	9/48 (19%)
Adjusted Rates (b)	21.1%	27.6%	23.8%
Terminal Rates (c)	8/38 (21%)	9/35 (26%)	7/35 (20%)
Week of First Observation	104	100	92
Life Table Tests (d)	P=0.375	P=0.324	P=0.430
Incidental Tumor Tests (d)	P=0.409	P=0.333	P=0.471
Cochran-Armitage Trend Test (d)	P=0.448		
Fisher Exact Test (d)		P=0.435	P=0.500
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	10/48 (21%)	10/50 (20%)	10/48 (21%)
Adjusted Rates (b)	26.3%	27.6%	26.5%
Terminal Rates (c)	10/38 (26%)	9/35 (26%)	8/35 (23%)
Week of First Observation	104	100	92
Life Table Tests (d)	P=0.469	P=0.520	P=0.521
Incidental Tumor Tests (d)	P=0.504	P=0.530	P=0.561
Cochran-Armitage Trend Test (d)	P=0.550		
Fisher Exact Test (d)		P=0.558N	P=0.599

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE (Continued)

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

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE RECEIVING NO TREATMENT

TABLE F1. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies at this laboratory are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 325/1,614 (20.1%)	(c) 38/1,614 (2.4%)	(b,c) 363/1,614 (22.5%)
SD (d)	11.14%	3.04%	10.98%
Range (e)			
High	24/46	5/45	25/46
Low	2/39	0/50	2/39

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes all diagnoses of NOS, chromophobe, acidophil, or basophil adenoma
(c) Includes all diagnoses of adenocarcinoma and NOS, chromophobe, acidophil, or basophil carcinoma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE F2. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

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

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

TABLE F3. HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL STROMAL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls	
	Polyps	Polyps or Sarcoma
No 2-year studies at this laboratory are included in the historical data base.		
Overall Historical Incidence		
TOTAL	383/1,750 (21.9%)	396/1,750 (22.6%)
SD (b)	7.57%	7.61%
Range (c)		
High	18/49	18/49
Low	4/50	4/50

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

TABLE F4. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls			
	Fibroadenoma	All Benign (b)	All Malignant (c)	All Benign or Malignant (b,c)
No 2-year studies at this laboratory are included in the historical data base.				
Overall Historical Incidence				
TOTAL	470/1,772 (26.5%)	492/1,772 (27.8%)	45/1,772 (2.5%)	520/1,772 (29.3%)
SD (d)	10.62%	9.61%	2.45%	9.29%
Range (e)				
High	24/49	24/49	4/49	24/49
Low	5/50	5/50	0/50	6/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes fibroadenoma, cystfibroadenoma, adenoma, NOS, cystadenoma, and papillary cystadenoma
(c) Includes all adenocarcinomas; no carcinomas have been observed.
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE F5. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls	
	Adenoma (b)	Adenoma or Carcinoma (b)
No 2-year studies at this laboratory are included in the historical data base.		
Overall Historical Incidence		
TOTAL	41/1,716 (2.4%)	43/1,716 (2.5%)
SD (c)	2.62%	2.70%
Range (d)		
High	4/46	4/46
Low	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes cortical adenomas and adenoma, NOS, of the adrenal and adrenal capsule
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F6. HISTORICAL INCIDENCE OF OVARIAN TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence of Granulosa Cell Tumors in Controls
No 2-year studies at this laboratory are included in the historical data base.	
Overall Historical Incidence	
TOTAL	(b) 6/1,610 (0.4%)
SD (c)	1.04%
Range (d)	
High	2/49
Low	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) No luteomas or granulosa carcinomas have been observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

APPENDIX G

GENETIC TOXICOLOGY OF EPHEDRINE SULFATE

TABLE G1. MUTAGENICITY OF EPHEDRINE SULFATE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	96 ± 8.7	75 ± 3.5	94 ± 9.0
	100	92 ± 5.0	77 ± 5.8	80 ± 3.4
	333	97 ± 6.7	75 ± 2.2	88 ± 5.2
	1,000	94 ± 6.1	74 ± 6.4	81 ± 1.3
	3.333	88 ± 3.8	81 ± 2.9	78 ± 1.2
	10,000	96 ± 5.1	85 ± 6.4	78 ± 1.5
TA1535	0	27 ± 3.8	14 ± 2.0	15 ± 1.0
	100	26 ± 1.5	20 ± 2.0	14 ± 3.8
	333	37 ± 2.8	16 ± 0.6	16 ± 1.0
	1,000	34 ± 3.8	9 ± 0.9	13 ± 0.9
	3,333	30 ± 2.7	16 ± 3.5	16 ± 0.6
	10,000	36 ± 2.7	11 ± 1.3	17 ± 2.7
TA97	0	94 ± 4.7	154 ± 4.6	181 ± 3.8
	100	107 ± 6.2	160 ± 2.3	179 ± 2.8
	333	99 ± 3.6	147 ± 1.7	185 ± 8.8
	1,000	101 ± 5.9	150 ± 11.4	190 ± 11.7
	3,333	98 ± 4.4	154 ± 2.4	161 ± 6.9
	10,000	86 ± 8.7	148 ± 3.1	161 ± 4.2
TA98	0	17 ± 1.2	31 ± 2.4	36 ± 3.2
	100	14 ± 1.2	30 ± 0.9	34 ± 2.2
	333	19 ± 1.3	31 ± 1.8	27 ± 3.5
	1,000	18 ± 0.6	32 ± 2.3	38 ± 2.0
	3,333	19 ± 1.7	36 ± 2.0	35 ± 4.0
	10,000	16 ± 0.9	35 ± 3.0	41 ± 5.3

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

TABLE G2. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY EPHEDRINE SULFATE (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	SCE/Cell (d)	Dose (µg/ml)	SCE/Cell (d)
Medium	7.2	Medium	9.5
1,000	8.0	6,500	10.7
1,250	8.2	7,000	10.3
1,490	9.6	8,000	10.5

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

TABLE G3. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY EPHEDRINE SULFATE (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)	Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)
Medium	1 (1)	Medium	1 (1)
1,490	4 (4)	5,600	2 (2)
1,740	7 (7)	6,000	3 (3)
1,990	2 (2)	6,400	10 (6)
2,490	2 (2)	7,000	14 (5)
2,760	1 (1)	7,600	3 (3)
3,000	5 (3)	8,000	2 (2)

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

APPENDIX H

CHEMICAL CHARACTERIZATION OF EPHEDRINE SULFATE

APPENDIX H. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Lot No. 926EW Performed by the Analytical Chemistry Laboratory

A. Physical properties	Determined	Literature Values
1. **Melting point:**	247°-250° C, decomposes (visual, capillary, Büchi 510 melting-point apparatus)	245°-248° C, decomposes
2. **Appearance:**	White microcrystalline powder	

B. Spectral data

1. Infrared

Instrument:	Beckman IR-12	
Phase:	1% in potassium bromide pellet	
Results:	See Figure 5	Consistent with literature spectrum (Sammul et al., 1964)

