NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 387

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *dl*-AMPHETAMINE SULFATE (CAS NO. 60-13-9) 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

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): 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. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

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 NTP toxicology and carcinogenesis studies 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.

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NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF *dl*-AMPHETAMINE SULFATE

(CAS NO. 60-13-9)

IN F344/N RATS AND B6C3F$_1$ MICE

(FEED STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
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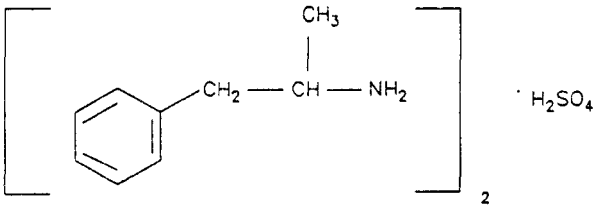
ABSTRACT



***dl*-Amphetamine Sulfate**

CAS No. 60-13-9

$C_{18}H_{28}N_2O_4S$ Molecular Weight: 368.5

Synonyms: (±)-amphetamine sulfate, (±)-2-amino-1-phenylpropane sulfate, amphamine sulfate, deoxynorephedrine, desoxynorephedrine, (±)-α-methylphenethylamine sulfate, (±)-phenisopropylamine sulfate, ß-phenyl isopropylamine sulfate

Trade Names: Acedron, Adipan, Adiparthrol, Aketdrin, Aktedrin, Alentol, Amfetamina, Amfetamine, Amphaetamin, Amphamed, Amphatamin, Amphate, Amphedrine, Amphetaminum, Amphezamin, Amphoids-S, Anara, Anfetamina, Anorexine, Astedin, Benzafinyl, Benzamphetamine,Benzebar, Benzedrina, Benzedryna, Benzolone, Benzpropamine, Betafen, Betaphen, Bluzedrin, Centramina, Didrex, Dietamine, Durophet, Elastonin, Elastonon, Euphobine, Euphodine, Euphodyn, Fabedrine, Fenamin, Fenara, Fenedrin, Fenopromin, Halloo-Wach, Ibiozedrine, Isamin, Isoamin, Isoamyne, Isomyn, Leodrin, Levonor, Linampheta, Mecodrin, Mimetina, Monetamine, Noclon, Norephedrane, Norphedrane, Novydrine, Oktedrin, Oraldrina, Ortenal, Orthedrin, Percomon, Pharmamedrine, Pharmedrine, Phenamine, Phenedrine, Phenopromin, Phenpromin, Profamina, Profetamine, Propenyl, Propisamine, Psychedrine, Psychedryna, Psychedrinum, Psychoton, Racephen, Rhinalator, Sedolin, Simpamina, Simpamine, Simpatedrin, Stimulan, Sympametin, Sympamine, Sympatedrine, Synsatedrine, Theptine, Vapedrine, Weckamine, Zedrine

Slang for Amphetamines: bennies, benzies, cartwheels, hearts, peaches, roses

dl-Amphetamine sulfate is used for the treatment of narcolepsy in adults and behavioral syndromes in children. Toxicology and carcinogenesis studies were conducted by administering *dl*-amphetamine sulfate (USP grade) in feed to groups of F344/N rats and B6C3F$_1$ mice of each sex for 14 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and Chinese hamster ovary (CHO) cells.

14-Day Studies: The chemical was administered at dietary concentrations of 0, 47, 94, 188, 375, or 750 ppm for rats and 0, 125, 250, 500, 1,000, or 2,000 ppm for mice. Decreased body weight gain was seen at the higher concentrations, but no chemical-related deaths or toxic lesions were observed.

13-Week Studies: The chemical was administered at dietary concentrations of 0, 47, 94, 188, 375, or 750 ppm for rats and 0, 125, 250, 500, 1,000, or 2,000 ppm for mice. None of the rats died, but 6/10 male mice and 7/10 female mice that received 2,000 ppm, 3/10 male mice that received 1,000 ppm, and 8/10 male mice that received 500 ppm died before the end of the studies. Decreased body weight gain and hyperactivity were seen in dosed rats and mice. Final body weights of rats receiving 188 ppm or more were 62% to 89% those of

controls, and final body weights of mice receiving 250 ppm or more were 70% to 86% those of controls. There were no lesions that were considered to be a primary effect of the chemical.

Based on decreased body weight gain and hyperactivity in the 13-week studies, 2-year studies were conducted by feeding diets containing 0, 20, or 100 ppm *dl*-amphetamine sulfate to groups of 50 rats or 50 mice of each sex.

Body Weights and Survival in the 2-Year Studies: No significant differences in survival were observed between any groups of rats or mice (male rats: control, 30/50; low dose, 31/50; high dose, 33/50; female rats: 33/50; 42/50; 37/50; male mice: 48/50; 48/50; 49/50; female mice: 35/50; 36/50; 44/50).

Final body weights of dosed rats and mice were decreased relative to those of controls. Final body weights were 92% and 86% those of controls for low- and high-dose male rats, 89% and 70% those of controls for low- and high-dose female rats, 85% and 72% those of controls for low- and high-dose male mice, and 81% and 66% those of controls for low- and high-dose female mice. Hyperactivity was observed in all dosed groups.

Feed consumption was similar among control and exposed groups with the exception of high-dose female rats (84% of controls) and high-dose male mice, for which hyperactivity resulted in scattering of feed and overestimation of feed consumption. The average amount of *dl*-amphetamine sulfate consumed per day was estimated to be 1 or 5 mg/kg for low- and high-dose rats, 4 or 30 mg/kg for low- or high-dose male mice, and 3 or 19 mg/kg for low- or high-dose female mice.

Nonneoplastic and Neoplastic Effects in the 2-Year Studies: Myelofibrosis, cataracts, and retinal atrophy in female rats, and ovarian atrophy in female mice occurred in a larger proportion of high-dose animals than in controls.

Dose-related increases in neoplasms did not occur in rats or mice receiving amphetamine. The administration of *dl*-amphetamine sulfate was associated with decreases in the incidence of total neoplasms and in the incidences of certain site-specific neoplasms, including pheochromocytomas of the adrenal gland in male rats (23/49, 15/44, 7/50), fibroadenomas of the mammary gland in female rats (21/50, 11/50, 2/50), adenomas of the anterior pituitary gland in male and female rats and female mice (male rats: 15/49, 15/48, 9/49; female rats: 31/50, 24/48, 19/50; female mice: 12/49, 6/49, 1/46), endometrial stromal polyps of the uterus of female rats (10/50, 6/50, 3/50), adenomas or carcinomas (combined) of the liver in male and female mice (male: 14/50, 12/50, 2/50; female: 5/50, 1/50, 1/47), adenomas of the harderian gland in male and female mice (male: 4/50, 2/50, 0/50; female: 5/50, 2/50, 0/47), and adenomas or carcinomas (combined) of the lung in male and female mice (male: 8/50, 3/50, 4/50; female: 8/50, 6/50, 1/47).

Genetic Toxicology: *dl*-Amphetamine sulfate was tested for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with and without exogenous metabolic activation (S9); the only response observed was in strain TA98 in the presence of S9, and it was judged to be equivocal. No induction of sister chromatid exchanges or chromosomal aberrations occurred in Chinese hamster ovary cells treated with amphetamine sulfate in either the presence or the absence of S9.

Conclusions: Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity*• of *dl*-amphetamine sulfate for male or female F344/N rats or male or female B6C3F$_1$ mice fed 20 or 100 ppm. The administration of *dl*-amphetamine sulfate was associated with decreased body weight. There were decreased incidences of total neoplasms in dosed rats and mice, of adrenal pheochromocytomas in male rats, of mammary gland fibroadenomas and uterine polyps in female rats, of pituitary gland adenomas in male and female rats and female mice, and of harderian gland adenomas, liver neoplasms, and lung neoplasms in male and female mice.

• Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the peer review comments and the public discussion on this Technical Report appears on page 10.

Summary of the 2-Year Feed and Genetic Toxicology Studies of *dl*-Amphetamine Sulfate

Variable	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 20, or 100 ppm *dl*-amphetamine sulfate	0, 20, or 100 ppm *dl*-amphetamine sulfate	0, 20, or 100 ppm *dl*-amphetamine sulfate	0, 20, or 100 ppm *dl*-amphetamine sulfate
Body weights	Dosed groups markedly lower than controls	Dosed groups markedly lower than controls	Dosed groups markedly lower than controls	Dosed groups markedly lower than controls
2-Year survival rates	30/50, 31/50, 33/50	33/50, 42/50, 37/50	48/50, 48/50, 49/50	35/50, 36/50, 44/50
Nonneoplastic effects	None	None	None	None
Neoplasms decreasing	Adrenal pheochromocytomas: 23/49, 15/44, 6/50 Anterior pituitary gland adenomas: 15/49, 15/48, 7/49	Mammary gland fibroadenomas: 21/50, 11/50, 2/50 Anterior pituitary gland adenomas: 31/50, 24/48, 19/50 Endometrial stromal polyps: 10/50, 6/50, 3/50	Harderian gland adenomas: 4/50, 2/50, 0/50 Lung adenomas or carcinomas (combined): 8/50, 3/50, 4/50 Liver adenomas or carcinomas (combined): 14/50, 12/50, 2/50)	Anterior pituitary gland adenomas: 12/49, 6/49, 1/46 Harderian gland adenomas: 5/50, 2/50, 0/47 Lung adenomas or carcinomas (combined): 8/50, 6/50, 1/47 Liver adenomas or carcinomas (combined): 5/50, 1/50, 1/47
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutation:	Negative with and without S9 in strains TA100, TA1535, and TA1537. Equivocal with S9 in strain TA98; negative without S9			
Sister chromatid exchanges Chinese hamster ovary cells *in vitro*:	Negative with and without S9			
Chromosomal aberrations Chinese hamster overy cells *in vitro*:	Negative with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

- **Clear evidence of carcinogenic activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence of carcinogenic activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence of carcinogenic activity** describes studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.
- **No evidence of carcinogenic activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate study of carcinogenic activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

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

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

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on November 20, 1989, and on April 25, 1990, 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:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the technical report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS

On November 20, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of *dl*-amphetamine sulfate received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Committee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC. During the review, there was a suggestion that animals might have become tolerant to the amphetamine-induced body weight effects and might have been able to tolerate higher doses without increasing the body weight-reducing effects of the drug. Accordingly, the Subcommittee moved to defer the Report to examine any new information available on tolerance to body weight effects.

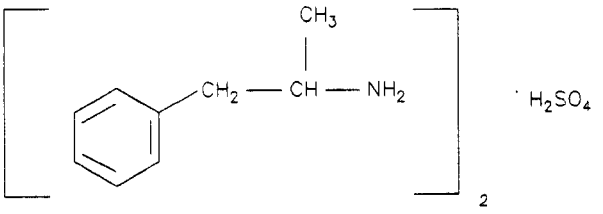
On April 25, 1990, a revised draft Technical Report was reviewed. Dr. J. Dunnick, NIEHS, NTP Study Scientist, began by reporting that the staff thoroughly reviewed the literature on the pharmacologic effects of the drug and found no data to indicate that rats and mice in the NTP 2-year studies could have tolerated higher doses of *dl*-amphetamine without increasing the weight decrements. She noted that in these studies, dosed animals continued to show weight effects throughout the course of the study and the weight effect became more marked with increasing age of the animals. Based on these studies and the findings of other investigators, the staff thought that the dose selection for the 2-year studies on *dl*-amphetamine was appropriate. Dr. Dunnick added that the revised Technical Report responded to previous comments of the Subcommittee by including further discussion on tolerance, the body weight effects observed, pathology procedures, and recording of clinical signs. The proposed conclusions were *no evidence of carcinogenic activity* of *dl*-amphetamine sulfate for male or female F344/N rats or male or female B6C3F$_1$ mice.

Dr. Carlson, a principal reviewer, agreed with the conclusions. He commented that effects seen at the high dose such as excessive hyperactivity and reduction in body weight should be labeled "toxicologic effects" and not "pharmacologic effects" even though these endpoints may reflect an extension of the latter.

Dr. Silbergeld, the second principal reviewer, agreed with the conclusions. However, she remained concerned that the high dose used was not far from the therapeutic range (the range of doses taken by humans for certain prescribed conditions) and that the chemical is also a street drug of abuse. Dr. Silbergeld noted that the observations of reduced incidences of hormone dependent adrenergic tumors were consistent with the demonstration that dopamine inhibits release of prolactin, and amphetamine facilitates dopaminergic neurotransmission.

Dr. Carlson moved that the draft Technical Report on *dl*-amphetamine be accepted with the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*, and with the decreased incidences of several neoplasms that were listed. Dr. Silbergeld seconded the motion, which was accepted unanimously with 11 votes.

INTRODUCTION



***dl*-Amphetamine Sulfate**

CAS No. 60-13-9

$C_{18}H_{28}N_2O_4S$ Molecular Weight: 368.5

Synonyms: (±)-amphetamine sulfate, (±)-2-amino-1-phenylpropane sulfate, amphamine sulfate, deoxynorephedrine, desoxynorephedrine, (±)-α-methylphenethylamine sulfate, (±)-phenisopropylamine sulfate, ß-phenyl isopropylamine sulfate

Trade Names: Acedron, Adipan, Adiparthrol, Aketdrin, Aktedrin, Alentol, Amfetamina, Amfetamine, Amphaetamin, Amphamed, Amphatamin, Amphate, Amphedrine, Amphetaminum, Amphezamin, Amphoids-S, Anara, Anfetamina, Anorexine, Astedin, Benzafinyl, Benzamphetamine,Benzebar, Benzedrina, Benzedryna, Benzolone, Benzpropamine, Betafen, Betaphen, Bluzedrin, Centramina, Didrex, Dietamine, Durophet, Elastonin, Elastonon, Euphobine, Euphodine, Euphodyn, Fabedrine, Fenamin, Fenara, Fenedrin, Fenopromin, Halloo-Wach, Ibiozedrine, Isamin, Isoamin, Isoamyne, Isomyn, Leodrin, Levonor, Linampheta, Mecodrin, Mimetina, Monetamine, Noclon, Norephedrane, Norphedrane, Novydrine, Oktedrin, Oraldrina, Ortenal, Orthedrin, Percomon, Pharmamedrine, Pharmedrine, Phenamine, Phenedrine, Phenopromin, Phenpromin, Profamina, Profetamine, Propenyl, Propisamine, Psychedrine, Psychedryna, Psychedrinum, Psychoton, Racephen, Rhinalator, Sedolin, Simpamina, Simpamine, Simpatedrin, Stimulan, Sympametin, Sympamine, Sympatedrine, Synsatedrine, Theptine, Vapedrine, Weckamine, Zedrine

Slang for Amphetamines: bennies, benzies, cartwheels, hearts, peaches, roses

Amphetamine was first synthesized in the 1920's, and the pharmacologic actions of the drug were described in the 1930's. Amphetamine and its congeners are derivatives of β-phenethylamine. Any substitution on the phenyl ring alters the pharmacologic action of this class of compounds. The addition of a methyl group on the α-carbon of phenethylamine is essential for the central nervous system actions of amphetamine and protects the compound from destruction by monoamine oxidase (Alles, 1933; Moore, 1978).

Use

Amphetamine is taken orally for the treatment of narcolepsy (sudden attacks of sleep), behavioral syndromes in children (hyperactivity, including restlessness, distractability, and impulsive behavior), and weight control. Some of the first amphetamine products were Benzedrine® (*dl*-amphetamine sulfate), marketed in 1936, and Dexedrine®, marketed in 1944 (Gross, 1976). Benzedrine® was withdrawn from the market in 1982 (A.S. Murabito, Smith Kline & French Laboratories, personal communi-

cation to J. K. Dunnick, NTP, 1989). The numbers of prescriptions dispensed in the United States in 1987 were: for Dexedrine® (*dl*-amphetamine sulfate), 329,000 (S.D. McCollough, IMS America Ltd., personal communication to J.K. Dunnick, NTP, 1988); for Biphetamine® (*dl*-amphetamine sulfate), 47,000 (R.L. Bader, Fisons Pharmaceuticals, personal communication to J.K. Dunnick, NTP, 1988); and for Obetrol® (*dl*-amphetamine saccharate and *dl*-amphetamine aspartate), 5,000 (T.D. Demos, Rexar Pharmacal Corp., personal communication to J.K. Dunnick, NTP, 1988).

Recommended doses for treatment are 5 to 60 mg/day for narcolepsy, 2 to 10 mg/day for hyperkinesis in children, and 5 to 30 mg/day for obesity. A 60-kg adult treated with 60 mg/day receives a dose of 1 mg/kg body weight, or approximately 35 mg/m^2 body surface area per day. A 30-kg child taking 10 mg/day receives a dose of approximately 0.3 mg/kg, or 12 mg/m^2 body surface area per day (PDR, 1989).

Amphetamine raises both systolic and diastolic blood pressure; the *levo* isomer is slightly more potent that the *dextro* isomer in its cardiovascular action. Amphetamine stimulates the central nervous system and decreases the degree of central depression; amphetamine is thought to exert these effects by releasing biogenic amines at the nerve terminals. The *dextro* isomer is three to four times as potent as the *levo* isomer in eliciting central nervous system excitatory effects. Amphetamine is used to treat obesity and is thought to depress the appetite through action at the lateral hypothalamic feeding center (Weiner, 1985).

METABOLISM

After oral administration, amphetamines are rapidly absorbed and distributed to the major organ systems, including the brain. During the first 24 hours, the primary route of excretion of amphetamines and their metabolites is via the urine. Routes of metabolism involve hydroxylation of the nitrogen, the α-carbon, the aromatic 4-carbon, and the β-carbon (Cho and Wright, 1978) (Figure 1). The extent to which each of these metabolic pathways is seen in rodents and humans is variable (Table 1). In rats, the major urinary metabolite is *p*-hydroxyamphetamine, whereas in humans, the major urinary metabolites are benzoic acid and hippuric acid; aromatic hydroxylation predominates in rats, and deamination predominates in humans (Caldwell, 1981; Green *et al.*, 1986).

In humans, peak plasma levels are reached 2 to 3 hours after oral dosing. After an oral dose of 0.5 mg/kg, peak plasma levels were approximately 65 ng/mL; after an oral dose of 0.25 mg/kg, peak plasma levels were approximately 35 ng/mL (Angrist *et al.*, 1987).

Table 1
Amphetamine Metabolite Profiles *In Vivo*

Species	Dose (mg/kg)	Dose Excreted in Urine (percent)[a]				Total Dose Recovered in Urine (percent)	Reference
		BA + HA	PA	pHA	Amphetamine		
Rat (female Wistar)	10	3	0	60	13	85	Dring *et al.*, 1970
Rabbit (female New Zealand)	10	25	22	6	4	72	Dring *et al.*, 1970
Dog (female greyhound	5	28	1	6	30	75	Dring *et al.*, 1970
Squirrel monkey	2	5	–[b]	1	23	34	Ellison *et al.*, 1966
Human (male)	0.66	45	2	9	37	66	Dring *et al.*, 1970; Caldwell *et al.*, 1977

[a] Urine was collected for 48 hours from rats and for 24 hours from all other species. BA = benzoic acid, HA = hippuric acid, pHA = *p*-hydroxyamphetamine, PA = phenylacetone

[b] Not determined, although an unidentified metabolite that accounted for 5% of the dose was also detected.

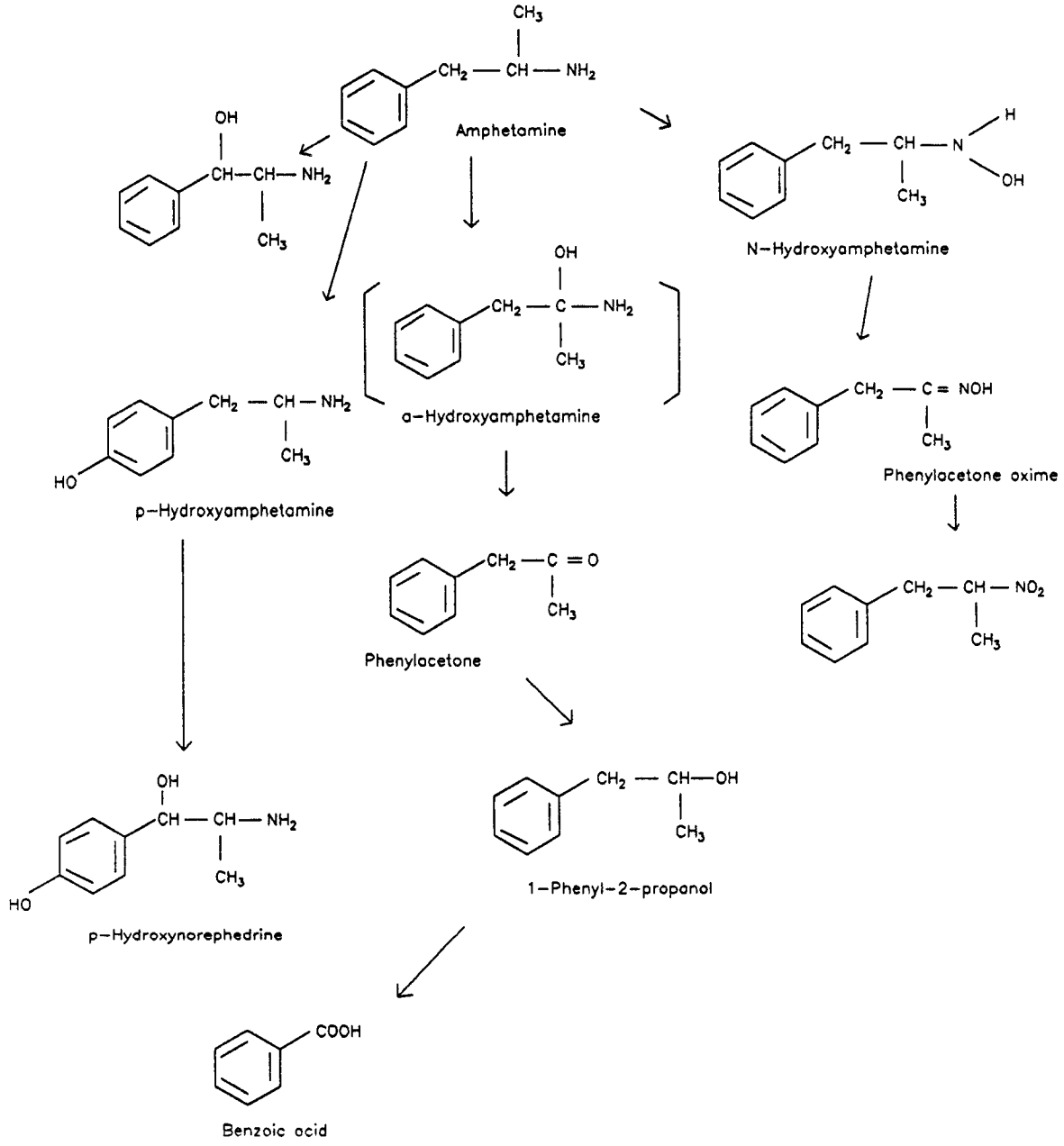


Figure 1
Some Possible Pathways of Metabolism of Amphetamine
(Adapted from Cho and Wright, 1978)

After an intravenous injection of *dl*-amphetamine (0.5 mg/kg) in rats, the half-life was reported to be 87 minutes in plasma and 62 minutes in the brain (Cho *et al.*, 1973). A tissue half-life of 5 to 9 hours was observed in rats after an intraperitoneal injection of *dl*-amphetamine sulfate (Kuhn and Schanberg, 1978). The half-life and plasma concentration of amphetamine sulfate after oral administration to rodents are not reported in the literature.

Toxicity in Humans

Amphetamine toxicity in humans generally results from an oral overdose and is manifested as an extension of the pharmacologic actions of the drug. Central nervous system toxicity includes restlessness, irritability, tension, weakness, and insomnia; cardiovascular toxicity includes chills, fever, and anginal pain; gastrointestinal complaints include dry mouth, cramps, and diarrhea. Amphetamine poisoning results in coma, convulsions, and death.

Amphetamine has been found in human breast milk at levels three to seven times higher than those in maternal plasma (Steiner *et al.*, 1984). No effects were observed on the newborn of a mother who took amphetamines for treatment of narcolepsy at a dose of 140 mg/day during pregnancy (Briggs *et al.*, 1975).

Toxicity in Animals

The oral LD_{50} of *dl*-amphetamine sulfate reported for rats is 55 mg/kg; for mice, 24 mg/kg (Behrendt and Deininger, 1963); and for dogs, 23 mg/kg (Hazleton *et al.*, 1953). The short-term toxicity of amphetamine in rats and mice is manifested by hyperactivity, piloerection, salivation, and hyperpnea (Davis *et al.*, 1978).

Oral administration of amphetamines to rodents has been shown to cause biochemical and behavioral changes. *d*-Amphetamine administered at 1 mg/kg per hour to Sprague-Dawley rats (by means of a minipump implanted subcutaneously) for 12 days produced a marked increase in motor movements and stereotypic behavior (as measured by grooming, scratching, rearing, limb flicks, and biting); these effects were reversible when dosing was stopped. Brain norepinephrine and cardiac catecholamine levels were decreased (Vogel *et al.*, 1985).

Mechanism of Action

Amphetamine crosses the blood-brain barrier, and the major site of the pharmacologic activities of this drug is in the brain. The effects of amphetamine are thought to be mediated by release of catecholamines in the brain (Angrist *et al.*, 1987); amphetamine stimulates the central nervous system, resulting in increased motor activity (Schaefer and Michael, 1988). In rats, this increased activity abolishes REM sleep (Radulovacki and Zak, 1981) and decreases feed intake (Hoebel *et al.*, 1981). Metabolites of amphetamine found in the rat brain include *p*-hydroxyamphetamine, norepinephrine, and *p*-hydroxynorephedrine (Kuhn and Schanberg, 1978). Amphetamine analogs have been found to destroy brain serotonin nerve terminals in rats (Ricaurte *et al.*, 1985; Kuczenski *et al.*, 1987).

Teratogenic and Behavioral Effects

A series of studies indicated that *d*-amphetamine sulfate given orally at high doses increases the incidences of congenital malformations in the heart and large vessels (Nora *et al.*, 1965, 1968). Pregnant ICR mice receiving injections of 50 or 100 mg/kg *d*-amphetamine on days 9 to 11 of gestation were killed on day 15 or 19 of gestation, and the fetuses and uterus were examined (Fein *et al.*, 1987). The heart of exposed embryos showed a large number of undifferentiated cardiac myoblasts, suggesting that the drug may affect embryonic development and delay the histodifferentiation of the myocardium. The drug given at 100 mg/kg killed 40% of the dams, increased the resorption rate in survivors, and increased the number of malformed fetuses. *d*-Amphetamine sulfate has also been shown to cause cardiovascular malformations in 3- or 4-day-old chick embryos (Kolesari and Kaplan, 1979; Cameron *et al.*, 1983).

d-Amphetamine given at low doses to pregnant rats can cause behavioral alterations in their offspring. Offspring of Sprague-Dawley rats given subcutaneous injections of 0, 0.5, 1, or 2 mg/kg *d*-amphetamine sulfate on days 12 to 15 of gestation were evaluated in a behavioral test battery; the 38- to 41-day-old pups were found to have significant deficits in ability to escape from a maze and a lower baseline locomotor activity (Adams *et al.*, 1982; Vorhees, 1985). At the doses used, no effects on body

weights or mortality of offspring early in life and no teratogenic effects were seen. A follow-up study was performed to evaluate further the behavioral teratogenic effects of *d*-amphetamine in Sprague-Dawley rats (Holson *et al.*, 1985). In this study, pregnant rats were given subcutaneous injections of 0, 0.5, 1, 2, or 3 mg/kg *dl*-amphetamine on gestational days 12-15. Some dose-related effects were seen on the auditory startle amplitude in the 47- and 120-day-old offspring, but these effects were subtle and depended on the type of test used.

GENETIC TOXICITY

dl-Amphetamine sulfate gave an equivocal response in an NTP *Salmonella* gene mutation assay in the frameshift strain TA98 in the presence of S9 metabolic activation (Zeiger *et al.*, 1987). No increase in sister chromatid exchanges or chromosomal aberrations occurred in Chinese hamster ovary cells treated with amphetamine sulfate with or without S9 (Appendix I).

STUDY RATIONALE

No long-term studies in rodents have been reported for the amphetamine drugs in the literature. The National Toxicology Program conducted 14-day, 13-week, and 2-year studies to determine the toxic and carcinogenic properties of *dl*-amphetamine sulfate. The *dl*- mixture was chosen since it has been widely used in the past and would be representative of either *dl*- or *d*-amphetamine. The drug was administered orally, since humans receive the drug by the oral route.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *dl*-AMPHETAMINE SULFATE

dl-Amphetamine sulfate, USP grade, was obtained in one lot (lot no. 1087 AM) from Arenol, Inc. (Long Island City, NY). Purity, identity, and stability analyses were conducted at the analytical chemistry laboratory (Midwest Research Institute, Kansas City, MO) (Appendix H).

The study chemical, a white, microcrystalline powder labeled as a racemic mixture, was identified as *dl*-amphetamine sulfate by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. Lot no. 1087 AM was found to be 99% pure, as determined by elemental analysis, Karl Fischer water analysis, optical rotation measurements, potentiometric titration, thin-layer chromatography, and high-performance liquid chromatography. This lot met all USP/NF XX compendial requirements.

Stability studies performed by high-performance liquid chromatography indicated that *dl*-amphetamine sulfate, when protected from light, was stable as a bulk chemical for at least 2 weeks at temperatures up to 60° C. During the 2-year studies, the stability of the bulk chemical was monitored by high-performance liquid chromatography and by titration; no degradation of the study material was seen throughout the studies.

CHARACTERIZATION OF FORMULATED DIETS

The formulated diets were prepared by mixing appropriate amounts of *dl*-amphetamine sulfate and feed (Table H1). Stability studies showed no decrease in concentration after storage for 21 days in the dark at 5° C or under simulated animal cage conditions (open to air and light) for 3 days. During the 2-year studies, the formulated diets were stored at 5° C for no longer than 3 weeks and the feed hoppers were changed at midweek.

Periodic analysis of the formulated diets of *dl*-amphetamine sulfate was conducted at the study laboratory and the analytical chemistry laboratory. During the 2-year studies, the formulated diets were analyzed at a minimum of every 8 weeks by gas chromatography. For the *dl*-amphetamine sulfate studies, it was estimated that the formulations were prepared within ± 10% of the target concentrations throughout the entire studies (Table H3). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results from the study laboratory (Table H4).

14-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries. Rats were held for 19 days before the studies began, and mice were held for 20 days. The rats were 7 weeks old when placed on study, and the mice were 9 weeks old.

Groups of five rats of each sex were fed diets containing 0, 47, 94, 188, 375, or 750 ppm *dl*-amphetamine sulfate for 14 consecutive days. Groups of five mice of each sex were fed diets containing 0, 125, 250, 500, 1,000, or 2,000 ppm on the same schedule.

Animals were housed five per cage. Water and feed were available *ad libitum*. The rats and mice were observed twice per day and were weighed on day 0 and then once per week. A necropsy was performed on all animals.

The brain, heart, liver, lung, right kidney, and thymus of all animals surviving to the end of the studies were weighed. Histopathologic examinations were performed on controls, rats fed 750 ppm, male mice fed 1,000 or 2,000 ppm, and female mice fed 2,000 ppm. Tissues and groups examined and details of animal maintenance are presented in Table 2.

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of *dl*-Amphetamine Sulfate

14-Day Studies	13-Week Studies	2-Year Studies
Study Laboratory		
Microbiological Associates, Inc.	Microbiological Associates, Inc.	Microbiological Associates, Inc.
Strain and Species		
F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source		
Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)
Time Held Before Study		
Rats: 19 days Mice: 20 days	19 days	19 days
Age When Placed on Study		
Rats: 7 weeks Mice: 9 weeks	Rats: 7-8 weeks Mice: 8-9 weeks	Rats: 7-8 weeks Mice: 8-9 weeks
Date of First Dose		
Rats: 6 April 1981 Mice: 7 April 1981	13 July 1981	Rats: 21 June 1982 Mice: 28 June 1982
Duration of Dosing		
14 consecutive days	13 weeks	103 weeks
Date of Last Dose		
Rats: 20 April 1981 Mice: 21 April 1981	Rats: 12 or 13 October 1981 Mice: 13 or 14 October 1981	Rats: 8 June 1984 Mice: 13 June 1984
Necropsy Dates		
Rats: 21-22 April 1981 Mice: 23 April 1981	Rats: 12-13 October 1981 Mice: 13-14 October 1981	Rats: 18-22 June 1984; Mice: 25 June-3 July 1984 (one-third of the high-dose female mice were killed on 3 July 1984, 5 days after the last day of the terminal kill for the rest of the mice)
Age at Sacrifice		
Rats: 9 weeks Mice: 11 weeks	Rats: 20-21 weeks Mice: 21-22 weeks	Rats: 112 weeks Mice: 113 weeks
Size of Study Groups		
5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Method of Animal Distribution		
Animals distributed to weight classes and then assigned to groups according to a table of random numbers	Same as 14-day studies	Same as 14-day studies

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of *dl*-Amphetamine Sulfate (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Animals per Cage		
5	5; male mice receiving 1,000 or 2,000 ppm housed individually after week 4	Rats and female mice: 5; male mice: 1
Method of Animal Identification		
Ear punch	Ear punch and clip	Ear tag
Feed		
Powdered NIH-07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available *ad libitum*	Same as 14-day studies	Same as 14-day studies
Water		
Automatic watering system (Edstrom Industries, Waterford, WI); available *ad libitum*	Same as 14-day studies	Same as 14-day studies
Cages		
Polycarbonate (Hazleton Systems, Inc., Aberdeen, MD, or Lab Products, Inc., Rochelle Park, NJ)	Same as 14-day studies	Same as 14-day studies
Bedding		
Sani-chips (P.J. Murphy Forest Products Corp., Rochelle Park, NJ)	Same as 14-day studies	Same as 14-day studies
Cage Filters		
Spun-bonded polyester. Dupont 2024® (Snow Filtration, Cincinnati, OH)	Same as 14-day studies	Same as 14-day studies
Animal Room Environment		
Temperature: 68°-70° F; humidity: 32%-80%; fluorescent light 12 hours/day; 12-15 room air changes/hour	Temperature: 69°-83° F; humidity: 39%-84%; fluorescent light 12 hours/day; 12-15 room air changes/hour	Temperature: 60°-80° F (rats) or 60°-79° F (mice); humidity: 12%-86% (rats) or 15%-97% (mice); fluorescent light 12 hours/day; 12-15 room air changes/hour
Other Chemicals on Study in the Same Room		
None	None	None
Doses		
Rats: 0, 47, 94, 188, 375, or 750 ppm *dl*-amphetamine sulfate in feed; mice: 0, 125, 250, 500, 1,000, or 2,000 ppm	Rats: 0, 47, 94, 188, 375, or 750 ppm *dl*-amphetamine sulfate in feed; mice: 0, 125, 250, 500, 1,000, or 2,000 ppm	0, 20, or 100 ppm *dl*-amphetamine sulfate in feed
Type and Frequency of Observation		
Observed 2 times/day; weighed initially and 1 time/week thereafter	Observed 1 time/day; weighed initially and 1 time/week thereafter	Observed 2 times/day; weighed 1 time/week for 13 weeks and at least 1 time/month thereafter

TABLE 2
Experimental Design and Materials and Methods in the Feed Studies of *dl*-Amphetamine Sulfate (continued)

14-Day Studies	13-Week Studies	2-Year Studies
Necropsy, Histologic Examinations, and Supplemental Studies		
Necropsy performed on all animals; histologic exams performed on all controls, all animals in the high-dose groups, and all male mice in the 1,000 ppm group; tissues examined include adrenal glands, brain, cecum, colon, costochondral junction, duodenum, esophagus, eyes, femur or sternebrae or vertebrae including marrow, gallbladder (mice), gross lesions, heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, mammary gland, manidibular and mesenteric lymph nodes, nasal passage, pancreas, parathyroid glands, pituitary gland, prostate/testes/seminal vesicles or ovaries/uterus, rectum, salivary glands, sciatic nerve, skin, spinal cord, spleen, stomach, thigh muscle, thymus, thyroid gland, tissue masses, trachea, and urinary bladder. Organ weights obtained for all animals surviving to the end of the studies.	Necropsy performed on all animals; histologic exams performed on all controls, all high-dose rats, all mice that died before the end of the studies, male mice in the 1,000 and 2,000 ppm groups, and all female mice in the 2,000 ppm group; tissues examined include adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), gross lesions and tissue masses, heart, kidneys, liver, lungs and bronchi, mammary gland, mandibular lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes or ovaries/uterus, salivary glands, skin, small intestine, spinal cord (if neurologic signs present), spleen, sternebrae, stomach, thymus, thyroid gland, trachea, and urinary bladder. Tissues examined in lower dose rat groups include thymus for males in the 94 ppm group and thymus and spleen for females in the 47 and 94 ppm groups. Organ weights obtained for all animals surviving to the end of the studies.	Necropsy and histologic exams performed on all animals; the following tissues were examined: adrenal glands, bone marrow, brain, colon, costochondral junction, duodenum, esophagus, gallbladder (mice), gross lesions, heart, ileum, jejunum, kidneys, larynx, liver, lungs and bronchi, mammary gland, mandibular and mesenteric lymph nodes, pancreas, parathyroid glands, pituitary gland, prostate/testes/seminal vesicles or ovaries/uterus, salivary glands, skin, spleen, stomach, thymus, thyroid gland, tissue masses with abnormal regional lymph nodes, trachea, and urinary bladder.

