NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 373

TOXICOLOGY AND CARCINOGENESIS STUDIES OF SUCCINIC ANHYDRIDE

(CAS NO. 108-30-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE 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. All NTP toxicology and carcinogenesis studies are subjected to a comprehensive audit before being presented for public review. This Technical Report has been reviewed and approved by the NTP Board of Scientific Counselors' Peer Review Panel in public session; the interpretations described herein represent the official scientific position of the NTP.

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 SUCCINIC ANHYDRIDE

(CAS NO. 108-30-5)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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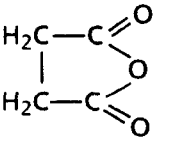

SUCCINIC ANHYDRIDE

CAS No. 108-30-5

$C_4H_4O_3$ Molecular weight 100.1

Synonyms: butanedioic anhydride; dihydro-2,5-furandione; 2,5-diketotetrahydrofuran; succinic acid anhydride; succinyl anhydride; succinyl oxide; tetrahydro-2,5-dioxofuran

ABSTRACT

Succinic anhydride, a food additive, is also used in the manufacture of polymeric materials, pharmaceuticals, and agricultural and industrial chemicals. Toxicology and carcinogenesis studies were conducted by administering suspensions of succinic anhydride (97% pure) in corn oil by gavage to groups of F344/N rats and B6C3F$_1$ mice of each sex for 16 or 20 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and Chinese hamster ovary (CHO) cells.

Twenty-Day or Sixteen-Day and Thirteen-Week Studies: In the 20-day studies in rats, doses of succinic anhydride given on 14 exposure days ranged from 47 to 750 mg/kg. Compound-related deaths occurred in the groups of males that received 375 mg/kg or higher doses and in females that received 187 mg/kg or higher doses. Necrosis and inflammation of the upper respiratory tract were seen in 3/10 male and 3/10 female rats given 750 mg/kg and 2/10 female rats given 375 mg/kg.

In the 16-day studies in mice, doses of succinic anhydride given on 12 exposure days ranged from 219 to 3,500 mg/kg. All animals that received 875 mg/kg or higher doses of succinic anhydride died before the end of the studies. No compound-related lesions were seen in male or female mice examined from the 438 mg/kg dose group.

In the 13-week studies in rats, doses of succinic anhydride ranged from 25 to 400 mg/kg for males and from 12.5 to 200 mg/kg for females. Deaths of 8/10 male rats that received 400 mg/kg and 4/10 males and 5/10 females that received 200 mg/kg were compound related. At necropsy, the mean body weights of male rats that received 200 or 400 mg/kg were 9% or 15% lower than that of vehicle controls, whereas the mean body weights of dosed and vehicle control female rats were similar. No compound-related gross or microscopic lesions were observed.

In the 13-week studies in mice, doses of succinic anhydride ranged from 37 to 600 mg/kg. All 10 males and 8/10 females that received 600 mg/kg and 2/10 males and 2/10 females that received 300 mg/kg died before the end of the studies. The final mean body weights of mice that received 150 or 300 mg/kg were 13% or 9% lower than that of vehicle controls for males and 8% or 7% lower for females. Mild inflammation of the stomach was observed in 7/10 male mice that received 150 mg/kg and 5/10 males that received 300 mg/kg compared with 2/10 vehicle controls.

Based primarily on the effects of administration of succinic anhydride on survival and mean body weights of rats and mice, doses for the 2-year studies were 0, 50, or 100 mg/kg to groups of 60 rats of each sex; 0, 38, or 75 mg/kg to groups of 50 male mice; and 0, 75, or 150 mg/kg to groups of 50 female mice. Succinic anhydride was administered as a suspension in corn oil by gavage, 5 days per week for 103 weeks.

Body Weights and Survival in the Two-Year Studies: Mean body weights of high dose rats were 5%-11% lower than those of vehicle controls during the second year of the studies. No significant differences in survival after 2 years were observed between any groups of rats of either sex (male: vehicle control, 36/60; low dose, 33/60; high dose, 32/60; female: 31/60; 27/60; 27/60). For mice, mean body weights of high dose males were generally 5%-12% lower than those of vehicle controls throughout the study. Mean body weights of high dose female mice were 10%-32% lower than those of vehicle controls; mean body weights of low dose female mice were 10%-20% lower than those of vehicle controls. The survival of high dose male mice was significantly greater than that of vehicle controls after week 77 (survival after 2 years--male: 27/50; 30/50; 42/50; female: 37/50; 38/50; 41/50). No other differences in survival were observed between any groups of mice of either sex.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: At no site in rats or mice was there a chemical-related increase in the incidence of nonneoplastic or neoplastic lesions. A sufficient number of animals in each dose group lived long enough to allow evaluation of the potential carcinogenicity of succinic anhydride.

Genetic Toxicology: Succinic anhydride was not mutagenic in *S. typhimurium* with or without exogenous metabolic activation. The chemical did not induce sister chromatid exchanges or chromosomal aberrations in cultured CHO cells in the presence or absence of exogenous metabolic activation.

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of succinic anhydride for male or female F344/N rats given 50 or 100 mg/kg succinic anhydride. There was *no evidence of carcinogenic activity* for male B6C3F$_1$ mice given 38 or 75 mg/kg succinic anhydride or for female B6C3F$_1$ mice given 75 or 150 mg/kg.

SUMMARY OF THE TWO-YEAR GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Doses			
0, 50, or 100 mg/kg succinic anhydride in corn oil, 5 d/wk	0, 50, or 100 mg/kg succinic anhydride in corn oil, 5 d/wk	0, 38, or 75 mg/kg succinic anhydride in corn oil, 5 d/wk	0, 75, or 150 mg/kg succinic anhydride in corn oil, 5 d/wk
Body weights in the 2-year study			
High dose lower than vehicle controls	High dose lower than vehicle controls	High dose lower than vehicle controls	Dosed lower than vehicle controls
Survival in the 2-year study			
36/60; 33/60; 32/60	31/60; 27/60; 27/60	27/50; 30/50; 42/50	37/50; 38/50; 41/50
Nonneoplastic effects			
None	None	None	None
Neoplastic effects			
None	None	None	None
Level of evidence of carcinogenic activity			
No evidence	No evidence	No evidence	No evidence

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 5.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 8.