2. Ultraviolet/visible

Instrument:	Cary 118 No absorbance from 800 to 350 nm		
Solvent:	0.1 N HCl		
Results:	λ_{max} (nm)	$\varepsilon \times 10^{-2}$	No literature reference found; spectrum consistent with structure
	262	2.78 ± 0.04	
	257	3.63 ± 0.05	
	251	2.92 ± 0.04	
	(shoulder) 246	2.05 ± 0.02	

3. Nuclear magnetic resonance

Instrument:	Varian EM-360A
Solvent:	Deuterium oxide with internal sodium trimethylsilylpropionate-2,2,3,3,-d_4

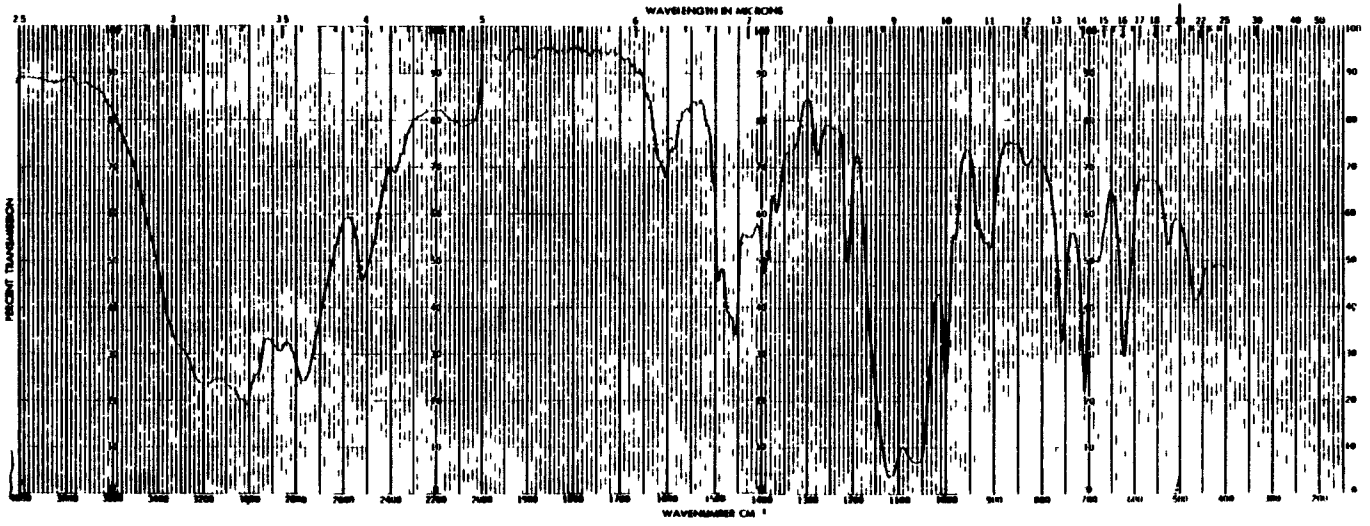


FIGURE 5. INFRARED ABSORPTION SPECTRUM OF EPHEDRINE SULFATE (LOT NO. 926EW)

3. Nuclear magnetic resonance (Continued)	Determined	Literature Values
Assignments:	See Figure 6	Consistent with structure of ephedrine sulfate. Literature spectrum of free base (The Aldrich Chemical Co., Inc., 1974) done in different solvent (deuterated chloroform) has different chemical shifts but similar spectrum, as expected.
Chemical shift (δ):	a d, 1.19 ppm, J_{a-c} = 7 Hz b s, 2.80 ppm c d of q, 3.56 ppm, J_{c-d} = 3 Hz d d, 5.16 ppm e s, 7.46 ppm f s, 4.76 ppm (HDO)	
Integration ratios:	a 3.19 b 3.13 c 1.30 d 1.18 e 5.20 f HDO	

C. **Titration:** Nonaqueous titration of the amine group with perchloric acid (U.S.P. Method [United States Pharmacopeia, 1975]), calculated on dry basis--99.3% ± 0.3 (δ)%

D. **Water analysis:** Weight loss on drying (U.S.P. Method)--0.14%. U.S.P specifies the loss of not more than 2% of weight.

E. **Elemental analyses**

Element	C	H	N	S
Theory (T)	56.05	7.53	6.54	7.48
Determined (D)	56.43 56.25	7.56 7.70	6.47 6.37	7.50 7.47
Percent D/T	100.52	101.33	98.16	100.07