13-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to *dl*-amphetamine 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 5- to 6-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 19 days before the studies began. Groups of 10 rats of each sex were fed diets containing 0, 47, 94, 188, 375, or 750 ppm *dl*-amphetamine sulfate for 13 weeks. Groups of 10 mice of each sex were fed diets containing 0, 125, 250, 500, 1,000, or 2,000 ppm on the same schedule. Further experimental details are summarized in Table 2.

Animals were observed once per day; moribund animals were killed. Feed consumption was measured once per week by cage. After week 4, male mice in the 1,000- and 2,000-ppm groups were housed individually. Individual animal weights were recorded once per week (except for week 9).

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals. The brain, liver, lung, right kidney, heart, and thymus of all animals surviving to the end of the studies were weighed. Histologic examinations were performed on all controls, rats fed 750 ppm, male mice fed 1,000 or 2,000 ppm, female mice fed 2,000 ppm, and all mice that died before the end of the studies. Tissues and groups examined are listed in Table 2.

2-YEAR STUDIES

Study Design

Groups of 50 rats and 50 mice of each sex were fed diets containing 0, 20, or 100 ppm *dl*-amphetamine sulfate for 103 weeks.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female X C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 4 to 5 (rats) or 5 to 6 (mice) weeks of age. The animals were quarantined at the study laboratory for 3 weeks. Before the start of the 2-year studies, a complete necropsy was performed on five animals of each sex and species to assess their health status. Rats were placed on study at 7 to 8 weeks of age and mice at 8 to 9 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix E).

Animal Maintenance

Animals were housed five per cage, with the exception of male mice, which were housed individually. Cages were rotated throughout the studies. Feed (Appendix G) and water were available *ad libitum*. Further details of animal maintenance are given in Table 2.

Clinical Examinations and Pathology

All animals were observed twice per day. Body weights were recorded once per week for the first 13 weeks of the study and at least once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals, including those found dead, except for three high-dose female mice. Seventeen high-dose female mice received water (but no feed) for 5 days after the scheduled terminal kill; a necropsy was performed on the 14 surviving mice at day 736.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined are listed in Table 2.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue

trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all target tissues (eye in rats and thyroid gland in mice), and all tissues from a randomly selected 10% of the animals from each control and high-dose group were re-evaluated microscopically by a quality assessment pathologist. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the target organs in the randomly selected 10% of animals.

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

Statistical Methods

Survival Analyses

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be dead from other than natural causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. All reported P values for the survival analysis are two-sided.

Calculation of Incidence

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

Analysis of Tumor Incidence

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

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

procedures based on the overall proportion of tumor-bearing animals.

Tests of significance include pairwise comparisons of each dosed group with controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, see Haseman, 1984.

Analysis of Continuous Variables

For analysis of organ weights, dosed groups were compared with the control group using the nonparametric multiple comparison test of Dunn (1964) or Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons.

Historical Control Data

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

Quality Assurance Methods

The 13-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR Part 58). In addition, as study records were submitted to the NTP Archives, they were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and preliminary review draft of this NTP Technical Report were conducted. Audit procedures are presented in the reports, which are on file at the NIEHS. The audit findings were reviewed and assessed by NTP staff so that all had been resolved or were otherwise addressed during the preparation of this Technical Report.

RESULTS

RATS

14-Day Studies

None of the rats died before the end of the studies (Table 3). Final mean body weights of rats that received 375 or 750 ppm were 7% or 9% lower than that of controls for males and 5% or 16% lower for females. Feed consumption by all but the 47 ppm groups was decreased during week 1; feed consumption by male rats that received 750 ppm was marginally lower than that by controls during week 2. Rats that received 375 or 750 ppm were hyperactive, particularly when handled. The absolute heart weights were decreased in female rats that received 375 or 750 ppm (Table J1). No compound-related lesions were observed.

13-Week Studies

All rats lived to the end of the studies (Table 4). The final mean body weights of all groups of rats that received *dl*-amphetamine sulfate were lower than those of controls; final mean body weights of rats that received 188, 375, or 750 ppm were 11%, 18%, or 38% lower than that of controls for males and 15%, 26%, or 32% lower for females. Feed consumption was similar in all groups, except that feed consumption by 750 ppm males was 20% lower than that by controls. Hyperactivity was observed in all dosed groups, and the severity increased with the concentration of amphetamine. Changes in organ weights were a consequence of lower body weights in the dosed groups (Table J2).

TABLE 3
Survival, Mean Body Weights, and Feed Consumption of Rats in the 14-Day Feed Studies of *dl*-Amphetamine Sulfate

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)	Feed Consumption[d]	
		Initial[b]	Final	Change[c]		Week 1	Week 2
Male							
0	5/5	141	188	+47		14	16
47	5/5	149	191	+42	101.6	14	16
94	5/5	142	188	+46	100.0	11	16
188	5/5	146	187	+41	99.5	11	15
375	5/5	146	174	+28	92.6	11	15
750	5/5	147	171	+24	91.0	9	14
Female							
0	5/5	118	136	+18		11	11
47	5/5	117	139	+22	102.2	11	11
94	5/5	113	127	+14	93.4	8	10
188	5/5	113	132	+19	97.1	8	11
375	5/5	117	129	+12	94.9	7	10
750	5/5	114	114	0	83.8	5	10

[a] Number surviving/number initially on study
[b] Initial group mean body weight
[c] Mean body weight change of survivors
[d] Grams per animal per day; not corrected for scatter.

TABLE 4
Survival, Mean Body Weights, and Feed Consumption of Rats in the 13-Week Feed Studies of *dl*-Amphetamine Sulfate

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)	Feed Consumption[d]	
		Initial[b]	Final	Change[c]		Week 6	Week 13
Male							
0	10/10	127 ± 2	359 ± 7	+232 ± 6		17	17
47	10/10	128 ± 2	326 ± 8	+198 ± 7	91	17	16
94	10/10	126 ± 2	332 ± 7	+206 ± 6	92	16	15
188	10/10	127 ± 2	321 ± 12	+194 ± 10	89	17	15
375	10/10	124 ± 2	294 ± 7	+170 ± 6	82	16	15
750	10/10	128 ± 2	223 ± 5	+95 ± 4	62	14	13
Female							
0	10/10	113 ± 2	210 ± 2	+97 ± 2		11	10
47	10/10	114 ± 1	197 ± 3	+83 ± 2	94	12	11
94	10/10	111 ± 2	188 ± 3	+77 ± 2	90	10	10
188	10/10	111 ± 2	178 ± 4	+67 ± 3	85	12	9
375	10/10	112 ± 2	156 ± 4	+44 ± 4	74	12	11
750	10/10	113 ± 2	142 ± 4	+29 ± 4	68	10	11

[a] Number surviving/number initially on study
[b] Initial group mean body weight ± standard error of the mean
[c] Mean body weight change of ± standard error of the mean
[d] Grams per animal per day; not corrected for scatter

Dose Selection Rationale

Because of hyperactivity and decreased body weight gain seen at 188 ppm and above, dietary concentrations selected for rats in the 2-year studies were 20 and 100 ppm *dl*-amphetamine sulfate.

2-Year Studies

Body Weights, Feed Consumption, and Clinical Findings

Mean body weights of high-dose males and low- and high-dose females were markedly lower (10% to 34%) than those of controls throughout most of the studies (Table 5 and Figure 2). The average daily feed consumption by high-dose females was 84% that by controls (Table F2). The average amount of *dl*-amphetamine sulfate consumed per day was approximately 1 or 5 mg/kg for low-dose or high-dose rats, respectively (Tables F1 and F2).

Survival

Estimates of the probabilities of survival for rats are shown in Table 6 and in the Kaplan and Meier curves in Figure 3. No significant differences in survival were seen between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the thyroid gland, testis, eye, bone marrow, adrenal gland, mammary gland, anterior pituitary gland, and uterus.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at

TABLE 5
Mean Body Weights and Survival of Male Rats in the 2-Year Feed Study of *dl*-Amphetamine Sulfate

Week on Study	0 ppm		20 ppm			100 ppm		
	Av. Wt. (g)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors	Av. Wt. (g)	Wt. (% of controls)	Number of Survivors
1	145	50	144	99	50	143	99	50
2	180	50	176	98	50	176	98	50
3	215	50	206	96	50	203	95	50
4	234	50	229	98	50	222	95	50
5	254	50	249	98	50	242	95	50
6	268	50[a]	272	102	50	255	95	50
7	285	50	280	98	50	268	94	50
8	297	50	292	98	50	281	95	50
9	311	50	304	98	50	293	94	50
10	324	50	315	97	50[a]	302	93	50
11	332	50	322	97	50	307	92	50[a]
12	345	50	334	97	50	319	93	50
13	349	50	340	98	50	323	92	50[a]
17	379	50	369	97	50	344	91	50
21	392	50	385	98	50	355	91	50
25	410	50	403	98	50	369	90	50
31	422	50	411	97	50	385	91	50
35	444	50	430	97	49	399	90	50[a]
36	438	50[a]	426	97	49	395	90	50[a]
39	448	50	437	98	49	406	91	50
43	450	50	436	97	49	401	89	50
47	466	49	453	97	49	415	89	50
51	468	49	456	97	49	416	89	50
55	476	49	466	98	49	417	88	50
59	479	49	470	98	48	417	87	50
63	481	49	467	97	47	419	87	48
67	480	49	471	98	46	418	87	48
71	483	49	477	99	45	421	87	48
75	489	48	474	97	45	418	86	47
79	488	47	475	97	44	419	86	47
83	483	46	470	97	43	414	86	47
87	484	45	463	96	42	409	85	46
91	476	44	457	96	42	407	85	43
96	477	39	447	94	38	408	86	39
100	473	35	431	91	34	399	85	38
102	463	33	427	92	32	393	85	36
104	461	31	424	92	32	397	86	34
Mean for weeks								
1-13	272		266	98		256	94	
17-51	432		421	97		389	90	
55-104	478		459	96		411	86	

[a] The number of animals weighed was less than the number of animals surviving.

TABLE 5
Mean Body Weights and Survival of Female Rats in the 2-Year Feed Study of *dl*-Amphetamine Sulfate (continued)

Week on Study	0 ppm Av. Wt. (g)	0 ppm Number of Survivors	20 ppm Av. Wt. (g)	20 ppm Wt. (% of controls)	20 ppm Number of Survivors	100 ppm Av. Wt. (g)	100 ppm Wt. (% of controls)	100 ppm Number of Survivors
1	113	50	114	101	50	113	100	50
2	132	50	129	98	50	125	95	50
3	143	50	140	98	50	138	96	50
4	152	50	148	97	50	146	96	50
5	162	50	157	97	50	148	91	50
6	169	50	167	99	50	158	94	50
7	176	50	169	96	50	162	92	50
8	181	50	174	96	50	167	93	50
9	186	50	180	97	50	171	92	50
10	191	50	184	96	50	177	92	50
11	194	50	187	96	50	180	93	50
12	200	50	190	95	50	182	91	50
13	202	50	192	95	50	183	91	50[a]
17	212	50	201	94	50	191	90	50
21	216	50	200	93	50	192	89	50
25	220	50	204	93	50	197	90	50
31	237	50	213	90	50	204	86	50
35	246	50	229	93	50	203	83	49
36	240	50	223	93	50[a]	206	86	49
39	241	50	223	93	50	205	85	49
43	249	50	227	91	50	211	85	49
47	258	50	229	89	50	216	84	49
51	265	50	234	88	49	219	83	49
55	277	50	241	87	49	214	77	49
59	288	50	249	87	49	222	77	49
63	293	50	254	87	49	222	76	49[a]
67	302	50	261	87	49	224	74	47
71	313	48	270	86	49	227	73	47
75	323	48	276	85	49	226	70	46
79	331	46	283	85	49	231	70	45
83	335	46	282	84	49	228	68	45
87	344	45	287	83	47	230	67	44
91	351	45	293	83	46	231	66	44[a]
96	346	42	298	86	44	234	68	43
100	350	38	300	86	43	236	67	40
102	339	37	300	88	42	227	67	39
104	349	34	309	88	42	243	70	37
Mean for weeks								
1-13	169		164	97		158	93	
17-51	238		218	92		204	86	
55-104	324		279	86		228	70	

[a] The number of animals weighed for this week is less than the number of animals surviving.

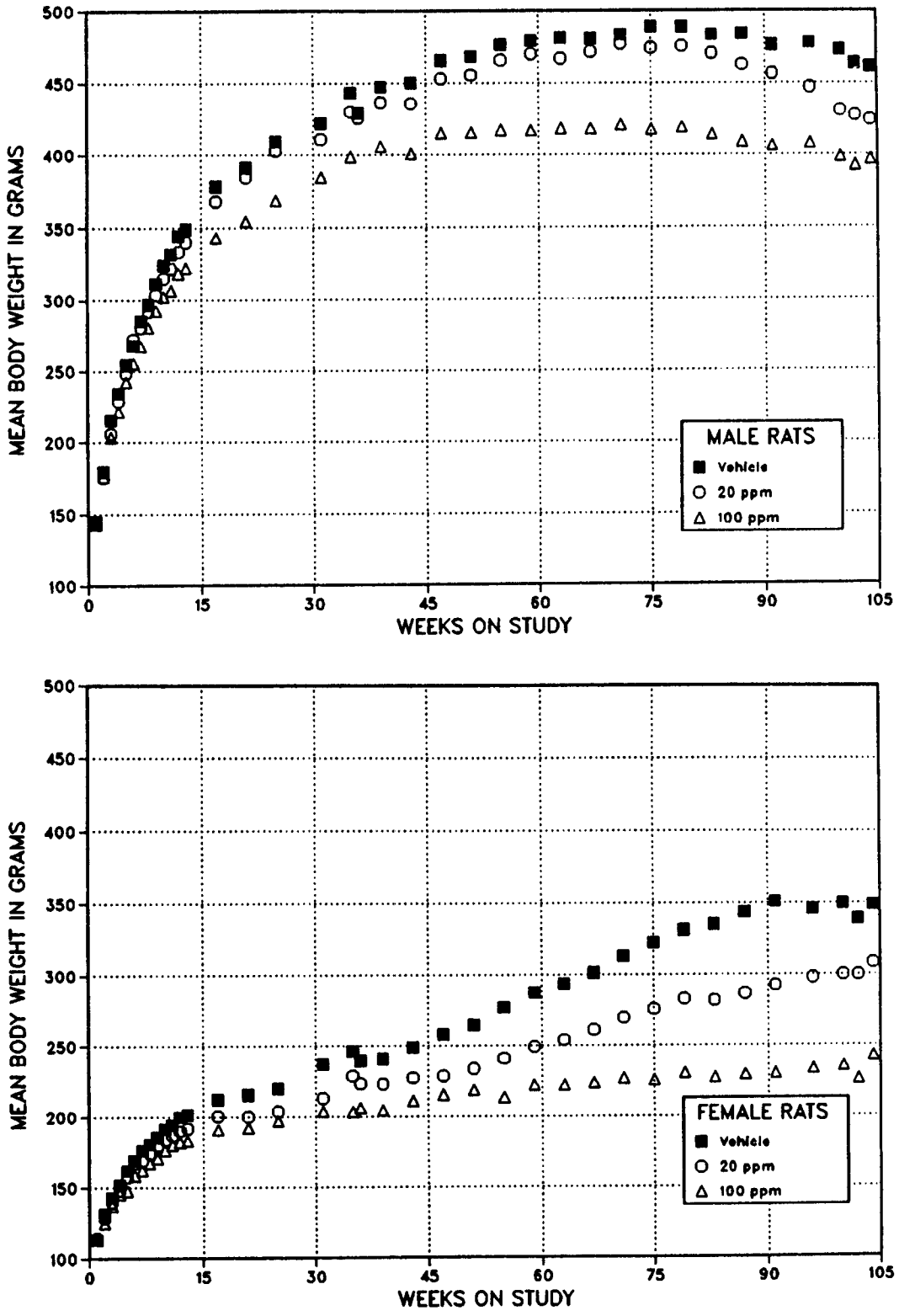


FIGURE 2
Growth Curves for Rats Fed Diets Containing *dl*-Amphetamine Sulfate for 2 Years

TABLE 6
Survival of Rats in the 2-Year Feed Studies of *dl*-Amphetamine Sulfate

	0 ppm	20 ppm	100 ppm
Male[a]			
Animals initially in study	50	50	50
Natural deaths	8	11	9
Moribund kills	12	8	8
Animals surviving to study termination	30	31	33
Mean survival (days)[b]	691	675	694
Survival P values[c]	0.623	1.000	0.680
Female[a]			
Animals initially in study	50	50	50
Natural deaths	7	4	6
Moribund kills	10	4	7
Animals surviving to study termination	33	42	37
Mean survival (days)[b]	701	710	693
Survival P values[c]	0.965	0.078	0.560

[a] First day of termination period: male - 729; female - 731
[b] Mean of all deaths (uncensored, censored, terminal sacrifice)
[c] The entry under the "0 ppm" column is the trend test (Tarone, 1975) result. Subsequent entries are the results of pairwise tests (Cox, 1972).

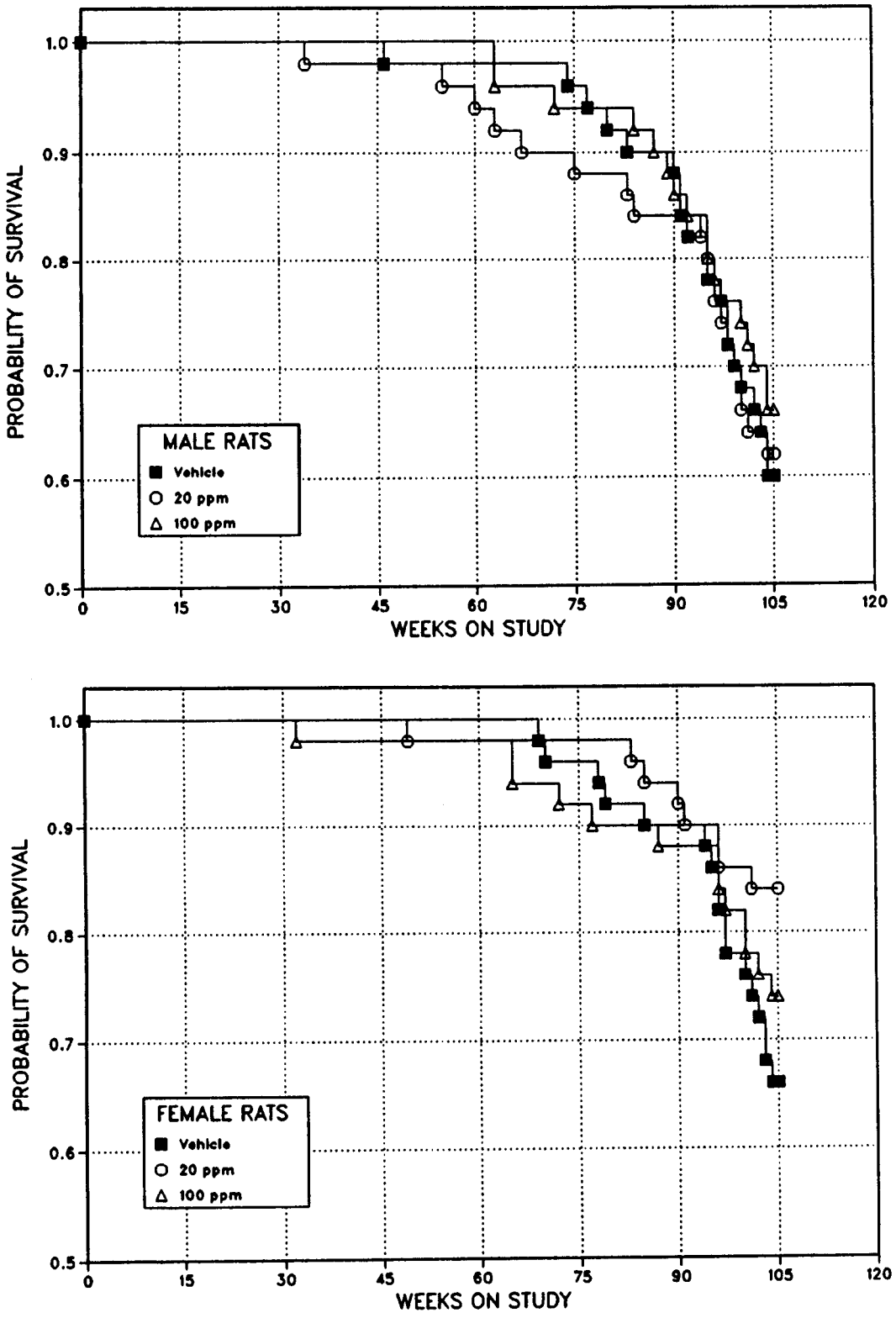


FIGURE 3
Kaplan-Meier Survival Curves for Rats Fed Diets Containing *dl*-Amphetamine Sulfate for 2 Years

least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

Thyroid Gland: Follicular cell adenomas were seen in 2/50 low-dose female rats; a follicular cell carcinoma was seen in a third low-dose female rat. The historical incidence of thyroid gland follicular cell neoplasms in untreated control female F344/N rats is 16/1,612 (1%), and the highest observed incidence is 2/49. There were no follicular cell neoplasms in the control or high-dose female rats. One follicular cell adenoma occurred in a control male, and one occurred in a high-dose male. Follicular cell hyperplasia was not observed in either the control or exposed male or female rats. Due to the lack of a dose-related increase in follicular cell neoplasms and the complete absence of focal follicular cell hyperplasia, a lesion generally considered to be a precursor to adenoma, the three follicular cell neoplasms in the low-dose female group were not considered related to chemical exposure.

Testis: There was a marginally significant increase in interstitial cell adenomas in male rats (control, 34/50; low dose, 43/50; high dose, 48/50) (Table A3). This slight increase in the incidence of a commonly occurring neoplasm was not considered to be related to chemical exposure.

Eye: Cataracts and retinal atrophy were observed at increased incidences in high-dose female rats (cataracts--male: control, 6/50; low dose, 10/50; high dose, 6/48; female: 12/50; 7/50; 36/50; atrophy--male: 14/50; 9/50; 3/48; female: 25/50; 17/50; 42/50). The cataracts and retinal atrophy were similar in dosed and control rats. The cataracts were generally subcapsular, involving the outer cortex and often extending the full circumference of the lens. The less severe lesions were characterized by swelling and granular degeneration of the lens fibers, with irregularity of the nuclei in the bow area near the equator. In more advanced lesions, the outer cortex exhibited complete loss of structure and consisted of an amorphous coagulum of lens protein. The retinal atrophy was diffuse and characterized by mild-to-marked reduction in cellularity of the inner and outer nuclear cell layers. The eye lesions observed were similar to those reported to be associated with exposure to excessive illumination intensity. Furthermore, the NTP has observed higher incidences of cataracts and retinal atrophy in rats housed in the top rows of the cage rack (nearest the light source) compared with those near the bottom. The incidences of cataracts and retinal atrophy, which were increased only in high-dose female rats, are probably not compound induced. Although cages were rotated during these studies, racks were not rotated, and the high-dose female rats may have been exposed to more light than the animals in other rows.

Bone Marrow: Myelofibrosis was observed at an increased incidence in high-dose female rats (control, 1/50; low dose, 2/50; high dose, 11/49). The change was of minimal-to-mild severity and appeared histologically as an increase in the amount of fibrous tissue elements in the bone marrow. Generally, the affected marrow lacked the adipose tissue that is normally a constituent of the bone marrow. This change was interpreted as being secondary to the low body weight in the high-dose animals, which resulted in an absence of fat in the marrow. The lack of fat, in turn, led to prominence of the normal connective tissue elements.

Adrenal Gland, Mammary Gland, Anterior Pituitary Gland, and Uterus: Significantly decreased incidences of a variety of neoplasms occurred in exposed rats of each sex; the neoplasms included adrenal gland pheochromocytomas in males and mammary gland fibroadenomas, pituitary gland neoplasms, and endometrial stromal polyps in females (Table 7).

Table 7
Decreased Incidences of Naturally Occurring Neoplasms in Rats in the 2-Year Feed Studies of *dl*-Amphetamine Sulfate

	0 ppm	20 ppm	100 ppm
Male			
Estimated dose in milligrams per kilogram per day[a]	0	1	5
Final body weight (percent of controls)		92	86
Final survival	30/50	31/50	33/50
Neoplasm site			
Adrenal gland			
Hyperplasia	8/49	4/44	2/50
Pheochromocytoma	23/49	15/44	7/50
Anterior pituitary gland			
Adenoma	15/49	15/48	9/49
Total animals with primary neoplasms[b]	46	45	38
Total animals with benign neoplasms[b]	40	31	25
Total animals with malignant neoplasms	25	25	28
Female			
Estimated dose in milligrams per kilogram per day[a]	0	1	5
Final body weight (percent of controls)		88	70
Final survival	33/50	42/50	37/50
Neoplasm site			
Mammary gland			
Fibroadenoma	21/50	11/50	2/50
Anterior pituitary gland			
Adenoma	31/50	24/48	19/50
Uterus			
Endometrial stromal polyp	10/50	6/50	3/50
Total animals with primary neoplasms	48	42	30
Total animals with benign neoplasms	42	36	23
Total animals with malignant neoplasms	16	14	10

[a] Therapeutic dose range of *dl*-amphetamine sulfate in humans is 0.1-2 mg/kg per day.
[b] Excludes interstitial cell tumors of the testis.

MICE

14-Day Studies

Male mice that received 500, 1,000, or 2,000 ppm lost weight (Table 8). Final mean body weights of females that received 250 to 2,000 ppm were 12% to 13% lower than that of controls. Feed consumption by all groups was similar throughout the studies. Mice that received 1,000 or 2,000 ppm were hyperactive or lethargic and hyporesponsive. Liver weight to body weight ratios for males receiving 250 ppm or more and for females receiving 2,000 ppm were significantly greater than those for controls (Table J3). No compound-related lesions were seen; deaths of dosed male mice were not clearly related to chemical administration.

13-Week Studies

Six of 10 male mice and 7/10 female mice that received 2,000 ppm, 3/10 male mice that received 1,000 ppm, and 8/10 male mice that received 500 ppm died before the end of the studies (Table 9). Final mean body weights of male mice that received 250, 500, 1,000, or 2,000 ppm were 18% to 30% lower than that of controls; final mean body weights were 13% to 19% lower for exposed females. All groups of dosed mice were hyperactive; hyperactivity increased as the concentration increased. Fighting was seen among male mice at the four highest dietary concentrations. Increased relative organ weights were a consequence of significantly reduced body weights (Table J4).

TABLE 8
Survival, Mean Body Weights, and Feed Consumption of Mice in the 14-Day Feed Studies of *dl*-Amphetamine Sulfate

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)	Feed Consumption[d]	
		Initial[b]	Final	Change[c]		Week 1	Week 2
Male							
0	5/5	23.7	26.4	+2.7		3.3	4.0
125	5/5	22.2	25.6	+3.4	97.0	3.2	4.0
250	5/5	24.5	24.8	+0.3	93.9	3.2	4.4
500	5/5	24.1	23.9	-0.2	90.5	3.0	4.8
1,000	1/5[e]	24.7	21.3	-3.4	80.7	2.9	–
2,000	4/5[f]	24.2	21.7	-2.5	82.2	3.0	4.4
Female							
0	5/5	19.1	21.6	+2.5		3.3	3.8
125	5/5	19.0	20.7	+1.7	95.8	3.2	3.7
250	5/5	18.5	19.1	+0.6	88.4	3.2	4.3
500	5/5	18.2	19.1	+0.9	88.4	3.0	4.2
1,000	5/5	18.6	18.8	+0.2	87.0	3.6	4.6
2,000	5/5	18.5	19.0	+0.5	88.0	3.6	4.6

[a] Number surviving/number initially on study
[b] Initial group mean body weight.
[c] Mean body weight change of the survivors
[d] Grams per animal per day; not corrected for scatter
[e] Day of death: all 7
[f] Day of death: 4

TABLE 9
Survival, Mean Body Weights, and Feed Consumption of Mice in the 13-Week Feed Studies of *dl*-Amphetamine Sulfate

Concentration (ppm)	Survival[a]	Mean Body Weights (g)			Final Weight Relative to Controls (%)	Feed Consumption[d]	
		Initial[b]	Final	Change[c]		Week 7	Week 13
Male							
0	10/10	24.0 ± 0.3	33.1 ± 0.4	+9.1 ± 0.5		4.0	3.8
125	10/10	23.8 ± 0.4	30.8 ± 0.8	+7.0 ± 0.6	93.1	3.9	4.3
250	10/10	23.4 ± 0.5	27.0 ± 0.6	+3.6 ± 0.7	81.6	3.9	4.3
500	2/10[e]	23.3 ± 0.4	25.3 ± 0.4	+2.3 ± 0.5	76.4	4.5	15.0
1,000	7/10[f]	23.0 ± 0.5	23.1 ± 0.5	+0.3 ± 0.3	69.8	8.2	8.0
2,000	4/10[g]	22.5 ± 0.4	23.5 ± 0.5	+0.5 ± 0.7	71.0	6.1	12.0
Female							
0	10/10	18.0 ± 0.3	24.7 ± 0.5	+6.7 ± 0.4		3.7	4.7
125	10/10	17.9 ± 0.3	21.6 ± 0.4	+3.7 ± 0.3	87.4	3.5	4.4
250	10/10	17.9 ± 0.3	20.7 ± 0.3	+2.8 ± 0.3	83.8	4.2	4.6
500	10/10	17.8 ± 0.3	20.9 ± 0.2	+3.1 ± 0.3	84.6	4.1	4.9
1,000	10/10	17.6 ± 0.2	21.3 ± 0.3	+3.7 ± 0.4	86.2	3.9	5.2
2,000	3/10[h]	18.3 ± 0.3	19.9 ± 0.8	+2.0 ± 1.7	80.6	6.3	9.9

[a] Number surviving/number initially on study
[b] Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
[c] Mean body weight change of survivors ± standard error of the mean
[d] Grams per animal per day; not corrected for scatter
[e] Week of death: 1,3,5,5,5,9,9,9
[f] Week of death: all 1; this group was housed individually after week 4 to reduce fighting. Consequently, feed consumption was highly variable, especially toward the end of the study.
[g] Week of death: 1,1,1,2,2,3
[h] Week of death: 1,1,1,2,5,7,9

Feed consumption was similar for exposed and control groups except for high-dose male mice in the last half of the study, when scattering of feed, probably due to increased activity, occurred.

Dose Selection Rationale: Because of hyperactivity and decreased body weight gain at higher concentrations, dietary concentrations selected for mice in the 2-year studies were 20 and 100 ppm *dl*-amphetamine sulfate. Male mice were housed separately during the 2-year study because of the fighting seen in the 13-week study.

2-Year Studies

Body Weights, Feed Consumption, and Clinical Findings

Mean body weights of high-dose male mice were 10% to 20% lower than those of controls from week 7 to week 13 and 20% to 36% lower thereafter; mean body weights of low-dose male mice were 10% to 19% lower than those of controls after week 11 (Table 10 and Figure 4). Mean body weights of high-dose female mice were 10% to 25% lower than those of controls from week 10 to week 43 and 25% to 34% lower thereafter; mean body weights of low-

TABLE 10
Mean Body Weights and Survival of Male Mice in the 2-Year Feed Study of *dl*-Amphetamine Sulfate

Week on Study	0 ppm Av. Wt. (g)	0 ppm Number of Survivors	20 ppm Av. Wt. (g)	20 ppm Wt. (% of controls)	20 ppm Number of Survivors	100 ppm Av. Wt. (g)	100 ppm Wt. (% of controls)	100 ppm Number of Survivors
1	23.7	50	23.3	98	50	23.5	99	50[a]
2	24.6	50	24.0	98	49	23.5	96	50
3	25.8	50	24.9	97	49	23.9	93	50
4	27.2	50	25.7	95	49	24.9	92	50
5	26.7	50	26.6	100	49	25.1	94	50
6	28.1	49	27.2	97	49	25.7	92	50
7	28.6	49	27.4	96	49	25.5	89	50
8	28.7	49	28.3	99	49	25.5	89	50
9	29.7	49	27.3	92	49[a]	25.8	87	50
10	30.8	49	27.9	91	49	26.1	85	50
11	31.8	49	28.3	89	49	26.3	83	50
12	32.6	49	29.0	89	49	26.0	80	50
13	32.9	49	29.3	89	49	26.4	80	50
17	34.2	49[a]	30.4	89	49[a]	27.0	79	50
21	35.2	49	30.8	88	49	27.5	78	50[a]
25	37.3	49	32.9	88	49	29.0	78	50[a]
31	38.6	49	34.0	88	49	29.7	77	50
35	39.6	49	34.9	88	49	27.9	71	50
39	41.2	49	35.9	87	49	29.2	71	50
43	42.1	49	36.9	88	49	29.5	70	50
48	42.5	49	38.0	89	49	29.2	69	50
51	42.6	49	37.7	89	49	29.4	69	50
55	44.4	49	39.6	89	49	30.2	68	50
59	46.3	48	40.6	88	49	31.5	68	50
63	46.8	48	40.5	87	49[a]	31.4	67	50
67	46.0	48	40.2	87	49	30.4	66	50
71	45.9	48	40.0	87	49	30.7	67	50
75	46.2	48	39.5	86	49	31.3	68	50
79	46.2	48	39.6	86	49	31.7	69	50
83	47.3	48	39.0	83	49	30.4	64	50[a]
88	46.3	48	39.2	85	49	30.4	66	50
91	45.3	48	38.4	85	49	30.6	68	49
96	45.8	48	38.5	84	49	31.0	68	49
100	45.5	48	38.2	84	49	31.4	69	49
102	43.4	48	35.2	81	48	28.9	67	49
104	43.4	48	37.0	85	48	31.3	72	49
Mean for weeks								
1-13	28.6		26.9	94		25.2	88	
17-51	39.3		34.6	88		28.7	73	
55-104	45.6		39.0	86		30.8	68	

[a] The number of animals weighed was less than the number of animals surviving.