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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

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

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

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

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

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

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Succinic Anhydride is based on 13-week studies that began in March 1980 and ended in June 1980 or that began in October 1981 and ended in January 1982 (rats only) and on 2-year studies that began in August 1982 and ended in August 1984 (rats) or that began in May 1981 and ended in May 1983 (mice) at Microbiological Associates, Inc. (Bethesda, MD).

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The members of the Peer Review Panel who evaluated the draft Technical Report on succinic anhydride on June 27, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF SUCCINIC ANHYDRIDE

On June 27, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of succinic anhydride received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

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

Because Dr. Newberne, a principal reviewer, was unable to attend the meeting, Dr. L. Hart, NIEHS, read his review into the record. Dr. Newberne agreed with the conclusions but questioned the gavage route of exposure. Dr. Melnick said the route used was selected because that is the route of human exposure. Dr. Newberne stated that the usage data were available and that including the weight or percentage used in foods would be helpful.

Dr. Gold, the second principal reviewer, agreed with the conclusions. She commented on finding oil droplets in the lungs of some rats and mice during retrospective examination. She suggested that the possible role of gavage accidents in early deaths or moribund states needed further discussion and that it should be clearly stated that survival was considered adequate to detect a carcinogenic effect. Dr. Melnick pointed out that there were sufficient numbers of animals to evaluate carcinogenicity, as stated in the Discussion, Results and Abstract. Dr. Gold also thought that more information on human exposure should be added, including more recent estimates on worker exposure from the NIOSH National Occupational Exposure Survey (NOES). Dr. Melnick said that the NOES data would be included in the Report.

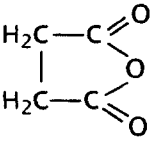
Dr. McKnight, the third principal reviewer, agreed with the conclusions. She said that she could support a conclusion of equivocal evidence of carcinogenic activity in male rats based on a statistically significant positive dose-related trend in the incidence of keratoacanthomas of the skin. Dr. Melnick explained that the incidence in high dose animals was not significantly different from vehicle control values and that the incidence was slightly lower than the highest historical incidence observed in male corn oil gavage control F344 rats. With regard to early deaths due to to gavage accidents, Dr. McKnight noted there was a clear dose-related trend, presumably because dosed animals become harder to handle and are thus more prone to accident. Thus, she proposed that these "accidental" deaths could be classified as deaths due to toxic effects of the chemical as it is administered under study conditions. Dr. Melnick said an additional survival curve of total survival without censoring for gavage accidents would be included.

Dr. Gold moved that the Technical Report on succinic anhydride be accepted with the conclusions as written for male and female rats and mice, no evidence of carcinogenic activity. Dr. Popp seconded the motion, which was accepted by seven yes votes and one abstention (Dr. McKnight).

I. INTRODUCTION

Properties, Production, and Use
Animal Toxicity
Developmental Toxicity
Carcinogenicity
Genetic Toxicology
Study Rationale

I. INTRODUCTION



SUCCINIC ANHYDRIDE

CAS No. 108-30-5

$C_4H_4O_3$ Molecular weight 100.1

Synonyms: butanedioic anhydride; dihydro-2,5-furandione; 2,5-diketotetrahydrofuran; succinic acid anhydride; succinyl anhydride; succinyl oxide; tetrahydro-2,5-dioxofuran

Properties, Production, and Use

Succinic anhydride is a colorless and odorless organic solid (melting point 119.6° C) that is soluble in ethanol, chloroform, and carbon tetrachloride but only very slightly soluble in water. In boiling water, succinic anhydride is converted almost instantaneously to succinic acid, an endogenous metabolic intermediate (Winstrom, 1983), whereas at 21° C, hydrolysis of an aqueous suspension of succinic anhydride requires 30 minutes (Furia, 1972). The half-life for succinic anhydride in carbonate buffer (pH 7.4) was reported to be 2 minutes (Brown et al., 1978). Succinic anhydride has been produced by hydrogenation of maleic anhydride; by dehydration of succinic acid at elevated temperatures and pressure; by treating succinic acid with diketene, succinyl chloride, or acetic anhydride; or by reacting the diethyl ester with boron chloride (IARC, 1977; Winstrom, 1983). Approximately 19 million pounds (8.6×10^6 kg) of succinic anhydride derivatives was produced in the United States in 1987 (USITC, 1988).

Succinic anhydride is used in the manufacture of polymeric materials (adhesives; alkyd, casting, molding, and laminating resins; cross-linking agents; curing agents; and specialty elastomers), pharmaceuticals (chemotherapeutic agents, vitamins A and B_6, antihemorrhagic drugs, anticonvulsants, muscle relaxants, and steroids), and agricultural chemicals (plant growth regulators, insecticides, and herbicides) and as a chemical intermediate in the manufacture of dyestuffs, photographic chemicals, surface-active agents, lubricant additives, and fire retardants for paper (IARC, 1977; Winstrom, 1983). Succinic anhydride may be used as a food starch modifier at levels up to 4% in food (CFR, 1977); there was no reported use of succinic anhydride as a food additive in the United States during the year 1987 (FDA unpublished data). Approximately 3,060 workers in the United States are potentially exposed to succinic anhydride, as estimated from data complied from the National Occupational Exposure Survey (NIOSH unpublished data).

Succinylation of protein amino groups or of other macromolecules by succinic anhydride is a well-established procedure in biochemistry and protein physical chemistry (Klotz, 1967).

Animal Toxicity

The oral LD_{50} of succinic anhydride suspended in corn oil is 2,160 mg/kg in male Sprague Dawley rats and 1,510 mg/kg in female rats (USEPA, 1982). The LD_{50} of succinic anhydride in CD®-1 mice is 0.62 mmol/kg per day (62.1 mg/kg per day) when administered as three consecutive daily intraperitoneal injections in 0.5% carboxymethyl cellulose (Fabro et al., 1982). In the red-winged blackbird, the oral LD_{50} of succinic anhydride is 96 mg/kg (Schafer et al., 1983).

Succinic anhydride is an eye irritant. Carpenter and Smyth (1946) developed a system to score injury to the rabbit eye 18-24 hours after application of a test material. Application of 5 µl of a solution of 15% succinic anhydride in propylene glycol to the center of the cornea (while the lids were retracted) caused necrosis that covered

about 75% of the cornea. On a grading system of 1 (least severe) to 10 (most severe), the severity of succinic anhydride was rated as 8.