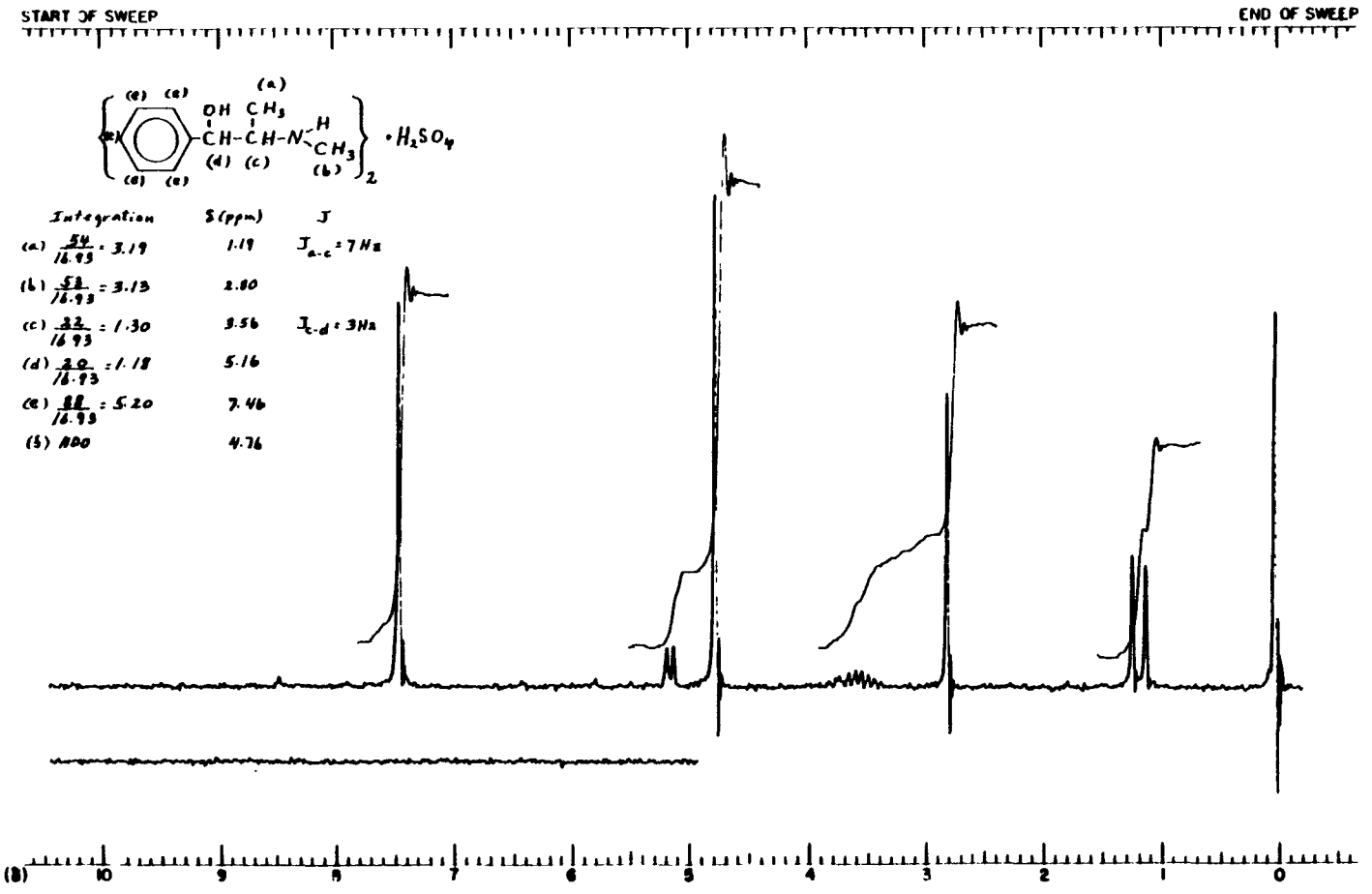


FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF EPHEDRINE SULFATE (LOT NO. 926EW)

F. Chromatographic analyses

1. Thin-layer chromatography

Plates: Silica Gel 60 without fluorescence indicator, 0.25 mm layer thickness
Amount spotted: 300 µg and 100 µg (10 µg/µl in 95% ethanol)
Reference standard: Phenylpropanolamine, 40 µg (2 µg/µl in 95% ethanol)
Visualization: Ultraviolet (254 nm) and ninhydrin spray
Solvent system 1: *n*-Butanol:ethanol:water:ammonium hydroxide (40:20:20:20)
R_f: 0.72
R_{st}: 1.04

Solvent system 2: *n*-Butanol:water:acetic acid (4:2:1)
R_f: 0.57
R_{st}: 1.19

2. High-performance liquid chromatography

Instrumental system
Pump: Waters 6000A
Programmer: Waters 660
Detector: Waters 440
Injector: Waters U6K
Detection: Ultraviolet, 254 nm
Column: µBondapak C_{18}, 300 mm × 3.9 mm ID
Guard column: CO:PELL, ODS, 72 mm × 2.3 mm ID
Solvent system
A: Water with 5 mM heptanesulfonic acid sodium salt and 1% acetic acid (v/v)
B: Methanol with 5 mM heptanesulfonic acid sodium salt and 1% acetic acid (v/v)
Program
System I: 83% A:17% B, isocratic
System II: 58% A:42% B, isocratic

Results: Peak no. 1 in System I corresponds by chromatographic profile to peak no. 1 in System II. Peak nos. 2 and 3 in System I are obscured by the major peak in System II. Peak no. 3 in System II is obscured by the major peak in System I.

System I: Major peak and three impurities, all before the major peak, with areas totaling 0.36% of the major peak

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	3.0	0.19	0.28
2	4.8	0.30	0.04
3	11.3	0.70	0.04
4	16.0	1.00	100

System II: Major peak and two impurities, one before and one after the major peak, with a total relative area of 0.36%

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	3.0	0.57	0.13
2	5.2	1.00	100
3	8.5	1.62	0.23

G. **Summary of analytical data:** Results of the elemental analyses for carbon, hydrogen, nitrogen and sulfur were in agreement with the theoretical values. Weight loss on drying indicated 0.14% water. Nonaqueous titration of the amine groups (U.S.P. Method), calculated on dry basis, indicated a purity of 99.3% ± 0.3 (δ)%. Thin-layer chromatography by two systems both indicated a single major spot. High-performance liquid chromatography by one system indicated three impurities before the major peak with a total combined area of 0.36% that of the major peak. A second high-performance liquid chromatographic system indicated two impurities, one before and one after the major peak, with a combined area of 0.36% that of the major peak. The combined data indicate a total of four different impurities detected in the two systems. Peak no. 1 in both systems is the same impurity. Peak nos. 2 and 3 in System I are not seen in System II. Peak no. 3 in System II is not seen in System I. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra are consistent with the structure of ephedrine sulfate.

H. **Conclusion:** Analyses identified the sample as ephedrine sulfate (spectroscopy) of a purity consistent with the U.S.P. specifications of 98% to 101% (titration) and four small impurities detected by chromatography with areas totaling less than 0.7% that of the major peak.

II. Study Chemical Stability Study Performed by the Analytical Chemistry Laboratory

A. Sample storage: Ephedrine sulfate was stored for 2 weeks in glass tubes with Teflon®-lined caps at temperatures of −20°, 5°, 25°, and 60° C.

B. Analytical method: Samples from each storage temperature were analyzed by the same high-performance liquid chromatographic system as in Section F.2. The only differences in parameters were the following:

Solvent program: 55% A:45% B, isocratic
Samples injected: Solutions (10 µl) of 10 mg/ml ephedrine sulfate per milliliter water

The areas of the major peaks of each storage temperature were compared with the area of the −20° C major peak.

C. Results

Storage Temperature	Percent of Ephedrine Sulfate Normalized to −20° C Sample
−20° C	100.0 ± 1.7
5° C	100.2 ± 1.7
25° C	100.3 ± 1.7
60° C	101.1 ± 1.7

D. Conclusion: Ephedrine sulfate is stable as the bulk chemical, within the limits of error of this analysis, when stored for 2 weeks at temperatures up to 60° C.

III. Study Chemical Stability Study Performed by the Study Laboratory

A. Analytical methods

1. **Nonaqueous titration:** An accurately weighed amount of compound (300 mg) was added to a 125-ml separatory funnel and dissolved in 10 ml of water. Sodium chloride (40 g) and 5.0 ml of 1 N sodium hydroxide were added to the separatory funnel and the mixture extracted with four 25-ml aliquots of chloroform by shaking each aliquot for 5 minutes. The combined chloroform aliquots were transferred to another 125-ml separatory funnel. The chloroform solution was washed with 10 ml of saturated sodium chloride by shaking for 5 minutes; then the chloroform layer was filtered through a glass wool plug into a 150-ml beaker. The leftover saturated sodium chloride was rewashed with 10 ml of chloroform, which was also used to wash the glass wool plug. The combined chloroform extracts were titrated with 0.1 N perchloric acid.

2. **High-performance liquid chromatography:** An accurately weighed amount of compound (100 mg) was transferred to a 10-ml volumetric flask and diluted to volume with water. Duplicate injections were made on the following high-performance liquid chromatographic system:

Instrument: Varian 5060 with Vista 401
Column: 300 mm × 3.9 mm μBondapak C_{18}
Guard column: 72 mm × 2.3 mm CO:PELL
Detector: 254 nm
Solvent system:
45% methanol with 1% acetic acid and 5 mM heptanesulfonic acid
55% water with 1% acetic acid and 5 mM heptanesulfonic acid
Flow rate: 1 ml/min

Retention volume: 7.157 ml

The height response was measured and divided by the milligrams of the original sample. Then the relative percent purity was calculated.