TABLE 10
Mean Body Weights and Survival of Female Mice in the 2-Year Feed Study of *dl*-Amphetamine Sulfate (continued)

Week on Study	0 ppm Av. Wt. (g)	0 ppm Number of Survivors	20 ppm Av. Wt. (g)	20 ppm Wt. (% of controls)	20 ppm Number of Survivors	100 ppm Av. Wt. (g)	100 ppm Wt. (% of controls)	100 ppm Number of Survivors
1	18.9	50	18.9	100	50	18.9	100	50
2	19.7	50[a]	20.2	103	50	19.9	101	50[a]
3	21.4	50	20.6	96	50	20.3	95	50
4	22.9	50	22.2	97	50	21.4	93	50
5	22.6	50	22.2	98	50	21.9	97	50
6	23.4	50	23.2	99	50	22.2	95	50
7	23.6	50	23.6	100	50	21.9	93	50
8	24.3	50	24.0	99	50	22.6	93	50
9	24.7	50	23.7	96	50	22.7	92	50
10	25.0	50	24.2	97	50	22.5	90	50
11	25.1	50	24.1	96	50	22.7	90	50
12	25.2	50	24.4	97	50	22.5	89	50
13	25.4	50	24.6	97	50	22.4	88	50
18	27.4	50	26.4	96	50	24.2	88	50
21	28.0	50	25.9	93	50	24.0	86	50
25	29.9	50	27.7	93	50	25.4	85	50[a]
31	30.5	50	28.1	92	50	25.7	84	50
35	32.0	50	28.2	88	50	24.4	76	50
39	32.8	50	29.6	90	50	25.7	78	48
43	34.4	50	30.0	87	50	25.8	75	48
48	34.4	50	30.0	87	50	25.9	75	48
51	35.6	50	30.4	85	50	26.1	73	48
55	36.6	50	32.4	89	50	26.6	73	48
59	38.0	50	33.3	88	50	26.7	70	48
63	38.9	50	33.2	85	50	27.5	71	48
67	39.2	50	33.4	85	50	26.8	68	48
71	40.9	50	34.1	83	50	27.1	66	48
75	41.6	50	34.5	83	47	27.4	66	48
79	43.4	47	34.5	80	47	27.7	64	48
83	43.5	47	33.1	76	47	27.5	63	47
88	44.7	45	33.7	75	47	27.4	61	47
91	42.6	45	33.7	79	46	27.1	64	47
96	43.7	43	34.7	79	42	27.3	63	47
100	43.2	39	34.4	80	41	28.1	65	46
102	41.3	39	32.5	79	37	25.7	62	46
104	41.5	36	33.5	81	36	27.4	66	44
Mean for weeks								
1-13	23.2		22.8	98		21.7	94	
18-51	31.7		28.5	90		25.2	80	
55-104	41.4		33.6	81		27.2	66	

[a] The number of animals weighed for this week is less than the number of animals surviving.

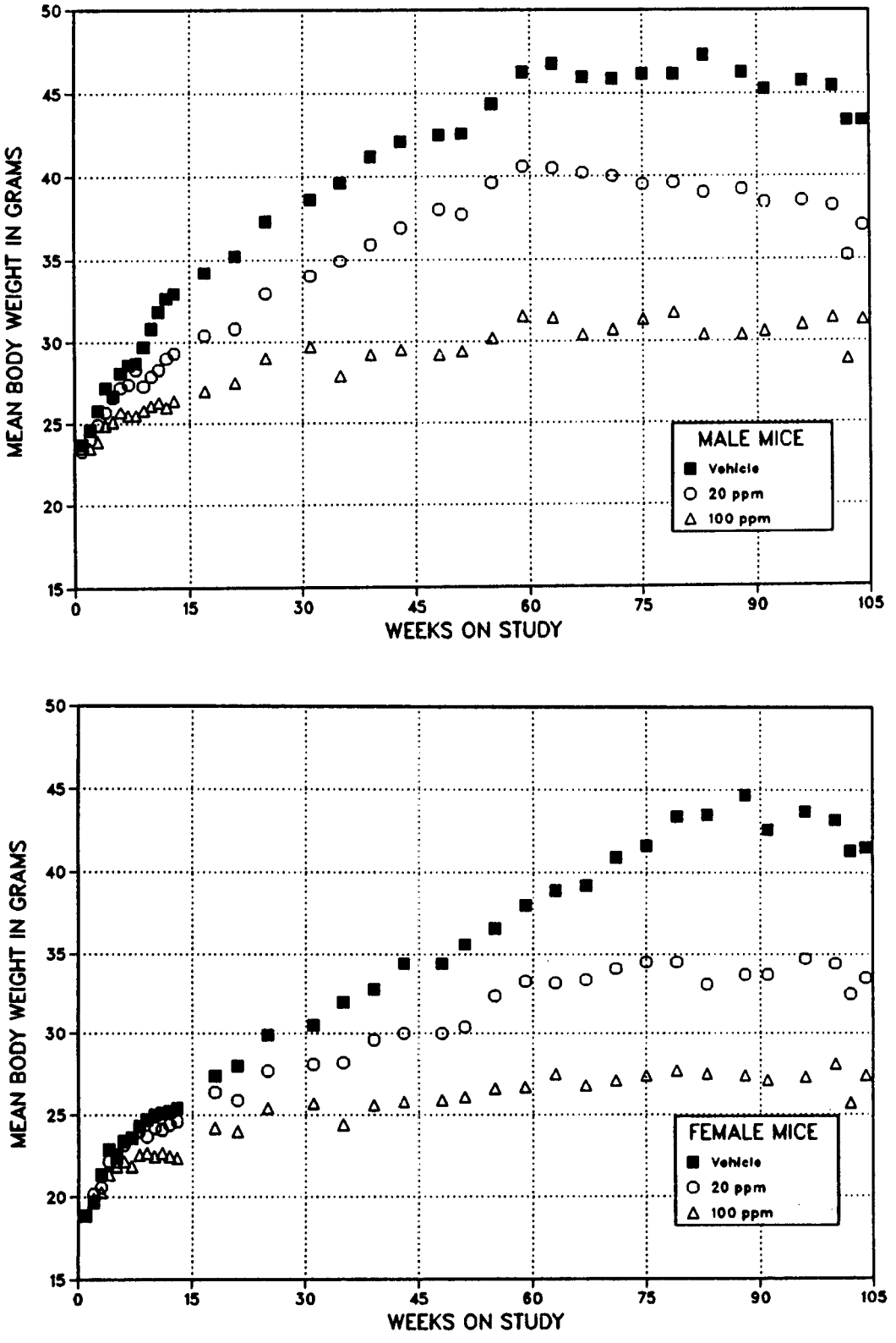


FIGURE 4
Growth Curves for Mice Fed Diets Containing *dl*-Amphetamine Sulfate for 2 Years

dose female mice were 10% to 19% lower than those of controls after week 35. The average daily feed consumption (not corrected for scatter) by low-dose and high-dose mice was 130% and 180%, respectively, that by controls for males and 110% and 120% for females (Tables F3 and F4). The average amount of *dl*-amphetamine sulfate consumed per day was approximately 4 or 30 mg/kg for low-dose or high-dose male mice, respectively, and 3 or 19 mg/kg for low-dose or high-dose female mice. Dosed male and female mice were hyperactive.

Survival

Estimates of the probabilities of survival for male and female mice fed diets containing *dl*-amphetamine sulfate at the concentrations used in these studies and for controls are shown in Table 11 and in the Kaplan and Meier curves in Figure 5. Seventeen high-dose female mice were inadvertently not killed at the end of the study; they received water but no feed for 5 days, and necropsies were then performed on 14 of these animals. No significant differences in survival were observed between any groups of either sex.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the thyroid gland, ovary, liver, harderian gland, lung, and anterior pituitary gland. In the current studies, final body weights of high-dose mice were only 60% to 70% those of controls.

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

TABLE 11
Survival of Mice in the 2-Year Feed Studies of *dl*-Amphetamine Sulfate

	0 ppm	20 ppm	100 ppm
Male[a]			
Animals initially in study	50	50	50
Natural deaths	2	1	1
Moribund kills	0	0	0
Killed accidentally	0	1	0
Animals surviving to study termination	48	48	49
Mean survival (days)[b]	708	714	727
Survival P values[c]	0.986	1.000	0.986
Female[a]			
Animals initially in study	50	50	50
Natural deaths	10	11	5
Moribund kills	5	3	1
Animals surviving to study termination	35	36	44
Mean survival (days)[b]	704	705	708
Survival P values[c]	0.035	0.971	0.051

[a] First day of termination period: male - 729; female - 732
[b] Mean of all deaths (uncensored, censored, terminal sacrifice)
[c] The entry under the "0 ppm" column is the trend test (Tarone, 1975) result. Subsequent entries are the results of pairwise tests (Cox, 1972).

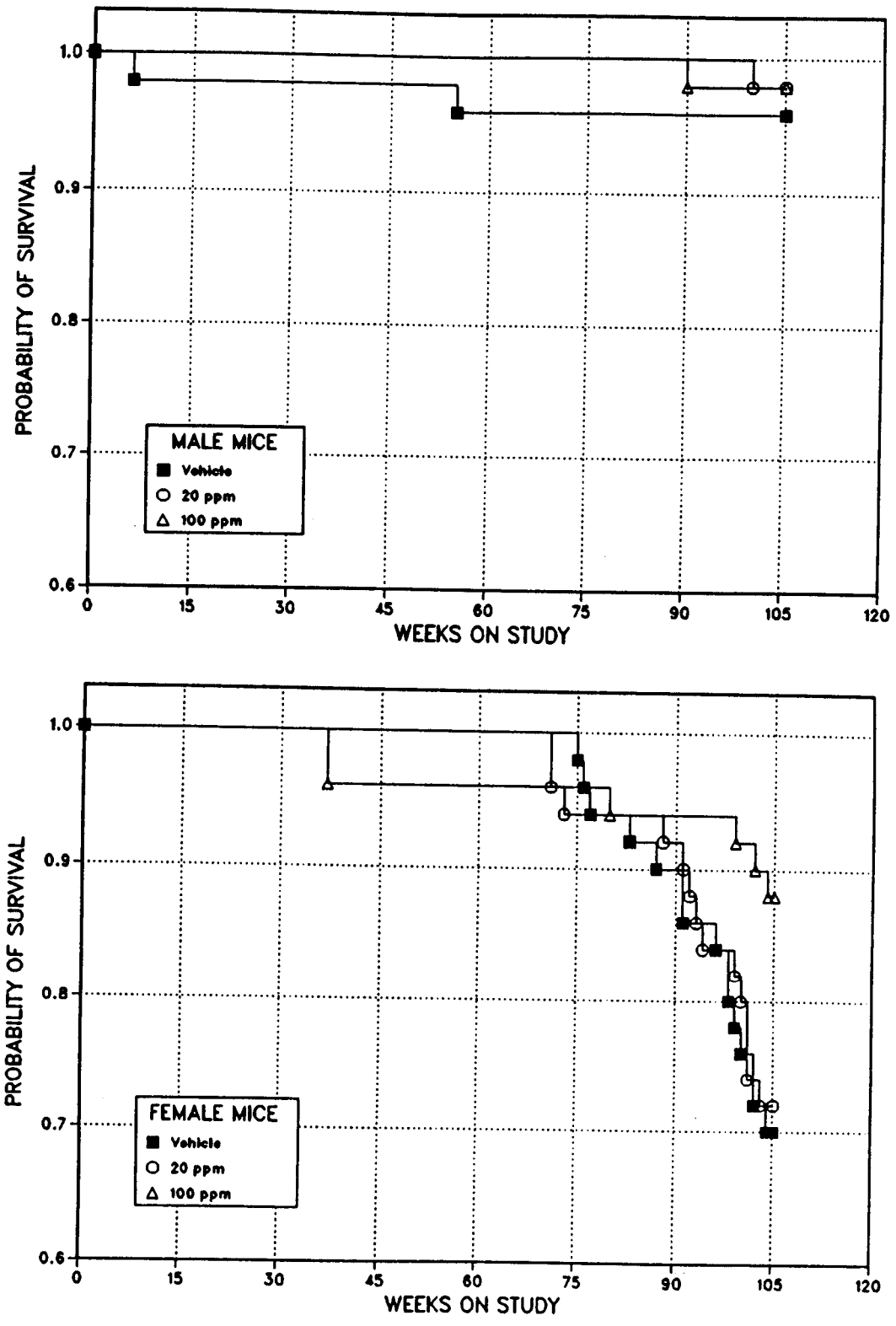


FIGURE 5
Kaplan-Meier Survival Curves for Mice Fed Diets Containing *dl*-Amphetamine Sulfate for 2 Years

Thyroid Gland: Follicular cell adenomas were seen in two high-dose male mice; follicular cell carcinomas were seen in one low-dose male mouse and one high-dose male mouse (Table 12). Follicular cell hyperplasia was seen in one control, one low-dose, and one high-dose male mouse. Follicular cell adenomas were seen in one control, one low-dose, and one high-dose female mouse. The historical incidence of follicular cell adenomas or carcinomas (combined) in male mice is 32/1,630 (2%), and the highest observed incidence is 3/42.

Although there was a slight increase in follicular cell neoplasms in exposed male mice, there was no increase in focal follicular cell hyperplasia, a lesion generally considered to be a precursor to adenoma. In addition, there were no dose-related increased incidences of follicular cell neoplasms in female mice, and the incidences of follicular cell hyperplasia were decreased in exposed females (control, 8/50; low dose, 5/49; high dose, 3/47). Consequently, the increase in follicular cell neoplasms in male mice was not considered to be related to chemical exposure.

Ovary: Atrophy was observed at an increased incidence in high-dose female mice (control, 14/49; low dose, 12/48; high dose, 25/46).

Liver, Harderian Gland, Lung, and Anterior Pituitary Gland: Significantly decreased incidences of a variety of neoplasms occurred in exposed mice of each sex; the neoplasms included hepatocellular neoplasms in male mice and harderian gland adenomas, lung neoplasms, and pituitary adenomas in female mice (Table 13).

TABLE 12
Thyroid Gland Follicular Cell Lesions in Male Mice in the 2-Year Feed Study of *dl*-Amphetamine Sulfate[a]

	0 ppm	20 ppm	100 ppm
Hyperplasia			
Overall rates	1/50 (2%)	1/50 (2%)	1/50 (2%)
Adenoma			
Overall rates	0/50 (0%)	0/50 (0%)	2/50 (4%)
Carcinoma			
Overall rates	0/50 (0%)	1/50 (2%)	1/50 (2%)
Adenoma or Carcinoma[b]			
Overall rates	0/50 (0%)	1/50 (2%)	3/50 (6%)
Terminal rates	0/48 (0%)	1/48 (2%)	3/49 (6%)
Day of first observation		729	729
Logistic regression tests	P=0.084	P=0.500	P=0.125

(T)Terminal sacrifice
[a] For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods). The estimated doses in milligrams per kilogram per day are 4 and 30 mg/kg for the 20 and 100 ppm dose groups.
[b] Historical incidence in NTP studies: 32/1,630 (2% ± 2%)

Table 13
Decreased Incidences of Naturally Occurring Neoplasms in Mice in the 2-Year Feed Studies of *dl*-Amphetamine Sulfate

	0 ppm	20 ppm	100 ppm
Male			
Estimated dose in milligrams per kilogram per day[a]	0	4	30
Final body weight (percent of controls)		85	72
Final survival	48/50	48/50	49/50
Neoplasm site			
Liver			
Adenoma	10/50	7/50	1/50
Carcinoma	4/50	6/50	1/50
Harderian gland			
Adenoma	4/50	2/50	0/50
Lung			
Adenoma	6/50	2/50	3/50
Adenoma or carcinoma	8/50	3/50	4/50
Total animals with primary neoplasms	30	25	18
Total animals with benign neoplasms	23	15	9
Total animals with malignant neoplasms	13	17	9
Female			
Estimated dose in milligrams per kilogram per day[a]	0	3	19
Final body weight (percent of controls)		81	66
Final survival	35/50	36/50	44/50
Neoplasm site			
Anterior pituitary gland			
Adenoma	12/49	6/49	1/46
Liver			
Adenoma	5/50	1/50	1/47
Harderian gland			
Adenoma	5/50	2/50	0/47
Lung			
Adenoma	7/50	4/50	1/47
Adenoma or carcinoma	8/50	6/50	1/47
Total animals with primary neoplasms	40	27	15
Total animals with benign neoplasms	30	13	5
Total animals with malignant neoplasms	19	17	11

[a] Therapeutic dose range of *dl*-amphetamine sulfate in humans is 0.1-2 mg/kg per day.

GENETIC TOXICOLOGY

dl-Amphetamine sulfate (maximum concentration of 10 mg/plate) was tested for induction of gene mutations in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 according to a preincubation protocol both in the presence and the absence of Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Zeiger *et al.*, 1987). The only response observed in the four strains occurred in TA98 in the presence of rat liver S9. Because of the variable nature of this response in the presence of different concentrations of the S9 mix, the overall assay call was judged to be equivocal. In cytogenetic tests with Chinese hamster ovary cells, amphetamine sulfate did not induce sister chromatid exchanges (SCEs) (Table I2) or chromosomal aberrations (Table I3) in either the presence or the absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9. In the SCE test, the first trial conducted with S9 produced a significant increase in SCEs at three of the four doses tested, but this response was not repeated in two subsequent trials performed with the same doses; the test results were therefore considered negative. The experimental procedures and results are presented in Appendix I.

DISCUSSION AND CONCLUSIONS

Amphetamine is taken orally for the treatment of narcolepsy, for behavioral syndromes in children, and for weight control. The U.S. Food and Drug Administration nominated this drug for 2-year carcinogenesis studies because there were no adequate studies on the long-term effects in rodents and the drug was widely used in the United States. Amphetamine is available in several forms and both the *dl-* and *d-* isomers have been widely used. *dl-*Amphetamine sulfate was selected as the representative drug for study. Doses in humans vary with use and body weight of patients, but a typical dose might be between 0.2 and 2 mg/kg body weight.

Fourteen-day and 13-week toxicity studies were conducted in F344/N rats and B6C3F$_1$ mice to determine toxicity and to set doses for the 2-year studies. In the 14-day and 13-week studies, *dl-*amphetamine sulfate was administered in the feed at concentrations from 47 to 750 ppm for rats and from 125 to 2,000 ppm for mice. In the 14-day studies, decreased body weight gain was seen at the high concentrations but no toxic lesions were seen; the same concentrations were used in the 13-week studies.

In the 13-week studies, there were no dose-related deaths in rats, but some male mice that received 500 to 2,000 ppm and female mice that received 2,000 ppm died before the end of the studies. The pattern of deaths in male mice is similar to that observed by other investigators (Moore, 1963; James *et al.*, 1978). The single-dose response curve for lethality in mice is triphasic rather than the usual hyperbolic shape, since for a short portion of the curve mortality decreases with increasing dose. James and Franklin (1978) showed that three inhibitors of hepatic metabolism changed the lethal dose response curve to a more typical curvilinear response or rectangular hyperbolic curve. Further, stress factors such as crowding, noise, and elevated room temperature enhance the lethality of amphetamine and contribute to the susceptibility of individual mice and fluctuations in the dose response curve (Moore, 1963). Although the immediate cause of death in rodents receiving lethal doses of amphetamine is unknown, the central and peripheral release of catecholamines is believed to be an important factor in the events leading to the animals' death (Lewander, 1977).

There were no histological lesions that were considered to be a primary effect of amphetamine in the 13-week studies. Therefore, the decreased body weight gain and the hyperactivity seen in dosed rats and mice were the primary factors used in selection of dietary concentrations for the 2-year studies. In the 13-week studies, final body weight of rats receiving 188 ppm or more were 62% to 89% those of controls, and final body weights of mice receiving 250 ppm or more were 70% to 86% those of controls. One of the characteristics of the physiological and behavioral effects of repeated exposure to amphetamine which impacts on dose selection for the 2-year studies is the development of tolerance. Tolerance has been shown to develop to the lethal effects in mice (Abdallah, 1973) and rats (Lewander, 1968; Magour *et al.*, 1974), to the hyperthermic and anorexic effects (Tormey and Lasagna, 1960; Götestam and Lewander, 1975; Götestam, 1976; Thornhill *et al.*, 1977), and to some, but not all, of the behavioral effects (Lewander, 1977). Tolerance to the effects of amphetamine on food responding patterns (food consumption, anorexia) develops, but the rate and degree of tolerance is greatly influenced by the frequency, route, and time of administration of the drug, as well as the nature of the food (palatability, etc.) and whether the diet is restricted (Lewander, 1977). However, studies in which body weights are reported show that complete tolerance to the body weight effects of amphetamine does not occur. That is, following an initial drop in body weight the growth curves of dosed animals may approach and parallel those of controls, but a decrement remains despite the recovery of food intake (Lewander, 1971; Lu *et al.*, 1973; Magour *et al.*, 1974; Jenner *et al.*, 1978; Levitsky *et al.*, 1981; Wolgin, 1983; Wolgin *et al.*, 1985).

The results of the 13-week studies reported here provide further evidence that tolerance to body weight effects is not complete, particularly under the conditions of these studies. A low dose of 20 ppm

was selected for the 2-year studies to approximate human doses, and a high dose of 100 ppm was selected which, based on the results of the 13-week studies, was expected to give a final body weight of approximately 90% that of controls. In the 2-year studies, the estimated daily dose of drug at the dietary concentration of 20 ppm in rats was 1 mg/kg and in mice 3 to 4 mg/kg, and the estimated daily dose at 100 ppm was 5 mg/kg in rats and 19 to 30 mg/kg in mice. In the 2-year studies there were dose-related decrements in body weight for both rats and mice administered amphetamine. In general, body weight decrements in dosed animals were apparent by week 15 and increased as the study progressed. At week 104, the final mean body weights of low- and high-dose groups relative to controls were 92% and 86% for male rats, 89% and 70% for female rats, 85% and 72% for male mice, and 81% and 66% for female mice. It is apparent from these studies not only that there was a lack of tolerance to the body weight effects of amphetamine, but that aging rats and mice became more susceptible to the effects of continuous dietary administration. Aging animals are often more susceptible to the adverse effects of drugs or chemicals due to a variety of factors including altered rates of metabolism, longer biological half-life or greater plasma concentrations. Truex and Schmidt (1980) have shown that amphetamine concentrations in the brain are twice as high in 24-month-old rats as that of 3-month-old rats receiving the same dose on a mg/kg body weight basis. Further, it has been demonstrated that mice become more sensitive to the acute lethal effects of amphetamine as they grow older (Alhava, 1972).

It is unknown if the decreased weight gain in these 2-year studies is due to the increased activity shown by the dosed animals, direct effects on metabolism, or combinations of various factors. Amphetamine has been shown to affect oxygen consumption, lipid, carbohydrate, and protein metabolism, and secretion of insulin from the pancreas and of corticosteroids from the adrenal gland (Lewander, 1977). Decreased food consumption does not seem to be the primary factor since only high-dose female rats showed a decrease in consumption relative to the controls. However, since the chemical-related hyperactivity may have caused increased spillage of the feed, consumption may have been overestimated in the dosed groups.

Lethal doses of amphetamine have been reported to cause petechial hemorrhages in a variety of organs and necrosis of the myocardium (Lewander, 1978). Other studies have reported hyperemia, hemorrhages, and glial proliferation in the brain of monkeys (Duarte-Escalante and Ellinwood, 1972), enlargement and chromatolysis of neurons in the medulla oblongata of cats (Escalante and Ellinwood, 1970), and swelling of cell bodies in the caudate nucleus, cortex, and hypothalamus during motor excitation in the rat (Popova *et al.*, 1972).

In the 13-week studies there were no histological lesions associated with the administration of amphetamine, although in the 2-year studies there were increases in bone marrow myelofibrosis, cataracts and retinal atrophy in high-dose female rats and ovarian atrophy in high-dose female mice. The cataracts and retinal atrophy are not believed to be directly caused by amphetamine. The spectrum, location, and type of lesions in the lens and retina of high-dose female rats are similar to those seen in aging rats exposed to high illumination intensity. Further, factors such as body temperature and stress are known to increase the rate and extent of these degenerative lesions (Lai *et al.*, 1978). Since amphetamine is known to cause hyperthermia, increased activity, and pupil dilation in some species, the drug may have contributed to the increased incidences of these age- and light-related lesions through a nonspecific mechanism. Similarly, the increased incidence of ovarian atrophy in high-dose female mice may be related to the marked reduction in body weight (34% lower than controls at the end of the study) rather than a direct effect of the drug on the ovary.

In addition to the chemical-related decrements in weight gain and hyperactivity, the major effect of chronic amphetamine administration was a decrease in the occurrence of certain site-specific neoplasms that occur naturally at incidences of 3% or more (Tables 7 and 13). Although the mechanisms involved in the inhibition of the development of spontaneous neoplasms are unknown, reduced body weights and/or feed restriction have been associated with similar decreases in tumor incidences.

Rous (1914) first observed that tumor growth is retarded in animals consuming less feed, with

concomitant reduced body weight gain. In the succeeding years the relationship between feed restriction and tumor growth has been investigated using transplanted or induced tumors (Sylvester *et al.*, 1981; Gross and Dreyfus, 1984; Ershler *et al.*, 1986) or by studying the effects of feed restriction on the development of naturally occurring tumors.

A lifespan study in F344/N rats in which the feed restricted group received 60% of the feed received by the controls resulted in decreased incidences of interstitial cell tumors of the testis, bile duct hyperplasia, myocardial fibrosis, and myocardial degeneration (Yu *et al.*, 1982). From the body weight curves given in the report, it is estimated that the final body weight of the feed-restricted group was approximately 70% that of controls.

In a study using Charles River rats, dietary restriction over the lifespan of the animals resulted in reduced incidences of benign connective tissue neoplasms and neoplasms of epithelial tissue including reduction in neoplasms of the lung, pituitary gland, pancreas, and thyroid gland (Ross and Bras, 1971). A 20% restriction of feed in Wistar rats or Swiss mice for 24 months caused decreases in neoplasms of the pituitary gland, mammary gland, and skin in rats and pituitary gland in mice (Tucker, 1979). Spontaneous lymphomas were inhibited by feed restriction in mice (Weindruck and Walford, 1982).

Rao *et al.* (1987) reviewed a series of National Cancer Institute/National Toxicology Program 2-year studies in rodents and found that among control groups lower mean body weight was associated with lower incidences of naturally occurring benign neoplasms of the mammary gland in female rats. However, comparison of control with treated groups showed that chemical-related decreases in maximum mean body weights were associated with decreases in benign mammary gland tumors and pituitary tumors in female rats and leukemia in male rats.

It appears from the work of others that reduced body weight is closely associated with reduced neoplasm incidence at certain sites (Schneider and Reed, 1985). In contrast to the above studies, however, the reduced body weight gain in F344/N rats and $B6C3F_1$ mice given *dl*-amphetamine was likely due to the pharmacologic effects of the drug and possibly an increase in the activity of the animals, rather than reduced feed intake. Whether the lower incidences of neoplasms are related to the reduced body weights or a more direct effect of the drug cannot be determined from these studies.

Although survival of rats and mice was not affected by the administration of amphetamine in the feed for 2 years and there were few nonneoplastic toxic lesions, there were substantial reductions in body weights in dosed groups. Therefore, we feel the doses were sufficiently high to draw conclusions regarding the potential carcinogenic activity of amphetamine.

Under the conditions of these 2-year feed studies, there was *no evidence of carcinogenic activity** of *dl*-amphetamine sulfate for male or female F344/N rats or male or female $B6C3F_1$ mice fed 20 or 100 ppm. The administration of *dl*-amphetamine sulfate was associated with decreased body weight. There were decreased incidences of total neoplasms in dosed rats and mice, of adrenal pheochromocytomas in male rats, of mammary gland fibroadenomas and uterine polyps in female rats, of pituitary gland adenomas in male and female rats and female mice, and of harderian gland adenomas, hepatocellular neoplasms, and lung neoplasms in male and female mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 8. A summary of the peer review comments and the public discussion on this Technical Report appears on page 10.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDIES OF *dl*-AMPHETAMINE SULFATE

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

	Untreated Control	20 ppm	100 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Dead	8	11	9
Moribund	12	8	8
Survivors			
Terminal sacrifice	30	31	33
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Intestine small, jejunum	(49)	(49)	(46)
Adenocarcinoma	1 (2%)		
Liver	(50)	(50)	(50)
Carcinoma, metastatic, testes		1 (2%)	
Neoplastic nodule			1 (2%)
Mesentery	(6)	(5)	(5)
Fibrous histiocytoma		1 (20%)	
Pancreas	(49)	(49)	(49)
Fibrous histiocytoma		1 (2%)	
Salivary glands	(50)	(48)	(50)
Schwannoma malignant	1 (2%)		2 (4%)
Stomach, glandular	(50)	(50)	(50)
Tooth		(1)	(1)
Gingiva, neoplasm, NOS		1 (100%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	(49)	(50)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(49)	(48)	(50)
Adenoma			1 (2%)
Adrenal gland, medulla	(49)	(44)	(50)
Pheochromocytoma malignant			1 (2%)
Pheochromocytoma benign	17 (35%)	10 (23%)	6 (12%)
Pheochromocytoma benign, multiple	6 (12%)	5 (11%)	
Islets, pancreatic	(50)	(47)	(50)
Adenoma	1 (2%)	1 (2%)	1 (2%)
Carcinoma	1 (2%)	1 (2%)	2 (4%)
Parathyroid gland	(41)	(39)	(49)
Adenoma		1 (3%)	
Pituitary gland	(49)	(48)	(49)
Pars distalis, adenoma	15 (31%)	15 (31%)	9 (18%)
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	9 (18%)	4 (8%)	5 (10%)
C-cell, adenoma, multiple	1 (2%)		
C-cell, carcinoma	3 (6%)		1 (2%)
Follicle, adenoma	1 (2%)		1 (2%)
GENERAL BODY SYSTEM			
None			

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

	Untreated Control	20 ppm	100 ppm
GENITAL SYSTEM			
Epididymis	(50)	(50)	(50)
Preputial gland	(48)	(47)	(49)
Adenoma	2 (4%)	5 (11%)	1 (2%)
Carcinoma		1 (2%)	2 (4%)
Prostate	(49)	(49)	(50)
Adenoma		1 (2%)	
Seminal vesicle	(49)	(49)	(49)
Testes	(50)	(50)	(50)
Interstitial cell, adenoma	10 (20%)	10 (20%)	4 (8%)
Interstitial cell, adenoma, multiple	33 (66%)	33 (66%)	44 (88%)
Interstitial cell, carcinoma		1 (2%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Lymph node	(50)	(50)	(50)
Lymph node, mandibular	(48)	(45)	(49)
Lymph node, mesenteric	(48)	(49)	(50)
Spleen	(50)	(49)	(50)
Carcinoma, metastatic, testes		1 (2%)	
Hemangioma			1 (2%)
Thymus	(39)	(45)	(43)
INTEGUMENTARY SYSTEM			
Mammary gland	(37)	(44)	(48)
Fibroadenoma	3 (8%)		
Skin	(50)	(50)	(50)
Basal cell adenoma		1 (2%)	
Keratoacanthoma	1 (2%)	1 (2%)	1 (2%)
Papilloma squamous	1 (2%)	1 (2%)	1 (2%)
Subcutaneous tissue, fibroma	2 (4%)	3 (6%)	1 (2%)
Subcutaneous tissue, fibroma, multiple	1 (2%)		
Subcutaneous tissue, keratoacanthoma		1 (2%)	
Subcutaneous tissue, neurofibrosarcoma	1 (2%)		
Subcutaneous tissue, sarcoma		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Femur, osteosarcoma			1 (2%)
Skeletal muscle		(1)	
Diaphragm, fibrous histiocytoma		1 (100%)	
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Cerebrum, astrocytoma malignant			1 (2%)
Spinal cord	(50)	(50)	(50)
Nerve, schwannoma malignant	1 (2%)	1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	2 (4%)
Alveolar/bronchiolar carcinoma		3 (6%)	
Carcinoma, metastatic, preputial gland		1 (2%)	
Chordoma, metastatic, uncertain primary site			1 (2%)
Fibrous histiocytoma		1 (2%)	
Osteosarcoma, metastatic, uncertain primary site			1 (2%)

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

	Untreated Control	20 ppm	100 ppm
RESPIRATORY SYSTEM (Continued)			
Nose	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
Mucosa, squamous cell carcinoma	2 (4%)		
SPECIAL SENSES SYSTEM			
Eye	(50)	(50)	(48)
Zymbal gland			(1)
Carcinoma			1 (100%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Fibrous histiocytoma		1 (2%)	
Liposarcoma	1 (2%)		
Urinary bladder	(50)	(49)	(50)
Transitional epithelium, papilloma	1 (2%)	1 (2%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	20 (40%)	16 (32%)	18 (36%)
Mesothelioma malignant	2 (4%)	1 (2%)	2 (4%)
TUMOR SUMMARY			
Total animals with primary neoplasms **	49	50	49
Total primary neoplasms	140	127	110
Total animals with benign neoplasms	48	45	49
Total benign neoplasms	107	95	79
Total animals with malignant neoplasms	25	25	27
Total malignant neoplasms	33	31	31
Total animals with secondary neoplasms ***		2	3
Total secondary neoplasms		3	4
Total animals with malignant neoplasms--uncertain primary site			2
Total animals with neoplasms--uncertain benign or malignant		1	
Total uncertain neoplasms		1	

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: UNTREATED CONTROL

DAYS ON STUDY	311	512	533	558	579	625	634	637	638	659	664	676	684	684	691	695	708	717	722	726	729	729	729	729
CARCASS ID	021	075	035	034	105	074	055	032	045	054	063	015	025	073	023	044	014	065	024	103	011	012	013	022	031
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery						+				+		+				+								+	
Pancreas	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign					X					X	X		X	X	X		X			X					X
Pheochromocytoma benign, multiple																X									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X						X								X			X	X			X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X			X															
C-cell, adenoma, multiple																		X							
C-cell, carcinoma							X								X										
Follicle, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Adenoma																						X			
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma						X		X						X		X				X	X		X		
Interstitial cell, adenoma, multiple				X	X					X	X	X	X		X			X	X			X	X		X

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

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

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

DAYS ON STUDY	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	TOTAL:
CARCASS ID	033	041	042	043	051	052	053	061	062	064	071	072	081	082	083	084	085	091	092	093	094	095	101	102	104	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma										X																1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery													+													6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant													X													1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign		X		X			X						X			X		X					X		X	17
Pheochromocytoma benign, multiple															X				X	X	X			X		6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X																					1
Carcinoma								X																		1
Parathyroid gland	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X		X		X		X		X	X										X			X	15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X				X			X		X	X			X	X									9
C-cell, adenoma, multiple																										1
C-cell, carcinoma						X																				3
Follicle, adenoma										X																1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma							X																			2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma															X			X							X	10
Interstitial cell, adenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X	X	X	X		33