Succinic anhydride inhibited the motility of *Proteus mirabilis* and *Azospirillum brasilense* and the growth of *Bacillus thuringiensis* (Lenz and Sussmuth, 1987). Succinylation of biologic membranes by succinic anhydride may impair membrane transport properties of Ehrlich ascites tumor cells, intact yeast cells, and erythrocytes (Brossmer et al., 1973; Bohn and Brossmer, 1974; Brossmer and Bohn, 1974).

Developmental Toxicity

In an abstract, Fabro et al. (1976) reported that intraperitoneal injections of succinic anhydride (50 mg/kg) given to CD®-1 mice on days 8-10 of gestation produced a teratogenic response. No increases in resorptions or decreases in birth weight occurred; however, 23% of the viable pups exhibited branched ribs, fused vertebrae, or cleft palate.

In a study of several anhydrides, fetal abnormalities were observed in CD®-1 mice administered succinic anhydride by intraperitoneal injection on gestational days 8-10 or 11-13 (Brown et al., 1978). The minimally effective dose of succinic anhydride which produced a significant increase in defects after administration on gestational days 11-13 was reported to be 0.25 mmol/kg. Succinic anhydride was more potent than phthalic or maleic anhydride but was less active than propionic or acetic anhydride.

Fabro et al. (1982) reported that succinic anhydride induces malformations in mice at doses nearly lethal to adults. This conclusion was based on a determination of a relative teratogenic index, defined as the ratio of minimum lethal dose to minimum teratogenic dose (LD_{01}/tD_{05}), equal to 1.0. In the teratogenicity study, pregnant CD®-1 mice were given intraperitoneal injections of succinic anhydride as a freshly prepared suspension in 0.5% carboxymethyl cellulose once per day on days 8-10 of gestation. Only major structural defects were included in the evaluation of teratogenic potency. For succinic anhydride, the median effective teratogenic dose, tD_{50}, was 0.8 mmol/kg per day, and the tD_{05} was 0.3 mmol/kg per day.

Carcinogenicity

In the one available long-term study, six male rats were given subcutaneous injections of 2 mg succinic anhydride in 0.5 ml arachis oil twice per week for 65 weeks; the total dose was 260 mg/animal (Dickens and Jones, 1965). Local transplantable sarcomas were induced in all three rats that survived 93-106 weeks. The authors concluded that succinic anhydride was carcinogenic in rats because no subcutaneous sarcomas occurred in 24 control rats injected with arachis oil only. There were too few animals in this study to adequately evaluate the carcinogenicity of succinic anhydride. The International Agency for Research on Cancer considered this study to be inadequate for evaluation of the carcinogenicity of succinic anhydride (IARC, 1977).

Morphologically transformed colonies of Syrian golden hamster embryo cells were induced in primary cell cultures incubated for 8 days at 37° C with 0.1 or 1.0 µg/ml of succinic anhydride (Pienta et al., 1977; Pienta, 1980).

Bakale and McCreary (1987) determined the rate at which excess electrons produced in liquid cyclohexane by a short pulse of ionizing radiation attach to carcinogens and noncarcinogens as a potential screen of electrophilic carcinogens; the response of succinic anhydride was negative as an electrophile because the rate of electron attachment to succinic anhydride was less than the diffusion-controlled rate constant for electron attachment.

Genetic Toxicology

Succinic anhydride was not mutagenic or clastogenic in a variety of bacterial, yeast, or mammalian cell culture systems. Succinic anhydride was not mutagenic to *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1536, or TA1537 with or without exogenous metabolic activation (McCann et al., 1975; Kawachi et al., 1978; Rosenkranz and Poirier, 1979; Simmon, 1979a; Kawachi et al., 1980; Ishidate et al., 1981; Zeiger et al., 1987). In a host-mediated

assay, male Swiss Webster mice were administered 125 mg/kg succinic anhydride by intramuscular injection or 689 mg/kg by gavage (Simmon et al., 1979). The mutation frequency was not increased in cells of the detector organisms (*S. typhimurium* strains TA1530, TA1535, or TA1538) recovered from the mice.

Succinic anhydride was reported to be positive in the RK (replicative killing) test because incubation of *Escherichia coli* strain CHY832 with this compound produced an increase in the frequency of cells that survived incubation at 42° C (Hayes et al., 1984). This strain of bacteria carries a fragment of the λ phage genome that imparts a temperature-sensitive phenotype; i.e., cells of the selector strain are killed upon incubation at 42° C due to thermal derepression of the integrated RK λ genes.

Succinic anhydride did not induce *umu* gene expression (demonstrated by an increase in β-galactosidase activity) in *S. typhimurium* TA1535/pSK 1002, a new tester strain in which an *umuC-lacZ* fused gene had been introduced (Nakamura et al., 1987). Because the *umu* gene is activated in response to DNA damage, the lack of an increase in the activity of β-galactosidase (the protein coded by the *lacZ* gene) indicates that incubation of this Salmonella strain with succinic anhydride did not induce a DNA repair response.

The lack of preferential killing by succinic anhydride in a DNA polymerase-deficient strain of *E. coli* (polA$^-$) compared with the wild-type strain (polA$^+$) indicates that succinic anhydride does not act as a DNA-modifying agent (Rosenkranz and Poirier, 1979; Rosenkranz and Leifer, 1980; Leifer et al., 1981). Succinic anhydride did not induce increases in mitotic recombination in *Saccharomyces cerevisiae* strain D3 when tested either directly (Simmon, 1979b) or in a host-mediated assay (Simmon et al., 1979).

Succinic anhydride was not mutagenic in mouse L5178Y lymphoma cells (Clive et al., 1979). Succinic anhydride did not induce chromosomal aberrations in cultured Chinese hamster lung cells, whereas maleic anhydride, a structural analog of succinic anhydride, was positive (Ishidate et al., 1981). Kawachi et al. (1978, 1980) reported that succinic anhydride did not induce chromosomal aberrations or sister chromatid exchanges in hamster lung fibroblast cells in vitro or chromosomal aberrations in rat bone marrow cells in vivo. DNA single-strand breaks were not induced in rat hepatocytes exposed to succinic anhydride (Sina et al., 1983).