B. Results

1. **Nonaqueous titration**

Sample	#1	#2	Mean
−20° C	98.63	99.14	98.88
25° C	98.49	99.15	98.82

2. **Purity analysis based on perchloric acid titration (a)**

Date of Analysis	Percent Purity Bulk	Percent Purity Reference	Bulk/Reference (percent) (b)
06/11/79	98.20	98.25	--
11/08/79	98.65	98.79	--
02/13/80	99.65	99.61	--
06/12/80	98.86	98.98	--
10/04/80	98.76	99.23	--
02/13/81	98.82	(c) 98.88	100.2
06/22/81	98.2	(d) 97.3	98.9
10/15/81	98.88	(e) 98.46	99.7
02/04/82	96.69	(f) 97.10	98.5
06/10/82	96.70	(g) 96.85	99.5
09/01/82	94.85	(h)	100.0

(a) Average of two samples
(b) Determined by HPLC
(c) 2/11/81
(d) Possible condensation
(e) 10/20/81
(f) 2/15/82
(g) 6/11/82
(h) Not reported as percent purity

3. **Infrared purity analysis:** Results identical to those provided by the analytical chemistry laboratory

APPENDIX I

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES AND FORMULATED DIETS

APPENDIX I. PREPARATION AND CHARACTERIZATION

I. Stability in Drinking Water

A. Stability study parameters

Concentration: 0.2%
Vehicle: Distilled water
Duration: 7 days
Temperature: Room

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

Solutions were prepared by weighing 50-mg amounts of chemical to the nearest 0.01 mg and dissolving in a few milliliters of water in a 25-ml volumetric flask. After being diluted to volume with water and mixed, about 4 ml of each solution was filtered through a 0.5-μ Millipore filter into an 8.5-ml septum vial and sealed. The concentration of ephedrine sulfate in the solutions was approximately 2 mg/ml.

C. Analysis: On day 7, storage samples, sealed in the septum vials, were analyzed by the high-performance liquid chromatographic system described below:

Instrument: Waters Associates components
Column: μBondapak C_{18}, 300 mm × 4 mm ID
Detector: Ultraviolet - 254 nm
Solvent: 35% A: 5 mM heptanesulfonic acid and 1% acetic acid in water
65% B: 5 mM heptanesulfonic acid and 1% acetic acid in methanol
Solvent flow rate: 1 ml/min
Injection volume: 14 μl
Retention time of study chemical: 4.1 min

D. Quality control: Analyses were carried out by making duplicate injections of duplicate sample weighings. High-performance liquid chromatographic linearity was determined with standard solutions of ephedrine sulfate in water at 1.2, 2.0, and 2.4 mg/ml concentrations. The correlation coefficient was greater than 0.9999.

E. Results

Storage Time (days)	Determined Amount of Chemical in Solution (mg/ml)	Target Amount of Chemical in Solution (mg/ml)	Percent Recovery (determined/target)
0	2.0484	2.0044	
0	2.0308	2.0048	(a) 101.8 ± 0.5
1	2.0362	2.0052	
1	2.0220	1.9948	101.4 ± 0.1
5	2.0562	2.0116	
5	2.0008	2.0044	101.0 ± 1.2
6	2.0252	2.0012	
6	2.0300	2.0116	101.1 ± 0.2
7	2.0384	2.0288	
7	1.9996	1.9952	100.4 ± 0.2

(a) Error values are deviations from the mean.

F. Conclusions: Ephedrine sulfate in water solutions at a concentration of 0.2% (w/v) was stable during 7 days' storage at room temperature.

II. Homogeneity in Feed

A. Premix preparation: Ephedrine sulfate (3.00 g) was transferred to a tared 600-ml beaker and intimately mixed by spatula with 5 g of feed. Additional 10-, 20-, and 50-g amounts of feed were added and blended in the same manner. A final portion of feed was incorporated so that the total weight of the premix was 200 g. The concentration of the chemical in the final premix was 15.0 mg/g.

B. Bulk mixing and sampling: A 600-g quantity of feed was layered evenly in a Patterson-Kelly®, twin-shell, 4-quart blender; then the premix was added in roughly equal amounts to both sides. The fine material adhering to the beaker walls was taken up by stirring 100 g of feed in the beaker briefly and adding it to the blender. After an additional 600 g of feed was layered over the premix, the blender ports were sealed.

Blending was conducted with the intensifier bar turned on for the first 5 minutes and turned off for the next 10 minutes of mixing. At the end of the 15-minute mixing period, approximately 50 g was sampled from the upper left- and right-hand shells and from the bottom discharge port.

Duplicate 10 ± 0.01-g aliquots of each sample were transferred to individual 200-ml centrifuge bottles for analysis. The target concentration of ephedrine sulfate in the final blend was 2.00 mg/g.

C. Analysis

1. Special reagents

Extraction solution: Methanol, acetic acid, and water were mixed together in the proportion of 93:5:2 (v/v/v).
Internal standard solution: 146 mg of *n*-hexadecane was dissolved in chloroform and diluted to 100 ml. The solution was reduced to working concentration by diluting 10 ml to 100 ml with chloroform.
TRI-SIL/BSA Formula D reagent: Pierce Chemical Company, Catalog No. 49008.
BSTFA (N,O-bis(trimethylsilyl)trifluoroacetamide): Pierce Chemical Company, Catalog No. 38828.

2. Procedure: Samples (10 g) were extracted with 50 ml of extracting solution by sonicating for 1 minute and shaking 30 minutes on a Burrell® wrist-action shaker. After the extracts were clarified by centrifugation, 2-ml aliquots were transferred to 10-ml septum vials and evaporated to dryness under a stream of nitrogen.

A 0.5-ml volume of TRI-SIL/BSA reagent and 1 ml of BSTFA were added to each vial; then the vials were sealed and heated in a 60° C bath for 30 minutes.

After the sample vials cooled to room temperature and were uncapped, 2 ml of internal standard solution was added to each vial, and the vials were sealed again and reserved. The gas chromatographic system described below was used to determine the ephedrine sulfate content of the samples.

Instrument: Varian 3700 with CDS111 integrator
Column: 3% SP-2100 on 100/120 mesh Supelcoport, 1.8 m × 2 mm ID, glass, silanized
Detector: Flame ionization
Temperatures
Oven: 120° C for 7 min, then 20° C/min to 265° C
Inlet: 180° C
Detector: 300° C
Carrier gas: Nitrogen, 30 cc/min
Amount injected: 3.5 µl
Retention times
Study chemical: 4.0 min
Internal standard: 5.0 min

D. **Quality control measures:** Analyses were performed by making duplicate injections of duplicate sample extracts. Spiked feed recovery yield (100.2%) was determined independently in quadruplicate at the same dose level as the samples. The linearity of the gas chromatograph detector system was evaluated with derivatized standard solutions of ephedrine sulfate at concentrations of 0.28, 0.23, and 0.14 mg/ml. The correlation coefficient was 0.99995.

E. **Results**

15-Min Blend Sampling Location	Determined Amount of Chemical in Solution (mg/g) (a)	Percent Recovery (determined/target) (b)
Right Port	2.02	101.8 ± 0.8
	2.15	
Left Port	2.06	100.5 ± 2.5
	1.96	
Bottom Port	2.03	102.5 ± 1.0
	2.07	

(a) Target ephedrine sulfate content was 2.00 mg/g. Results were not corrected for recovery because the spiked feed recovery yield determined in quadruplicate was 100.2% ± 0.5%.
(b) Error values are deviations from the mean and are the sum of the analytical method errors plus feed blend variations.