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

DAYS ON STUDY	316	512	533	558	579	625	634	637	638	659	664	676	684	684	691	695	708	717	722	726	729	729	729	729
CARCASS ID	0021	0075	0035	0034	1005	0074	0055	0032	0045	0054	0063	0155	0225	0733	0223	0444	0144	0665	0224	1003	0111	0112	0113	0222	0331
HEMATOPOIETIC SYSTEM																									
Blood										+															
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	M	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	M	M	+	M	+	+	+	+	+	M	+	+	+	+	M	+	M	+	M	+	+
Fibroadenoma																								X	X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Papilloma squamous																									
Subcutaneous tissue, fibroma																	X								
Subcutaneous tissue, fibroma, multiple																									
Subcutaneous tissue, neurofibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nerve, schwannoma malignant																									
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X			X					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucosa, squamous cell carcinoma								X			X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma													X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X			X	X	X					X	X	X	X	X		X	X		X		X	X	X
Mesothelioma malignant											X														

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

DAYS ON STUDY	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	TOTAL:
CARCASS ID	033	041	042	043	051	052	053	061	062	064	071	072	081	082	083	084	085	091	092	093	094	095	101	102	104	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	48
Lymph node, mesenteric	+	+	M	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	M	+	+	+	39
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	M	+	M	+	+	M	+	+	+	+	37
Fibroadenoma																	X									3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma							X																			1
Papilloma squamous								X																		1
Subcutaneous tissue, fibroma			X																							2
Subcutaneous tissue, fibroma, multiple						X																				1
Subcutaneous tissue, neurofibrosarcoma																		X								1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nerve, schwannoma malignant																							X			1
RESPIRATORY SYSTEM																										
Larynx	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																					X					3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mucosa, squamous cell carcinoma																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma						X																				1
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X	X			X					X							X	20
Mesothelioma malignant													X													2

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: 20 ppm

DAYS ON STUDY	236	384	415	437	467	524	576	585	655	660	666	667	674	682	688	694	695	705	723	729	729	729	729	729	730
CARCASS ID	11 1	15 5	12 5	18 5	19 5	18 4	11 5	12 4	13 5	18 3	13 4	20 5	12 3	14 5	14 4	18 2	20 4	17 5	15 4	12 1	12 2	13 1	13 2	13 3	14 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, testes																									
Mesentery											+		+												
Fibrous histiocytoma													X												
Pancreas	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma													X												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth							+																		
Gingiva, neoplasm, NOS							X																		
CARDIOVASCULAR SYSTEM																									
Blood vessel		+																+							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+
Pheochromocytoma benign														X								X	X		
Pheochromocytoma benign, multiple									X			X									X				
Islets, pancreatic	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma																		X							
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	M
Adenoma																									
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X			X		X										X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																						X			
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+
Adenoma										X											X				
Carcinoma									X																
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma					X	X	X		X													X			
Interstitial cell, adenoma, multiple								X		X	X	X	X		X	X	X	X		X	X		X	X	X
Interstitial cell, carcinoma																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 20 ppm (Continued)

DAYS ON STUDY	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	TOTAL:
CARCASS ID	142	143	151	152	153	161	162	163	164	165	171	172	173	174	181	191	192	193	194	201	202	203	212	213	214	TISSUES / TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, testes								X																		1
Mesentery	+														+				+							5
Fibrous histiocytoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
Gingiva, neoplasm, NOS																										1
CARDIOVASCULAR SYSTEM																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	49
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			48
Adrenal gland, medulla	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+			44
Pheochromocytoma benign					X								X		X	X		X			X	X				10
Pheochromocytoma benign, multiple						X								X												5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Carcinoma																						X				1
Parathyroid gland	+	+	M	+	+	M	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	M	39
Adenoma							X																			1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma	X			X	X	X		X	X	X				X	X					X			X			15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma						X																X			X	4
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma												X							X		X					5
Carcinoma																										1
Prostate	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Seminal vesicle	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma			X		X	X			X											X						10
Interstitial cell, adenoma, multiple	X	X		X			X	X		X	X	X	X	X		X	X	X	X		X	X	X	X	X	33
Interstitial cell, carcinoma								X																		1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 20 ppm (Continued)

DAYS ON STUDY	236	384	415	437	467	524	576	585	655	660	666	667	674	682	688	694	695	705	723	729	729	729	729	729	730
CARCASS ID	11 1	15 5	12 5	18 5	19 5	18 4	11 5	12 4	13 5	18 3	13 4	20 5	12 3	14 5	14 4	18 2	20 4	17 5	15 4	12 1	12 2	13 1	13 2	13 3	14 1
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Carcinoma, metastatic, testes																									
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Keratoacanthoma																									
Papilloma squamous																									
Subcutaneous tissue, fibroma												X										X			
Subcutaneous tissue, keratoacanthoma											X														
Subcutaneous tissue, sarcoma				X																					
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+												
Diaphragm, fibrous histiocytoma													X												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nerve, schwannoma malignant		X																							
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X															
Alveolar/bronchiolar carcinoma																						X			
Carcinoma, metastatic, preputial gland									X																
Fibrous histiocytoma													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear					+						M														
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma													X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																		X							
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X		X			X			X	X				X	X		X	X			X	X	
Mesothelioma malignant													X												

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 20 ppm (Continued)

DAYS ON STUDY	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	TOTAL:
CARCASS ID	142	143	151	152	153	161	162	163	164	165	171	172	173	174	181	191	192	193	194	201	202	203	112	113	114	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, testes								X																		1
Thymus	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	M	+	+	+	+	+	+	+	45
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	44
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																					X					1
Keratoacanthoma														X												1
Papilloma squamous						X																				1
Subcutaneous tissue, fibroma										X																3
Subcutaneous tissue, keratoacanthoma																										1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Diaphragm, fibrous histiocytoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nerve, schwannoma malignant																										1
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																		X								2
Alveolar/bronchiolar carcinoma									X							X										3
Carcinoma, metastatic, preputial gland																										1
Fibrous histiocytoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																									M	1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma																										1
Urinary bladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional epithelium, papilloma																										1
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear									X			X					X		X							16
Mesothelioma malignant																										1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: 100 ppm

DAYS ON STUDY	436	436	498	582	607	621	627	639	659	660	666	675	695	703	711	722	726	729	729	729	729	729	729	729	729
CARCASS ID	21 5	30 4	22 5	23 5	25 3	24 5	22 4	27 5	26 5	25 5	22 3	24 4	27 4	26 4	23 4	29 5	23 2	28 1	28 2	28 3	28 4	28 5	29 1	29 2	29 3
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	M	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Mesentery								+											+	+			+		
Mesothelioma malignant, metastatic																							X		
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant							X							X											
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									X
Pheochromocytoma benign											X				X									X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X							X	X			X				X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma	X																X	X							
C-cell, carcinoma																	X								•
Follicle, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Serosa, mesothelioma malignant, metastatic																							X		
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma				X			X											X							
Interstitial cell, adenoma, multiple			X		X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 100 ppm (Continued)

DAYS ON STUDY	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	TOTAL:
CARCASS ID	294	301	302	303	211	212	213	214	221	222	231	233	241	242	243	251	252	254	261	262	263	271	272	273	305	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	46
Intestine large, cecum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	44
Intestine large, colon	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	46
Intestine large, rectum	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule					X																					1
Mesentery			+																							5
Mesothelioma malignant, metastatic																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										2
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																			+							1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																							X			1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign		X	X																						X	6
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma		X								X																2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma												X										X	X		X	9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma											X				X											5
C-cell, carcinoma																										1
Follicle, adenoma									X																	1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Serosa, mesothelioma malignant, metastatic																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma									X																	1
Carcinoma				X											X											2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																							X			4
Interstitial cell, adenoma, multiple	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	44

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 100 ppm (Continued)

DAYS ON STUDY	436	436	498	582	607	621	627	639	659	660	666	675	695	703	711	722	726	729	729	729	729	729	729	729	729
CARCASS ID	215	304	225	235	253	245	224	275	265	255	223	244	274	264	234	295	232	281	282	283	284	285	291	292	293
HEMATOPOIETIC SYSTEM																							+		
Blood																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Thymus	+	+	+	M	+	+	+	+	M	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma												X													
Papilloma squamous																									
Subcutaneous tissue, fibroma																X									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma											X														
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebrum, astrocytoma malignant															X										
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Chordoma, metastatic, uncertain primary site							X																		
Osteosarcoma, metastatic, uncertain primary site																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Eye	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal gland									+																
Carcinoma									X																
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X			X		X		X		X	X					X			X		X		X
Mesothelioma malignant																							X	X	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 100 ppm (Continued)

DAYS ON STUDY	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	TOTAL:
CARCASS ID	294	301	302	303	211	212	213	214	221	222	231	233	241	242	243	251	252	254	261	262	263	271	272	273	305	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma										X																1
Thymus	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										1
Papilloma squamous											X															1
Subcutaneous tissue, fibroma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femur, osteosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cerebrum, astrocytoma malignant																										1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X												X								2
Chordoma, metastatic, uncertain primary site																										1
Osteosarcoma, metastatic, uncertain primary site								X																		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear						M																M				
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Zymbal gland																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X											X		X				X	X		X		X	X	18
Mesothelioma malignant																										2

TABLE A3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

	Control	20 ppm	100 ppm
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	23/49 (47%)	15/44 (34%)	6/50 (12%)
Adjusted Rates (b)	59.5%	50.2%	16.7%
Terminal Rates (c)	14/29 (48%)	12/26 (46%)	4/33 (12%)
Day of First Observation	579	655	666
Life Table Tests (d)	P<0.001N	P=0.143N	P<0.001N
Logistic Regression Tests (d)	P<0.001N	P=0.204N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.147N	P<0.001N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	23/49 (47%)	15/44 (34%)	7/50 (14%)
Adjusted Rates (b)	59.5%	50.2%	19.6%
Terminal Rates (c)	14/29 (48%)	12/26 (46%)	5/33 (15%)
Day of First Observation	579	655	666
Life Table Tests (d)	P<0.001N	P=0.143N	P<0.001N
Logistic Regression Tests (d)	P<0.001N	P=0.204N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.147N	P<0.001N
Preputial Gland: Adenoma			
Overall Rates (a)	2/48 (4%)	5/47 (11%)	1/49 (2%)
Adjusted Rates (b)	6.7%	15.9%	3.0%
Terminal Rates (c)	2/30 (7%)	4/29 (14%)	1/33 (3%)
Day of First Observation	729	660	729
Life Table Tests (d)	P=0.214N	P=0.206	P=0.467N
Logistic Regression Tests (d)	P=0.225N	P=0.180	P=0.467N
Cochran-Armitage Trend Test (d)	P=0.240N		
Fisher Exact Test (d)		P=0.209	P=0.492N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	2/48 (4%)	6/47 (13%)	3/49 (6%)
Adjusted Rates (b)	6.7%	17.9%	9.1%
Terminal Rates (c)	2/30 (7%)	4/29 (14%)	3/33 (9%)
Day of First Observation	729	655	729
Life Table Tests (d)	P=0.499N	P=0.130	P=0.544
Logistic Regression Tests (d)	P=0.522N	P=0.107	P=0.544
Cochran-Armitage Trend Test (d)	P=0.540N		
Fisher Exact Test (d)		P=0.127	P=0.510
Pancreatic Islets: Adenoma or Carcinoma			
Overall Rates (a)	2/50 (4%)	2/47 (4%)	3/50 (6%)
Adjusted Rates (b)	6.7%	6.2%	8.7%
Terminal Rates (c)	2/30 (7%)	1/31 (3%)	2/33 (6%)
Day of First Observation	729	705	722
Life Table Tests (d)	P=0.471	P=0.688N	P=0.543
Logistic Regression Tests (d)	P=0.461	P=0.679	P=0.533
Cochran-Armitage Trend Test (d)	P=0.439		
Fisher Exact Test (d)		P=0.668	P=0.500
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	9.2%	5.6%	6.1%
Terminal Rates (c)	1/30 (3%)	1/31 (3%)	2/33 (6%)
Day of First Observation	708	660	729
Life Table Tests (d)	P=0.463N	P=0.497N	P=0.461N
Logistic Regression Tests (d)	P=0.483N	P=0.516N	P=0.478N
Cochran-Armitage Trend Test (d)	P=0.500N		
Fisher Exact Test (d)		P=0.500N	P=0.500N

TABLE A3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (*Continued*)

	Control	20 ppm	100 ppm
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	9.7%	0.0%
Terminal Rates (c)	0/30 (0%)	3/31 (10%)	0/33 (0%)
Day of First Observation		729	
Life Table Tests (d)	P=0.368N	P=0.126	(e)
Logistic Regression Tests (d)	P=0.368N	P=0.126	(e)
Cochran-Armitage Trend Test (d)	P=0.394N		
Fisher Exact Test (d)		P=0.121	(e)
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	9.2%	15.0%	6.1%
Terminal Rates (c)	1/30 (3%)	4/31 (13%)	2/33 (6%)
Day of First Observation	708	660	729
Life Table Tests (d)	P=0.287N	P=0.368	P=0.461N
Logistic Regression Tests (d)	P=0.303N	P=0.338	P=0.478N
Cochran-Armitage Trend Test (d)	P=0.325N		
Fisher Exact Test (d)		P=0.357	P=0.500N
Mammary Gland: Fibroadenoma			
Overall Rates (f)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	10.0%	0.0%	0.0%
Terminal Rates (c)	3/30 (10%)	0/31 (0%)	0/33 (0%)
Day of First Observation	729		
Life Table Tests (d)	P=0.127N	P=0.114N	P=0.104N
Logistic Regression Tests (d)	P=0.127N	P=0.114N	P=0.104N
Cochran-Armitage Trend Test (d)	P=0.140N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	15/49 (31%)	15/48 (31%)	9/49 (18%)
Adjusted Rates (b)	43.1%	44.7%	25.4%
Terminal Rates (c)	11/30 (37%)	12/30 (40%)	7/33 (21%)
Day of First Observation	533	660	660
Life Table Tests (d)	P=0.052N	P=0.579	P=0.085N
Logistic Regression Tests (d)	P=0.059N	P=0.526	P=0.103N
Cochran-Armitage Trend Test (d)	P=0.080N		
Fisher Exact Test (d)		P=0.560	P=0.120N
Subcutaneous Tissue: Fibroma			
Overall Rates (f)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	9.4%	8.9%	2.9%
Terminal Rates (c)	2/30 (7%)	2/31 (6%)	0/33 (0%)
Day of First Observation	708	667	722
Life Table Tests (d)	P=0.215N	P=0.656N	P=0.279N
Logistic Regression Tests (d)	P=0.224N	P=0.648	P=0.290N
Cochran-Armitage Trend Test (d)	P=0.237N		
Fisher Exact Test (d)		P=0.661	P=0.309N
Subcutaneous Tissue: Fibroma, Sarcoma, or Neurofibrosarcoma			
Overall Rates (f)	4/50 (8%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	12.6%	10.8%	2.9%
Terminal Rates (c)	3/30 (10%)	2/31 (6%)	0/33 (0%)
Day of First Observation	708	437	722
Life Table Tests (d)	P=0.120N	P=0.637N	P=0.158N
Logistic Regression Tests (d)	P=0.132N	P=0.644N	P=0.165N
Cochran-Armitage Trend Test (d)	P=0.133N		
Fisher Exact Test (d)		P=0.643	P=0.181N

TABLE A3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Control	20 ppm	100 ppm
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	43/50 (86%)	43/50 (86%)	48/50 (96%)
Adjusted Rates (b)	97.7%	97.7%	100.0%
Terminal Rates (c)	29/30 (97%)	30/31 (97%)	33/33 (100%)
Day of First Observation	558	467	498
Life Table Tests (d)	P=0.405	P=0.528N	P=0.459
Logistic Regression Tests (d)	P=0.047	P=0.349	P=0.034
Cochran-Armitage Trend Test (d)	P=0.056		
Fisher Exact Test (d)		P=0.613N	P=0.080
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	10/50 (20%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	29.1%	12.9%	13.5%
Terminal Rates (c)	7/30 (23%)	4/31 (13%)	3/33 (9%)
Day of First Observation	634	729	436
Life Table Tests (d)	P=0.175N	P=0.070N	P=0.107N
Logistic Regression Tests (d)	P=0.201N	P=0.082N	P=0.130N
Cochran-Armitage Trend Test (d)	P=0.213N		
Fisher Exact Test (d)		P=0.074N	P=0.131N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	8.2%	0.0%	2.9%
Terminal Rates (c)	1/30 (3%)	0/31 (0%)	0/33 (0%)
Day of First Observation	634		726
Life Table Tests (d)	P=0.388N	P=0.127N	P=0.289N
Logistic Regression Tests (d)	P=0.404N	P=0.120N	P=0.304N
Cochran-Armitage Trend Test (d)	P=0.407N		
Fisher Exact Test (d)		P=0.121N	P=0.309N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	12/50 (24%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	34.1%	12.9%	13.5%
Terminal Rates (c)	8/30 (27%)	4/31 (13%)	3/33 (9%)
Day of First Observation	634	729	436
Life Table Tests (d)	P=0.092N	P=0.027N	P=0.044N
Logistic Regression Tests (d)	P=0.107N	P=0.031N	P=0.054N
Cochran-Armitage Trend Test (d)	P=0.115N		
Fisher Exact Test (d)		P=0.027N	P=0.054N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (f)	20/50 (40%)	16/50 (32%)	18/50 (36%)
Adjusted Rates (b)	47.5%	38.4%	44.9%
Terminal Rates (c)	9/30 (30%)	7/31 (23%)	12/33 (36%)
Day of First Observation	512	236	498
Life Table Tests (d)	P=0.412N	P=0.301N	P=0.349N
Logistic Regression Tests (d)	P=0.519N	P=0.230N	P=0.418N
Cochran-Armitage Trend Test (d)	P=0.500N		
Fisher Exact Test (d)		P=0.266N	P=0.418N
All Sites: Benign Tumors			
Overall Rates (f)	48/50 (96%)	45/50 (90%)	49/50 (98%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	30/30 (100%)	31/31 (100%)	33/33 (100%)
Day of First Observation	533	467	436
Life Table Tests (d)	P=0.451N	P=0.327N	P=0.397N
Logistic Regression Tests (d)	P=0.303	P=0.632N	P=0.392
Cochran-Armitage Trend Test (d)	P=0.251		
Fisher Exact Test (d)		P=0.218N	P=0.500

TABLE A3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Control	20 ppm	100 ppm
All Sites: Malignant Tumors			
Overall Rates (f)	25/50 (50%)	25/50 (50%)	28/50 (56%)
Adjusted Rates (b)	57.1%	54.3%	61.9%
Terminal Rates (c)	12/30 (40%)	11/31 (35%)	16/33 (48%)
Day of First Observation	512	236	498
Life Table Tests (d)	P=0.445	P=0.562N	P=0.478
Logistic Regression Tests (d)	P=0.270	P=0.513N	P=0.347
Cochran-Armitage Trend Test (d)	P=0.298		
Fisher Exact Test (d)		P=0.579N	P=0.344
All Sites: All Tumors			
Overall Rates (f)	49/50 (98%)	50/50 (100%)	49/50 (98%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	30/30 (100%)	31/31 (100%)	33/33 (100%)
Day of First Observation	512	236	436
Life Table Tests (d)	P=0.287N	P=0.531	P=0.336N
Logistic Regression Tests (d)	P=0.430N	P=0.266	P=0.581N
Cochran-Armitage Trend Test (d)	P=0.629N		
Fisher Exact Test (d)		P=0.500	P=0.753N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(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 logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in controls is indicated by (N).
(e) No P value is reported because no tumors were observed in the 100-ppm and control groups.
(f) Number of tumor-bearing animals/number of animals examined grossly at the site

TABLE A4a. HISTORICAL INCIDENCE OF TESTICULAR INTERSTITIAL CELL NEOPLASMS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence of Interstitial Cell Tumors in Controls
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.	
Overall Historical Incidence	
TOTAL	1,401/1,582 (88.6%)
SD (b)	7.33%
Range (c)	
High	49/49
Low	32/50

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

TABLE A4b. HISTORICAL INCIDENCE OF ADRENAL MEDULLARY NEOPLASMS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	432/1,583 (27.3%)	36/1,583 (2.3%)	460/1,583 (29.1%)
SD (b)	12.59%	2.97%	13.21%
Range (c)			
High	31/49	6/50	32/49
Low	4/50	0/50	4/50

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

TABLE A4c. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND NEOPLASMS IN MALE F344/NRATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 377/1,540 (24.5%)	(c) 23/1,540 (1.5%)	(b,c) 400/1,540 (26.0%)
SD (d)	10.33%	2.05%	10.24%
Range (e)			
High	24/46	3/39	25/46
Low	4/50	0/50	4/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Includes 12 chromophobe adenomas and 1 acidophil adenoma
(c) Includes five chromophobe carcinomas and one adenocarcinoma, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

	Untreated Control	20 ppm	100 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Dead	8	11	9
Moribund	12	8	8
Survivors			
Terminal sacrifice	30	31	33
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(50)	(49)	(50)
Inflammation, subacute	1 (2%)		
Intestine small, duodenum	(49)	(50)	(48)
Ectopic tissue			1 (2%)
Intestine small, ileum	(49)	(49)	(48)
Inflammation, chronic, multifocal	1 (2%)		
Intestine small, jejunum	(49)	(49)	(46)
Inflammation, chronic, focal	1 (2%)		
Liver	(50)	(50)	(50)
Basophilic focus			2 (4%)
Degeneration, cystic, focal	4 (8%)	6 (12%)	3 (6%)
Degeneration, cystic, multifocal	1 (2%)	2 (4%)	
Fatty change	5 (10%)	9 (18%)	6 (12%)
Focal cellular change	29 (58%)	23 (46%)	32 (64%)
Hematopoietic cell proliferation, multifocal	2 (4%)		
Hepatodiaphragmatic nodule	6 (12%)	4 (8%)	2 (4%)
Hyperplasia, focal	3 (6%)	1 (2%)	
Hyperplasia, multifocal		1 (2%)	2 (4%)
Inflammation, chronic, multifocal	7 (14%)	2 (4%)	2 (4%)
Necrosis, acute, multifocal		1 (2%)	1 (2%)
Bile duct, hyperplasia, multifocal	46 (92%)	47 (94%)	45 (90%)
Centrilobular, congestion, chronic			1 (2%)
Centrilobular, necrosis, acute	1 (2%)	2 (4%)	
Vein, thrombus		1 (2%)	
Mesentery	(6)	(5)	(5)
Inflammation, chronic, multifocal	1 (17%)		
Fat, necrosis	4 (67%)	2 (40%)	4 (80%)
Pancreas	(49)	(49)	(49)
Acinus, atrophy, diffuse	1 (2%)		2 (4%)
Acinus, atrophy, focal	14 (29%)	11 (22%)	7 (14%)
Acinus, atrophy, multifocal	11 (22%)	8 (16%)	8 (16%)
Acinus, focal cellular change	1 (2%)	1 (2%)	
Acinus, hyperplasia, focal	1 (2%)	2 (4%)	
Artery, inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Salivary glands	(50)	(48)	(50)
Hemorrhage, focal	1 (2%)		
Inflammation, chronic	1 (2%)		
Stomach, forestomach	(48)	(50)	(50)
Erosion			1 (2%)
Hyperplasia, squamous	1 (2%)		
Hyperplasia, squamous, multifocal	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, chronic active, diffuse			1 (2%)
Inflammation, subacute			1 (2%)
Ulcer	1 (2%)	2 (4%)	2 (4%)
Stomach, glandular	(50)	(50)	(50)
Erosion, focal		1 (2%)	2 (4%)
Erosion, multifocal		1 (2%)	
Ulcer	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
CARDIOVASCULAR SYSTEM			
Blood vessel		(2)	
Aorta, arteriosclerosis		2 (100%)	
Heart	(50)	(49)	(50)
Cardiomyopathy, multifocal	40 (80%)	40 (82%)	40 (80%)
Mineralization, multifocal		1 (2%)	
Atrium, thrombus	1 (2%)	3 (6%)	4 (8%)
Coronary artery, inflammation, chronic			2 (4%)
Valve, inflammation, chronic		2 (4%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(49)	(48)	(50)
Accessory adrenal cortical nodule		1 (2%)	
Degeneration, focal	6 (12%)	6 (13%)	3 (6%)
Degeneration, multifocal			1 (2%)
Hematopoietic cell proliferation, multifocal	2 (4%)		5 (10%)
Hemorrhage	1 (2%)		
Hyperplasia, focal	4 (8%)	8 (17%)	3 (6%)
Hyperplasia, multifocal	2 (4%)		2 (4%)
Adrenal gland, medulla	(49)	(44)	(50)
Hemorrhage	1 (2%)		
Hyperplasia, focal	5 (10%)	2 (5%)	2 (4%)
Hyperplasia, multifocal	3 (6%)	2 (5%)	
Islets, pancreatic	(50)	(47)	(50)
Hyperplasia, focal	1 (2%)		2 (4%)
Pituitary gland	(49)	(48)	(49)
Hemorrhage			1 (2%)
Pars distalis, abscess	1 (2%)		
Pars distalis, angiectasis		2 (4%)	1 (2%)
Pars distalis, cyst	1 (2%)	1 (2%)	3 (6%)
Pars distalis, hemorrhage	1 (2%)		
Pars distalis, hyperplasia, focal	7 (14%)	6 (13%)	7 (14%)
Pars distalis, hyperplasia, multifocal		1 (2%)	2 (4%)
Pars intermedia, cyst	1 (2%)		
Thyroid gland	(50)	(50)	(50)
C-cell, hyperplasia, focal	3 (6%)	6 (12%)	5 (10%)
C-cell, hyperplasia, multifocal	3 (6%)	3 (6%)	
Follicle, cyst	1 (2%)	1 (2%)	2 (4%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(50)	(50)	(50)
Granuloma sperm			1 (2%)
Preputial gland	(48)	(47)	(49)
Abscess	1 (2%)		2 (4%)
Hyperplasia, focal		2 (4%)	1 (2%)
Inflammation, acute, focal	1 (2%)		
Inflammation, acute, multifocal	1 (2%)	1 (2%)	
Inflammation, chronic, diffuse		3 (6%)	1 (2%)
Inflammation, chronic, focal	3 (6%)	1 (2%)	5 (10%)
Inflammation, chronic, multifocal	15 (31%)	21 (45%)	17 (35%)
Inflammation, chronic active, focal	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic active, multifocal	1 (2%)	6 (13%)	5 (10%)
Inflammation, subacute, multifocal	1 (2%)		
Prostate	(49)	(49)	(50)
Hyperplasia, focal	7 (14%)	3 (6%)	3 (6%)
Hyperplasia, multifocal			2 (4%)
Inflammation, acute, focal	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
GENITAL SYSTEM			
Prostate (Continued)	(49)	(49)	(50)
Inflammation, acute, multifocal			1 (2%)
Inflammation, chronic, focal	4 (8%)	2 (4%)	
Inflammation, chronic, multifocal	1 (2%)		
Inflammation, chronic active, diffuse		1 (2%)	
Inflammation, chronic active, multifocal	1 (2%)		1 (2%)
Inflammation, subacute, focal		1 (2%)	
Epithelium, hyperplasia, multifocal		1 (2%)	
Seminal vesicle	(49)	(49)	(49)
Atrophy, diffuse	27 (55%)	30 (61%)	36 (73%)
Dilatation	1 (2%)		1 (2%)
Inflammation, acute		1 (2%)	
Inflammation, chronic, focal			1 (2%)
Inflammation, chronic, multifocal	1 (2%)		
Testes	(50)	(50)	(50)
Atrophy	1 (2%)		
Atrophy, diffuse	4 (8%)	5 (10%)	1 (2%)
Atrophy, focal	1 (2%)		1 (2%)
Granuloma sperm	1 (2%)		
Interstitial cell, hyperplasia, multifocal	5 (10%)	8 (16%)	2 (4%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(50)
Hyperplasia	3 (6%)	6 (12%)	6 (12%)
Infiltration cellular, histiocytic, focal	1 (2%)		
Lymph node	(50)	(50)	(50)
Mediastinal, hemorrhage		1 (2%)	
Lymph node, mandibular	(48)	(45)	(49)
Congestion		1 (2%)	1 (2%)
Degeneration, cystic	3 (6%)	1 (2%)	1 (2%)
Hyperplasia, lymphoid		1 (2%)	3 (6%)
Hyperplasia, plasma cell	1 (2%)		1 (2%)
Lymph node, mesenteric	(48)	(49)	(50)
Congestion	1 (2%)		
Degeneration, cystic	1 (2%)	1 (2%)	
Hemorrhage		1 (2%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Infiltration cellular, histiocytic	3 (6%)	3 (6%)	5 (10%)
Spleen	(50)	(49)	(50)
Atrophy, focal	1 (2%)		
Congestion		1 (2%)	
Fibrosis, diffuse	1 (2%)		
Fibrosis, focal	3 (6%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	2 (4%)	3 (6%)	1 (2%)
Artery, thrombus		1 (2%)	
Lymphoid follicle, atrophy	1 (2%)		4 (8%)
INTEGUMENTARY SYSTEM			
Mammary gland	(37)	(44)	(48)
Inflammation, chronic	1 (3%)		
Acinus, hyperplasia, diffuse		1 (2%)	
Acinus, hyperplasia, focal	1 (3%)	1 (2%)	
Duct, ectasia	8 (22%)	8 (18%)	4 (8%)
Skin	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)		
Inflammation, acute, focal	1 (2%)		
Inflammation, chronic, focal	1 (2%)		
Inflammation, chronic active, focal		1 (2%)	
Hair follicle, atrophy			1 (2%)
Subcutaneous tissue, fibrosis, focal	1 (2%)		

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
INTEGUMENTARY SYSTEM			
Skin (Continued)	(50)	(50)	(50)
Subcutaneous tissue, inflammation, chronic, focal		1 (2%)	
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Hyperostosis	2 (4%)	2 (4%)	
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Hydrocephalus	1 (2%)		
Cerebellum, necrosis, focal	1 (2%)		
Cerebrum, necrosis, focal			1 (2%)
Hypothalamus, compression	3 (6%)	4 (8%)	1 (2%)
Spinal cord	(50)	(50)	(50)
Cyst	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Abscess, multifocal			1 (2%)
Fibrosis, focal	1 (2%)		
Foreign body	2 (4%)		1 (2%)
Hemorrhage, multifocal		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
Infiltration cellular, histiocytic, focal		1 (2%)	
Infiltration cellular, histiocytic, multifocal	4 (8%)	9 (18%)	6 (12%)
Inflammation, acute, multifocal	1 (2%)	1 (2%)	1 (2%)
Inflammation, granulomatous, multifocal	1 (2%)		
Leukocytosis		1 (2%)	
Alveolar epithelium, hyperplasia, focal	3 (6%)		4 (8%)
Alveolar epithelium, hyperplasia, multifocal		2 (4%)	
Interstitium, inflammation, chronic, multifocal	2 (4%)	2 (4%)	
Peribronchiolar, hyperplasia, lymphoid	1 (2%)		
Nose	(50)	(50)	(50)
Foreign body	2 (4%)		3 (6%)
Fungus	7 (14%)	9 (18%)	4 (8%)
Inflammation, chronic active, multifocal		2 (4%)	
Metaplasia, squamous, focal			1 (2%)
Mucosa, cytoplasmic alteration, multifocal	2 (4%)		
Mucosa, foreign body, focal	1 (2%)		
Mucosa, inflammation, acute, focal	1 (2%)	1 (2%)	
Mucosa, inflammation, acute, multifocal	2 (4%)	2 (4%)	
Mucosa, inflammation, chronic, focal		2 (4%)	
Mucosa, inflammation, chronic, multifocal	2 (4%)	2 (4%)	1 (2%)
Mucosa, inflammation, chronic active, multifocal	5 (10%)	8 (16%)	5 (10%)
Mucosa, inflammation, subacute, focal	1 (2%)		
Mucosa, inflammation, subacute, multifocal	2 (4%)		2 (4%)
Mucosa, metaplasia, squamous, focal		1 (2%)	
Mucosa, metaplasia, squamous, multifocal	1 (2%)		1 (2%)
Nasolacrimal duct, inflammation, chronic	7 (14%)	10 (20%)	6 (12%)
Nasolacrimal duct, inflammation, chronic active	2 (4%)	2 (4%)	1 (2%)
Nasolacrimal duct, inflammation, subacute			1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(50)	(50)	(48)
Inflammation, chronic			1 (2%)
Anterior chamber, hemorrhage		1 (2%)	
Cornea, inflammation, chronic active		1 (2%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
SPECIAL SENSES SYSTEM			
Eye (Continued)	(50)	(50)	(48)
Lens, cataract	6 (12%)	10 (20%)	6 (13%)
Retina, atrophy	14 (28%)	9 (18%)	3 (6%)
Sclera, metaplasia, osseous, focal	21 (42%)	13 (26%)	14 (29%)
Sclera, metaplasia, osseous, multifocal	22 (44%)	30 (60%)	26 (54%)
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Cyst	1 (2%)	1 (2%)	1 (2%)
Nephropathy, chronic, multifocal	47 (94%)	46 (92%)	45 (90%)
Papilla, necrosis		1 (2%)	
Pelvis, dilatation		2 (4%)	
Renal tubule, mineralization, multifocal		1 (2%)	
Renal tubule, pigmentation	2 (4%)	3 (6%)	4 (8%)
Transitional epithelium, hyperplasia	1 (2%)		
Urinary bladder	(50)	(49)	(50)
Calculus micro observation only		1 (2%)	
Dilatation	1 (2%)		
Inflammation, hemorrhagic		1 (2%)	
Inflammation, subacute		1 (2%)	

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDIES

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

	Untreated Control	20 ppm	100 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Moribund	10	4	7
Dead	7	4	6
Survivors			
Terminal sacrifice	33	42	37
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(49)	(49)	(50)
Osteosarcoma, metastatic, uncertain primary site	1 (2%)		
Intestine small, ileum	(47)	(50)	(50)
Leiomyosarcoma			1 (2%)
Liver	(50)	(50)	(50)
Pancreas	(49)	(49)	(49)
Acinus, carcinoma	1 (2%)		
Salivary glands	(48)	(49)	(49)
Schwannoma malignant			1 (2%)
Tongue	(1)		
Papilloma squamous	1 (100%)		
CARDIOVASCULAR SYSTEM			
Heart	(49)	(50)	(50)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(47)	(50)
Adenoma		2 (4%)	
Adrenal gland, medulla	(49)	(47)	(49)
Pheochromocytoma benign	2 (4%)	3 (6%)	2 (4%)
Pheochromocytoma benign, multiple		1 (2%)	
Islets, pancreatic	(50)	(48)	(50)
Carcinoma	1 (2%)	1 (2%)	
Parathyroid gland	(45)	(44)	(47)
Adenoma		1 (2%)	
Pituitary gland	(50)	(48)	(50)
Pars distalis, adenoma	31 (62%)	24 (50%)	19 (38%)
Pars distalis, carcinoma		2 (4%)	
Thyroid gland	(50)	(50)	(50)
C-cell, adenoma	5 (10%)	2 (4%)	2 (4%)
Follicular cell, adenoma		2 (4%)	
Follicular cell, carcinoma		1 (2%)	
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(39)	(37)	(39)
Adenoma	2 (5%)	1 (3%)	
Ovary	(50)	(50)	(50)
Uterus	(50)	(50)	(50)
Endometrium, polyp stromal	10 (20%)	5 (10%)	3 (6%)
Endometrium, polyp stromal, multiple		1 (2%)	
Endometrium, sarcoma stromal	1 (2%)		
Vagina	(1)	(1)	
Sarcoma, metastatic	1 (100%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
HEMATOPOIETIC SYSTEM			
Blood			(1)
Bone marrow	(50)	(50)	(49)
Lymph node, mandibular	(47)	(49)	(48)
Lymph node, mesenteric	(46)	(49)	(49)
Spleen	(50)	(50)	(49)
Thymus	(45)	(47)	(47)
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	(49)	(47)
Adenocarcinoma	3 (6%)	1 (2%)	1 (2%)
Adenoma	2 (4%)	1 (2%)	
Fibroadenoma	17 (35%)	10 (20%)	2 (4%)
Fibroadenoma, multiple	4 (8%)	1 (2%)	
Skin	(50)	(50)	(50)
Lipoma		1 (2%)	
Papilloma squamous	1 (2%)		
Sebaceous gland, papilloma		1 (2%)	
Subcutaneous tissue, fibroma	2 (4%)		
Subcutaneous tissue, fibrosarcoma	1 (2%)		
Subcutaneous tissue, lipoma		1 (2%)	
Subcutaneous tissue, sarcoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Cerebrum, astrocytoma malignant			1 (2%)
Pons, carcinoma, metastatic		1 (2%)	
Spinal cord	(50)	(49)	(49)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma		3 (6%)	2 (4%)
SPECIAL SENSES SYSTEM			
Zymbal gland	(1)		
Carcinoma	1 (100%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Urinary bladder	(50)	(48)	(50)
Leiomyoma		1 (2%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	7 (14%)	8 (16%)	7 (14%)
Lymphoma malignant histiocytic		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
TUMOR SUMMARY			
Total animals with primary neoplasms **	48	42	30
Total primary neoplasms	93	75	41
Total animals with benign neoplasms	42	36	23
Total benign neoplasms	77	61	30
Total animals with malignant neoplasms	15	14	10
Total malignant neoplasms	16	14	11
Total animals with secondary neoplasms ***	2	1	
Total secondary neoplasms	2	1	
Total animals with malignant neoplasms--uncertain primary site	1		