Study Rationale

Succinic anhydride was nominated by the National Cancer Institute for toxicology and carcinogenicity studies because of its potential to be a direct-acting acylating agent, because its extensive use may lead to human exposure, and because there was a lack of long-term toxicity and carcinogenicity information on this chemical. The gavage route of administration was selected because human exposure occurs by the oral route.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF SUCCINIC ANHYDRIDE

PREPARATION AND CHARACTERIZATION OF DOSE FORMULATIONS

TWENTY-DAY STUDIES IN RATS

SIXTEEN-DAY STUDIES IN MICE

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II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF SUCCINIC ANHYDRIDE

Succinic anhydride was obtained as a white, flaky solid in two lots from Aldrich Chemical Company, with purity indicated as 99%. Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G). Both lots of the study chemical were identified as succinic anhydride by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy.

The purity of both lots studied was determined by elemental analysis, Karl Fischer water analysis, gas chromatography, potentiometric titration with 0.1 N sodium methoxide to determine total acid and acid anhydride content, and potentiometric acid back-titration of excess added amine to determine acid anhydride content. Gas chromatography by two different systems detected no impurities with areas 0.2% or greater than the area of the major peak. Comparison of the results of the two titration methods indicated the presence of approximately 3.3% succinic acid in lot no. PE072797 and approximately 2.2% succinic acid in lot no. LC081487. Based on the results of all of the analyses, lot no. LC081487 was 98.0% pure, and lot no. PE072797 was 96.6% pure. Lot no. PE072797 was used in the 2-year studies in rats and mice.

The identity of the chemical at the study laboratory was confirmed by infrared analysis. The stability of the bulk chemical during the toxicology studies was monitored by gas chromatography and analysis of total anhydride. No deterioration of succinic anhydride was observed throughout the studies.

PREPARATION AND CHARACTERIZATION OF DOSE FORMULATIONS

Dose formulations of succinic anhydride in corn oil (w/v) were prepared every 2 weeks and used within 3 weeks. Because succinic anhydride forms a suspension in corn oil, the formulations were constantly stirred with a magnetic stirrer during dosing to maintain uniformity. Before the beginning of the 2-year studies, the dose formulation procedure was modified to use a Polytron® homogenizer to reduce particle size and produce more stable suspensions. However, the resulting formulations proved to be more toxic to rats than those prepared with the original method, necessitating the repetition of the short-term studies to select new doses for the 2-year studies in this species. Results of the second short-term studies in rats are presented in this report.

The stability of succinic anhydride in corn oil at concentrations of 15 or 25 mg/ml was determined at the study laboratory. The chemical was found to be stable as a suspension in corn oil for at least 18 days when stored at room temperature.

Periodic gas chromatographic analysis of the dose formulations was conducted at the study laboratory and the analytical chemistry laboratory. During the 13-week studies in mice, the concentrations of all formulations were found to be 20%-39% higher than the target concentrations (Table G3). During the 13-week studies in rats, all dose formulations except one were found to be within $\pm 10\%$ of the target concentrations by the study laboratory. The analytical chemistry (referee) laboratory analyzed one dose formulation and found that, although it was not within specifications, their result was within 10% of the study laboratory result.

During the 2-year studies, the dose formulations were analyzed at intervals of approximately 8 weeks. For the succinic anhydride studies, the formulations were estimated to have been prepared within $\pm 10\%$ of the target concentrations approximately 98% of the time throughout the studies (Table G4). Results of periodic referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results from the study laboratory (Table G5).

TWENTY-DAY STUDIES IN RATS

Twenty-day studies were conducted to evaluate the toxicity of succinic anhydride/corn oil formulations that were prepared in a Polytron® mixer. Male and female F344/N rats were obtained from Charles River Breeding Laboratories and were held for 21 days before the studies began.

The rats were 7-8 weeks old when placed on study.

Groups of 10 male and female rats were administered 0, 47, 94, 187, 375, or 750 mg/kg succinic anhydride (lot no. PE072797) in corn oil by gavage, 5 days per week, for 14 doses over 20 days.

Animals were housed five per cage. Water and feed were available ad libitum. The rats were observed once per day. Animals were weighed initially and then once per week until the end of the studies. A necropsy was performed on all rats in the 0, 187, 375, and 750 mg/kg dose groups. Histologic examinations were performed on vehicle controls, rats in the 375 and 750 mg/kg groups, and those in the 187 mg/kg groups which died before the end of the studies. Further details are presented in Table 1.

SIXTEEN-DAY STUDIES IN MICE

Male and female $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories and were held for 18 days before the studies began. The mice were 7-9 weeks old when placed on study.

Groups of five mice of each sex were administered 0, 219, 438, 875, 1,750, or 3,500 mg/kg succinic anhydride (lot no. LC081487) in corn oil by gavage, 5 days per week, for 12 doses over 16 days.

Animals were housed five per cage. Water and feed were available ad libitum. The mice were observed once per day and were weighed on the first day of dose administration each week. A necropsy was performed on all animals dying before the end of the studies. Histologic examinations were performed on four males and two females from the 438 mg/kg groups. Further details are presented in Table 1.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of succinic anhydride and to determine the doses to be used in the 2-year studies.

Four- to 6-week-old male and female F344/N rats and $B6C3F_1$ mice were obtained from Charles River Breeding Laboratories, observed for 18 days (rats) or 19 days (mice), distributed to cages from weight classes, and assigned to dose groups according to a table of random numbers. Rats were approximately 7-8 weeks old when placed on study, and mice were 7-9 weeks old.

Groups of 10 male rats were administered 0, 25, 50, 100, or 400 mg/kg succinic anhydride (lot no. PE072797) in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 female rats were administered 0, 12.5, 25, 50, 100, or 200 mg/kg and groups of 10 mice of each sex were administered 0, 37, 75, 150, 300, or 600 mg/kg succinic anhydride (lot no. LC081487) on the same schedule.

Rats and mice were housed five per cage. Feed and water were available ad libitum. Further experimental details are summarized in Table 1.

Rats were observed once per day, and mice were observed twice per day. Clinical observations were recorded once per week. Animals were weighed at the beginning of the studies and then once per week.

At the end of the 13-week studies, survivors were humanely killed. A necropsy was performed on all animals. Tissues and groups examined microscopically are listed in Table 1.

TWO-YEAR STUDIES

Study Design

Groups of 60 male and 60 female rats were administered 0, 50, or 100 mg/kg succinic anhydride in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 male mice were administered 0, 38, or 75 mg/kg and groups of 50 female mice were administered 0, 75, or 150 mg/kg on the same schedule. Both rats and mice received the same lot of succinic anhydride (lot no. PE072797).