F. **Conclusion:** Ephedrine sulfate was blended into rodent feed with satisfactory uniformity. Maximum difference in chemical concentration between three sampling locations in the blender was 2% of the target level.

III. Stability in Feed

A. Stability study parameters

Concentration: 0.2%
Vehicle: NIH 07 Rat and Mouse Ration
Duration: 14 days
Temperature: −20°, 5°, 25°, or 45° C

B. Sample preparation and storage: Four screw-cap bottles were each filled with about 200 g of the dosed feed blend prepared as in II. A and were tightly sealed. Single bottles were placed under −20°, 5°, 25°, or 45° C storage conditions for 2 weeks' stability study.

C. Analysis: Samples (10 ± 0.01 g) from each storage condition were weighed in triplicate and transferred to 200-ml centrifuge bottles. Ephedrine sulfate content was determined by the analysis procedure described in II.C.

D. Quality control: Quality control measures were the same as those in II.D. except that samples were analyzed in triplicate.

E. Results

Storage Temperature	Determined Amount of Chemical in Feed (mg/g) (a)	Percent Recovery (determined/target)
−20° C	1.96 ± 0.07	98.0 ± 3.5
5° C	2.04 ± 0.04	102.0 ± 2.0
25° C	2.02 ± 0.02	101.0 ± 1.0
45° C	1.82 ± 0.06	91.0 ± 3.0

(a) Mean ± maximum deviation for three determinations except at 25° C where two determinations were made. Target ephedrine sulfate content was 2.00 mg/g. Results were not corrected for recovery because the spiked feed recovery yield determined was 100.2 ± 0.5%.

F. Conclusion: Ephedrine sulfate blended with rodent feed at a level of 2 mg/g (0.2%) showed no apparent decomposition, within the limits of study errors (±3%), after 2 weeks' storage at temperatures up to 25° C. There was a 9% loss of chemical in feed stored 2 weeks at 45° C.

APPENDIX J

METHODS OF ANALYSIS OF FORMULATED DIETS

APPENDIX J. METHODS OF ANALYSIS

I. Study Laboratory

A. Reagents

1. **Extracting solution:** methanol:acetic acid:water (93:5:2)
2. **Internal standard solution:** 20 mg of hexadecane dissolved in 500 ml of chloroform
3. **10% Sodium chloride solution:** 50 g sodium chloride dissolved in 450 ml water
4. **Silylating:** Five parts BSTFA (N,O-bis(trimethylsilyl)trifluoroacetamide) and one part TMCS (trimethylchlorosilane); both were fresh lots obtained from Pierce Chemical Co.

B. Preparation of spiked feed standards

1. Ephedrine sulfate in extracting solution (1.32 mg/ml) was prepared.
2. 1.0 ml and 2.0 ml of the ephedrine sulfate solution were added to 10.0-g feed samples.
3. Feed samples then were extracted with an additional 50-ml portion of extracting solution

C. Preparation of ephedrine sulfate standard solution

1. Ephedrine sulfate standard solution (1.0 ml) was added to extracting solution (7.0 ml) and evaporated to about 1.0 ml.
2. Ephedrine sulfate standard solution (2.0 ml) was added to extracting solution (6.0 ml) and evaporated to about 1.0 ml.
3. The evaporated extracts were treated as sample solutions.

D. Sample analysis

1. Feed (10 g) was extracted with 50 ml extracting solution by shaking 30 minutes on a Kraft Shaker® and centrifuging 7 minutes at 2,000 rpm.
2. The extract (8.0 ml) was transferred to a 100-ml beaker and evaporated to about 1.0 ml at 72° C under nitrogen.
3. Ten percent sodium chloride solution (10 ml) was added to each beaker; the beaker was swirled. Then 20 ml of hexane was added to each beaker; the beaker was swirled again to mix.
4. The sodium chloride/hexane mix was transferred to a 125-ml separatory funnel. The 100-ml beaker was rinsed with 5.0 ml sodium chloride and 20 ml hexane; the rinse was combined with the initial extract.
5. The separatory funnel was shaken thoroughly for at least 30 seconds.
6. After the hexane and aqueous layers separated, the aqueous layer was transferred to another 125-ml separatory funnel.
7. The first separatory funnel was rinsed with 1.0 ml sodium chloride solution to clear the stopcock. The hexane was then discarded.
8. Sodium chloride (3.0 g) was added to the second separatory funnel containing the aqueous fraction. The sodium chloride was dissolved and then 2.0 ml of the 10 N sodium hydroxide was added and mixed. Additional 1 N sodium hydroxide was added to adjust the pH to greater than 12.
9. Internal standard (10.0 ml) was added to the separatory funnel, shaken for at least 60 seconds, and allowed to separate.
10. After separation, the chloroform layer was transferred to a 15-ml centrifuge tube and centrifuged at least 3 minutes at 2,000 rpm.
11. Water or particulate matter was aspirated from the surface of the chloroform.
12. The chloroform solution (5.0 ml) was transferred to a 10.0-ml septum vial and sealed, and then 2.0 ml of the silylating solution was added.

13. The samples were allowed to react for 30 minutes at 60° C, cooled, transferred to 2.0-ml sampling vials (with Teflon® caps), and analyzed on one of the following gas chromatographic systems:

	System 1	System 2
Instrument:	Hewlett-Packard 5880	Varian 3700 GLC;HP 3388 Integrator
Detector:	Flame ionization	Flame ionization
Detector temp:	350° C	300° C
Column:	3% OV101 on 80/100 mesh Chromosorb W HP	SP 2100; 10 m capillary
Oven conditions:	120° for 1 min; 20° C/min; to 250° C, then 250° C for 3 min	150° C for 4.0 min; 30° C/min; to 280° C
Carrier gas:	Nitrogen	Helium
Flow rate:	32 ml/min	1 ml/min
Injection port:	225° C	210° C
Retention times:	Ephedrine sulfate--5.34 min Hexadecane--5.54 min	

II. Analytical Chemistry Laboratory

Note: Ephedrine sulfate has been reported to be light sensitive. All operations, therefore, were performed in subdued light with foil-covered or amber glassware.

A. Special reagents

1. **Extracting solution:** Prepared by pipetting 50 ml of reagent-grade, glacial acetic acid into a 1-liter volumetric flask containing 20 ml of distilled water and diluting to volume with reagent-grade methanol
2. **Sodium chloride solution (10%):** Prepared by dissolving 50 g of reagent-grade sodium chloride in 450 ml of distilled water
3. **Silylating reagent:** Supelco brand Sylon BT or Pierce brand Tri-Sil BT are satisfactory; both contain five parts of BSA(N,O-bis(trimethylsilyl)acetamide) and one part TMCS (trimethylchlorosilane).

B. Preparation of spiked feed standards: Two standard solutions of ephedrine sulfate were prepared independently in extracting solution; these solutions were diluted with extracting solution to make four additional standards. Aliquots (20-50 ml) of the six standard solutions were pipetted into individual 200-ml centrifuge bottles containing 10 g of undosed feed to make spiked feed standards bracketing the specified dose range of the referee sample. One 200-ml centrifuge bottle containing 10 g of undosed feed was treated with 20-50 ml of extracting solution for use as a blank. The spiked feed standards and the feed blank were sealed and allowed to stand overnight at room temperature before being used in the analysis procedure described below.