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: UNTREATED CONTROL

DAYS ON STUDY	478	485	541	547	593	655	660	666	667	677	677	694	701	710	719	719	726	731	731	731	731	731	731	731	731
CARCASS ID	3155	3555	3144	3355	3455	3135	3655	3446	3857	3995	4055	3129	3646	3544	3255	3433	3553	3111	3211	3223	3234	3241	3311	3323	3332	3333
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma, metastatic, uncertain primary site												X														
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																+										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinus, carcinoma																										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue					+																					
Papilloma squamous					X																					
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+	
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																				X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X	X					X	X				X	X		X	X	X	X		X		X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																X			X							
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Adenoma																	X									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal			X	X						X								X							X	X
Endometrium, sarcoma stromal	X																									
Vagina	+																									
Sarcoma, metastatic	X																									

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue
M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

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

DAYS ON STUDY	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	TOTAL:
CARCASS ID	334	341	342	351	352	361	362	363	371	372	373	374	375	381	382	383	384	391	392	393	394	401	402	403	404	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Osteosarcoma, metastatic, uncertain primary site																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+	+				+												+					+			6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	49
Acinus, carcinoma					X																					1
Salivary glands	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	49
Tongue																										1
Papilloma squamous																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign												X														2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma						X																				1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	M	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X	X	X	X	X		X		X	X	X	X		X	X			X	X		X		31
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma													X		X							X				5
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	M	M	M	+	+	+	+	+	+	+	M	+	M	+	M	+	M	+	+	+	+	+	+	+	M	39
Adenoma												X														2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrium, polyp stromal					X												X					X			X	10
Endometrium, sarcoma stromal																										1
Vagina																										1
Sarcoma, metastatic																										1

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

DAYS ON STUDY	478	485	541	547	593	655	660	666	667	677	677	694	701	710	719	719	726	731	731	731	731	731	731	731	731	731
CARCASS ID	315	355	314	335	345	313	365	344	385	395	405	312	364	354	325	343	353	311	321	322	323	324	331	332	333	334
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma				X						X																
Adenoma																										
Fibroadenoma										X	X	X	X		X	X			X			X			X
Fibroadenoma, multiple								X									X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous													X													
Subcutaneous tissue, fibroma								X													X					
Subcutaneous tissue, fibrosarcoma			X																							
Subcutaneous tissue, sarcoma									X																	
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																										
Ear																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal gland																										
Carcinoma																										
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X							X												

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

DAYS ON STUDY	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	TOTAL:
CARCASS ID	334	341	342	351	352	361	362	363	371	372	373	374	375	381	382	383	384	391	392	393	394	401	402	403	404	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	47
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma			X																							3
Adenoma									X															X		2
Fibroadenoma		X			X		X	X		X				X					X	X						17
Fibroadenoma, multiple						X					X															4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																										1
Subcutaneous tissue, fibroma																										2
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, sarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear												M														
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal gland					+																					1
Carcinoma					X																					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear										X						X		X							X	7

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: 20 ppm

DAYS ON STUDY	340	578	590	624	632	666	669	706	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732
CARCASS ID	473	465	505	485	445	435	484	434	111	112	113	114	115	121	122	123	124	125	131	132	133	171	172	174	175
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery				+																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pharynx																					+				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, *forestomach*	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth		+																							
CARDIOVASCULAR SYSTEM																									
Blood vessel						+												+							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									X
Pheochromocytoma benign, multiple						X																			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																			X						
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X					X				X	X			X				X			X	X	X	X
Pars distalis, carcinoma				X																					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma									X																
Follicular cell, adenoma													X												
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	M
Adenoma																						X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal						X	X														X				
Endometrium, polyp stromal, multiple										X															
Vagina														+											

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 20 ppm (Continued)

DAYS ON STUDY	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
CARCASS ID	4 8 1	4 8 2	4 8 3	4 9 1	4 9 2	4 9 3	4 9 4	4 9 5	5 0 1	5 0 2	5 0 3	5 0 4	4 4 1	4 4 2	4 4 3	4 4 4	4 5 1	4 5 2	4 5 3	4 5 4	4 5 5	4 6 1	4 6 2	4 6 3	4 6 4	TOTAL: TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pharynx																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										1
CARDIOVASCULAR SYSTEM																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	M		+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	47
Adenoma										X				X												2
Adrenal gland, medulla	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	47
Pheochromocytoma benign										X					X											3
Pheochromocytoma benign, multiple																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																										1
Parathyroid gland	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma									X																	1
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma				X	X		X		X	X		X	X			X			X		X	X	X		X	24
Pars distalis, carcinoma																		X								2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																									X	2
Follicular cell, adenoma		X																								2
Follicular cell, carcinoma							X																			1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	M	+	+	+	+	+	M	+	M	+	M	+	+	M	M	+	M	M	+	+	+	+	+	+	+	37
Adenoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrium, polyp stromal				X																		X				5
Endometrium, polyp stromal, multiple																										1
Vagina																										1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 20 ppm (Continued)

DAYS ON STUDY	340	578	590	624	632	666	669	706	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732
CARCASS ID	473	465	505	485	445	435	484	434	111	112	113	114	115	421	422	423	424	425	431	432	433	471	472	474	475
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma															X										
Adenoma																									X
Fibroadenoma											X			X									X		X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Lipoma																									
Sebaceous gland, papilloma															X										
Subcutaneous tissue, lipoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pons, carcinoma, metastatic				X																					
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear														M											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland		+																							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X				X	X								X							X		
Lymphoma malignant histiocytic		X																							

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 20 ppm (Continued)

DAYS ON STUDY	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	733	TOTAL:
CARCASS ID	481	482	483	491	492	493	494	495	501	502	503	504	441	442	443	444	451	452	453	454	455	461	462	463	464	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Adenocarcinoma																										1
Adenoma																										1
Fibroadenoma				X								X	X		X	X	X									10
Fibroadenoma, multiple			X																							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma								X																		1
Sebaceous gland, papilloma																										1
Subcutaneous tissue, lipoma									X																	1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pons, carcinoma, metastatic																										1
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X										X									X				3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear												M									M					
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland			+																							2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leiomyoma		X																								1
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X						X		X													8
Lymphoma malignant histiocytic																										1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: 100 ppm

DAYS ON STUDY	220	453	453	504	535	604	666	669	676	694	696	710	724	731	731	731	731	731	731	731	731	731	731	731	732
CARCASS ID	543	521	591	565	555	535	585	534	605	595	604	545	544	511	512	513	514	515	522	523	524	525	572	531	532
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																	X								
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery													+												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant																					X				
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign											X							X							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X			X			X		X	X	X	X			X	X			X	X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X								
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	M	+	M	+	+	M
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrium, polyp stromal														X					X						
HEMATOPOIETIC SYSTEM																									
Blood						+																			
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cerebrum, astrocytoma malignant																	X								
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma												X							X						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear		+																							
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+																							
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X		X	X			X					X											

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 100 ppm (Continued)

DAYS ON STUDY	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	TOTAL:
CARCASS ID	533	541	542	551	552	553	554	561	562	563	564	571	573	574	575	581	582	583	584	592	593	594	601	602	603	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																									+	1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X				X									X		X	X			X				19
Thyroid gland	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X																		2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	39
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrium, polyp stromal									X																	3
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	47
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	47
Adenocarcinoma																			X							1
Fibroadenoma												X								X						2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cerebrum, astrocytoma malignant																										1
Spinal cord	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland																										2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X														7

TABLE B3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

	Control	20 ppm	100 ppm
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	2/49 (4%)	4/47 (9%)	2/49 (4%)
Adjusted Rates (b)	6.3%	9.7%	5.2%
Terminal Rates (c)	2/32 (6%)	3/39 (8%)	1/37 (3%)
Day of First Observation	731	666	710
Life Table Tests (d)	P=0.469N	P=0.419	P=0.649N
Logistic Regression Tests (d)	P=0.491N	P=0.341	P=0.676N
Cochran-Armitage Trend Test (d)	P=0.493N		
Fisher Exact Test (d)		P=0.319	P=0.691N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	0.0%	7.1%	5.2%
Terminal Rates (c)	0/33 (0%)	3/42 (7%)	1/37 (3%)
Day of First Observation		731	710
Life Table Tests (d)	P=0.426	P=0.167	P=0.258
Logistic Regression Tests (d)	P=0.415	P=0.167	P=0.239
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.121	P=0.247
Mammary Gland: Adenocarcinoma			
Overall Rates (e)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	7.4%	2.4%	2.7%
Terminal Rates (c)	1/33 (3%)	1/42 (2%)	1/37 (3%)
Day of First Observation	547	731	731
Life Table Tests (d)	P=0.336N	P=0.259N	P=0.292N
Logistic Regression Tests (d)	P=0.321N	P=0.316N	P=0.287N
Cochran-Armitage Trend Test (d)	P=0.337N		
Fisher Exact Test (d)		P=0.309N	P=0.309N
Mammary Gland: Fibroadenoma			
Overall Rates (e)	21/50 (42%)	11/50 (22%)	2/50 (4%)
Adjusted Rates (b)	51.0%	26.2%	5.4%
Terminal Rates (c)	13/33 (39%)	11/42 (26%)	2/37 (5%)
Day of First Observation	666	731	731
Life Table Tests (d)	P<0.001N	P=0.006N	P<0.001N
Logistic Regression Tests (d)	P<0.001N	P=0.014N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.026N	P<0.001N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (e)	23/50 (46%)	11/50 (22%)	2/50 (4%)
Adjusted Rates (b)	55.9%	26.2%	5.4%
Terminal Rates (c)	15/33 (45%)	11/42 (26%)	2/37 (5%)
Day of First Observation	666	731	731
Life Table Tests (d)	P<0.001N	P=0.002N	P<0.001N
Logistic Regression Tests (d)	P<0.001N	P=0.004N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.010N	P<0.001N
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (e)	25/50 (50%)	12/50 (24%)	3/50 (6%)
Adjusted Rates (b)	59.3%	28.6%	8.1%
Terminal Rates (c)	16/33 (48%)	12/42 (29%)	3/37 (8%)
Day of First Observation	547	731	731
Life Table Tests (d)	P<0.001N	P=0.001N	P<0.001N
Logistic Regression Tests (d)	P<0.001N	P=0.003N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.006N	P<0.001N

TABLE B3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Control	20 ppm	100 ppm
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	31/50 (62%)	24/48 (50%)	19/50 (38%)
Adjusted Rates (b)	77.0%	55.4%	45.0%
Terminal Rates (c)	24/33 (73%)	21/40 (53%)	14/37 (38%)
Day of First Observation	541	340	504
Life Table Tests (d)	P=0.017N	P=0.021N	P=0.007N
Logistic Regression Tests (d)	P=0.020N	P=0.150N	P=0.015N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test (d)		P=0.160N	P=0.014N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	31/50 (62%)	26/48 (54%)	19/50 (38%)
Adjusted Rates (b)	77.0%	58.7%	45.0%
Terminal Rates (c)	24/33 (73%)	22/40 (55%)	14/37 (38%)
Day of First Observation	541	340	504
Life Table Tests (d)	P=0.013N	P=0.049N	P=0.007N
Logistic Regression Tests (d)	P=0.013N	P=0.271N	P=0.015N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.281N	P=0.014N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (e)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.3%	0.0%	0.0%
Terminal Rates (c)	1/33 (3%)	0/42 (0%)	0/37 (0%)
Day of First Observation	541		
Life Table Tests (d)	P=0.142N	P=0.106N	P=0.120N
Logistic Regression Tests (d)	P=0.111N	P=0.121N	P=0.096N
Cochran-Armitage Trend Test (d)	P=0.140N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Subcutaneous Tissue: Fibroma, Sarcoma, or Fibrosarcoma			
Overall Rates (e)	4/50 (8%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	9.5%	0.0%	0.0%
Terminal Rates (c)	1/33 (3%)	0/42 (0%)	0/37 (0%)
Day of First Observation	541		
Life Table Tests (d)	P=0.082N	P=0.056N	P=0.064N
Logistic Regression Tests (d)	P=0.060N	P=0.063N	P=0.048N
Cochran-Armitage Trend Test (d)	P=0.080N		
Fisher Exact Test (d)		P=0.059N	P=0.059N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	14.6%	4.8%	5.4%
Terminal Rates (c)	4/33 (12%)	2/42 (5%)	2/37 (5%)
Day of First Observation	71[illegible]	731	731
Life Table Tests (d)	P=0.248N	P=0.136N	P=0.177N
Logistic Regression Tests (d)	P=0.254N	P=0.161N	P=0.189N
Cochran-Armitage Trend Test (d)	P=0.262N		
Fisher Exact Test (d)		P=0.218N	P=0.218N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	7.1%	0.0%
Terminal Rates (c)	0/33 (0%)	3/42 (7%)	0/37 (0%)
Day of First Observation		731	
Life Table Tests (d)	P=0.384N	P=0.167	(f)
Logistic Regression Tests (d)	P=0.384N	P=0.167	(f)
Cochran-Armitage Trend Test (d)	P=0.394N		
Fisher Exact Test (d)		P=0.121	(f)

TABLE B3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Control	20 ppm	100 ppm
Uterus: Endometrial Stromal Polyp			
Overall Rates (e)	10/50 (20%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	26.3%	13.5%	8.1%
Terminal Rates (c)	7/33 (21%)	4/42 (10%)	3/37 (8%)
Day of First Observation	541	666	731
Life Table Tests (d)	P=0.043N	P=0.121N	P=0.028N
Logistic Regression Tests (d)	P=0.044N	P=0.217N	P=0.037N
Cochran-Armitage Trend Test (d)	P=0.044N		
Fisher Exact Test (d)		P=0.207N	P=0.036N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (e)	7/50 (14%)	8/50 (16%)	7/50 (14%)
Adjusted Rates (b)	18.3%	17.7%	15.3%
Terminal Rates (c)	4/33 (12%)	5/42 (12%)	2/37 (5%)
Day of First Observation	655	590	453
Life Table Tests (d)	P=0.533N	P=0.576N	P=0.572N
Logistic Regression Tests (d)	P=0.476N	P=0.498	P=0.554N
Cochran-Armitage Trend Test (d)	P=0.543N		
Fisher Exact Test (d)		P=0.500	P=0.613N
All Sites: Benign Tumors			
Overall Rates (e)	42/50 (84%)	36/50 (72%)	23/50 (46%)
Adjusted Rates (b)	95.4%	78.2%	54.5%
Terminal Rates (c)	31/33 (94%)	32/42 (76%)	18/37 (49%)
Day of First Observation	541	340	504
Life Table Tests (d)	P<0.001N	P=0.004N	P<0.001N
Logistic Regression Tests (d)	P<0.001N	P=0.084N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.114N	P<0.001N
All Sites: Malignant Tumors			
Overall Rates (e)	16/50 (32%)	14/50 (28%)	10/50 (20%)
Adjusted Rates (b)	36.2%	29.6%	22.5%
Terminal Rates (c)	7/33 (21%)	9/42 (21%)	5/37 (14%)
Day of First Observation	478	578	453
Life Table Tests (d)	P=0.135N	P=0.261N	P=0.126N
Logistic Regression Tests (d)	P=0.077N	P=0.487N	P=0.093N
Cochran-Armitage Trend Test (d)	P=0.116N		
Fisher Exact Test (d)		P=0.414N	P=0.127N
All Sites: All Tumors			
Overall Rates (e)	48/50 (96%)	42/50 (84%)	30/50 (60%)
Adjusted Rates (b)	98.0%	85.7%	63.6%
Terminal Rates (c)	32/33 (97%)	35/42 (83%)	20/37 (54%)
Day of First Observation	478	340	453
Life Table Tests (d)	P<0.001N	P=0.006N	P<0.001N
Logistic Regression Tests (d)	P<0.001N	P=0.045N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.046N	P<0.001N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(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 logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined grossly at the site
(f) No P value is reported because no tumors were observed in the 100-ppm and control groups.

TABLE B4a. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL NEOPLASMS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 12/1,612 (0.7%)	4/1,612 (0.2%)	(b) 16/1,612 (1.0%)
SD (c)	0.99%	0.67%	1.15%
Range (d)			
High	1/48	1/49	2/49
Low	0/50	0/50	0/50

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

TABLE B4b. HISTORICAL INCIDENCE OF MAMMARY GLAND NEOPLASMS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Fibroadenoma	Adenocarcinoma	Fibroadenoma or Adenocarcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 520/1,643 (31.6%)	(c) 49/1,643 (3.0%)	(b,c) 552/1,643 (33.6%)
SD (d)	12.23%	2.07%	11.95%
Range (e)			
High	30/50	4/50	32/50
Low	5/50	0/50	6/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Includes 510 fibroadenomas, 11 adenomas, NOS, 2 cystadenomas, NOS, and 1 papillary cystadenoma; more than 1 tumor was observed in some animals.
(c) Includes two carcinomas, NOS, two papillary adenocarcinomas, and one papillary cystadenocarcinoma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE B4c. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND NEOPLASMS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 731/1,617 (45.2%)	(c) 42/1,617 (2.6%)	(b,c) 771/1,617 (47.7%)
SD (d)	10.79%	2.76%	11.00%
Range (e)			
High	33/47	6/50	33/47
Low	10/49	0/50	12/49

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Includes 39 chromophobe adenomas
(c) Includes three adenocarcinomas, NOS, and three chromophobe carcinomas
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE B4d. HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL STROMAL POLYPS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

	Incidence in Controls
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.	
Overall Historical Incidence	
TOTAL	342/1,632 (21.0%)
SD (b)	7.20%
Range (c)	
High	18/50
Low	4/50

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

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

	Untreated Control	20 ppm	100 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Moribund	10	4	7
Dead	7	4	6
Survivors			
Terminal sacrifice	33	42	37
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(49)	(49)	(49)
Inflammation, acute		1 (2%)	
Submucosa, hemorrhage		1 (2%)	
Intestine large, colon	(50)	(50)	(49)
Ulcer	1 (2%)		
Intestine small, duodenum	(50)	(49)	(50)
Ulcer, chronic	1 (2%)		
Liver	(50)	(50)	(50)
Basophilic focus	1 (2%)		
Fatty change	12 (24%)	4 (8%)	2 (4%)
Focal cellular change	42 (84%)	42 (84%)	41 (82%)
Granuloma	1 (2%)		
Hematopoietic cell proliferation, multifocal	1 (2%)	1 (2%)	1 (2%)
Hepatodiaphragmatic nodule	5 (10%)	9 (18%)	9 (18%)
Hyperplasia, focal		2 (4%)	1 (2%)
Hyperplasia, multifocal	1 (2%)	2 (4%)	1 (2%)
Infiltration cellular, lymphocytic, multifocal	1 (2%)		
Inflammation, chronic, multifocal	28 (56%)	25 (50%)	19 (38%)
Inflammation, granulomatous, focal			1 (2%)
Necrosis, multifocal			1 (2%)
Bile duct, hyperplasia, focal			1 (2%)
Bile duct, hyperplasia, multifocal	27 (54%)	36 (72%)	30 (60%)
Centrilobular, necrosis, acute		1 (2%)	
Vein, thrombus			1 (2%)
Mesentery	(6)	(1)	(1)
Fat, necrosis	6 (100%)	1 (100%)	
Pancreas	(49)	(49)	(49)
Metaplasia, focal	2 (4%)		
Necrosis, acute, multifocal		1 (2%)	
Acinus, atrophy, diffuse	2 (4%)	1 (2%)	
Acinus, atrophy, focal	10 (20%)	5 (10%)	9 (18%)
Acinus, atrophy, multifocal	6 (12%)	1 (2%)	9 (18%)
Acinus, focal cellular change	1 (2%)		
Pharynx		(1)	
Palate, ulcer		1 (100%)	
Salivary glands	(48)	(49)	(49)
Atrophy, diffuse		1 (2%)	
Stomach	(49)	(50)	(50)
Ulcer		1 (2%)	
Stomach, forestomach	(49)	(49)	(50)
Erosion, focal			1 (2%)
Hyperplasia, squamous, diffuse	2 (4%)		1 (2%)
Hyperplasia, squamous, focal	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, chronic active			1 (2%)
Ulcer, multiple	1 (2%)		
Stomach, glandular	(49)	(50)	(50)
Erosion, focal	2 (4%)		
Ulcer			1 (2%)
Tongue	(1)		
Abscess	1 (100%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
ALIMENTARY SYSTEM (Continued)			
Tooth		(1)	(1)
Abscess		1 (100%)	
CARDIOVASCULAR SYSTEM			
Blood vessel		(2)	
Aorta, inflammation, chronic, focal		1 (50%)	
Artery, thrombus		1 (50%)	
Heart	(49)	(50)	(50)
Cardiomyopathy, multifocal	30 (61%)	27 (54%)	28 (56%)
Inflammation, acute, multifocal		1 (2%)	
Mineralization, multifocal	2 (4%)		
Atrium, thrombus		1 (2%)	1 (2%)
Valve, inflammation, chronic active		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(48)	(50)
Hematocyst		1 (2%)	
Adrenal gland, cortex	(50)	(47)	(50)
Degeneration, focal	9 (18%)	6 (13%)	3 (6%)
Degeneration, multifocal	1 (2%)	3 (6%)	
Fibrosis, focal	1 (2%)		
Hematocyst	1 (2%)	3 (6%)	4 (8%)
Hematocyst, focal		1 (2%)	
Hematopoietic cell proliferation, multifocal	1 (2%)		
Hyperplasia, focal	6 (12%)	7 (15%)	6 (12%)
Hyperplasia, multifocal	5 (10%)	3 (6%)	1 (2%)
Necrosis, multifocal	1 (2%)		
Adrenal gland, medulla	(49)	(47)	(49)
Hyperplasia, focal	2 (4%)	8 (17%)	3 (6%)
Hyperplasia, multifocal	4 (8%)	1 (2%)	1 (2%)
Islets, pancreatic	(50)	(48)	(50)
Hyperplasia, focal	1 (2%)	1 (2%)	
Pituitary gland	(50)	(48)	(50)
Pars distalis, angiectasis, focal	2 (4%)	3 (6%)	1 (2%)
Pars distalis, cyst	11 (22%)	4 (8%)	8 (16%)
Pars distalis, fibrosis			1 (2%)
Pars distalis, hemorrhage		1 (2%)	
Pars distalis, hyperplasia, focal	5 (10%)	1 (2%)	4 (8%)
Thyroid gland	(50)	(50)	(50)
C-cell, hyperplasia, diffuse	1 (2%)		
C-cell, hyperplasia, focal	4 (8%)	4 (8%)	3 (6%)
C-cell, hyperplasia, multifocal	7 (14%)		1 (2%)
Follicle, cyst	1 (2%)		
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(39)	(37)	(39)
Ectasia	1 (3%)		
Hyperplasia	1 (3%)		
Hyperplasia, focal	3 (8%)	2 (5%)	
Inflammation, acute, focal	1 (3%)		
Inflammation, chronic, focal	2 (5%)		1 (3%)
Inflammation, chronic, multifocal	2 (5%)	2 (5%)	
Inflammation, chronic active, multifocal		3 (8%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
GENITAL SYSTEM (Continued)			
Ovary	(50)	(50)	(50)
Cyst	4 (8%)	4 (8%)	1 (2%)
Inflammation, chronic, multifocal	1 (2%)		
Uterus	(50)	(50)	(50)
Abscess		1 (2%)	
Amyloid deposition		1 (2%)	
Dilatation	3 (6%)		4 (8%)
Cervix, cyst	3 (6%)	1 (2%)	
Cervix, dilatation		2 (4%)	
Cervix, inflammation, acute		1 (2%)	
Cervix, inflammation, chronic	1 (2%)		
Cervix, inflammation, chronic active	3 (6%)		
Cervix, metaplasia, squamous	3 (6%)		
Endometrium, cyst			4 (8%)
Endometrium, cyst, multiple	2 (4%)	4 (8%)	11 (22%)
Endometrium, hyperplasia	1 (2%)		
Endometrium, inflammation, subacute, focal			1 (2%)
Lumen, hemorrhage	1 (2%)		
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(49)
Atrophy	1 (2%)		1 (2%)
Hyperplasia	8 (16%)	2 (4%)	1 (2%)
Myelofibrosis, focal			1 (2%)
Myelofibrosis, multifocal	1 (2%)	2 (4%)	10 (20%)
Lymph node	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Mediastinal, pigmentation			1 (2%)
Lymph node, mandibular	(47)	(49)	(48)
Congestion			1 (2%)
Degeneration, cystic, focal		1 (2%)	
Hyperplasia, lymphoid	2 (4%)		
Pigmentation		1 (2%)	
Lymph node, mesenteric	(46)	(49)	(49)
Congestion		1 (2%)	4 (8%)
Hemorrhage	1 (2%)		
Hyperplasia, lymphoid	2 (4%)	1 (2%)	
Infiltration cellular, histiocytic	10 (22%)		3 (6%)
Spleen	(50)	(50)	(49)
Congestion		1 (2%)	
Hematopoietic cell proliferation	3 (6%)	2 (4%)	
Infarct	3 (6%)		2 (4%)
Pigmentation	1 (2%)		
Lymphoid follicle, atrophy	2 (4%)	1 (2%)	
Lymphoid follicle, hyperplasia, focal	3 (6%)	1 (2%)	
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	(49)	(47)
Acinus, hyperplasia, focal	2 (4%)	1 (2%)	1 (2%)
Duct, ectasia	27 (56%)	20 (41%)	5 (11%)
Skin	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Inflammation, chronic active			2 (4%)
Ulcer		1 (2%)	
Subcutaneous tissue, hemorrhage	1 (2%)		
Subcutaneous tissue, inflammation, chronic active, focal	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(49)
Hyperostosis	4 (8%)	4 (8%)	6 (12%)
Osteomalacia	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Cerebrum, hydrocephalus	1 (2%)		1 (2%)
Cerebrum, infiltration cellular, lymphocytic, focal	1 (2%)		
Cerebrum, necrosis, focal		1 (2%)	
Hypothalamus, compression	6 (12%)	7 (14%)	2 (4%)
Spinal cord	(50)	(49)	(49)
Cyst	1 (2%)		
RESPIRATORY SYSTEM			
Larynx	(50)	(50)	(50)
Inflammation, chronic, focal			1 (2%)
Lung	(50)	(50)	(50)
Congestion	1 (2%)		
Infiltration cellular, histiocytic, multifocal	19 (38%)	22 (44%)	20 (40%)
Pigmentation, multifocal		1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia, focal	2 (4%)	3 (6%)	
Interstitium, inflammation, chronic, diffuse		1 (2%)	
Interstitium, inflammation, chronic, focal	1 (2%)		
Peribronchial, hyperplasia, lymphoid	1 (2%)		
Pleura, fibrosis, focal		1 (2%)	
Pleura, inflammation, chronic, focal	1 (2%)		
Pleura, inflammation, proliferative, multifocal	1 (2%)		
Nose	(50)	(50)	(50)
Foreign body	1 (2%)	1 (2%)	
Fungus	2 (4%)	3 (6%)	1 (2%)
Mucosa, cytoplasmic alteration, multifocal	37 (74%)	39 (78%)	34 (68%)
Mucosa, inflammation, acute, multifocal	2 (4%)		2 (4%)
Mucosa, inflammation, chronic, focal		1 (2%)	
Mucosa, inflammation, chronic, multifocal	1 (2%)		
Mucosa, inflammation, chronic active, focal			1 (2%)
Mucosa, inflammation, chronic active, multifocal	1 (2%)	4 (8%)	
Mucosa, inflammation, subacute, multifocal	2 (4%)	3 (6%)	
Mucosa, metaplasia, squamous, focal	1 (2%)	2 (4%)	1 (2%)
Nasolacrimal duct, inflammation, chronic	2 (4%)	4 (8%)	2 (4%)
Nasolacrimal duct, inflammation, chronic active	4 (8%)	1 (2%)	3 (6%)
SPECIAL SENSES SYSTEM			
Eye	(50)	(50)	(50)
Lens, cataract	12 (24%)	7 (14%)	36 (72%)
Retina, atrophy	25 (50%)	17 (34%)	42 (84%)
Sclera, metaplasia, osseous, focal	11 (22%)	10 (20%)	12 (24%)
Sclera, metaplasia, osseous, multifocal	8 (16%)	15 (30%)	5 (10%)
Harderian gland		(2)	(2)
Infiltration cellular, lymphocytic, multifocal			1 (50%)
Inflammation, acute		1 (50%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Bacterium		1 (2%)	1 (2%)
Cyst		1 (2%)	1 (2%)
Inflammation, acute, multifocal		1 (2%)	1 (2%)
Nephropathy, chronic, multifocal	32 (64%)	18 (36%)	
Papilla, necrosis	1 (2%)		
Pelvis, mineralization, multifocal	1 (2%)	2 (4%)	
Renal tubule, pigmentation	2 (4%)	1 (2%)	
Urinary bladder	(50)	(48)	(50)
Calculus gross observation			1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, subacute	1 (2%)		
Transitional epithelium, hyperplasia	1 (2%)		1 (2%)

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDIES OF *dl*-AMPHETAMINE SULFATE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

	Untreated Control	20 ppm	100 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Dead	2	1	1
Accident		1	
Survivors			
Terminal sacrifice	48	48	49
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(48)	(48)	(48)
Adenoma, papillary	1 (2%)		1 (2%)
Intestine large, cecum	(49)	(48)	(50)
Intestine small, duodenum	(49)	(48)	(50)
Intestine small, ileum	(49)	(48)	(50)
Intestine small, jejunum	(49)	(48)	(50)
Carcinoma		1 (2%)	
Liver	(50)	(50)	(50)
Hemangiosarcoma	3 (6%)	1 (2%)	
Hemangiosarcoma, multiple			1 (2%)
Hepatocellular carcinoma	4 (8%)	5 (10%)	1 (2%)
Hepatocellular carcinoma, multiple		1 (2%)	
Hepatocellular adenoma	10 (20%)	7 (14%)	1 (2%)
Mesentery	(1)	(3)	
Hemangiosarcoma		1 (33%)	
Pancreas	(50)	(50)	(50)
Salivary glands	(50)	(50)	(49)
CARDIOVASCULAR SYSTEM			
None			
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(49)	(49)
Capsule, adenoma	4 (8%)	1 (2%)	
Adrenal gland, cortex	(50)	(49)	(49)
Adenoma		1 (2%)	
Adrenal gland, medulla	(49)	(49)	(47)
Neuroblastoma benign		1 (2%)	
Pheochromocytoma benign		1 (2%)	1 (2%)
Islets, pancreatic	(50)	(50)	(50)
Adenoma	1 (2%)		
Thyroid gland	(50)	(50)	(50)
Follicular cell, adenoma			2 (4%)
Follicular cell, carcinoma		1 (2%)	1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(50)	(50)	(50)
Seminal vesicle	(50)	(50)	(50)
Testes	(50)	(50)	(50)
Interstitial cell, adenoma			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
HEMATOPOIETIC SYSTEM			
Lymph node	(50)	(50)	(50)
Lymph node, mandibular	(41)	(44)	(45)
Lymph node, mesenteric	(47)	(49)	(48)
Spleen	(48)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	
Thymus	(44)	(44)	(41)
INTEGUMENTARY SYSTEM			
None			
MUSCULOSKELETAL SYSTEM			
None			
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Spinal cord	(49)	(50)	(50)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	6 (12%)	2 (4%)	3 (6%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple	1 (2%)		
Hepatocellular carcinoma, metastatic, liver	2 (4%)	3 (6%)	
SPECIAL SENSES SYSTEM			
Harderian gland	(4)	(2)	
Adenoma	4 (100%)	2 (100%)	
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Renal tubule, adenoma		1 (2%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Lymphoma malignant histiocytic			1 (2%)
Lymphoma malignant mixed	4 (8%)	5 (10%)	4 (8%)
TUMOR SUMMARY			
Total animals with primary neoplasms**	30	25	18
Total primary neoplasms	41	33	18
Total animals with benign neoplasms	23	15	9
Total benign neoplasms	26	16	9
Total animals with malignant neoplasms	13	17	9
Total malignant neoplasms	15	17	9
Total animals with secondary neoplasms***	2	3	
Total secondary neoplasms	2	3	

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: UNTREATED CONTROL

DAYS ON STUDY	036	383	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
CARCASS ID	061	011	021	031	041	051	071	081	091	101	111	121	131	141	151	161	171	181	191	201	211	221	231	241	251
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenoma, papillary																					X				
Intestine large	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Intestine small	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X										X											
Hepatocellular carcinoma							X				X														
Hepatocellular adenoma										X					X			X							
Mesentery																								+	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+														+					
CARDIOVASCULAR SYSTEM																									
Blood vessel																			+						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma			X		X						X			X											
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Parathyroid gland	M	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+
Pituitary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+
Lymph node, mesenteric	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma												X													
Thymus	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma										X		X											X		
Alveolar/bronchiolar carcinoma												X													
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Eye	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed							X																		

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically

I: Insufficient tissue
M: Missing

A: Autolysis precludes examination
X: Incidence of listed morphology

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

DAYS ON STUDY	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	TOTAL:
CARCASS ID	261	271	281	291	301	311	321	331	341	351	361	371	381	391	401	411	421	431	441	451	461	471	481	491	501	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, papillary																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																				X						3
Hepatocellular carcinoma										X		X														4
Hepatocellular adenoma	X	X			X				X					X			X							X		10
Mesentery																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth						+	+												+							5
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																										4
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland																				+						1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	M	41
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										1
Thymus	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	44
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X																X	X							6
Alveolar/bronchiolar carcinoma																						X				2
Alveolar/bronchiolar carcinoma, multiple									X																	1
Hepatocellular carcinoma, metastatic, liver										X																2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear		+																								1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland																+						+	+		+	4
Adenoma																X						X	X		X	4
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed								X			X													X		4