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female $\times$ C3H/HeN MTV^-, male)

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

Sixteen-Day Studies in Mice	Twenty-Day Studies in Rats	Thirteen-Week Studies in Mice	Thirteen-Week Studies in Rats	Two-Year Studies
EXPERIMENTAL DESIGN				
Size of Study Groups				
5 male and 5 female mice	10 male and 10 female rats	10 male and 10 female mice	10 male and 10 female rats	60 male and 60 female rats; 50 male and 50 female mice
Doses				
0, 219, 438, 875, 1,750, or 3,500 mg/kg succinic anhydride in corn oil by gavage; dose vol--10 ml/kg	0, 47, 94, 187, 375, or 750 mg/kg succinic anhydride in corn oil by gavage; dose vol--5 ml/kg	0, 37, 75, 150, 300, or 600 mg/kg succinic anhydride in corn oil by gavage; dose vol--10 ml/kg	Male--0, 25, 50, 100, 200, or 400 mg/kg succinic anhydride in corn oil by gavage; female--0, 12 5, 25, 50, 100, or 200 mg/kg; dose vol--5 ml/kg	Rats--0, 50, or 100 mg/kg succinic anhydride in corn oil by gavage; mice--male: 0, 38, or 75 mg/kg; female: 0, 75, or 150 mg/kg; dose vol--rats: 5 ml/kg; mice: 10 ml/kg
Date of First Dose				
11/26/79	7/9/81	3/31/80	10/5/81	Rats--8/30/82; mice--5/18/81
Date of Last Dose				
12/11/79	7/28/81	6/27/80	1/3/82	Rats--8/17/84, mice--5/6/83
Duration of Dosing				
12 doses over 16 d	14 doses over 20 d	5 d/wk for 13 wk	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation				
Observed 1 × d; weighed 1 × wk	Same as 16-d studies in mice	Observed 2 × d; weighed initially and 1 × wk thereafter	Same as 13-wk studies in mice, except observed 1 × d	Observed 2 × d, weighed 1 × wk for 13 wk (rats) or 12 wk (mice) and 1 × mo thereafter
Necropsy and Histologic Examinations				
Necropsy performed on all animals; histologic exams performed on 4 males and 2 females from the 438 mg/kg groups	Necropsy performed on all animals in the 0, 187, 375, and 750 mg/kg groups, histologic exams performed on all vehicle controls, animals from the 375 and 750 mg/kg groups, and animals in the 187 mg/kg groups dying before the end of the studies. Tissues examined include esophagus, kidneys, larynx, lungs, parathyroid glands, stomach, and trachea; nasal cavity or intestinal tract for rats with gross lesions	Necropsy performed on all animals; the following tissues examined histologically for all vehicle control and high dose animals and for animals dying before the end of the studies: adrenal glands, bone, bone marrow, brain, colon, esophagus, gallbladder, heart, kidneys, liver, lungs, mammary gland, mandibular and mesenteric lymph nodes, pancreas, parathyroid glands, pituitary gland, salivary glands, skin, small intestine, spleen, stomach, testes/epididymis/prostate or ovaries/uterus, thymus, thyroid gland, trachea, and urinary bladder	Necropsy performed on all animals; histologic exams performed on all vehicle controls, 200 and 400 mg/kg males, 100 and 200 mg/kg females, and animals dying before the end of the studies. The following tissues were examined microscopically: brain, cecum, esophagus, heart, kidneys, larynx, liver, lungs, mediastinum, mesenteric lymph nodes, pancreas, salivary glands, spleen, stomach, thymus, thyroid gland, and trachea. Liver weights obtained at necropsy	Necropsy performed on all animals; histologic exams performed on all vehicle control and high dose animals, all rats that died before the end of the studies, all mice that died before wk 92, and all animals with gross lesions, the following tissues were examined adrenal glands, bone, bone marrow, brain, clitoral or preputial gland, epididymis/prostate/testes or ovaries/uterus, esophagus, heart, kidneys, large and small intestines, larynx, liver, lungs, lymph nodes, mammary gland, nose, pancreas, pancreatic islets, parathyroid glands, pituitary gland, salivary glands, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Adrenal glands (male), kidneys, lungs (male), nose, pituitary gland (male), and thyroid gland (male) examined for low dose rats; kidneys, liver, and nasal cavity examined

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF SUCCINIC ANHYDRIDE (Continued)

Sixteen-Day Studies in Mice	Twenty-Day Studies in Rats	Thirteen-Week Studies in Mice	Thirteen-Week Studies in Rats	Two-Year Studies
Necropsy and Histologic Examinations				for low dose male mice, and pituitary gland and cecum examined for low dose female mice
ANIMALS AND ANIMAL MAINTENANCE				
Strain and Species				
$B6C3F_1$ mice	F344/N rats	$B6C3F_1$ mice	F344/N rats	F344/N rats, $B6C3F_1$ mice
Animal Source				
Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)	Charles River Breeding Laboratories (Kingston, NY)	Rats--Frederick Cancer Research Facility (Frederick, MD), mice--Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory				
Microbiological Associates, Inc	Microbiological Associates, Inc.	Microbiological Associates, Inc.	Microbiological Associates, Inc.	Microbiological Associates, Inc
Method of Animal Identification				
Ear punch	Ear tag/punch	Ear punch	Ear punch and clip	Ear tag
Time Held Before Study				
18 d	21 d	19 d	18 d	Rats--20 d; mice -19 d
Age When Placed on Study				
7-9 wk	7 8 wk	7 9 wk	7-8 wk	Rats 8-9 wk; mice--8-9 wk
Age When Killed				
9-11 wk	10-11 wk	20-22 wk	20-21 wk	112-114 wk
Necropsy Dates				
12/12/79	7/29/81-7/30/81	7/1/80-7/3/80	1/4/82-1/5/82	Rats--8/27/84-8/30/84; mice--5/16/83-5/20/83
Method of Animal Distribution				
Animals distributed to weight classes and then assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice
Diet				
NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc , Gardners, PA); available ad libitum	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice
Bedding				
Hardwood chips (P J. Murphy Forest Products Corp., Rochelle Park, NJ)	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF SUCCINIC ANHYDRIDE (Continued)