C. Preparation of referee sample: Triplicate weights of the referee feed sample (approximately 10 g weighed to the nearest 0.001 g) were transferred to individual 200-ml centrifuge bottles. Extracting solution (20-50 ml) was pipetted into each sample; then the bottles were sealed and allowed to stand overnight at room temperature before analysis.

D. Analysis procedure: Thirty milliliters of extracting solution (0 ml if 50 ml was added in the previous step) was pipetted into each blank, standard, and referee sample bottle, and the bottles were shaken at maximum stroke for 10-30 minutes on a wrist-action shaker. The extraction mixtures were centrifuged for 10 minutes; then 20- to 25-ml aliquots of the

supernatant solutions were pipetted into individual 100-ml glass beakers and evaporated to about 1 ml with a gentle stream of nitrogen and an 85° C oil bath.

A 10-ml volume of 10% sodium chloride solution and 20 ml of reagent-grade hexane were added to each beaker. The solutions were swirled briefly to mix and then were transferred to individual 125-ml separatory funnels with Teflon® stopcocks. The beakers were rinsed with 5-10 ml of 10% sodium chloride solution and 20 ml of hexane, and the rinse was added to its respective separatory funnel.

Each funnel was shaken for 30 seconds, and the layers were allowed to separate. The lower aqueous layer was tapped off into a clean 125-ml separatory funnel. An additional 1 ml of 10% sodium chloride solution was added to the first funnel containing the hexane layer and tapped off into the second funnel in order to rinse out any trapped extract in the stopcock and funnel stem; the hexane layer then was discarded.

Sodium chloride crystals (3 g) were dissolved in each funnel, and then 2 ml of 10 N sodium hydroxide was added. The solutions were swirled and their pH was checked with pH paper. The pH was adjusted to a minimum value of 12 with 1 N sodium hydroxide.

Ten milliliters of methylene chloride or heptadecane internal standard or 0.1 mg/ml of chloroform was pipetted into each funnel, and the solutions were shaken for 1 minute. Each lower layer was tapped off into a 15-ml centrifuge tube and centrifuged for 3 minutes at 2,000 rpm. The aqueous layer from each tube was aspirated off the top layer; then 2- to 5-ml aliquots of the clear extracts were pipetted into 10-ml septum vials and sealed with Teflon®-lined septa.

A 2-ml volume of silylating reagent was injected into each vial, and the vials were heated for 30 minutes in a 60° C water bath. After the vials were cooled, the concentration of silylated ephedrine was determined by the gas chromatographic system described below.

Instrument: Varian 3700 Gas Chromatograph with Autosampler and Varian CDS 111-C integrator
Column: 3% SP 2100 on 100/120 mesh Supelcoport, 1.8 m × 2 mm ID, glass, silanized
Detection: Flame ionization
Temperatures: Inlet--200° C; Oven--130° or 140° C, isothermal or 140° C for 15 min, then 10° C/min to 190° C and held at 190° C for 5 min; Detector--250° C
Carrier gas: Nitrogen
Flow rate: 30 cc/min
Volume of injection: 3 µl
Retention time: Silylated ephedrine--5.8-23.6

The total amount of ephedrine sulfate in the referee feed samples was determined from the linear regresion equation obtained from the standard data by relating the peak area of each spiked feed standard to the amount of chemical in the respective spiked feed standard.

III. Quality Assurance Measures

The referee feed sample was analyzed in triplicate, and the undosed feed sample was analyzed once. Individually spiked portions of undosed feed (six concentrations bracketing the specified concentration of the referee sample) were prepared from two independently weighed standards and were used for obtaining standard data. Triplicate injections of each standard and sample were made into the gas chromatograph in a randomized order.

APPENDIX K

RESULTS OF ANALYSIS OF FORMULATED DIETS

TABLE K1. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

Date Mixed	Determined Concentration for Target Concentration of 125 ppm	250 ppm	125 ppm	250 ppm
	Rats		Mice	
09/16/80	129	231	124	239
10/07/80	114	240	112	253
01/05/81	113	253	126	246
03/17/81	137	243	123	244
(a) 03/17/81	127	256	118	240
03/27/81	136	258	132	252
07/07/81	119	(b) 347	129	237
07/14/81		(c) 240		
08/18/81	126	267	131	264
10/06/81	128	261	125	(d)
10/09/81				(c) 258
11/17/81	124	255	123	240
01/02/82	117	258	132	266
03/30/82	121	254	137	261
06/01/82	123	(b) 281	132	256
06/07/82		(c) 260		
07/13/82	117	251	116	252
Mean (ppm)	123	261	126	251
Standard deviation	7.7	28.5	7.0	9.9
Coefficent of variation (percent)	6.3	10.9	5.6	3.9
Range (ppm)	113-137	231-347	112-137	237-266
No. of samples	13	13	13	12

(a) Analysis performed by Capsule Laboratories; not included in mean.
(b) Sample out of tolerance; not used; included in mean.
(c) Remix; not included in mean.
(d) Sample out of tolerance; data not reported.

TABLE K2. RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm) Testing Laboratory	Analytical Laboratory
(a) 08/27/80	125	146	154
03/17/81	125	118	(b) <250
08/18/81	250	267	210
03/30/82	125	121	155
07/13/82	250	252	234

(a) Preliminary mix
(b) Accidentally analyzed under conditions suitable for a higher concentration of ephedrine sulfate

APPENDIX L

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

Meal Diet: June 1980 to July 1982

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

TABLE L1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE L2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
d-α-Tocopheryl acetate	20,000 IU	
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Folic acid	2.2 g	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
B_{12}	4,000.0 mcg	
Biotin	140.0 mg	*d*-Biotin
K_3	2.8 g	Menadione activity
Choline	560.0 g	Choline chloride
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

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

TABLE L3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.20 ± 1.00	22.6-26.3	24
Crude fat (percent by weight)	5.02 ± 0.46	4.2-6.0	24
Crude fiber (percent by weight)	3.48 ± 0.41	2.4-4.3	24
Ash (percent by weight)	6.66 ± 0.41	5.97-7.42	24
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	11,087 ± 1,723	7,200-17,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	18.8 ± 0.36	7.4-26.0	(b) 23
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.27 ± 0.19	0.81-1.6	24
Phosphorous (percent)	1.00 ± 0.08	0.84-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