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: 20 ppm

DAYS ON STUDY	006	695	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731
CARCASS ID	07211	05711	05111	05211	05311	05411	05511	05611	05811	05911	06011	06111	06211	06311	06411	06511	06611	06711	06811	06911	07011	07111	07311	07411	07511
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Intestine small	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X																					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Hepatocellular carcinoma															X										X
Hepatocellular carcinoma, multiple									X																
Hepatocellular adenoma		X													X		X	X							
Mesentery																				+		+			
Hemangiosarcoma																				X					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth			+						+	+															
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																X									
Adrenal gland, cortex	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																					
Adrenal gland, medulla	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neuroblastoma benign																									
Pheochromocytoma benign																X									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	M	M	M	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X														
Alveolar/bronchiolar carcinoma																	X								
Hepatocellular carcinoma, metastatic, liver									X						X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma			X																						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed						X													X						

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 20 ppm
(Continued)

DAYS ON STUDY	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	731	TOTAL:
CARCASS ID	07761	07771	07781	07791	08001	08111	08221	08331	08441	08551	08661	08771	08881	08991	09001	09111	09221	09331	09441	09551	09661	09771	09881	09991	10001	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma												X									X		X			5
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma							X		X							X										7
Mesentery																				+						3
Hemangiosarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth						+	+																			5
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neuroblastoma benign				X																						1
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, carcinoma				X																						1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	44
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																X										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	44
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																							X			2
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver																					X					3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland						+					+															2
Adenoma						X					X															2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed	X						X																	X		5

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: 100 ppm

DAYS ON STUDY	624	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730
CARCASS ID	10911	10111	10211	10311	10411	10511	10611	10711	10811	11011	11111	11211	11311	11411	11511	11611	11711	11811	11911	12011	12111	12211	12311	12411	12511
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenoma, papillary												X													
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple																									
Hepatocellular carcinoma																								X	
Hepatocellular adenoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adrenal gland, medulla	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M
Pheochromocytoma benign																				X					
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	M	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma			X			X																			
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS								+																	
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland			+																						
Prostate	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	M	M	M	+	+	+	+	M
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X		X				
Alveolar/bronchiolar carcinoma																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic										X															
Lymphoma malignant mixed	X						X		X																

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 100 ppm (Continued)

DAYS ON STUDY	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	TOTAL:
CARCASS ID	12601	12711	12811	12901	13011	13111	13211	13311	13411	13511	13611	13711	13811	13911	14011	14111	14211	14311	14411	14511	14611	14711	14811	14911	15011	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, papillary																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple																			X							1
Hepatocellular carcinoma																										1
Hepatocellular adenoma																							X			1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										2
Follicular cell, carcinoma													X													1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma				X																						1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	+	M	2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																							3
Alveolar/bronchiolar carcinoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed								X																		4

TABLE C3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

	Control	20 ppm	100 ppm
Adrenal Capsule: Adenoma			
Overall Rates (a)	4/45 (9%)	1/46 (2%)	0/48 (0%)
Adjusted Rates (b)	9.3%	2.3%	0.0%
Terminal Rates (c)	4/43 (9%)	1/44 (2%)	0/47 (0%)
Day of First Observation	729	729	
Life Table Tests (d)	P=0.062N	P=0.173N	P=0.053N
Logistic Regression Tests (d)	P=0.062N	P=0.173N	P=0.053N
Cochran-Armitage Trend Test (d)	P=0.063N		
Fisher Exact Test (d)		P=0.174N	P=0.051N
Harderian Gland: Adenoma			
Overall Rates (e)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	8.3%	4.2%	0.0%
Terminal Rates (c)	4/48 (8%)	2/48 (4%)	0/49 (0%)
Day of First Observation	729	729	
Life Table Tests (d)	P=0.060N	P=0.337N	P=0.061N
Logistic Regression Tests (d)	P=0.060N	P=0.337N	P=0.061N
Cochran-Armitage Trend Test (d)	P=0.061N		
Fisher Exact Test (d)		P=0.339N	P=0.059N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	10/50 (20%)	7/50 (14%)	1/50 (2%)
Adjusted Rates (b)	20.8%	14.3%	2.0%
Terminal Rates (c)	10/48 (21%)	6/48 (13%)	1/49 (2%)
Day of First Observation	729	695	729
Life Table Tests (d)	P=0.005N	P=0.299N	P=0.005N
Logistic Regression Tests (d)	P=0.005N	P=0.287N	P=0.005N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P=0.298N	P=0.004N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	8.3%	12.5%	2.0%
Terminal Rates (c)	4/48 (8%)	6/48 (13%)	1/49 (2%)
Day of First Observation	729	729	729
Life Table Tests (d)	P=0.092N	P=0.370	P=0.174N
Logistic Regression Tests (d)	P=0.092N	P=0.370	P=0.174N
Cochran-Armitage Trend Test (d)	P=0.096N		
Fisher Exact Test (d)		P=0.370	P=0.181N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	14/50 (28%)	12/50 (24%)	2/50 (4%)
Adjusted Rates (b)	29.2%	24.5%	4.1%
Terminal Rates (c)	14/48 (29%)	11/48 (23%)	2/49 (4%)
Day of First Observation	729	695	729
Life Table Tests (d)	P<0.001N	P=0.410N	P=0.001N
Logistic Regression Tests (d)	P<0.001N	P=0.393N	P=0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.410N	P<0.001N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	6/50 (12%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	12.5%	4.2%	6.1%
Terminal Rates (c)	6/48 (13%)	2/48 (4%)	3/49 (6%)
Day of First Observation	729	729	729
Life Table Tests (d)	P=0.321N	P=0.135N	P=0.233N
Logistic Regression Tests (d)	P=0.321N	P=0.135N	P=0.233N
Cochran-Armitage Trend Test (d)	P=0.332N		
Fisher Exact Test (d)		P=0.134N	P=0.243N

TABLE C3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF dl-AMPHETAMINE SULFATE (Continued)

	Control	20 ppm	100 ppm
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	6.3%	2.1%	2.0%
Terminal Rates (c)	3/48 (6%)	1/48 (2%)	1/49 (2%)
Day of First Observation	729	729	729
Life Table Tests (d)	P=0.330N	P=0.306N	P=0.298N
Logistic Regression Tests (d)	P=0.330N	P=0.306N	P=0.298N
Cochran-Armitage Trend Test (d)	P=0.337N		
Fisher Exact Test (d)		P=0.309N	P=0.309N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	8/50 (16%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	16.7%	6.3%	8.2%
Terminal Rates (c)	8/48 (17%)	3/48 (6%)	4/49 (8%)
Day of First Observation	729	729	729
Life Table Tests (d)	P=0.253N	P=0.101N	P=0.169N
Logistic Regression Tests (d)	P=0.253N	P=0.101N	P=0.169N
Cochran-Armitage Trend Test (d)	P=0.264N		
Fisher Exact Test (d)		P=0.100N	P=0.178N
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	2.1%	6.1%
Terminal Rates (c)	0/48 (0%)	1/48 (2%)	3/49 (6%)
Day of First Observation		729	729
Life Table Tests (d)	P=0.084	P=0.500	P=0.125
Logistic Regression Tests (d)	P=0.084	P=0.500	P=0.125
Cochran-Armitage Trend Test (d)	P=0.080		
Fisher Exact Test (d)		P=0.500	P=0.121
Circulatory System: Hemangiosarcoma			
Overall Rates (e)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	8.3%	6.3%	2.0%
Terminal Rates (c)	4/48 (8%)	3/48 (6%)	1/49 (2%)
Day of First Observation	729	729	729
Life Table Tests (d)	P=0.151N	P=0.500N	P=0.174N
Logistic Regression Tests (d)	P=0.151N	P=0.500N	P=0.174N
Cochran-Armitage Trend Test (d)	P=0.156N		
Fisher Exact Test (d)		P=0.500N	P=0.181N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (e)	4/50 (8%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (b)	8.3%	10.4%	10.0%
Terminal Rates (c)	4/48 (8%)	5/48 (10%)	4/49 (8%)
Day of First Observation	729	729	624
Life Table Tests (d)	P=0.516	P=0.500	P=0.514
Logistic Regression Tests (d)	P=0.508	P=0.500	P=0.500
Cochran-Armitage Trend Test (d)	P=0.500		
Fisher Exact Test (d)		P=0.500	P=0.500
All Sites: Benign Tumors			
Overall Rates (e)	23/50 (46%)	15/50 (30%)	9/50 (18%)
Adjusted Rates (b)	47.9%	30.6%	18.4%
Terminal Rates (c)	23/48 (48%)	14/48 (29%)	9/49 (18%)
Day of First Observation	729	695	729
Life Table Tests (d)	P=0.004N	P=0.076N	P=0.002N
Logistic Regression Tests (d)	P=0.003N	P=0.065N	P=0.002N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P=0.074N	P=0.002N

TABLE C3. ANALYSIS OF PRIMARY NEOPLASMS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF dl-AMPHETAMINE SULFATE (Continued)

	Control	20 ppm	100 ppm
All Sites: Malignant Tumors			
Overall Rates (e)	13/50 (26%)	17/50 (34%)	9/50 (18%)
Adjusted Rates (b)	27.1%	35.4%	18.0%
Terminal Rates (c)	13/48 (27%)	17/48 (35%)	8/49 (16%)
Day of First Observation	729	729	624
Life Table Tests (d)	P=0.103N	P=0.256	P=0.220N
Logistic Regression Tests (d)	P=0.100N	P=0.256	P=0.217N
Cochran-Armitage Trend Test (d)	P=0.114N		
Fisher Exact Test (d)		P=0.257	P=0.235N
All Sites: All Tumors			
Overall Rates (e)	30/50 (60%)	25/50 (50%)	18/50 (36%)
Adjusted Rates (b)	62.5%	51.0%	36.0%
Terminal Rates (c)	30/48 (63%)	24/48 (50%)	17/49 (35%)
Day of First Observation	729	695	624
Life Table Tests (d)	P=0.012N	P=0.211N	P=0.011N
Logistic Regression Tests (d)	P=0.010N	P=0.182N	P=0.009N
Cochran-Armitage Trend Test (d)	P=0.014N		
Fisher Exact Test (d)		P=0.211N	P=0.014N

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

TABLE C4a. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL NEOPLASMS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls	
	Adenoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.		
Overall Historical Incidence		
TOTAL	(b) 30/1,630 (1.8%)	(b) 32/1,630 (2.0%)
SD (c)	2.16%	2.17%
Range (d)		
High	3/42	3/42
Low	0/50	0/50

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

TABLE C4b. HISTORICAL INCIDENCE OF HEPATOCELLULAR NEOPLASMS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	233/1,678 (13.9%)	285/1,678 (17.0%)	494/1,678 (29.4%)
SD (b)	7.50%	6.31%	8.04%
Range (c)			
High	22/50	15/50	29/50
Low	2/45	4/50	7/48

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

TABLE C4c. HISTORICAL INCIDENCE OF HARDERIAN GLAND NEOPLASMS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 61/1,692 (3.6%)	(c) 6/1,692 (0.4%)	(b,c) 67/1,692 (4.0%)
SD (d)	3.23%	0.78%	3.14%
Range (e)			
High	6/50	1/49	6/50
Low	0/50	0/50	0/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Includes five papillary adenomas, five cystadenomas, and one papillary cystadenoma, NOS
(c) Includes two ademocarcinomas. NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE C4d. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR NEOPLASMS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	204/1,684 (12.1%)	80/1,684 (4.8%)	277/1,684 (16.4%)
SD (b)	6.18%	2.70%	6.91%
Range (c)			
High	14/50	5/49	17/50
Low	1/50	0/49	4/50

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

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

	Untreated Control	20 ppm	100 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Dead	2	1	1
Accident		1	
Survivors			
Terminal sacrifice	48	48	49
Animals examined microscopically	50	50	50
ALIMENTARY SYSTEM			
Gallbladder	(48)	(48)	(48)
Inflammation, chronic	2 (4%)		
Intestine large, cecum	(49)	(48)	(50)
Hyperplasia, lymphoid	1 (2%)		2 (4%)
Intestine large, rectum	(47)	(46)	(50)
Inflammation, acute			1 (2%)
Inflammation, chronic active	1 (2%)		
Intestine small, duodenum	(49)	(48)	(50)
Hyperplasia, lymphoid			1 (2%)
Intestine small, ileum	(49)	(48)	(50)
Amyloid deposition		1 (2%)	
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Intestine small, jejunum	(49)	(48)	(50)
Hyperplasia, lymphoid		1 (2%)	
Inflammation, chronic		1 (2%)	
Liver	(50)	(50)	(50)
Basophilic focus	3 (6%)		
Clear cell focus		1 (2%)	
Cyst			1 (2%)
Cytologic alterations, focal	4 (8%)		3 (6%)
Fibrosis, focal	1 (2%)		
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, chronic	8 (16%)	3 (6%)	
Necrosis, focal	1 (2%)		
Centrilobular, vacuolization cytoplasmic	1 (2%)		
Mesentery	(1)	(3)	
Fat, necrosis	1 (100%)	1 (33%)	
Pancreas	(50)	(50)	(50)
Inflammation, chronic	2 (4%)	1 (2%)	1 (2%)
Acinus, inflammation, chronic	1 (2%)		
Acinus, vacuolization cytoplasmic			1 (2%)
Salivary glands	(50)	(50)	(49)
Infiltration cellular, lymphocytic	38 (76%)	27 (54%)	15 (31%)
Inflammation, chronic active			1 (2%)
Artery, inflammation, chronic	1 (2%)	3 (6%)	
Stomach, glandular	(49)	(50)	(50)
Cyst	1 (2%)		
Inflammation, acute			1 (2%)
Inflammation, chronic	1 (2%)		
Tooth	(5)	(5)	
Developmental malformation	1 (20%)	4 (80%)	
Inflammation, acute	3 (60%)	1 (20%)	
Inflammation, chronic active	1 (20%)		

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
CARDIOVASCULAR SYSTEM			
Blood vessel	(1)		
Aorta, inflammation, chronic	1 (100%)		
Heart	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Atrium, bacterium			1 (2%)
Atrium, thrombus			1 (2%)
Myocardium, infarct			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(49)	(49)
Capsule, hyperplasia	28 (56%)	32 (65%)	36 (73%)
Adrenal gland, cortex	(50)	(49)	(49)
Hyperplasia	2 (4%)	3 (6%)	
Hypertrophy	3 (6%)	1 (2%)	
Hypertrophy, focal	5 (10%)	2 (4%)	2 (4%)
Capsule, hyperplasia	1 (2%)		
Islets, pancreatic	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)	
Parathyroid gland	(42)	(44)	(41)
Cyst			1 (2%)
Pituitary gland	(48)	(49)	(50)
Pars distalis, cyst	1 (2%)	2 (4%)	1 (2%)
Pars distalis, hyperplasia		1 (2%)	
Thyroid gland	(50)	(50)	(50)
Cyst	7 (14%)	6 (12%)	7 (14%)
Inflammation, chronic		1 (2%)	
Follicular cell, hyperplasia	1 (2%)	1 (2%)	1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(50)	(50)	(50)
Inflammation, chronic	1 (2%)	2 (4%)	3 (6%)
Preputial gland	(1)		(1)
Cyst	1 (100%)		
Inflammation, acute			1 (100%)
Prostate	(50)	(50)	(49)
Inflammation, chronic		3 (6%)	2 (4%)
Seminal vesicle	(50)	(50)	(50)
Inflammation, acute			1 (2%)
Inflammation, chronic		1 (2%)	
Testes	(50)	(50)	(50)
Atrophy		3 (6%)	1 (2%)
HEMATOPOIETIC SYSTEM			
Lymph node	(50)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Lymph node, mandibular	(41)	(44)	(45)
Hyperplasia, lymphoid			2 (4%)
Lymph node, mesenteric	(47)	(49)	(48)
Amyloid deposition		1 (2%)	
Hematopoietic cell proliferation	2 (4%)		
Hemorrhage	2 (4%)	1 (2%)	
Hyperplasia, lymphoid	4 (9%)	4 (8%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(48)	(50)	(50)
Depletion lymphoid	1 (2%)		
Hematopoietic cell proliferation			1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Thymus	(44)	(44)	(41)
Cyst	2 (5%)		1 (2%)
Epithelial cell, hyperplasia		1 (2%)	1 (2%)
INTEGUMENTARY SYSTEM			
Skin	(50)	(50)	(50)
Inflammation, acute		2 (4%)	
Inflammation, chronic	2 (4%)		1 (2%)
Subcutaneous tissue, abscess		1 (2%)	
Tail, inflammation, chronic	1 (2%)		
Tail, epidermis, cyst			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)		1 (2%)
Osteomalacia		1 (2%)	
Cranium, hyperostosis		1 (2%)	
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Infiltration cellular, lymphocytic	1 (2%)		
Choroid plexus, infiltration cellular, lymphocytic			1 (2%)
Meninges, infiltration cellular, lymphocytic		1 (2%)	
Thalamus, mineralization	43 (86%)	33 (66%)	36 (72%)
Spinal cord	(49)	(50)	(50)
Infiltration cellular, lymphocytic	1 (2%)		
Meninges, infiltration cellular, lymphocytic		3 (6%)	4 (8%)
RESPIRATORY SYSTEM			
Larynx	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Lung	(50)	(50)	(50)
Congestion	1 (2%)		
Fibrosis, focal			1 (2%)
Hemorrhage		2 (4%)	
Hyperplasia, adenomatous	3 (6%)	3 (6%)	
Infiltration cellular, lymphocytic	39 (78%)	30 (60%)	33 (66%)
Infiltration cellular, histiocytic	4 (8%)		
Inflammation, acute		1 (2%)	
Pigmentation	1 (2%)		
Alveolar epithelium, hyperplasia, adenomatous	1 (2%)		1 (2%)
Interstitium, inflammation, chronic	1 (2%)		
Nose	(50)	(50)	(50)
Glands, inflammation, acute			1 (2%)
Nasolacrimal duct, inflammation, acute	2 (4%)		
Sinus, hemorrhage		1 (2%)	
Sinus, inflammation, acute	2 (4%)	1 (2%)	
Turbinate, inflammation, chronic		1 (2%)	

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
SPECIAL SENSES SYSTEM			
Eye	(49)	(49)	(50)
Cornea, inflammation, chronic	1 (2%)		
URINARY SYSTEM			
Kidney	(50)	(50)	(50)
Cyst	2 (4%)	3 (6%)	1 (2%)
Fibrosis, focal	1 (2%)		
Inflammation, chronic	34 (68%)	25 (50%)	27 (54%)
Metaplasia, osseous	1 (2%)	1 (2%)	
Artery, inflammation, chronic		1 (2%)	
Cortex, cyst	1 (2%)		
Cortex, necrosis, focal		1 (2%)	
Papilla, bacterium			1 (2%)
Papilla, necrosis			1 (2%)
Pelvis, dilatation		1 (2%)	
Renal tubule, hyperplasia		1 (2%)	
Renal tubule, regeneration	1 (2%)		

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDIES OF *dl*-AMPHETAMINE SULFATE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

	Untreated Control	20 ppm	100 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Dead	10	11	5
Moribund	5	3	1
Survivors			
Terminal sacrifice	35	36	44
Animals examined microscopically	50	50	47
ALIMENTARY SYSTEM			
Intestine large, cecum	(44)	(44)	(44)
Intestine small, jejunum	(45)	(43)	(44)
Liver	(50)	(50)	(47)
Hemangiosarcoma		1 (2%)	
Hepatocellular adenoma	5 (10%)	1 (2%)	1 (2%)
Histiocytic sarcoma	1 (2%)	2 (4%)	
Pancreas	(49)	(48)	(45)
Histiocytic sarcoma		1 (2%)	
Salivary glands	(49)	(46)	(43)
Stomach, forestomach	(50)	(49)	(46)
Papilloma squamous	1 (2%)		
Stomach, glandular	(50)	(49)	(46)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(47)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(46)	(46)
Adrenal gland, medulla	(48)	(43)	(43)
Histiocytic sarcoma		1 (2%)	
Pheochromocytoma benign		1 (2%)	
Parathyroid gland	(46)	(42)	(44)
Pituitary gland	(49)	(49)	(46)
Pars distalis, adenoma	12 (24%)	6 (12%)	1 (2%)
Pars intermedia, adenoma	1 (2%)		
Thyroid gland	(50)	(49)	(47)
Follicular cell, adenoma	1 (2%)	1 (2%)	1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(49)	(48)	(46)
Cystadenoma	1 (2%)	1 (2%)	
Granulosa cell tumor benign		1 (2%)	
Hemangiosarcoma	1 (2%)		
Histiocytic sarcoma		1 (2%)	
Neoplasm, NOS			1 (2%)
Uterus	(50)	(50)	(47)
Histiocytic sarcoma		2 (4%)	
Cervix, fibrosarcoma		1 (2%)	
Cervix, leiomyoma	1 (2%)		
Endometrium, polyp stromal	2 (4%)	1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(47)
Lymph node	(50)	(49)	(47)
Mediastinal, histiocytic sarcoma	1 (2%)		
Lymph node, mandibular	(47)	(43)	(41)
Histiocytic sarcoma	2 (4%)		
Lymph node, mesenteric	(50)	(46)	(40)
Histiocytic sarcoma	1 (2%)		
Spleen	(50)	(49)	(46)
Hemangiosarcoma	1 (2%)	1 (2%)	
Histiocytic sarcoma	1 (2%)	3 (6%)	
Thymus	(46)	(46)	(45)
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(48)	(45)
Adenocarcinoma		1 (2%)	1 (2%)
Adenoma	1 (2%)	1 (2%)	
Skin	(50)	(50)	(47)
Melanoma benign			1 (2%)
Subcutaneous tissue, fibrosarcoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(47)
Joint, neoplasm, NOS		1 (2%)	
Skeletal muscle		(5)	(1)
NERVOUS SYSTEM			
Brain	(50)	(49)	(47)
Spinal cord	(49)	(46)	(43)
RESPIRATORY SYSTEM			
Larynx	(50)	(49)	(47)
Lung	(50)	(50)	(47)
Alveolar/bronchiolar adenoma	7 (14%)	4 (8%)	1 (2%)
Alveolar/bronchiolar carcinoma	1 (2%)	2 (4%)	
Fibrosarcoma, metastatic, skin	1 (2%)		
Fibrous histiocytoma, metastatic, ear	1 (2%)		
Histiocytic sarcoma	1 (2%)	1 (2%)	
Nose	(50)	(50)	(47)
SPECIAL SENSES SYSTEM			
Ear	(1)	(1)	
Pinna, fibrous histiocytoma	1 (100%)		
Harderian gland	(7)	(2)	
Adenoma	5 (71%)	2 (100%)	
URINARY SYSTEM			
Kidney	(50)	(48)	(47)
Histiocytic sarcoma	1 (2%)	3 (6%)	
Urinary bladder	(48)	(47)	(45)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(47)
Histiocytic sarcoma	2 (4%)	3 (6%)	
Lymphoma malignant	1 (2%)		1 (2%)
Lymphoma malignant histiocytic	4 (8%)		
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)	2 (4%)
Lymphoma malignant mixed	10 (20%)	9 (18%)	7 (15%)
Lymphoma malignant undifferentiated cell			1 (2%)
TUMOR SUMMARY			
Total animals with primary neoplasms**	40	27	15
Total primary neoplasms	60	39	18
Total animals with benign neoplasms	30	13	5
Total benign neoplasms	37	19	5
Total animals with malignant neoplasms	19	17	11
Total malignant neoplasms	23	19	12
Total animals with secondary neoplasms***	2		
Total secondary neoplasms	2		
Total animals with neoplasms--uncertain benign or malignant		1	1
Total uncertain neoplasms		1	1

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: UNTREATED CONTROL

DAYS ON STUDY	519	527	534	579	603	632	632	671	681	686	687	699	711	711	728	732	732	732	732	732	732	732	732	732	732
CARCASS ID	15885	15775	15844	15445	15115	15664	15665	16005	15663	15625	15444	15955	15114	15554	15544	15112	15122	15132	15212	15222	15232	15242	15311	15322	15332
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	+	+	+	+	A	A	+	A	A	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	A	A	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	A	A	+	+	+	A	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	A	A	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	A	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	A	A	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	A	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	A	A	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	A	A	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X										X								X			
Histiocytic sarcoma																									
Mesentery		+																+				+			
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous					X																				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth													+			+									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma												X		X					X	X	X				X
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Hemangiosarcoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cervix, leiomyoma																		X							
Endometrium, polyp stromal										X															

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

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

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

DAYS ON STUDY	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	TOTAL:
CARCASS ID	15344	15355	15411	15422	15433	15511	15522	15533	15611	15622	15711	15722	15733	15744	15811	15822	15833	15911	15922	15933	15944	16001	16022	16033	16044	TISSUES TUMORS
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma					X						X															5
Histiocytic sarcoma																							X			1
Mesentery																+										4
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																										2
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma		X							X					X	X				X			X				12
Pars intermedia, adenoma																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma		X																								1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma												X														1
Hemangiosarcoma									X																	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cervix, leiomyoma																										1
Endometrium, polyp stromal																							X			2

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

DAYS ON STUDY	519	527	534	579	603	632	632	671	681	686	687	699	711	711	728	732	732	732	732	732	732	732	732	732	732
CARCASS ID	15885	15775	15844	15455	15155	15564	15665	16055	15633	15255	15444	15955	15144	15555	15544	15111	15122	15132	15211	15222	15232	15244	15311	15322	15333
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+
Histiocytic sarcoma																		X							
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																									
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma							X																		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma															X										
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic, skin															X										
Fibrous histiocytoma, metastatic, ear											X														
Histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear											+														
Pinna, fibrous histiocytoma											X														
Eye	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland			+	+			+						+												
Adenoma							X						X												
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Urinary bladder	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Lymphoma malignant				X																					
Lymphoma malignant histiocytic	X														X										
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed			X	X	X					X												X			

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

DAYS ON STUDY	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	TOTAL: TISSUES TUMORS
CARCASS ID	15334	15335	15341	15422	15433	15512	15522	15533	15611	15622	15711	15722	15733	15744	15811	15822	15833	15911	15922	15933	15944	16011	16022	16033	16044	
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, histiocytic sarcoma																							X			1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																							X			2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																							X			1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma									X																	1
Histiocytic sarcoma																							X			1
Thymus	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X			X					X			X				X		X								7
Alveolar/bronchiolar carcinoma																	X									1
Fibrosarcoma, metastatic, skin																										1
Fibrous histiocytoma, metastatic, ear																										1
Histiocytic sarcoma																							X			1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																									
Ear																										1
Pinna, fibrous histiocytoma																										1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	47
Harderian gland											+					+								+		7
Adenoma											X					X								X		5
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																							X			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																							X			2
Lymphoma malignant																										1
Lymphoma malignant histiocytic								X					X													4
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed						X			X	X					X						X					10

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: 20 ppm

DAYS ON STUDY	495	497	511	613	634	643	646	654	690	700	701	704	704	716	733	733	733	733	733	733	733	733	733	733	733	733
CARCASS ID	16655	16625	16553	16445	17005	16885	16995	16224	17004	16865	16664	16444	16634	16775	16111	16121	16131	16141	16151	16211	16221	16231	16311	16321	16331	16332
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	+	A	+	A	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	A	A	+	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	A	+	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	A	A	+	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	A	+	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	A	A	+	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	A	+	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	A	+	+	A	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	A	+	+	+	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																										
Hepatocellular adenoma												X														
Histiocytic sarcoma									X				X													
Mesentery																										
Pancreas	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Salivary glands	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																										
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																										
Adrenal gland	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	M	M	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X													
Pheochromocytoma benign																										
Islets, pancreatic	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	M	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X			X						X		
Thyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																						X				
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																										
Granulosa cell tumor benign																										
Histiocytic sarcoma													X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma													X													
Cervix, fibrosarcoma																									X	
Endometrium, polyp stromal															X											

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 20 ppm (Continued)

DAYS ON STUDY	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	TOTAL:
CARCASS ID	16334	16335	16341	16342	16343	16351	16352	16354	16361	16362	16371	16372	16373	16374	16381	16382	16383	16384	16391	16392	16393	16394	17001	17002	17003	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	40
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma										X																1
Hepatocellular adenoma																										1
Histiocytic sarcoma																										2
Mesentery															+											1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																X										1
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																+	+									2
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		46
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		46
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+		43
Histiocytic sarcoma																										1
Pheochromocytoma benign												X														1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+		42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		49
Pars distalis, adenoma												X								X				X		6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Follicular cell, adenoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Cystadenoma					X																					1
Granulosa cell tumor benign																				X						1
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																X										2
Cervix, fibrosarcoma																										1
Endometrium, polyp stromal																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 20 ppm (Continued)

DAYS ON STUDY	495	497	511	613	634	643	646	654	690	700	701	704	704	716	733	733	733	733	733	733	733	733	733	733
CARCASS ID	16555	16225	16533	16445	17005	16885	16995	16224	17004	16665	16664	16444	16633	16775	16111	16122	16133	16144	16155	16221	16223	16231	16232	16333
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	M	M	+
Lymph node, mesenteric	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Histiocytic sarcoma									X				X											
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																								
Mammary gland	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																X								
Adenoma																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Joint, neoplasm, NOS																								
Skeletal muscle										+				+										
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	M	+	+	M	M	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																								
Larynx	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X						
Alveolar/bronchiolar carcinoma																								X
Histiocytic sarcoma													X											
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																								
Ear				+																				
Eye	M	A	A	M	+	+	A	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland																								
Adenoma																								
URINARY SYSTEM																								
Kidney	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X				X											
Ureter														+										
Urinary bladder	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X				X											
Lymphoma malignant lymphocytic																								
Lymphoma malignant mixed	X			X								X				X								

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 20 ppm (Continued)

DAYS ON STUDY	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	TOTAL:
CARCASS ID	16334	16335	16341	16342	16343	16351	16352	16354	16361	16362	16371	16372	16373	16374	16381	16382	16383	16384	16391	16392	16393	16394	17001	17002	17003	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymph node, mesenteric	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma				X																						1
Histiocytic sarcoma																X										3
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																										1
Adenoma																	X									1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Joint, neoplasm, NOS															X											1
Skeletal muscle	+								+	+																5
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X										X	X							4
Alveolar/bronchiolar carcinoma												X														2
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Ear																										1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Harderian gland								+																	+	2
Adenoma								X																	X	2
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																X										3
Ureter																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	47
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																X										3
Lymphoma malignant lymphocytic										X																1
Lymphoma malignant mixed							X		X					X				X							X	9

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE: 100 ppm

DAYS ON STUDY	253	253	255	687	708	724	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732	732
CARCASS ID	17544	17555	17245	17445	17775	17665	17111	17112	17113	17114	17115	17211	17221	17233	17244	17311	17321	17333	17343	17353	17361	17362	17363	17364	17371
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	+	+	+	A	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Pancreas	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																+									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	A	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma					X																				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS																X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	M	+	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenocarcinoma					X																				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Melanoma benign																					X				
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	M	M	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye	M	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SYSTEMIC LESIONS																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant						X																			
Lymphoma malignant lymphocytic						X																			
Lymphoma malignant mixed			X	X				X						X							X				
Lymphoma malignant undifferentiated cell type																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 100 ppm (Continued)

DAYS ON STUDY	732	732	732	732	732	732	732	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	737	TOTAL:
CARCASS ID	17722	17733	17744	17811	17822	17833	17844	17855	17841	17852	17843	17844	17851	17852	17853	17891	17892	17893	17894	17895	18001	18002	18003	18004	18005	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	43
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	44
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	44
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	44
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Hepatocellular adenoma			X																							1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	45
Salivary glands	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	43
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	46
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	46
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	46
Tooth																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	46
Adrenal gland, medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+		+	+			+	+	43
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	45
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			M	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	46
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Follicular cell, adenoma																				X						1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	46
Neoplasm, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	41
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	M	+		+	+			+	M	40
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	46
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	45
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	45
Adenocarcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Melanoma benign																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Skeletal muscle						+																				1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	43
RESPIRATORY SYSTEM																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Alveolar/bronchiolar adenoma													X													1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
SPECIAL SENSES SYSTEM																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	45
SYSTEMIC LESIONS																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	47
Lymphoma malignant																										1
Lymphoma malignant lymphocytic						X																				2
Lymphoma malignant mixed		X																X								7
Lymphoma malignant undifferentiated cell type				X																						1

TABLE D3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

	Control	20 ppm	100 ppm
Harderian Gland: Adenoma			
Overall Rates (a)	5/50 (10%)	2/50 (4%)	0/47 (0%)
Adjusted Rates (b)	13.0%	5.6%	0.0%
Terminal Rates (c)	3/35 (9%)	2/36 (6%)	0/41 (0%)
Day of First Observation	632	732	
Life Table Tests (d)	P=0.029N	P=0.212N	P=0.027N
Logistic Regression Tests (d)	P=0.040N	P=0.215N	P=0.038N
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.218N	P=0.033N
Liver: Hepatocellular Adenoma			
Overall Rates (e)	5/50 (10%)	1/50 (2%)	1/47 (2%)
Adjusted Rates (b)	12.9%	2.6%	2.4%
Terminal Rates (c)	3/35 (9%)	0/36 (0%)	1/41 (2%)
Day of First Observation	579	704	732
Life Table Tests (d)	P=0.119N	P=0.105N	P=0.083N
Logistic Regression Tests (d)	P=0.157N	P=0.103N	P=0.118N
Cochran-Armitage Trend Test (d)	P=0.157N		
Fisher Exact Test (d)		P=0.102N	P=0.117N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (e)	7/50 (14%)	4/50 (8%)	1/47 (2%)
Adjusted Rates (b)	20.0%	11.1%	2.4%
Terminal Rates (c)	7/35 (20%)	4/36 (11%)	1/41 (2%)
Day of First Observation	732	732	732
Life Table Tests (d)	P=0.020N	P=0.241N	P=0.018N
Logistic Regression Tests (d)	P=0.020N	P=0.241N	P=0.018N
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.262N	P=0.036N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (e)	8/50 (16%)	6/50 (12%)	1/47 (2%)
Adjusted Rates (b)	22.9%	16.7%	2.4%
Terminal Rates (c)	8/35 (23%)	6/36 (17%)	1/41 (2%)
Day of First Observation	732	732	732
Life Table Tests (d)	P=0.008N	P=0.361N	P=0.009N
Logistic Regression Tests (d)	P=0.008N	P=0.361N	P=0.009N
Cochran-Armitage Trend Test (d)	P=0.020N		
Fisher Exact Test (d)		P=0.387N	P=0.019N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (e)	12/49 (24%)	6/49 (12%)	1/46 (2%)
Adjusted Rates (b)	32.2%	17.1%	2.3%
Terminal Rates (c)	10/35 (29%)	6/35 (17%)	0/41 (0%)
Day of First Observation	699	732	708
Life Table Tests (d)	P=0.001N	P=0.094N	P<0.001N
Logistic Regression Tests (d)	P=0.001N	P=0.095N	P=0.001N
Cochran-Armitage Trend Test (d)	P=0.003N		
Fisher Exact Test (d)		P=0.096N	P=0.001N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	15/50 (30%)	10/50 (20%)	10/47 (21%)
Adjusted Rates (b)	34.4%	24.7%	22.6%
Terminal Rates (c)	8/35 (23%)	7/36 (19%)	7/41 (17%)
Day of First Observation	519	495	555
Life Table Tests (d)	P=0.172N	P=0.184N	P=0.131N
Logistic Regression Tests (d)	P=0.292N	P=0.176N	P=0.224N
Cochran-Armitage Trend Test (d)	P=0.298N		
Fisher Exact Test (d)		P=0.178N	P=0.227N