Sixteen-Day Studies in Mice	Twenty-Day Studies in Rats	Thirteen-Week Studies in Mice	Thirteen-Week Studies in Rats	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)				
Water				
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice
Cages				
Polycarbonate (Lab Products, Inc., Rochelle Park, NJ, or Hazleton Systems, Inc., Aberdeen, MD)	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice
Cage Filters				
Spun-bonded polyester (Snow Filtration, Cincinnati, OH)	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice	Same as 16-d studies in mice
Animals per Cage				
5	5	5	5	5
Other Chemicals on Study in the Same Room				
None	None	None	None	None
Animal Room Environment				
Temp--62°-74° F; hum--45%-70%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--70°-80° F; hum--55%-73%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--68°-87° F; hum--35%-90%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--70°-80° F; hum--22%-74%; fluorescent light 12 h/d; 12-15 room air changes/h	Temp--64°-86° F; hum--22%-84%; fluorescent light 12 h/d; 12-15 room air changes/h

mice used in these studies were produced under strict barrier conditions at Frederick Cancer Research Facility (rats) or Charles River Breeding Laboratories (mice). Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats and mice were shipped to the study laboratory at 5-6 weeks of age. The animals were quarantined at the study laboratory for 3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats and mice were placed on study at 8-9 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. Cages of vehicle control animals were placed in the top two rows of the racks, cages of low dose animals were placed in the next two rows, and cages of high dose animals were placed in the bottom two rows. Cages were not rotated during the studies. Feed (Appendix F) and water were available ad libitum. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed two times per day. Body weights were recorded once per week for

the first 12 or 13 weeks of the study, except during week 7 for mice, and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals, including those found dead. One vehicle control male mouse was missing after week 92. The number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histopathologic examinations of tissues were performed according to an "inverse pyramid" design (McConnell, 1983a,b). That is, complete histopathologic examinations (Table 1) were performed on all high dose and vehicle control animals and on all low dose rats dying before the end of the studies and on all low dose mice dying before week 92. In addition, histopathologic examinations were performed on all grossly visible lesions in all dose groups. Potential target organs for chemically related neoplastic and nonneoplastic effects were determined by examination of the pathology data; these target organs/tissues in the low dose group were examined histopathologically.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System (rats) or the Carcinogenesis Bioassay Data System (mice), the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues (male rats: thyroid gland, pituitary gland, adrenal gland, kidney, testes; female rats: kidney; mice: none), and all tissues from a randomly selected 10% of the animals were re-evaluated microscopically by a quality assessment pathologist. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target organs, the randomly selected 10% of animals, and in tissues with unusual incidence patterns or trends.

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. For the rat studies, the PWG examined all lesions diagnosed as mesotheliomas, preputial gland adenomas, squamous cell papillomas of the skin, neoplastic nodules of the liver, and two renal nephroblastomas, as well as several sections of adrenal gland and kidney. For the mouse studies, the PWG examined sections of kidney, nasal cavity, and lung. The PWG included the quality assessment pathologist and other pathologists experienced in rodent toxicology, who examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final pathology data represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Statistical Methods

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found to be missing or dead from other than natural

causes; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. All reported P values for the survival analysis are two-sided.

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

Analysis of Tumor Incidence: The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was an incidental tumor analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals actually examined for tumors during the time interval. The individual time interval comparisons were then combined to obtain a single overall result.

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

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

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence.

III. RESULTS

RATS

TWENTY-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

III. RESULTS: RATS

TWENTY-DAY STUDIES

Six males and 10 females that received succinic anhydride died before the end of the studies (Table 2). The death of one female receiving 187 mg/kg was not compound related. Final mean body weights of male rats were not clearly related to the dose received. The final mean body weight of female rats that received 750 mg/kg was 11% lower than that of vehicle controls. Compound-related clinical signs included labored breathing, lethargy, distended abdomens, and rough hair coats. Necrosis and inflammation of the upper respiratory tract were seen in 3/10 males and 3/10 females receiving 750 mg/kg and 2/10 females receiving 375 mg/kg.

THIRTEEN-WEEK STUDIES

Deaths of 8/10 males that received 400 mg/kg and 4/10 males and 5/10 females that received 200 mg/kg were considered to be compound related (Table 3). Other deaths were considered to be the result of gavage error.

Lethargy and distended abdomens were seen at the two highest doses. The mean body weights at necropsy of male rats that received 200 or 400 mg/kg were 9% or 15% lower than that of vehicle controls. The mean body weights at necropsy of dosed and vehicle control female rats were similar. The relative liver weights for female rats that received 100 or 200 mg/kg were slightly greater than that for vehicle controls (Table 4). No compound-related lesions were seen microscopically

Dose Selection Rationale: Based primarily on the reduced survival for rats administered 200 mg/kg or higher doses of succinic anhydride in the 13-week studies, doses of succinic anhydride selected for the 2-year studies in rats were 50 and 100 mg/kg, administered in corn oil by gavage 5 days per week.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE TWENTY-DAY GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	127 ± 2	239 ± 7	+112 ± 6	
47	10/10	126 ± 3	229 ± 12	+103 ± 10	96
94	10/10	127 ± 2	229 ± 8	+102 ± 6	96
187	10/10	129 ± 2	226 ± 7	+97 ± 6	95
375	(d) 9/10	129 ± 2	234 ± 4	+104 ± 3	98
750	(e) 5/10	129 ± 2	231 ± 8	+99 ± 6	97
FEMALE					
0	10/10	110 ± 2	159 ± 2	+49 ± 1	
47	10/10	110 ± 2	149 ± 6	+39 ± 5	94
94	10/10	109 ± 2	154 ± 3	+45 ± 2	97
187	(f) 7/10	111 ± 2	155 ± 3	+45 ± 2	97
375	(g) 7/10	112 ± 1	155 ± 7	+43 ± 7	97
750	(h) 6/10	111 ± 2	142 ± 4	+30 ± 4	89

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Day of death: 6
(e) Day of death: 1,2,2,8,9
(f) Day of death: 6,7; an additional death was related to gavage trauma.
(g) Day of death: all 9
(h) Day of death: 6,8,9,20

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	143 ± 2	356 ± 6	+213 ± 6	
25	(d) 8/10	143 ± 2	352 ± 6	+210 ± 4	99
50	(d) 8/10	144 ± 3	357 ± 8	+212 ± 10	100
100	(d) 9/10	143 ± 2	340 ± 12	+197 ± 13	96
200	(e) 6/10	141 ± 1	324 ± 5	+183 ± 5	91
400	(f) 2/10	140 ± 2	302 ± 15	+163 ± 14	85
FEMALE					
0	10/10	114 ± 1	194 ± 2	+80 ± 2	
12.5	10/10	115 ± 0	199 ± 2	+84 ± 1	103
25	10/10	115 ± 1	201 ± 4	+86 ± 4	104
50	(d) 9/10	115 ± 1	198 ± 2	+83 ± 2	102
100	(d) 9/10	115 ± 1	189 ± 3	+74 ± 3	97
200	(g) 3/10	114 ± 1	192 ± 5	+78 ± 7	99

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Deaths may have been gavage related.
(e) Week of death: 1,10,12,12
(f) Week of death: 1,1,1,2,2,3,3,9
(g) Week of death: 1,1,2,2,3; two additional deaths may have been gavage related.