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

TABLE L4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.39 ± 0.17	0.13-0.93	24
Cadmium (ppm) (a)	<0.1		24
Lead (ppm)	1.09 ± 0.72	0.33-2.93	24
Mercury (ppm) (a)	0.05		
Selenium (ppm)	0.30 ± 0.07	0.16-0.48	24
Aflatoxins (ppb) (a, b)	<10		24
Nitrate nitrogen (ppm) (c)	8.50 ± 4.39	0.6-18.0	24
Nitrite nitrogen (ppm) (c)	2.05 ± 1.28	0.4-5.3	24
BHA (ppm) (d, e)	3.68 ± 2.71	0.4-11.0	24
BHT (ppm) (d)	2.65 ± 1.13	1.2-4.9	24
Aerobic plate count (CFU/g)	70,729 ± 49,351	7,000-210,000	21
Coliform (MPN/g) (f)	731 ± 880	<3-2,400	24
E. Coli (MPN/g)	7.50 ± 7.68	<3-23	24
Total nitrosamines (ppb) (g, h)	7.24 ± 6.70	1.8-24.5	22
Total nitrosamines (ppb) (g, i)	17.03 ± 28.20	1.8-101.6	24
N-Nitrosodimethylamine (ppb) (g, j)	5.55 ± 6.07	0.7-20.0	22
N-Nitrosodimethylamine (ppb) (g, k)	13.29 ± 26.86	0.7-99	24
N-Nitrosopyrrolidine (ppb)	1.32 ± 0.81	0.3-3.5	24
Pesticides (ppm)			
α-BHC (a, l)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a, m)	<0.01	0.05 (7/14/81)	24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (a, m)	<0.05	0.13 (8/25/81)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCB's (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (a)	<0.1		24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (n)	0.08 ± 0.05	<0.05-0.25	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

TABLE L4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) Detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: Alfalfa, grains, and fish meal
(d) Source of contamination: Soy oil and fish meal
(e) Two batches contained less than 0.5 ppm.
(f) MPN = most probable number
(g) All values were corrected for percent recovery.
(h) Mean, standard deviation, and range exclude two very high values of 101.6 and 100.3 ppb in batches produced on 1/26/81 and 4/27/81.
(i) Mean, standard deviation, and range include the very high values given in footnote h.
(j) Mean, standard deviation, and range exclude two very high values of 97.9 and 99 ppb in batches produced on 1/26/81 and 4/27/81.
(k) Mean, standard deviation, and range include the high values given in footnote j.
(l) BHC = hexachlorocyclohexane or benzene hexachloride
(m) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(n) Nine batches contained more than 0.05 ppm.

APPENDIX M

SENTINEL ANIMAL PROGRAM

APPENDIX M. SENTINEL ANIMAL PROGRAM

I. Methods

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

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

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

II. Results

A positive serologic reaction for Sendai occurred in 1/9 mice tested at 18 months. All other results were negative.

APPENDIX N

FEED AND COMPOUND CONSUMPTION BY RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF EPHEDRINE SULFATE

TABLE N1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

Week	Control		125 ppm				250 ppm			
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
2	17	236	16	235	0.9	9	16	233	0.9	17
7	16	324	16	315	1.0	6	16	313	1.0	13
12	18	373	16	357	0.9	6	15	355	0.8	11
18	15	400	15	379	1.0	5	15	376	1.0	10
21	14	416	14	395	1.0	4	14	390	1.0	9
27	20	428	15	409	0.8	5	15	399	0.8	9
29	16	442	16	421	1.0	5	15	411	0.9	9
34	14	450	13	424	0.9	4	10	415	0.7	6
39	16	457	15	431	0.9	4	15	423	0.9	9
43	17	460	16	432	0.9	5	15	420	0.9	9
47	17	467	16	438	0.9	5	16	427	0.9	9
51	16	472	15	445	0.9	4	15	430	0.9	9
56	15	472	14	444	0.9	4	14	432	0.9	8
60	15	479	14	450	0.9	4	14	441	0.9	8
65	14	475	14	447	1.0	4	14	438	1.0	8
68	14	480	14	453	1.0	4	14	443	1.0	8
73	14	471	14	444	1.0	4	14	437	1.0	8
76	15	462	15	438	1.0	4	14	428	0.9	8
81	13	462	12	431	0.9	3	12	421	0.9	7
85	14	450	12	429	0.9	3	12	421	0.9	7
89	14	450	14	436	1.0	4	13	427	0.9	8
94	14	441	13	416	0.9	4	13	408	0.9	8
98	14	437	13	410	0.9	4	13	407	0.9	8
102	14	425	13	398	0.9	4	13	400	0.9	8
Mean	15.3	434	14.4	411	0.9	4	14.0	404	0.9	9
SD (d)	1.6		1.3		0.1	1	1.4		0.1	2
CV (e)	10.7		9.3		11.1	25.0	10.0		11.1	22.2

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

TABLE N2. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	Control		125 ppm				250 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
2	11	154	11	152	1.0	9	11	152	1.0	18
7	11	194	10	188	0.9	7	10	186	0.9	13
12	10	212	9	203	0.9	6	9	200	0.9	11
18	10	219	8	206	0.8	5	8	203	0.8	10
21	10	228	9	214	0.9	5	9	211	0.9	11
27	10	235	9	220	0.9	5	9	215	0.9	10
29	10	237	9	223	0.9	5	9	218	0.9	10
34	10	242	9	224	0.9	5	9	218	0.9	10
39	11	249	10	230	0.9	5	10	225	0.9	11
43	11	255	10	234	0.9	5	10	226	0.9	11
47	11	264	10	237	0.9	5	9	229	0.8	10
51	11	272	10	242	0.9	5	9	234	0.8	10
56	11	279	10	249	0.9	5	9	238	0.8	9
60	12	296	10	260	0.8	5	9	245	0.8	9
65	11	301	10	266	0.9	5	9	248	0.8	9
68	11	311	11	271	1.0	5	10	252	0.9	10
73	12	319	11	278	0.9	5	9	255	0.8	9
76	11	317	11	278	1.0	5	10	254	0.9	10
81	10	313	10	287	1.0	4	10	263	1.0	10
85	12	330	10	294	0.8	4	10	267	0.8	9
89	11	332	10	299	0.9	4	10	270	0.9	9
94	12	332	11	299	0.9	5	10	272	0.8	9
98	11	332	11	293	1.0	5	12	271	1.1	11
102	14	331	14	295	1.0	6	15	275	1.1	14
Mean	11.0	273	10.1	248	0.9	5	9.8	234	0.9	11
SD (d)	0.9		1.2		0.1	1	1.4		0.1	2
CV (e)	8.2		12.0		11.1	20.0	14.0		11.1	18.2