TABLE D3. ANALYSIS OF PRIMARY NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Control	20 ppm	100 ppm
All Sites: Histiocytic Sarcoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/47 (0%)
Adjusted Rates (b)	5.7%	7.5%	0.0%
Terminal Rates (c)	2/35 (6%)	1/36 (3%)	0/41 (0%)
Day of First Observation	732	690	
Life Table Tests (d)	P=0.124N	P=0.517	P=0.204N
Logistic Regression Tests (d)	P=0.151N	P=0.503	P=0.204N
Cochran-Armitage Trend Test (d)	P=0.159N		
Fisher Exact Test (d)		P=0.500	P=0.263N
All Sites: Benign Tumors			
Overall Rates (a)	30/50 (60%)	13/50 (26%)	5/47 (11%)
Adjusted Rates (b)	71.1%	35.0%	11.9%
Terminal Rates (c)	23/35 (66%)	12/36 (33%)	4/41 (10%)
Day of First Observation	579	704	708
Life Table Tests (d)	P<0.001N	P<0.001N	P<0.001N
Logistic Regression Tests (d)	P<0.001N	P<0.001N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P<0.001N	P<0.001N
All Sites: Malignant Tumors			
Overall Rates (a)	19/50 (38%)	17/50 (34%)	11/47 (23%)
Adjusted Rates (b)	43.1%	40.8%	24.4%
Terminal Rates (c)	11/35 (31%)	12/36 (33%)	7/41 (17%)
Day of First Observation	519	495	555
Life Table Tests (d)	P=0.033N	P=0.396N	P=0.045N
Logistic Regression Tests (d)	P=0.078N	P=0.420N	P=0.091N
Cochran-Armitage Trend Test (d)	P=0.078N		
Fisher Exact Test (d)		P=0.418N	P=0.091N
All Sites: All Tumors			
Overall Rates (a)	40/50 (80%)	27/50 (54%)	15/47 (32%)
Adjusted Rates (b)	85.0%	65.5%	33.3%
Terminal Rates (c)	28/35 (80%)	22/36 (61%)	11/41 (27%)
Day of First Observation	519	495	555
Life Table Tests (d)	P<0.001N	P=0.012N	P<0.001N
Logistic Regression Tests (d)	P<0.001N	P=0.005N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.005N	P<0.001N

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

TABLE D4a. HISTORICAL INCIDENCE OF HEPATOCELLULAR NEOPLASMS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	100/1,683 (5.9%)	(b) 68/1,683 (4.0%)	(b) 163/1,683 (9.7%)
SD (c)	3.75%	2.30%	4.25%
Range (d)			
High	8/49	4/48	10/49
Low	0/50	0/49	2/50

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

TABLE D4b. HISTORICAL INCIDENCE OF HARDERIAN GLAND NEOPLASMS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 43/1,689 (2.5%)	(c) 8/1,689 (0.5%)	(b,c) 51/1,689 (3.0%)
SD (d)	2.89%	0.99%	2.93%
Range (e)			
High	6/50	2/50	6/50
Low	0/50	0/50	0/50

(a) Data as of March 1, 1989, for studies of at least 104 weeks
(b) Includes three papillary adenomas and two papillary cystadenomas, NOS
(c) Includes two adenocarcinomas, NOS, two papillary adenocarcinomas, and one papillary cystadenocarcinoma, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE D4c. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR NEOPLASMS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	73/1,676 (4.4%)	35/1,676 (2.1%)	107/1,676 (6.4%)
SD (b)	3.35%	1.68%	3.76%
Range (c)			
High	6/49	3/50	8/50
Low	0/50	0/50	0/50

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

TABLE D4d. HISTORICAL INCIDENCE OF ANTERIOR PITUITARY GLAND NEOPLASMS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
No 2-year studies by Microbiological Associates, Inc., are included in the historical data base.			
Overall Historical Incidence			
TOTAL	(b) 244/1,528 (16.0%)	(c) 12/1,528 (0.8%)	(b,c) 256/1,528 (16.8%)
SD (d)	10.80%	1.42%	11.09%
Range (e)			
High	18/49	3/50	19/49
Low	0/48	0/50	0/48

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

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

	Untreated Control	20 ppm	100 ppm
DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Early deaths			
Dead	10	11	5
Moribund	5	3	1
Survivors			
Terminal sacrifice	35	36	44
Animals examined microscopically	50	50	47
ALIMENTARY SYSTEM			
Gallbladder	(44)	(40)	(43)
Inflammation, chronic	1 (2%)	1 (3%)	
Intestine large, cecum	(44)	(44)	(44)
Hyperplasia, lymphoid	1 (2%)	5 (11%)	
Intestine small, jejunum	(45)	(43)	(44)
Inflammation, acute	1 (2%)		
Liver	(50)	(50)	(47)
Basophilic focus	1 (2%)		
Cytologic alterations, focal	1 (2%)		
Hematopoietic cell proliferation	4 (8%)	5 (10%)	
Inflammation, acute	3 (6%)	1 (2%)	1 (2%)
Inflammation, chronic	7 (14%)	11 (22%)	7 (15%)
Mitotic alteration			1 (2%)
Necrosis	3 (6%)	2 (4%)	1 (2%)
Vacuolization cytoplasmic	5 (10%)		
Serosa, inflammation, acute	1 (2%)	1 (2%)	
Mesentery	(4)	(1)	
Infiltration cellular, lymphocytic		1 (100%)	
Inflammation, acute	1 (25%)		
Fat, necrosis	3 (75%)		
Pancreas	(49)	(48)	(45)
Cyst	1 (2%)		
Inflammation, acute	2 (4%)	3 (6%)	
Inflammation, chronic		7 (15%)	5 (11%)
Acinus, atrophy, focal	2 (4%)		
Acinus, necrosis	1 (2%)		
Acinus, vacuolization cytoplasmic		2 (4%)	1 (2%)
Artery, inflammation, acute		1 (2%)	
Salivary glands	(49)	(46)	(43)
Infiltration cellular, lymphocytic	26 (53%)	25 (54%)	21 (49%)
Artery, inflammation, acute		1 (2%)	
Stomach, forestomach	(50)	(49)	(46)
Inflammation, acute	1 (2%)		
Epithelium, hyperplasia	2 (4%)		
Stomach, glandular	(50)	(49)	(46)
Erosion			1 (2%)
Infiltration cellular, lymphocytic		1 (2%)	
Inflammation, chronic		1 (2%)	
Ulcer	1 (2%)		
Tooth	(2)	(2)	(1)
Inflammation, acute	2 (100%)	1 (50%)	1 (100%)
Inflammation, chronic		1 (50%)	
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(47)
Fibrosis		2 (4%)	
Aortic valve, thrombus		1 (2%)	
Epicardium, inflammation, acute		2 (4%)	
Myocardium, inflammation, chronic		1 (2%)	
Myocardium, inflammation, chronic active	1 (2%)		

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
ENDOCRINE SYSTEM			
Adrenal gland	(50)	(46)	(47)
Capsule, hyperplasia	50 (100%)	42 (91%)	46 (98%)
Adrenal gland, cortex	(50)	(46)	(46)
Cyst	2 (4%)		
Hematopoietic cell proliferation		2 (4%)	
Infiltration cellular, lymphocytic		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, chronic		1 (2%)	
Vacuolization cytoplasmic	1 (2%)		
Adrenal gland, medulla	(48)	(43)	(43)
Hyperplasia		1 (2%)	
Parathyroid gland	(46)	(42)	(44)
Infiltration cellular, lymphocytic			1 (2%)
Pituitary gland	(49)	(49)	(46)
Pars distalis, angiectasis	1 (2%)		
Pars distalis, hyperplasia	11 (22%)	5 (10%)	3 (7%)
Pars intermedia, pigmentation	1 (2%)		
Thyroid gland	(50)	(49)	(47)
Cyst	8 (16%)	9 (18%)	10 (21%)
Inflammation, acute	2 (4%)		
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)
Follicular cell, hyperplasia	8 (16%)	5 (10%)	3 (6%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ovary	(49)	(48)	(46)
Abscess	2 (4%)		
Atrophy	14 (29%)	12 (25%)	25 (54%)
Cyst	11 (22%)	16 (33%)	12 (26%)
Hemorrhage	3 (6%)	1 (2%)	
Infiltration cellular, lymphocytic		2 (4%)	
Inflammation, acute	1 (2%)	4 (8%)	
Inflammation, chronic		1 (2%)	
Uterus	(50)	(50)	(47)
Abscess	2 (4%)		
Hemorrhage			1 (2%)
Inflammation, acute	8 (16%)	10 (20%)	4 (9%)
Artery, inflammation, acute		1 (2%)	1 (2%)
Cervix, inflammation, chronic	1 (2%)		
Endometrium, hyperplasia, cystic	35 (70%)	34 (68%)	34 (72%)
Endometrium, necrosis			1 (2%)
Serosa, inflammation, acute	1 (2%)		
Serosa, inflammation, chronic	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(47)
Hyperplasia	6 (12%)	6 (12%)	
Lymph node	(50)	(49)	(47)
Iliac, hyperplasia, lymphoid	2 (4%)		
Mediastinal, abscess	1 (2%)		
Lymph node, mandibular	(47)	(43)	(41)
Cyst		1 (2%)	
Hematopoietic cell proliferation	1 (2%)		
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)
Pigmentation		1 (2%)	
Thrombus	1 (2%)		
Lymphocyte, necrosis		1 (2%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
HEMATOPOIETIC SYSTEM (Continued)			
Lymph node, mesenteric	(50)	(46)	(40)
Dilatation	1 (2%)		
Hematopoietic cell proliferation	2 (4%)		
Hyperplasia, lymphoid	8 (16%)	4 (9%)	1 (3%)
Lymphocyte, necrosis	1 (2%)	2 (4%)	
Spleen	(50)	(49)	(46)
Amyloid deposition	1 (2%)		
Hematopoietic cell proliferation	8 (16%)	5 (10%)	1 (2%)
Hyperplasia, lymphoid	6 (12%)	5 (10%)	2 (4%)
Lymphocyte, necrosis	1 (2%)	1 (2%)	
Thymus	(46)	(46)	(45)
Atrophy	8 (17%)	1 (2%)	14 (31%)
Inflammation, acute		1 (2%)	
Mineralization		1 (2%)	
Necrosis		1 (2%)	
INTEGUMENTARY SYSTEM			
Skin	(50)	(50)	(47)
Abscess	1 (2%)		
Foreign body		1 (2%)	
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(47)
Fibrous osteodystrophy	18 (36%)	11 (22%)	11 (23%)
Metatarsal, inflammation, acute	1 (2%)		
Skeletal muscle		(5)	(1)
Inflammation, acute		1 (20%)	
Inflammation, chronic		2 (40%)	
Artery, inflammation, acute		1 (20%)	
NERVOUS SYSTEM			
Brain	(50)	(49)	(47)
Infiltration cellular, lymphocytic	1 (2%)	1 (2%)	3 (6%)
Thrombus		1 (2%)	
Meninges, infiltration cellular, lymphocytic	1 (2%)	3 (6%)	2 (4%)
Thalamus, mineralization	14 (28%)	7 (14%)	17 (36%)
Spinal cord	(49)	(46)	(43)
Meninges, infiltration cellular, lymphocytic	1 (2%)	7 (15%)	8 (19%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(47)
Congestion	1 (2%)		3 (6%)
Hemorrhage	1 (2%)	1 (2%)	
Hyperplasia, adenomatous	1 (2%)	2 (4%)	
Infiltration cellular	1 (2%)		
Infiltration cellular, lymphocytic	29 (58%)	36 (72%)	36 (77%)
Infiltration cellular, histiocytic	1 (2%)	3 (6%)	1 (2%)
Inflammation, chronic		1 (2%)	
Metaplasia, osseous	1 (2%)		
Alveolar epithelium, hyperplasia, adenomatous	1 (2%)		1 (2%)
Interstitium, inflammation, subacute			1 (2%)
Pleura, inflammation, acute	1 (2%)	2 (4%)	

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE (Continued)

	Untreated Control	20 ppm	100 ppm
RESPIRATORY SYSTEM (Continued)			
Nose	(50)	(50)	(47)
Hemorrhage	1 (2%)		
Nasolacrimal duct, inflammation	1 (2%)		
Nasolacrimal duct, inflammation, acute			1 (2%)
Sinus, inflammation, acute			1 (2%)
Trachea	(50)	(50)	(47)
Inflammation, acute	1 (2%)		
Artery, inflammation, chronic			1 (2%)
SPECIAL SENSES SYSTEM			
Eye	(47)	(44)	(45)
Cataract	1 (2%)		
Cornea, inflammation, acute		2 (5%)	
Harderian gland	(7)	(2)	
Hyperplasia	1 (14%)		
URINARY SYSTEM			
Kidney	(50)	(48)	(47)
Amyloid deposition		1 (2%)	
Inflammation, acute		2 (4%)	
Inflammation, chronic	16 (32%)	23 (48%)	14 (30%)
Glomerulus, inflammation, membranous		1 (2%)	
Pelvis, inflammation, acute	1 (2%)		
Renal tubule, degeneration			1 (2%)
Ureter		(1)	
Inflammation, acute		1 (100%)	
Urinary bladder	(48)	(47)	(45)
Infiltration cellular, lymphocytic	18 (38%)	13 (28%)	11 (24%)
Inflammation, acute	1 (2%)		
Artery, inflammation, acute			1 (2%)

APPENDIX E
SENTINEL ANIMAL PROGRAM

Methods

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

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

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

Results

Results are presented in Table E1.

TABLE E1. MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR FEED STUDIES OF *dl*-AMPHETAMINE SULFATE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	(b)	None positive
12	(b)	None positive
18	(c)	None positive
24	(b)	None positive
MICE		
6	5/9	*M. pul.* (d)
12	2/7	*M. pul.* (d)
18	(c)	None positive
24	(b)	None positive

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for determination of antibody titers.
(b) No positive antibody titers were observed for any of the 10 rodents tested.
(c) No positive antibody titers were observed for any of the nine rodents tested.
(d) Further evaluation of this assay indicated that it was not specific for *M. pulmonis*, and these results were considered to be false positive.

APPENDIX F
FEED AND COMPOUND CONSUMPTION BY RATS AND MICE IN THE TWO-YEAR STUDIES OF *dl*-AMPHETAMINE SULFATE

TABLE F1. FEED AND COMPOUND CONSUMPTION BY MALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

Week	Control		20 ppm			100 ppm		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
1	14	145	14	144	1.9	13	143	9
2	15	180	15	176	1.7	14	176	8
3	17	215	16	206	1.6	16	203	8
4	16	234	16	229	1.4	15	222	7
5	17	254	16	249	1.3	15	242	6
6	18	268	17	272	1.3	17	255	7
7	15	285	16	280	1.1	15	268	6
8	15	297	13	292	0.9	14	281	5
9	15	311	16	304	1.1	14	293	5
10	16	324	16	315	1.0	15	302	5
31	16	422	17	411	0.8	17	385	4
35	15	444	15	430	0.7	15	399	4
39	17	448	15	437	0.7	13	406	3
43	14	450	16	436	0.7	15	401	4
47	16	466	16	453	0.7	15	415	4
51	16	468	17	456	0.7	15	416	4
55	17	476	16	466	0.7	16	417	4
59	16	479	16	470	0.7	15	417	4
63	16	481	15	468	0.6	14	419	3
67	15	480	16	471	0.7	15	418	4
71	15	483	16	477	0.7	15	421	4
79	16	488	15	475	0.6	16	419	4
83	16	483	17	470	0.7	16	414	4
87	15	484	15	463	0.6	16	409	4
91	15	476	16	457	0.7	17	407	4
102	16	463	16	427	0.7	19	393	5
Mean for weeks								
1-10	15.8	251	15.5	247	1.3	14.8	239	6.6
31-51	15.7	450	16.0	437	0.7	15.0	404	3.8
55-102	15.7	479	15.8	464	0.7	15.9	413	4.0
Overall								
Mean	15.7	385	15.7	374	0.9	15.3	344	5.0
SD (c)	1.0		0.9		0.4	1.3		1.6
CV (d)	6.4		5.7		44.4	8.5		32.0

(a) Average grams of feed removed from feeder per animal per day; not corrected for scatter.
(b) Estimated milligrams of *dl*-amphetamine sulfate consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE F2. FEED AND COMPOUND CONSUMPTION BY FEMALE RATS IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

Week	Control		20 ppm			100 ppm		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
1	10	113	11	114	1.9	9	113	8
2	10	132	11	129	1.7	10	125	8
3	11	143	11	140	1.6	11	138	8
4	11	152	11	148	1.5	10	146	7
5	11	162	10	157	1.3	10	148	7
6	11	169	11	167	1.3	11	158	7
7	10	176	10	169	1.2	10	162	6
8	10	181	10	174	1.1	10	167	6
9	11	186	10	180	1.1	10	171	6
10	11	191	10	184	1.1	10	177	6
31	11	237	11	213	1.0	10	204	5
35	11	246	10	229	0.9	8	203	4
39	10	241	9	223	0.8	8	205	4
43	10	249	10	227	0.9	8	211	4
47	12	258	11	229	1.0	9	216	4
51	12	265	11	234	0.9	9	219	4
55	13	277	12	241	1.0	9	214	4
59	12	288	11	249	0.9	9	222	4
63	11	293	11	254	0.9	9	222	4
67	12	302	12	261	0.9	9	224	4
71	12	313	11	270	0.8	9	227	4
79	13	331	12	283	0.8	10	231	4
83	12	335	12	282	0.9	10	228	4
87	12	344	11	287	0.8	9	230	4
91	13	351	12	293	0.8	9	231	4
102	13	339	14	300	0.9	12	227	5
Mean for weeks								
1-10	10.6	161	10.5	156	1.4	10.1	151	6.9
31-51	11.0	249	10.3	226	0.9	8.7	210	4.2
55-102	12.3	317	11.8	272	0.9	9.5	226	4.1
Overall								
Mean	11.3	241	11.0	217	1.1	9.5	193	5.2
SD (c)	1.0		1.0		0.3	0.9		1.5
CV (d)	8.8		9.1		27.3	9.5		28.8

(a) Average grams of feed removed from feeder per animal per day; not corrected for scatter.
(b) Estimated milligrams of *dl*-amphetamine sulfate consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

TABLE F3. FEED AND COMPOUND CONSUMPTION BY MALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

Week	Control		20 ppm			100 ppm		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
1	4	23.7	4	23.3	3.4	3	23.5	13
2	4	24.6	4	24.0	3.3	4	23.5	17
3	4	25.8	4	24.9	3.2	5	23.9	21
4	4	27.2	6	25.7	4.7	6	24.9	24
5	4	26.7	4	26.6	3.0	5	25.1	20
6	4	28.1	5	27.2	3.7	6	25.7	23
7	4	28.6	5	27.4	3.6	7	25.5	27
8	4	28.7	6	28.3	4.2	7	25.5	27
9	4	29.7	4	27.3	2.9	6	25.8	23
31	5	38.6	6	34.0	3.5	8	29.7	27
35	6	39.6	8	34.9	4.6	9	27.9	32
39	5	41.2	5	35.9	2.8	8	29.2	27
43	5	42.1	7	36.9	3.8	12	29.5	41
48	6	42.5	6	38.0	3.2	10	29.2	34
51	5	42.6	7	37.7	3.7	11	29.4	37
55	6	44.4	7	39.6	3.5	12	30.2	40
59	5	46.3	7	40.6	3.4	11	31.5	35
63	6	46.8	7	40.5	3.5	11	31.4	35
67	6	46.0	8	40.2	4.0	13	30.4	43
71	7	45.9	9	40.0	4.5	12	30.7	39
75	6	46.2	8	39.5	4.1	11	31.3	35
79	7	46.2	10	39.6	5.1	13	31.7	41
83	6	47.3	8	39.0	4.1	13	30.4	43
88	5	46.3	8	39.2	4.1	10	30.4	33
91	5	45.3	7	38.4	3.6	10	30.6	33
96	5	45.8	8	38.5	4.2	11	31.0	35
102	7	43.4	9	35.2	5.1	14	28.9	48
Mean for weeks								
1-9	4.0	27.0	4.7	26.1	3.6	5.4	24.8	21.7
31-51	5.3	41.1	6.5	36.2	3.6	9.7	29.2	33.0
55-102	5.9	45.8	8.0	39.2	4.1	11.8	30.7	38.3
Overall								
Mean	5.1	38.5	6.6	34.2	3.8	(c) 9.2	28.4	(c) 31.6
SD (d)	1.0		1.7		0.6	3.1		8.8
CV (e)	19.6		25.8		15.8	33.7		27.8

(a) Average grams of feed removed from feeder per animal per day; not corrected for scatter.
(b) Estimated milligrams of *dl*-amphetamine sulfate consumed per day per kilogram of body weight
(c) Spillage of feed observed during the last half of the study.
(d) Standard deviation
(e) Coefficient of variation = (standard deviation/mean) × 100

TABLE F4. FEED AND COMPOUND CONSUMPTION BY FEMALE MICE IN THE TWO-YEAR FEED STUDY OF *dl*-AMPHETAMINE SULFATE

Week	Control		20 ppm			100 ppm		
	Grams Feed/ Day (a)	Body Weight (grams)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)	Grams Feed/ Day (a)	Body Weight (grams)	Dose/ Day (b)
1	3	18.9	3	18.9	3.2	3	18.9	16
2	6	19.7	3	20.2	3.0	4	19.9	20
3	3	21.4	3	20.6	2.9	3	20.3	15
4	3	22.9	3	22.2	2.7	3	21.4	14
5	3	22.6	4	22.2	3.6	4	21.9	18
6	3	23.4	3	23.2	2.6	3	22.2	14
7	2	23.6	2	23.6	1.7	2	21.9	9
8	3	24.3	4	24.0	3.3	4	22.6	18
9	3	24.7	3	23.7	2.5	3	22.7	13
18	4	27.4	5	26.4	3.8	6	24.2	25
31	2	30.5	3	28.1	2.1	3	25.7	12
35	4	32.0	5	28.2	3.5	5	24.4	20
39	4	32.8	4	29.6	2.7	5	25.7	19
43	4	34.4	5	30.0	3.3	5	25.8	19
48	4	34.4	5	30.0	3.3	6	25.9	23
51	4	35.6	5	30.4	3.3	5	26.1	19
55	4	36.6	5	32.4	3.1	5	26.6	19
59	4	38.0	4	33.3	2.4	5	26.7	19
63	4	38.9	5	33.2	3.0	5	27.5	18
67	4	39.2	5	33.4	3.0	5	26.8	19
71	4	40.9	5	34.1	2.9	5	27.1	18
75	4	41.6	5	34.5	2.9	5	27.4	18
79	5	43.4	6	34.5	3.5	6	27.7	22
83	4	43.5	5	33.1	3.0	6	27.5	22
88	5	44.7	5	33.7	3.0	7	27.4	26
91	4	42.6	4	33.7	2.4	5	27.1	18
96	4	43.7	5	34.7	2.9	5	27.3	18
102	5	41.3	6	32.5	3.7	7	25.7	27
Mean for weeks								
1-9	3.2	22.4	3.1	22.1	2.8	3.2	21.3	15.2
18-51	3.7	32.4	4.6	29.0	3.1	5.0	25.4	19.6
55-102	4.3	41.2	5.0	33.6	3.0	5.5	27.1	20.3
Overall								
Mean	3.8	33.0	4.3	28.7	3.0	4.6	24.8	18.5
SD (c)	0.9		1.0		0.5	1.3		4.1
CV (d)	23.7		23.3		16.7	28.3		22.2

(a) Average grams of feed removed from feeder per animal per day; not corrected for scatter.
(b) Estimated milligrams of *dl*-amphetamine sulfate consumed per day per kilogram of body weight
(c) Standard deviation
(d) Coefficient of variation = (standard deviation/mean) × 100

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

Meal Diet: May 1982 to June 1984
(Manufactured by Zeigler Bros., Inc., Gardners, PA)

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

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

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

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

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

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

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

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	22.95 ± 1.19	21.2-25.9	26
Crude fat (percent by weight)	5.08 ± 0.46	4.2-5.8	26
Crude fiber (percent by weight)	3.50 ± 0.60	2.8-4.5	26
Ash (percent by weight)	6.66 ± 0.21	6.3-7.1	26
Amino Acids (percent of total diet)			
Arginine	1.32 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.050	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.830-2.520	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	11,565 ± 4,265	4,200-22,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	18.46 ± 3.89	12.0-31.0	26
Riboflavin (ppm)	7.6 ± 0.85	6.10-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.80	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.70	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent)	1.24 ± 0.10	1.04-1.43	26
Phosphorus (percent)	0.96 ± 0.05	0.90-1.10	26
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.70-99.40	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

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

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.51 ± 0.14	0.18-0.74	26
Cadmium (ppm)	0.12 ± 0.04	0.10-0.20	26
Lead (ppm)	0.65 ± 0.52	0.27-2.93	26
Mercury (ppm) (a)	<0.05		26
Selenium (ppm)	0.31 ± 0.06	0.21-0.45	26
Aflatoxins (ppb) (a)	<5.0		26
Nitrate nitrogen (ppm) (b)	9.66 ± 4.49	2.50-19.0	26
Nitrite nitrogen (ppm) (b)	1.43 ± 1.50	0.10-6.10	26
BHA (ppm) (c)	4.04 ± 4.98	2.00-20.0	26
BHT (ppm) (c)	2.92 ± 2.59	1.00-13.0	26
Aerobic plate count (CFU/g) (d)	146,527 ± 143,387	6,200-420,000	26
Coliform (MPN/g) (e)	585 ± 859	<3.00-2,400	26
E. coli (MPN/g) (f)	3.83 ± 2.68	<3.00-15.00	25
E. coli (MPN/g) (g)	9.42 ± 28.79	<3.00-150.0	26
Total nitrosamines (ppb) (h)	5.30 ± 5.98	0.80-30.30	26
N-Nitrosodimethylamine (ppb) (h)	4.47 ± 5.91	0.50-30.00	26
N-Nitrosopyrrolidine (ppb) (h)	0.81 ± 0.65	0.30-2.20	26
Pesticides (ppm)			
α-BHC (a,i)	<0.01		26
β-BHC (a)	<0.02		26
γ-BHC-Lindane (a)	<0.01		26
δ-BHC (a)	<0.01		26
Heptachlor (a)	<0.01		26
Aldrin (a)	<0.01		26
Heptachlor epoxide (a)	<0.01		26
DDE (a)	<0.01		26
DDD (a)	<0.01		26
DDT (a)	<0.01		26
HCB (a)	<0.01		26
Mirex (a)	<0.01		26
Methoxychlor (j)	<0.05	0.06 (6/24/82)	26
Dieldrin (j)	<0.01	0.02 (7/27/82)	26
Endrin (a)	<0.01		26
Telodrin (a)	<0.01		26
Chlordane (a)	<0.05		26
Toxaphene (a)	<0.1		26
Estimated PCBs (a)	<0.2		26
Ronnel (a)	<0.01		26
Ethion (a)	<0.02		26
Trithion (a)	<0.05		26
Diazinon (a)	<0.1		26
Methyl parathion (a)	<0.02		26
Ethyl parathion (a)	<0.02		26
Malathion (k)	0.15 ± 0.17	<0.05-0.81	26
Endosulfan I (a)	<0.01		26
Endosulfan II (a)	<0.01		26
Endosulfan sulfate (a)	<0.03		26

(a) All values were less than the detection limit, listed in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source of contamination: soy oil and fish meal
(d) CFU = colony-forming unit
(e) MPN = most probable number
(f) Mean, standard deviation, and range exclude one high value of 150 MPN/g obtained for the lot milled on August 26, 1982.
(g) Mean, standard deviation, and range include the value listed in footnote (f).
(h) All values were corrected for percent recovery.
(i) BHC = hexachlorocyclohexane or benzene hexachloride
(j) There was one observation above the detection limit. The value and the date it was obtained are listed under the range.
(k) Fifteen lots contained more than 0.05 ppm.

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION

APPENDIX H. CHEMICAL CHARACTERIZATION

Procurement and Characterization of *dl*-Amphetamine Sulfate

dl-Amphetamine sulfate, NF, was obtained in one lot (lot no. 1087 AM) from Arenol, Inc. (Long Island City, NY). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on analyses performed in support of the *dl*-amphetamine sulfate studies are on file at the National Institute of Environmental Health Sciences.

The study chemical, a white, microcrystalline powder labeled as a racemic mixture, NF, was identified as *dl*-amphetamine sulfate by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure and with the literature spectra of *dl*-amphetamine sulfate (Figures H1 and H2) (Sadtler Standard Spectra; Warren et al., 1971).

The purity of lot no. 1087 AM was determined by elemental analysis, Karl Fischer water analysis, optical rotation measurements, potentiometric titration in glacial acetic acid of the amino group with 0.1 N perchloric acid, thin-layer chromatography, and high-performance liquid chromatography. Thin-layer chromatography was performed on silica gel plates with two solvent systems: ethyl acetate:cyclohexane:methanol:ammonium hydroxide:water (70:15:8:2:0.5) (system 1) and acetone:ammonium hydroxide (99:1) (system 2). Visualization was accomplished at 254 nm, at 366 nm with fluorescamine, and by 0.5% ninhydrin in butanol, followed by a 1 N sulfuric acid spray. High-performance liquid chromatography was performed with a μBondapak C_{18} column and a solvent ratio of aqueous 5 mM heptanesulfonic acid, sodium salt, pH adjusted to 2.02 with concentrated phosphoric acid:methanol containing 5 mM heptanesulfonic acid, sodium salt, and the same volume of concentrated phosphoric acid (75:25), with an isocratic program. Ultraviolet detection was at 254 nm.

Results of elemental analysis for carbon, hydrogen, nitrogen, and sulfur were in agreement with the theoretical values. Karl Fischer analysis indicated the presence of 0.18% water. Titration of the amino group indicated a purity of 101.5%. No impurities were detected by either thin-layer chromatographic system. High-performance liquid chromatography indicated four impurities, with a combined peak area of 0.77% relative to that of the major peak. No optical rotation was observed for a 4% aqueous solution in a 40-cm cell.

A complete battery of tests on *dl*-amphetamine sulfate were conducted to establish conformance to USP/NF XX compendial requirements. All tests indicated that this lot of chemical met specifications for identity and purity.

Stability studies performed by high-performance liquid chromatography with the system described above but with a solvent ratio of 60:40 and with propiophenone as an internal standard indicated that *dl*-amphetamine sulfate, when protected from light, was stable as a bulk chemical for at least 2 weeks at temperatures up to 60° C. During the 2-year studies, the stability of the bulk chemical was monitored by high-performance liquid chromatography and by titration; no degradation of the study material was seen throughout the studies.

Preparation and Characterization of Formulated Diets

Formulated diets were prepared by mixing the appropriate quantities of *dl*-amphetamine sulfate with feed in a blender (Table H1). Periodic analysis of the formulated diets of *dl*-amphetamine sulfate was conducted at the study laboratory and the analytical chemistry laboratory. Formulated diet samples were extracted with methanol:0.5 N hydrochloric acid (20:80). These extracts were then extracted with hexane; the aqueous portion was retained and extracted with sodium hydroxide and chloroform. The chloroform extract was centrifuged, tridecane was added as an internal standard, and *dl*-amphetamine sulfate was determined by gas chromatography performed with flame ionization detection, with a 10% Apiezon L + 2% potassium hydroxide column, and with nitrogen as the carrier

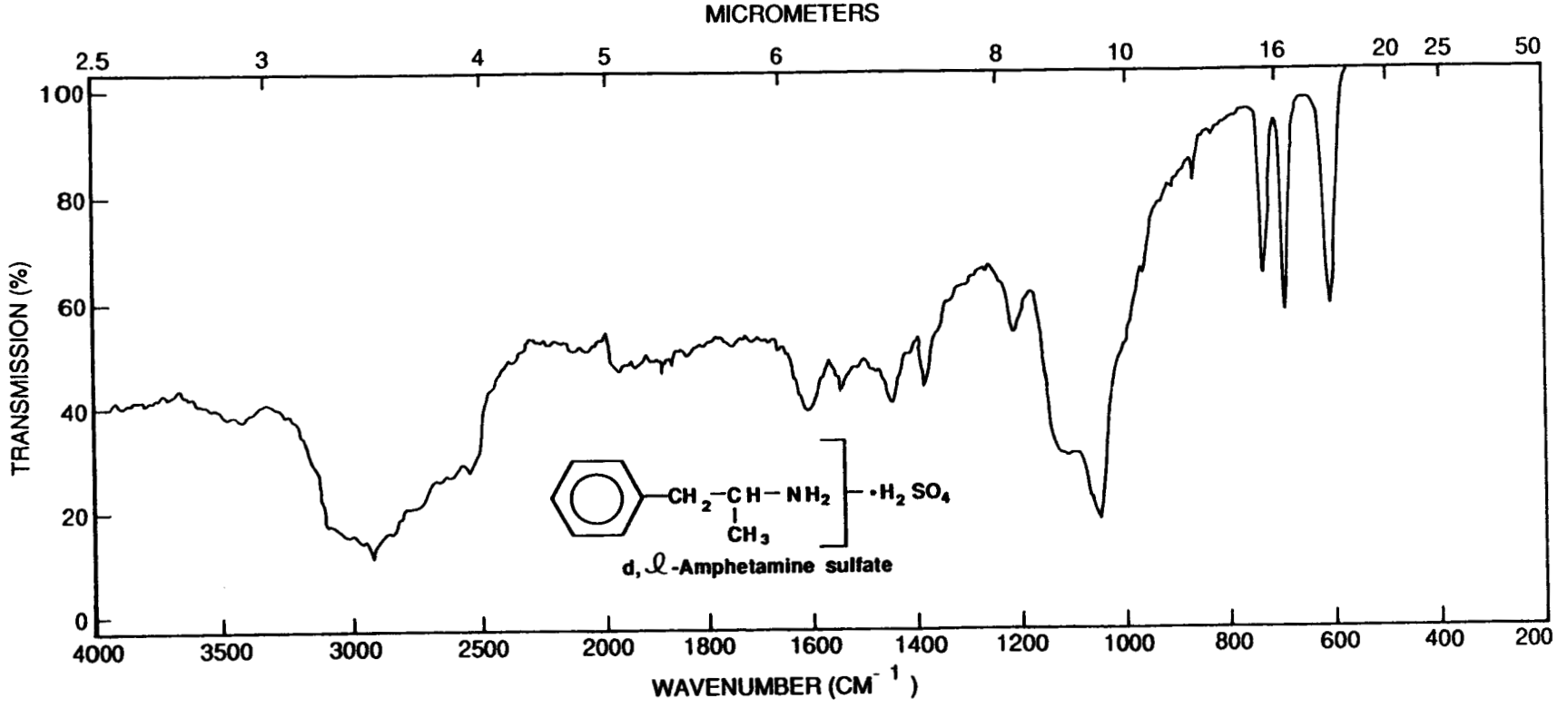

FIGURE H1. INFRARED ABSORPTION SPECTRUM OF *dl*-AMPHETAMINE SULFATE (LOT NO. 1087 AM)

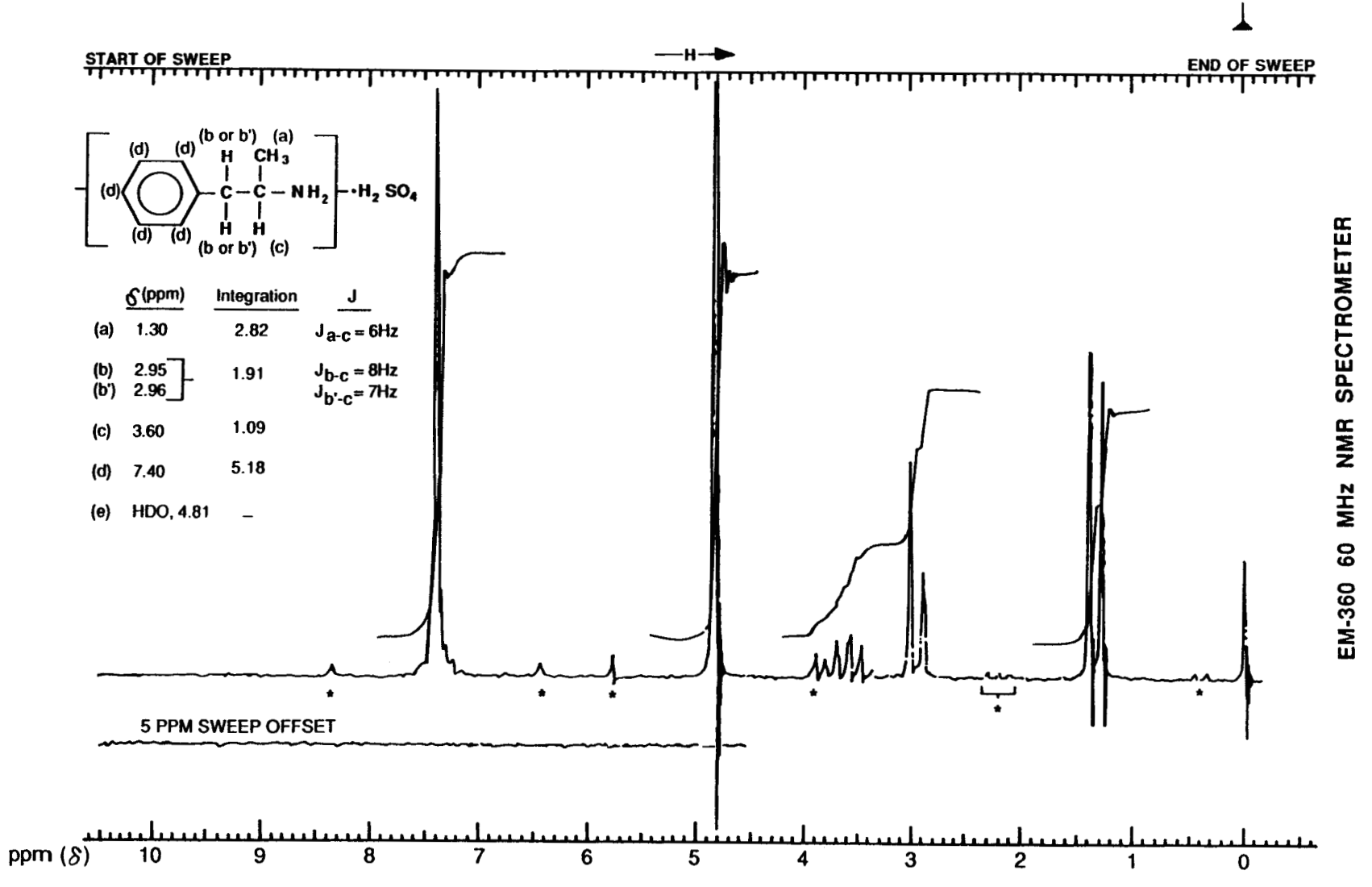

FIGURE H2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF *dl*-AMPHETAMINE SULFATE (LOT NO. 1087 AM)

TABLE H1. PREPARATION AND STORAGE OF FORMULATED DIETS IN THE FEED STUDIES OF *dl*-AMPHETAMINE SULFATE

Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation		
Appropriate amount of chemical was added to a small amount of feed in a premix bottle and shaken. Premix was layered between feed in a blender. Sample was mixed for 5 min with intensifier bar on and for 10 min with intensifier bar off	Similar to 14-d studies	Similar to 14-d studies
Maximum Storage Time		
2 wk	2 wk	3 wk
Storage Conditions		
5° C	5° C	5° C

at 30 ml/minute (system 1). This procedure was modified in June 1981 for formulated diets containing 50-250 ppm *dl*-amphetamine sulfate by changing the hexane extraction to a 0.5 N hydrochloric acid and cyclohexane extraction, extracting the aqueous layer with 10 ml of heptadecane in methylene chloride (approximately 36 µg/ml) as the internal standard, and determining the amount of *dl*-amphetamine sulfate present by gas chromatography with flame ionization detection, phenethylamine as the internal standard, a nitrogen carrier at 30 ml/minute, and a 10% Carbowax 20M + 2% potassium hydroxide column (system 2). The procedure was further modified in October 1982 by also using Waters C_{18} Sep-Pak® cartridges to purify the aqueous portion after cyclohexane extraction.