TABLE 4. LIVER WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF SUCCINIC ANHYDRIDE (a)

Dose (mg/kg)	Number Weighed	Necropsy Body Weight (grams)	Liver Weight (mg)	Liver Weight/ Necropsy Body Weight (mg/g)
MALE				
0	10	356.4 ± 5.7	14,125 ± 172.6	39.7 ± 0.70
25	8	352.1 ± 5.6	13,624 ± 554.0	38.7 ± 1.48
50	8	356.6 ± 8.0	14,363 ± 552.8	40.2 ± 1.02
100	(b) 8	336.5 ± 13.3	13,835 ± 788.1	41.0 ± 1.10
200	6	*323.8 ± 4.7	13,343 ± 386.5	41.2 ± 0.78
400	2	*302.0 ± 15.0	12,455 ± 135.0	41.4 ± 2.50
FEMALE				
0	10	193.5 ± 2.0	6,437 ± 138.4	33.3 ± 0.68
12.5	10	198.8 ± 1.7	6,765 ± 161.8	34.0 ± 0.66
25	10	201.2 ± 3.8	6,982 ± 125.1	34.7 ± 0.37
50	9	198.1 ± 2.4	6,829 ± 170.6	34.5 ± 0.85
100	9	188.8 ± 3.0	6,829 ± 182.9	*36.1 ± 0.62
200	3	192.3 ± 5.2	*7,303 ± 89.5	**38.0 ± 0.96

(a) Mean ± standard error; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1955).
(b) The liver of a ninth animal was not weighed; the necropsy body weight of this animal has been excluded from the analysis.
*P<0.05
**P<0.01

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were approximately 6% lower than those of vehicle controls during the second year of the study; mean body weights of high dose female rats were approximately 8% lower than those of vehicle controls during the second year of the study (Table 5 and Figure 1). Mean body weights of low dose and vehicle control rats were generally similar throughout the studies.

Survival

Estimates of the probabilities of survival for male and female rats administered succinic anhydride at the doses used in these studies and for vehicle controls are shown in Table 6 and in the Kaplan and Meier curves in Figure 2; standard (unadjusted) survival curves are presented for comparison in Figure 3. No significant differences in survival were observed between any groups of either sex. The interim evaluation of 10 rats per group scheduled after 15 months of exposure was canceled because of some early deaths due to gavage accidents. To determine whether gavage accidents were the possible cause of early death or the reason for the rats being killed in a moribund condition, a retrospective examination of sections of nose and lung, esophagus and trachea, and heart and mediastinum was performed on animals that died early. The detection of small oil droplets in the lung of certain animals coded as natural death or moribund kill indicates that some of these deaths may have been related to the dosing (gavage) procedure. A sufficient number of rats in each dose group lived long enough to allow evaluation of the potential carcinogenicity of succinic anhydride.

TABLE 5. MEAN BODY WEIGHTS OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

Week on Study	Vehicle Control		50 mg/kg			100 mg/kg		
	Av. Wt. (grams)	Number Weighed	Av Wt. (grams)	Wt. (percent of vehicle controls)	Number Weighed	Av. Wt. (grams)	Wt. (percent of vehicle controls)	Number Weighed
MALE								
1	169	(a) 53	168	99	60	170	101	(a) 59
2	201	60	198	99	59	202	100	60
3	223	60	226	101	59	229	103	60
4	248	60	243	98	(a) 57	244	98	(a) 55
5	267	60	263	99	59	261	98	60
6	282	60	279	99	59	277	98	60
7	290	60	294	101	59	294	101	60
8	307	60	304	99	59	302	98	(a) 58
9	316	60	304	96	59	302	96	60
10	324	60	315	97	59	311	96	60
11	334	60	325	97	59	320	96	(a) 54
12	344	60	332	97	59	328	95	59
13	348	60	344	99	59	335	96	58
17	377	60	369	98	59	363	96	57
21	396	60	385	97	59	378	95	57
25	419	59	401	96	59	396	95	57
29	428	59	415	97	58	410	96	55
33	437	59	423	97	58	421	96	54
41	456	59	448	98	57	438	96	54
45	469	59	457	97	57	452	96	53
49	476	59	465	98	57	457	96	53
53	484	58	473	98	56	460	95	53
57	486	58	477	98	56	462	95	53
61	488	58	480	98	56	465	95	53
65	491	58	483	98	56	463	94	52
69	491	58	481	98	55	465	95	51
73	493	(a) 56	482	98	54	470	95	51
77	497	(a) 56	481	97	54	464	93	49
81	489	(a) 54	479	98	53	466	95	48
86	490	(a) 52	478	98	50	464	95	47
89	482	51	480	100	49	456	95	45
93	482	47	474	98	43	446	93	43
97	478	46	469	98	41	442	92	41
101	474	41	475	100	37	435	92	37
104	470	36	468	100	33	446	95	32
Mean for weeks								
1 13	281 0		276 5	98		275 0	98	
17 49	432 3		420 4	97		414 4	96	
53 104	485 4		477 1	98		457 4	94	
FEMALE								
1	122	60	124	102	60	124	102	60
2	136	59	134	99	53	134	99	56
3	146	(a) 58	150	103	50	148	102	56
4	159	59	160	101	(a) 45	158	99	(a) 55
5	166	59	169	102	50	167	101	56
6	172	59	174	101	50	173	101	(a) 55
7	174	59	179	103	(a) 18	176	101	56
8	181	59	183	101	50	181	100	56
9	186	59	189	102	(a) 49	186	100	56
10	190	59	190	100	50	187	98	56
11	192	59	195	102	50	192	100	56
12	196	58	197	101	50	195	99	56
13	197	58	196	99	50	195	99	56
17	208	58	207	100	50	201	97	(a) 49
21	214	58	211	99	50	206	96	55
25	220	57	215	98	49	211	96	54
29	226	57	224	99	48	222	98	52
33	234	57	232	99	48	227	97	50
41	247	57	246	98	48	239	97	49
45	257	57	254	99	48	245	95	49
49	265	57	262	99	48	251	95	48
53	274	57	268	98	48	258	94	46
57	282	57	277	98	48	264	94	46
61	289	57	283	98	47	268	93	45
65	297	57	289	97	47	273	92	45
69	308	57	296	96	46	282	92	45
73	315	54	305	97	46	287	91	44
77	321	53	308	96	46	293	91	44
81	322	52	309	96	45	299	93	44
86	322	51	328	102	44	297	92	42
89	325	48	320	98	39	300	92	40
93	331	44	321	97	37	305	92	36
97	334	41	324	97	37	307	92	34
101	337	38	328	97	31	302	90	32
104	330	32	322	98	27	295	89	29
Mean for weeks								
1 13	170 5		172 3	101		170 5	100	
17 49	233 9		231 4	99		225 3	96	
53 104	313 2		305 6	98		287 9	92	