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

TABLE N3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	Control		125 ppm				500 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
3	3	26.0	3	26.1	1.0	14	3	25.2	1.0	30
8	4	29.3	4	28.5	1.0	18	4	27.2	1.0	37
13	4	32.9	4	30.1	1.0	17	4	29.4	1.0	34
19	4	34.5	4	31.8	1.0	16	4	29.9	1.0	33
22	4	37.2	4	33.9	1.0	15	4	32.0	1.0	31
28	4	37.9	4	35.7	1.0	14	4	33.5	1.0	30
30	4	39.6	4	36.7	1.0	14	4	34.4	1.0	29
35	4	42.1	4	39.6	1.0	13	4	37.0	1.0	27
40	4	41.1	4	38.8	1.0	13	4	35.5	1.0	28
44	4	40.9	4	38.7	1.0	13	4	35.4	1.0	28
48	4	41.9	4	39.6	1.0	13	4	36.3	1.0	28
52	4	40.7	4	38.5	1.0	13	4	35.1	1.0	28
57	4	42.8	4	40.9	1.0	12	4	36.9	1.0	27
61	4	41.8	4	39.9	1.0	13	4	36.3	1.0	28
66	4	43.0	5	40.2	1.3	16	4	37.0	1.0	27
70	4	41.5	4	39.9	1.0	13	4	36.6	1.0	27
74	4	42.4	4	39.5	1.0	13	4	36.2	1.0	28
77	4	41.3	4	38.4	1.0	13	4	35.5	1.0	28
81	4	41.5	4	38.1	1.0	13	4	34.8	1.0	29
86	4	39.4	4	38.2	1.0	13	4	34.2	1.0	29
90	6	41.8	4	38.2	0.7	13	4	34.2	0.7	29
95	4	40.4	4	36.7	1.0	14	4	33.5	1.0	30
99	4	39.5	4	36.3	1.0	14	4	33.4	1.0	30
103	4	39.2	4	35.5	1.0	14	4	33.2	1.0	30
Mean	4.0	39.1	4.0	36.7	1.0	14	4.0	33.9	1.0	29
SD (d)	0.5		0.3		0.1	1	0.2		0.1	2
CV (e)	12.5		7.5		10.0	7.1	5.0		10.0	6.9

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

TABLE N4. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF EPHEDRINE SULFATE

	Control		125 ppm				500 ppm			
Week	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Low/ Control (b)	Dose/ Day (c)	Grams Feed/ Day (a)	Body Weight (grams)	High/ Control (b)	Dose/ Day (c)
3	2	21.6	3	21.7	1.5	17	2	21.7	1.0	23
8	3	24.7	3	23.5	1.0	16	3	23.5	1.0	32
13	3	28.1	3	25.7	1.0	15	3	25.3	1.0	30
19	3	29.0	3	26.5	1.0	14	3	25.8	1.0	29
22	3	32.7	3	29.2	1.0	13	3	28.1	1.0	27
28	3	36.3	3	31.9	1.0	12	3	29.9	1.0	25
30	3	36.1	3	31.3	1.0	12	3	30.6	1.0	25
35	3	40.4	3	35.3	1.0	11	3	32.9	1.0	23
40	3	40.6	3	35.0	1.0	11	3	32.8	1.0	23
44	4	40.2	3	35.1	0.8	11	3	32.7	0.8	23
48	4	41.3	3	36.5	0.8	10	3	34.1	0.8	22
52	3	41.7	3	36.9	1.0	10	3	34.2	1.0	22
57	3	43.8	3	38.0	1.0	10	3	35.1	1.0	21
61	3	43.4	3	37.7	1.0	10	3	35.3	1.0	21
66	4	44.1	3	38.5	0.8	10	3	36.1	0.8	21
70	3	44.8	4	38.8	1.3	13	3	36.0	1.0	21
74	3	44.3	3	38.3	1.0	10	3	35.1	1.0	21
77	3	41.6	3	36.7	1.0	10	3	33.9	1.0	22
81	3	42.2	3	36.8	1.0	10	3	33.9	1.0	22
86	4	42.4	3	36.3	0.8	10	3	33.3	0.8	23
90	3	43.6	4	37.0	1.3	14	3	33.6	1.0	22
95	4	43.2	4	36.7	1.0	14	4	33.1	1.0	30
99	4	42.5	4	36.4	1.0	14	4	32.9	1.0	30
103	4	42.4	4	35.7	1.0	14	4	32.8	1.0	30
Mean	3.3	38.8	3.2	34.0	1.0	12	3.1	31.8	1.0	25
SD (d)	0.5		0.4		0.2	2	0.4		0.1	4
CV (e)	15.2		12.5		20.0	16.7	12.9		10.0	16.0

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

APPENDIX O

DATA AUDIT SUMMARY

APPENDIX O. DATA AUDIT SUMMARY

An audit was conducted of the archival data and pathology materials for the 2-year toxicology and carcinogenesis studies of ephedrine sulfate in rats and mice. The experimental studies were conducted at Physiological Research Laboratories, Minneapolis, Minnesota, under a subcontract with Tracor Jitco, Inc., from the National Cancer Institute. The studies were conducted from August 1980 to August 1982 and were initiated before the requirement of compliance to Good Laboratory Practices by NTP in October 1981. The audit was conducted March 11-15, 1985, at the NTP Archives, Research Triangle Park, North Carolina, and involved the following personnel from Argus Research Laboratories, Inc.: Jane E. Goeke, PhD.; James H. Hills, B.A.; David M. Willet, B.S.; Carol L. Viegle, H.T.; Diana S. Copeland, D.V.M., D.A.C.P. The audit report was approved by NTP personnel and is on file at NIEHS, NTP, Research Triangle Park, North Carolina.

The audit consisted of an indepth review of the data and pathology materials collected during the conduct of the studies as well as a review of the correspondence, laboratory final report, and draft Technical Report. Review of the inlife toxicology data involved examination of 100% of the records pertaining to animal receipt, acclimation/quarantine, randomization, identification, body weights, feed consumption, environmental conditions, and sentinel animal data; 10% of the study animal records were examined for clinical signs. Review of analytical chemistry involved examination of 100% of the data and verification of a randomly selected 10% of the calculations. The pathology review involved a 100% wet tissue bag count, a 100% slide block match for high dose and control animals, wet tissue examination and animal identification for a 10% random sample, and correlation of pathology tables and PWG Slide Review Worksheets for a 10% random sample of the entries.

Examination of the clinical observation data indicated that on occasion palpable masses were not consistently identified and recorded, and in a few instances the mode of death indicated on the Individual Animal Data Records (IADR's) did not correlate with the mode of death recorded in the clinical observation records. Review of the analytical chemistry data found that all appropriate data were present and verified that the feed mixtures were properly prepared and contained the correct concentrations of ephedrine sulfate. Review of the pathology materials revealed no significant problems in wet tissue bag count, slide/block match, or clerical errors on IADR's or individual pathology tables. Animal identification could not be verified from wet tissues, since no feet, ears, or carcasses were saved. (During the period in which these studies were initiated, it was not an NTP requirement to save feet, ears, or carcasses for identification purposes.) Although positive verification was not possible, examination of wet tissues and IADR's indicated no problems with animal identification. Several differences were found in the correlation of gross necropsy observations and microscopic diagnoses; all involved observations made at necropsy which would not necessarily correspond with microscopic pathologic changes, and none was found which involved potential target organs.

Examinations of wet tissues revealed numerous uncut lesions in the livers of both rats and mice. Subsequently 100% of the livers and uteri (a potential target site) from rats and mice were reexamined for the presence of uncut lesions by Experimental Pathology Laboratories at the NTP Archives in Research Triangle Park. The second review found uncut lesions in 10 rats and 22 mice, from which slides were prepared and analyzed. The results were then reviewed by the NTP Chemical Pathology Branch and submitted to the Carcinogenesis Bioassay Data System (CBDS). The updated CBDS tables have been incorporated into the Technical Report. None of the additions to the CBDS tables had an impact on the interpretation of the final results. In conclusion, data presented in the Technical Report are considered adequate to meet the objectives of these studies.

 ☆U.S. GOVERNMENT PRINTING OFFICE: 1986-491-292:41085