Stability and homogeneity studies were performed at the analytical chemistry laboratory with gas chromatographic system 1. *dl*-Amphetamine sulfate in feed (500 ppm) was found to be stable after storage for 2 weeks at −20° C or 5° C. Losses of 4% and 7% were seen in samples stored at 25° C or at 45° C. A stability test on formulated diets (20 ppm) was performed by the modified extraction procedure with determinations by gas chromatographic system 2. Formulated diet samples stored in sealed glass bottles at 5° C were stable for 21 days and when held under simulated animal cage conditions were stable for 3 days; samples stored at room temperature for 7, 14, or 21 days lost 4%-6% *dl*-amphetamine sulfate relative to the zero-time concentration.

Periodic analysis of formulated diet mixtures of *dl*-amphetamine sulfate was conducted at the study laboratory and the analytical chemistry laboratory. Formulated diets were analyzed once before and once during the 13-week studies. The results ranged from 90.4% to 109.8% of the target concentrations (Table H2). During the 2-year studies, the formulated diets were analyzed at least every 8 weeks. Based on the number of times that concentrations were within the specified ±10% of the target concentrations, it was estimated that the mixtures were formulated within ±10% of the target concentrations throughout the entire studies (Table H3). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated good agreement with the results from the study laboratory (Table H4).

TABLE H2. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE THIRTEEN-WEEK FEED STUDIES OF *dl*-AMPHETAMINE SULFATE

Date Mixed	Concentration of *dl*-Amphetamine Sulfate in Feed (ppm)		Determined as a Percent of Target
	Target	Determined (a)	
07/07/81-07/10/81	47	49	104.2
	94	94	100
	125	123.5	98.8
	188	183.5	97.6
	250	261	104.4
	376	392.5	104.4
	500	548	109.6
	1,000	1,054	105.4
	2,000	2,170	108.5
09/11/81-09/15/81	47	45	95.7
	94	88	93.6
	125	113	90.4
	188	189	100.5
	250	237	94.8
	376	397	105.6
	500	484	96.8
	1,000	996	99.6
	2,000	1984	99.2

(a) Results of duplicate analysis

TABLE H3. RESULTS OF ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF *dl*-AMPHETAMINE SULFATE

Date Mixed	Concentration of *dl*-Amphetamine Sulfate in Feed for Target Concentration (ppm) (a)	
	20	100
06/14/82	21.2	102
08/02/82	19.4	108
08/09/82	19.7	109
09/20/82	21.5	97.6
10/11/82	20.0	90.5
12/13/82	18.8	107
01/03/83	20.6	95.9
01/24/83	19.5	99.4
02/14/83	20.7	98.9
03/07/83	19.4	95.8
03/28/83	19.5	103
04/18/83	20.5	106
05/09/83	19.6	91.2
05/31/83	19.6	94.5
06/20/83	21.7	108
07/11/83	21.1	94.9
08/01/83	19.2	96.3
08/22/83	20.2	101
09/12/83	19.7	97.3
10/03/83	20.6	99.5
10/24/83	19.4	98.0
11/14/83	20.1	101
12/05/83	19.2	99.3
01/30/84	19.6	98.7
04/09/84	19.1	92.8
05/21/84	20.8	102
Mean (ppm)	20.0	99.5
Standard deviation	0.79	5.1
Coefficient of variation (percent)	4.0	5.1
Range (ppm)	18.8-21.7	90.5-109
Number of samples	26	26

(a) Results of duplicate analysis

TABLE H4. RESULTS OF REFEREE ANALYSIS OF FORMULATED DIETS IN THE TWO-YEAR FEED STUDIES OF *dl*-AMPHETAMINE SULFATE

Date Mixed	Target Concentration (ppm)	Determined Concentration (ppm)	
		Study Laboratory (a)	Referee Laboratory (b)
06/15/82	20	21	18
08/09/82	20	19.7	18.7
01/24/83	20	19.5	19.7
07/11/83	100	95.0	99.9
01/30/84	100	98.7	104
05/21/84	20	20.8	20.5

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

APPENDIX I
GENETIC TOXICOLOGY

METHODS

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

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

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

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

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

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

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

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 100 (more recently, 200) first-division metaphase cells were scored at each dose for the chromosomal aberration test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

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

RESULTS

The only response observed in the four strains occurred in TA98 in the presence of rat liver S9. Because of the variable nature of this response in the presence of different concentrations of the S9 mix, the overall assay call was judged to be equivocal. In cytogenetic tests with CHO cells, amphetamine sulfate did not induce SCEs (Table I2) or chromosomal aberrations (Table I3) in either the presence or the absence of Aroclor 1254-induced male Sprague Dawley rat liver S9. In the SCE test, the first trial conducted with S9 produced a significant increase in SCEs at three of the four doses tested, but this response was not repeated in two subsequent trials performed with the same doses; the test results were therefore considered negative.

TABLE I1. MUTAGENICITY OF *dl*-AMPHETAMINE SULFATE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)		
		−S9	+10% S9 (hamster)	+10% S9 (rat)
TA100	0	137 ± 1.8	143 ± 5.4	152 ± 5.8
	100	154 ± 7.1	156 ± 8.3	146 ± 8.1
	333	149 ± 15.3	173 ± 8.3	136 ± 2.5
	1,000	162 ± 11.2	166 ± 10.8	149 ± 7.1
	3,333	153 ± 8.4	167 ± 3.5	149 ± 9.4
	10,000	149 ± 9.2	159 ± 4.6	163 ± 1.2
Trial summary		Negative	Negative	Negative
Positive control (c)		266 ± 16	1,678 ± 18.1	890 ± 69.6
TA1535	0	16 ± 6.2	9 ± 1.9	6 ± 0.9
	100	15 ± 3.5	11 ± 3.9	8 ± 0.6
	333	13 ± 3.2	9 ± 1.3	6 ± 1.7
	1,000	13 ± 1.0	12 ± 1.8	10 ± 2.5
	3,333	14 ± 3.5	9 ± 2.4	6 ± 1.5
	10,000	13 ± 2.8	7 ± 0.3	11 ± 2.2
Trial summary		Negative	Negative	Negative
Positive control (c)		196 ± 7.4	268 ± 10.8	131 ± 30.2
TA1537	0	3 ± 0.3	5 ± 1.8	5 ± 0.9
	100	7 ± 0.9	6 ± 2.8	8 ± 2.0
	333	6 ± 0.9	6 ± 2.0	7 ± 0.9
	1,000	8 ± 3.2	5 ± 0.7	6 ± 0.9
	3,333	7 ± 0.9	7 ± 0.3	6 ± 2.3
	10,000	8 ± 1.2	7 ± 1.7	10 ± 1.3
Trial summary		Negative	Negative	Negative
Positive control (c)		157 ± 15.7	456 ± 19.4	238 ± 15.8

TA98	−S9	+S9 (hamster)			+S9 (rat)		
		4%	10%	20%	4%	10%	20%
0	18 ± 4.3	20 ± 1.5	25 ± 2.6	27 ± 2.6	19 ± 1.2	21 ± 1.5	19 ± 3.2
100	18 ± 4.6	31 ± 4.2	30 ± 2.4	33 ± 3.5	34 ± 3.6	33 ± 5.7	29 ± 6.1
333	21 ± 3.2	38 ± 4.1	35 ± 8.7	30 ± 2.1	44 ± 1.3	35 ± 1.3	37 ± 6.7
1,000	16 ± 0.6	31 ± 2.7	37 ± 2.6	36 ± 0.3	40 ± 1.5	30 ± 3.3	36 ± 2.2
3,333	19 ± 2.6	35 ± 3.2	40 ± 3.2	39 ± 6.1	50 ± 2.9	41 ± 1.2	38 ± 3.6
10,000	23 ± 2.6	36 ± 2.6	38 ± 3.7	41 ± 1.5	43 ± 1.5	40 ± 1.5	45 ± 0.6
Trial summary	Negative	Negative	Negative	Negative	Positive	Equivocal	Weakly positive
Positive control (c)	538 ± 124.9	(d)	1,276 ± 36.5	(d)	(d)	863 ± 31.6	(d)

(a) Study performed at SRI International. The detailed protocol and data are presented by Zeiger et al. (1987). Cells and study compound or solvent (water) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.
(d) The 10% hamster and rat S9 positive controls also served as controls for the other concentrations (4% and 20%) of S9 tested in TA98.

TABLE I2. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY AMPHETAMINE SULFATE (a)

Compound	Dose (μg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/ Chromosome (percent) (b)
−S9 (c) Summary: Negative								
Medium		50	1,050	381	0.36	7.6	26.0	
Amphetamine sulfate	5	50	1,046	388	0.37	7.8	26.0	2.23
	16	50	1,045	402	0.38	8.0	26.0	6.02
	50	50	1,048	351	0.33	7.0	26.0	−7.70
	160	50	1,048	359	0.34	7.2	26.0	−5.60
Mitomycin C	0.0005	50	1,047	500	0.47	10.0	26.0	31.61
	0.005	10	210	338	1.60	33.8	26.0	343.58
Trend test: P=0.90								
+S9 (d)								
Trial 1--Summary: Positive								
Medium		50	1,049	372	0.35	7.4	26.0	
Amphetamine sulfate	50	50	1,047	459	0.43	9.2	26.0	(e) 23.62
	160	50	1,047	449	0.42	9.0	26.0	(e) 20.93
	500	50	1,050	447	0.42	8.9	26.0	(e) 20.05
	1,600	50	1,050	399	0.38	8.0	26.0	7.16
Cyclophosphamide	0.1	50	1,048	475	0.45	9.5	26.0	27.81
	0.6	10	210	198	0.94	19.8	26.0	165.88
Trend test: P=0.27								
Trial 2--Summary: Negative								
Medium		50	1,047	396	0.37	7.7.9	26.0	
Amphetamine sulfate	50	50	1,041	412	0.39	8.2	26.0	4.64
	160	50	1,050	397	0.37	7.9	26.0	−0.04
	500	50	1,049	438	0.41	8.8	26.0	10.40
	1,600	50	1,043	400	0.38	8.0	26.0	1.40
Cyclophosphamide	0.1	50	1,049	547	0.52	10.9	26.0	37.87
	0.6	10	208	238	1.14	23.8	26.0	202.53
Trend test: P=0.53								
Trial 3--Summary: Negative								
Medium		50	1,044	375	0.35	7.5	26.0	
Amphetamine sulfate	50	50	1,045	388	0.37	7.8	26.0	3.37
	160	50	1,050	391	0.37	7.8	26.0	3.67
	500	50	1,041	399	0.38	8.0	26.0	6.71
	1,600	50	1,049	408	0.38	8.2	26.0	8.28
Cyclophosphamide	0.15	50	1,044	499	0.47	10.0	26.0	33.07
	0.6	10	207	182	0.87	18.2	26.0	144.78
Trend test: P=0.12								

TABLE I2. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY AMPHETAMINE SULFATE (Continued)

(a) Study performed at Environmental Health Research and Testing, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1987). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (medium) as described in (c) and (d) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) Percentage change in the value of SCEs/chromosome for exposed culture compared with that for solvent control culture. An increase of 20% or more was considered to be a significant response.
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(e) More than a 20% increase over solvent controls

TABLE 13. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY AMPHETAMINE SULFATE (a)

-S9 (b) Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	+S9 (c) Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time: 12 hours					Harvest time: 13 hours				
Medium					Medium				
	200	3	0.02	1.5	200	2	0.01	1.0	
Amphetamine sulfate					Amphetamine sulfate				
300	200	1	0.01	0.5	500	200	3	0.02	1.5
500	200	2	0.01	1.0	1,000	200	2	0.01	1.0
1,000	200	6	0.03	2.5	1,600	200	3	0.02	1.5
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.0625	200	39	0.20	15.0	2.5	200	22	0.11	10.5
0.25	50	22	0.44	36.0	7.5	50	21	0.42	36.0
Trend test: P=0.16					Trend test: P=0.40				

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

APPENDIX J
ORGAN WEIGHTS OF RATS AND MICE IN THE FOURTEEN-DAY AND THIRTEEN-WEEK FEED STUDIES OF *dl*-AMPHETAMINE SULFATE

TABLE J1. LIVER WEIGHTS OF RATS IN THE FOURTEEN-DAY FEED STUDIES OF *dl*-AMPHETAMINE SULFATE (a)

	Control	47 ppm	94 ppm	188 ppm	375 ppm	750 ppm
MALE						
Body weight (grams)	196 ± 7	197 ± 3	195 ± 7	199 ± 8	189 ± 6	173 ± 7
Absolute	9,592 ± 341	9,610 ± 128	10,148 ± 491	9,690 ± 352	9,978 ± 575	9,934 ± 540
Relative	49.0 ± 0.80	48.7 ± 0.63	51.9 ± 1.16	48.8 ± 0.75	52.9 ± 2.53	**57.4 ± 1.64
FEMALE						
Body weight (grams)	137 ± 2	143 ± 4	133 ± 2	137 ± 2	135 ± 2	**121 ± 5
Absolute	5,794 ± 264	6,226 ± 310	5,810 ± 121	6,374 ± 205	*6,590 ± 215	6,184 ± 209
Relative	42.4 ± 1.62	43.5 ± 1.03	43.5 ± 0.68	*46.6 ± 1.12	*48.9 ± 1.70	**51.4 ± 0.83

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

TABLE J2. ORGAN WEIGHTS OF RATS IN THE THIRTEEN-WEEK FEED STUDIES OF *dl*-AMPHETAMINE SULFATE (a)

Organ	Control	47 ppm	94 ppm	188 ppm	375 ppm	750 ppm
MALE						
Body weight (grams)	359 ± 7	**326 ± 8	*332 ± 7	**321 ± 12	**294 ± 7	**223 ± 5
Brain						
Absolute	1,912 ± 16	1,891 ± 17	1,910 ± 17	1,929 ± 20	1,958 ± 17	1,900 ± 12
Relative	5.3 ± 0.08	**5.8 ± 0.10	**5.8 ± 0.11	**6.1 ± 0.20	**6.7 ± 0.17	**8.5 ± 0.14
Heart						
Absolute	947 ± 22	891 ± 20	*892 ± 14	**845 ± 29	**797 ± 27	**618 ± 17
Relative	2.6 ± 0.04	2.7 ± 0.04	2.7 ± 0.06	2.6 ± 0.06	2.7 ± 0.07	2.8 ± 0.06
Right kidney						
Absolute	1,318 ± 37	*1,187 ± 39	*1,201 ± 18	*1,195 ± 34	**1,133 ± 34	**911 ± 26
Relative	3.7 ± 0.07	3.6 ± 0.06	3.6 ± 0.09	3.7 ± 0.05	3.9 ± 0.08	**4.1 ± 0.06
Liver						
Absolute	12,880 ± 420	*11,190 ± 410	11,920 ± 260	12,140 ± 470	**10,150 ± 380	**6,910 ± 340
Relative	35.9 ± 0.86	34.4 ± 0.99	36.1 ± 1.10	37.8 ± 0.82	34.6 ± 1.37	**30.8 ± 1.07
Lung						
Absolute	1,691 ± 37	1,609 ± 44	1,644 ± 33	1,643 ± 53	**1,487 ± 50	**1,217 ± 38
Relative	4.7 ± 0.07	*5.0 ± 0.09	5.0 ± 0.11	**5.1 ± 0.12	*5.1 ± 0.15	**5.5 ± 0.17
Thymus						
Absolute	(b) 375 ± 15	**309 ± 15	**295 ± 8	**274 ± 11	**256 ± 23	**151 ± 13
Relative	(b) 1.05 ± 0.040	0.95 ± 0.053	**0.89 ± 0.023	**0.86 ± 0.037	**0.87 ± 0.076	**0.67 ± 0.051
FEMALE						
Body weight (grams)	210 ± 2	**197 ± 3	**188 ± 3	**178 ± 4	**156 ± 4	**142 ± 4
Brain						
Absolute	1,804 ± 57	1,828 ± 64	**1,942 ± 23	**1,952 ± 25	*1,928 ± 25	*1,887 ± 44
Relative	8.6 ± 0.28	*9.3 ± 0.30	**10.3 ± 0.21	**11.0 ± 0.26	**12.4 ± 0.28	**13.3 ± 0.35
Heart						
Absolute	683 ± 19	*625 ± 12	**603 ± 12	**558 ± 16	**538 ± 16	**539 ± 10
Relative	3.3 ± 0.09	3.2 ± 0.06	3.2 ± 0.05	3.1 ± 0.08	3.5 ± 0.10	**3.8 ± 0.11
Right kidney						
Absolute	762 ± 21	736 ± 9	**684 ± 16	**670 ± 23	**667 ± 20	**672 ± 13
Relative	3.6 ± 0.10	3.7 ± 0.06	3.6 ± 0.05	3.8 ± 0.08	**4.3 ± 0.08	**4.7 ± 0.13
Liver						
Absolute	6,848 ± 202	6,290 ± 130	**5,499 ± 165	**5,386 ± 186	**5,378 ± 170	**5,215 ± 154
Relative	32.7 ± 0.88	31.9 ± 0.45	29.2 ± 0.74	30.2 ± 0.60	34.5 ± 1.02	*36.7 ± 1.01
Lung						
Absolute	1,299 ± 27	1,277 ± 21	1,301 ± 19	*1,166 ± 38	**(c) 1,180 ± 26	**1,149 ± 41
Relative	6.2 ± 0.11	6.5 ± 0.14	**6.9 ± 0.10	*6.5 ± 0.16	**(c) 7.5 ± 0.24	**8.1 ± 0.18
Thymus						
Absolute	286 ± 10	285 ± 8	294 ± 11	**241 ± 7	**175 ± 6	**(b) 111 ± 12
Relative	1.37 ± 0.055	1.44 ± 0.035	1.56 ± 0.049	1.36 ± 0.049	*1.13 ± 0.044	**(b) 0.76 ± 0.069

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

TABLE J3. ORGAN WEIGHTS OF MICE IN THE FOURTEEN-DAY FEED STUDIES OF *dl*-AMPHETAMINE SULFATE (a)

Organ	Control	125 ppm	250 ppm	500 ppm	1,000 ppm	2,000 ppm
MALE						
Number weighed	5	5	5	5	0	4
Body weight (grams)	26.9 ± 1.32	25.3 ± 1.07	26.4 ± 1.06	26.0 ± 0.72		24.3 ± 1.31
Brain						
Absolute	544 ± 5	*518 ± 6	536 ± 10	536 ± 12		*500 ± 14
Relative	20.4 ± 0.89	20.6 ± 0.83	20.4 ± 0.70	20.7 ± 0.78		20.7 ± 0.66
Heart						
Absolute	170 ± 14	142 ± 10	166 ± 7	166 ± 11		153 ± 9
Relative	6.3 ± 0.38	5.6 ± 0.42	6.3 ± 0.13	6.4 ± 0.44		6.3 ± 0.09
Right kidney						
Absolute	274 ± 16	260 ± 17	262 ± 12	272 ± 10		275 ± 17
Relative	10.2 ± 0.21	10.3 ± 0.34	9.9 ± 0.30	10.5 ± 0.45		*11.3 ± 0.10
Liver						
Absolute	1,620 ± 85	1,616 ± 42	1,756 ± 88	1,680 ± 39		1,830 ± 91
Relative	60.3 ± 1.59	64.1 ± 1.14	*66.4 ± 1.43	*64.6 ± 0.36		**75.4 ± 1.35
Lung						
Absolute	268 ± 15	254 ± 10	256 ± 7	266 ± 2		265 ± 6
Relative	10.0 ± 0.47	10.1 ± 0.48	9.7 ± 0.40	10.3 ± 0.34		11.0 ± 0.72
Thymus						
Absolute	64.0 ± 4.00	58.0 ± 5.83	68.0 ± 6.63	68.0 ± 8.60		*27.5 ± 8.54
Relative	2.4 ± 0.10	2.3 ± 0.31	2.6 ± 0.17	2.6 ± 0.27		1.1 ± 0.32
FEMALE						
Number weighed	5	5	5	5	5	5
Body weight (grams)	22.0 ± 0.29	21.8 ± 0.49	*20.0 ± 0.43	*19.9 ± 0.64	*20.3 ± 0.39	*21.2 ± 0.33
Brain						
Absolute	536 ± 9	512 ± 9	526 ± 10	534 ± 9	536 ± 14	538 ± 14
Relative	24.4 ± 0.27	23.5 ± 0.61	26.3 ± 0.81	26.9 ± 0.92	26.4 ± 1.01	25.3 ± 0.47
Heart						
Absolute	164 ± 8	*140 ± 5	*128 ± 8	**120 ± 5	*136 ± 8	*128 ± 10
Relative	7.5 ± 0.40	6.5 ± 0.37	6.4 ± 0.39	*6.0 ± 0.13	6.7 ± 0.52	*6.0 ± 0.48
Right kidney						
Absolute	206 ± 4	190 ± 8	172 ± 10	178 ± 12	190 ± 3	208 ± 12
Relative	9.4 ± 0.28	8.7 ± 0.37	8.6 ± 0.30	8.9 ± 0.48	9.4 ± 0.22	9.8 ± 0.46
Liver						
Absolute	1,306 ± 17	1,166 ± 49	1,128 ± 50	1,148 ± 48	1,286 ± 24	1,460 ± 27
Relative	59.5 ± 0.30	53.6 ± 2.40	56.2 ± 1.96	57.7 ± 1.23	63.3 ± 1.18	*68.8 ± 1.20
Lung						
Absolute	256 ± 7	246 ± 12	220 ± 6	240 ± 12	240 ± 11	244 ± 12
Relative	11.7 ± 0.30	11.3 ± 0.39	11.0 ± 0.45	12.0 ± 0.30	11.9 ± 0.73	11.5 ± 0.56
Thymus						
Absolute	82.0 ± 4.90	86.0 ± 2.45	86.0 ± 6.78	86.0 ± 2.45	72.0 ± 4.90	84.0 ± 7.48
Relative	3.7 ± 0.25	4.0 ± 0.16	4.3 ± 0.34	4.3 ± 0.21	3.6 ± 0.30	4.0 ± 0.33

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

TABLE J4. ORGAN WEIGHTS OF MICE IN THE THIRTEEN-WEEK FEED STUDIES OF *dl*-AMPHETAMINE SULFATE (a)

Organ	Control	125 ppm	250 ppm	500 ppm	1,000 ppm	2,000 ppm
MALE						
Number weighed (b)	10	10	10	2	6	4
Body weight (grams)	33.1 ± 0.42	*30.8 ± 0.80	**27.0 ± 0.61	**25.3 ± 0.35	**(c) 23.1 ± 0.46	**23.5 ± 0.48
Brain						
Absolute	504 ± 15	485 ± 13	489 ± 26	537 ± 5	(c) 496 ± 8	536 ± 27
Relative	15.2 ± 0.47	15.8 ± 0.51	**18.3 ± 1.00	**21.3 ± 0.49	**(c) 21.6 ± 0.63	**23.2 ± 1.61
Heart						
Absolute	171 ± 4	*149 ± 6	**133 ± 4	*144 ± 16	**137 ± 7	**145 ± 3
Relative	5.1 ± 0.11	4.8 ± 0.11	4.9 ± 0.16	5.7 ± 0.71	*6.1 ± 0.34	*6.2 ± 0.22
Right kidney						
Absolute	328 ± 8	**272 ± 11	**248 ± 11	*272 ± 17	**261 ± 13	**282 ± 12
Relative	9.9 ± 0.16	8.8 ± 0.25	9.2 ± 0.35	10.8 ± 0.51	*11.9 ± 0.44	12.0 ± 0.73
Liver						
Absolute	1,618 ± 32	**1,357 ± 60	**1,286 ± 80	*1,245 ± 171	**1,159 ± 48	**1,220 ± 121
Relative	48.9 ± 0.94	43.9 ± 1.19	47.8 ± 2.90	49.2 ± 6.07	52.1 ± 1.83	52.0 ± 5.02
Lung						
Absolute	257 ± 8	(d) 253 ± 9	244 ± 6	224 ± 17	*222 ± 10	**(e) 211 ± 8
Relative	7.8 ± 0.26	(d) 8.3 ± 0.18	**9.0 ± 0.25	8.8 ± 0.53	**9.9 ± 0.57	*(e) 9.1 ± 0.34
Thymus						
Absolute	(f) 47.9 ± 3.48	(f) 63.1 ± 2.56	57.6 ± 3.79	37.0 ± 6.00	39.6 ± 5.07	43.8 ± 4.66
Relative	(f) 1.5 ± 0.11	*(f) 2.1 ± 0.12	**2.1 ± 0.14	1.5 ± 0.22	1.8 ± 0.26	1.9 ± 0.22
FEMALE						
Number weighed	10	10	10	10	10	3
Body weight (grams)	24.7 ± 0.45	**21.6 ± 0.45	**20.7 ± 0.27	**20.9 ± 0.21	**21.3 ± 0.31	**19.9 ± 0.76
Brain						
Absolute	517 ± 10	509 ± 11	530 ± 5	539 ± 7	521 ± 14	504 ± 20
Relative	21.0 ± 0.50	**23.6 ± 0.55	**25.7 ± 0.42	**25.7 ± 0.29	**24.6 ± 0.85	*25.3 ± 0.25
Heart						
Absolute	142 ± 4	133 ± 6	**124 ± 5	**124 ± 4	**123 ± 5	122 ± 19
Relative	5.8 ± 0.21	6.2 ± 0.18	6.0 ± 0.23	5.9 ± 0.20	5.8 ± 0.21	6.1 ± 0.77
Right kidney						
Absolute	204 ± 7	203 ± 8	198 ± 6	190 ± 7	195 ± 9	211 ± 6
Relative	8.2 ± 0.24	*9.3 ± 0.26	**9.5 ± 0.27	*9.1 ± 0.33	*9.2 ± 0.36	**10.6 ± 0.29
Liver						
Absolute	1,268 ± 41	*1,147 ± 42	**1,092 ± 31	**1,000 ± 28	**991 ± 53	**1,062 ± 29
Relative	51.3 ± 1.48	52.9 ± 1.17	52.8 ± 1.88	47.8 ± 1.40	46.4 ± 1.83	53.5 ± 2.49
Lung						
Absolute	234 ± 9	244 ± 10	225 ± 7	230 ± 12	238 ± 14	217 ± 12
Relative	9.5 ± 0.34	*11.3 ± 0.51	*10.9 ± 0.39	*11.0 ± 0.54	*11.2 ± 0.68	10.9 ± 0.52
Thymus						
Absolute	69.8 ± 5.05	66.1 ± 2.40	*58.4 ± 3.13	60.0 ± 2.85	*59.1 ± 2.91	53.3 ± 9.96
Relative	2.8 ± 0.21	3.1 ± 0.14	2.8 ± 0.14	2.9 ± 0.13	2.8 ± 0.13	2.7 ± 0.39

(a) Mean ± standard error in milligrams (absolute) or milligrams per gram (relative); P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Unless otherwise specified
(c) Seven brains were weighed.
(d) Lungs of nine animals were weighed.
(e) Lungs of three animals were weighed.
(f) Nine thymuses were weighed.
*P<0.05
**P<0.01

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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Dermal)
206	1,2-Dibromo-3-chloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butyl Benzyl Phthalate
214	Caprolactam
215	Bisphenol A
216	11-Aminoundecanoic Acid
217	Di(2-ethylhexyl)phthalate
219	2,6-Dichloro-p-phenylenediamine
220	C.I. Acid Red 14
221	Locust Bean Gum
222	C.I. Disperse Yellow 3
223	Eugenol
224	Tara Gum
225	D & C Red No. 9
226	C.I. Solvent Yellow 14
227	Gum Arabic
228	Vinylidene Chloride
229	Guar Gum
230	Agar
231	Stannous Chloride
232	Pentachloroethane
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	*D*-Mannitol
237	1,1,1,2-Tetrachloroethane
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
243	Trichloroethylene (Rats and Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
246	Chrysotile Asbestos (Hamsters)
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos (Hamsters)
250	Benzyl Acetate
251	2,4- & 2,6-Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
254	Dichloromethane (Methylene Chloride)
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	1,2-Propylene Oxide
269	1,3-Dichloropropane (Telone II®)
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four Rat Strains)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
277	Tremolite
278	2,6-Xylidine
279	Amosite Asbestos
280	Crocidolite Asbestos
281	HC Red No. 3
282	Chlorodibromomethane
284	Diallylphthalate (Rats)
285	C.I. Basic Red 9 Monohydrochloride
287	Dimethyl Hydrogen Phosphite
288	1,3-Butadiene
289	Benzene
291	Isophorone
293	HC Blue No. 2
294	Chlorinated Trisodium Phosphate
295	Chrysotile Asbestos (Rats)
296	Tetrakis(hydroxymethyl) phosphonium Sulfate & Tetrakis(hydroxymethyl) phosphonium Chloride
298	Dimethyl Morpholinophosphoramidate
299	C.I. Disperse Blue 1
300	3-Chloro-2-methylpropene
301	*o*-Phenylphenol
303	4-Vinylcyclohexene
304	Chlorendic Acid
305	Chlorinated Paraffins (C_{23}, 43% chlorine)
306	Dichloromethane (Methylene Chloride)
307	Ephedrine Sulfate
308	Chlorinated Paraffins (C_{12}, 60% chlorine)
309	Decabromodiphenyl Oxide
310	Marine Diesel Fuel and JP-5 Navy Fuel
311	Tetrachloroethylene (Inhalation)
312	*n*-Butyl Chloride
313	Mirex
314	Methyl Methacrylate
315	Oxytetracycline Hydrochloride
316	1-Chloro-2-methylpropene
317	Chlorpheniramine Maleate
318	Ampicillin Trihydrate
319	1,4-Dichlorobenzene
320	Rotenone
321	Bromodichloromethane
322	Phenylephrine Hydrochloride
323	Dimethyl Methylphosphonate
324	Boric Acid
325	Pentachloronitrobenzene
326	Ethylene Oxide
327	Xylenes (Mixed)
328	Methyl Carbamate
329	1,2-Epoxybutane
330	4-Hexylresorcinol
331	Malonaldehyde, Sodium Salt
332	2-Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3
336	Penicillin VK
337	Nitrofurazone

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338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
340	Iodinated Glycerol
341	Nitrofurantoin
342	Dichlorvos
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
346	Chloroethane
347	D-Limonene
348	*a*-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
351	*p*-Chloroaniline Hydrochloride
352	N-Methylolacrylamide
353	2,4-Dichlorophenol
354	Dimethoxane
355	Diphenhydramine Hydrochloride
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
360	N,N-Dimethylaniline
361	Hexachloroethane
362	4-Vinyl-1-Cyclohexene Diepoxide
363	Bromoethane (Ethyl Bromide)
364	Rhodamine 6G (C.I. Basic Red 1)
365	Pentaerythritol Tetranitrate
366	Hydroquinone
367	Phenylbutazone
368	Nalidixic Acid
369	Alpha-Methylbenzyl Alcohol
370	Benzofuran
371	Toluene
372	3,3'-Dimethoxybenzidine Dihydrochloride
373	Succinic Anhydride
374	Glycidol
375	Vinyl Toluene
376	Allyl Glycidyl Ether
377	*o*-Chlorobenzalmalononitrile
378	Benzaldehyde
379	2-Chloroacetophenone
380	Epinephrine Hydrochloride
381	*d*-Carvone
382	Furfural
386	Tetranitromethane
393	Sodium Fluoride

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