(a) The number of animals weighed was lower than the number of animals surviving

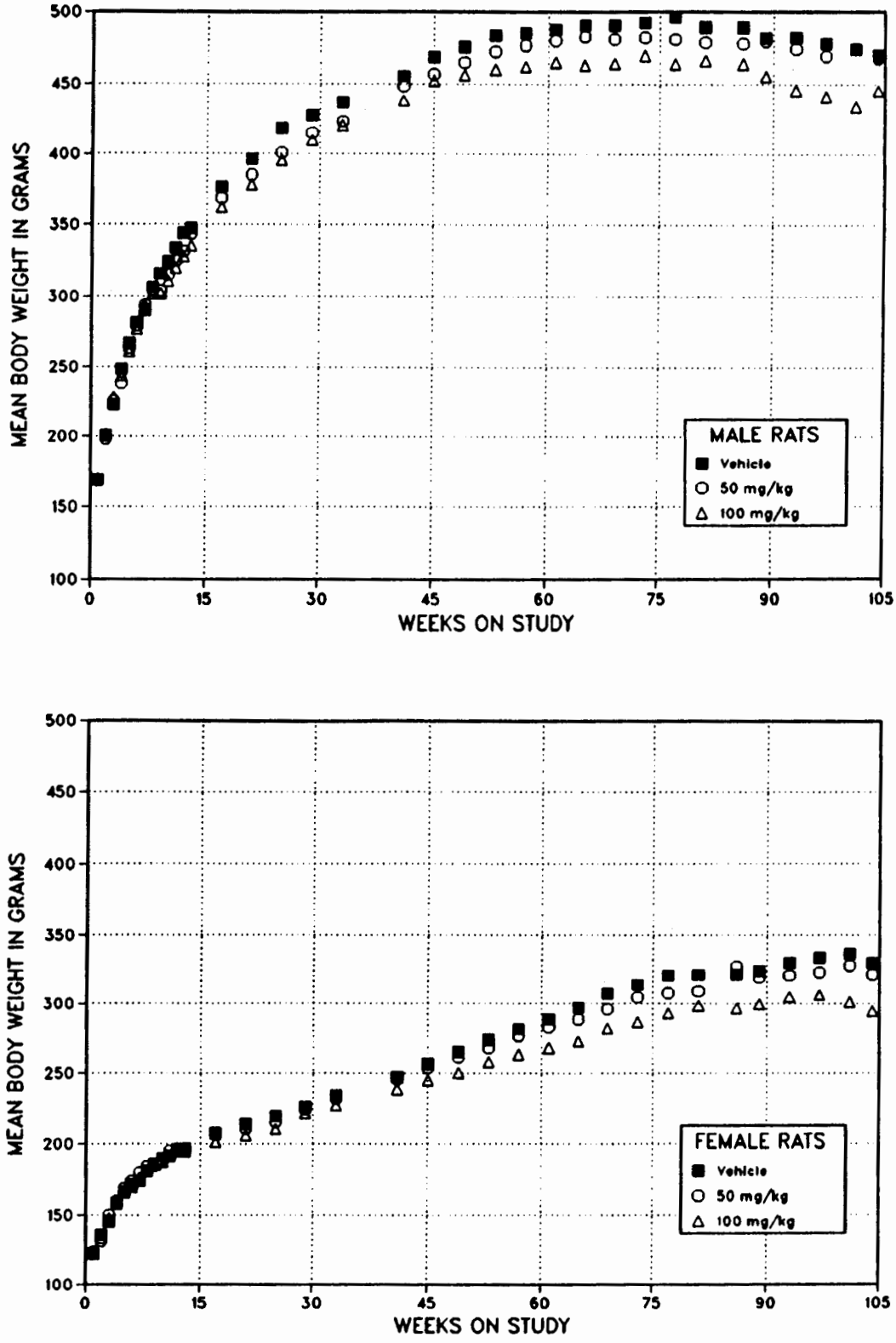


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED SUCCINIC ANHYDRIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

TABLE 6. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

	Vehicle Control	50 mg/kg	100 mg/kg
MALE (a)			
Animals initially in study	60	60	60
Natural deaths (b)	8	9	14
Moribund kills (b)	15	16	10
Killed accidentally	1	2	4
Animals surviving until study termination	36	33	32
Mean survival (days)	682	658	628
Survival P values (c)	0.656	0.690	0.718
Survival P values, unadjusted (d)	0.388	0.594	0.434
FEMALE (a)			
Animals initially in study	60	60	60
Natural deaths (b)	10	11	10
Moribund kills (b)	18	15	14
Killed accidentally	1	7	9
Animals surviving until study termination	(e) 31	27	(e) 27
Mean survival (days)	657	558	571
Survival P values (c)	0.983	0.873	0.920
Survival P values, unadjusted (d)	0.312	0.339	0.337

(a) First day of termination period: 729
(b) The possibility that some of these early deaths were gavage related cannot be excluded.
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns; animals killed accidentally were censored from the analyses.
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns; animals killed accidentally were not censored from the analyses.
(e) One animal died or was killed in a moribund condition during the termination period and was combined, for statistical purposes, with those killed at termination.

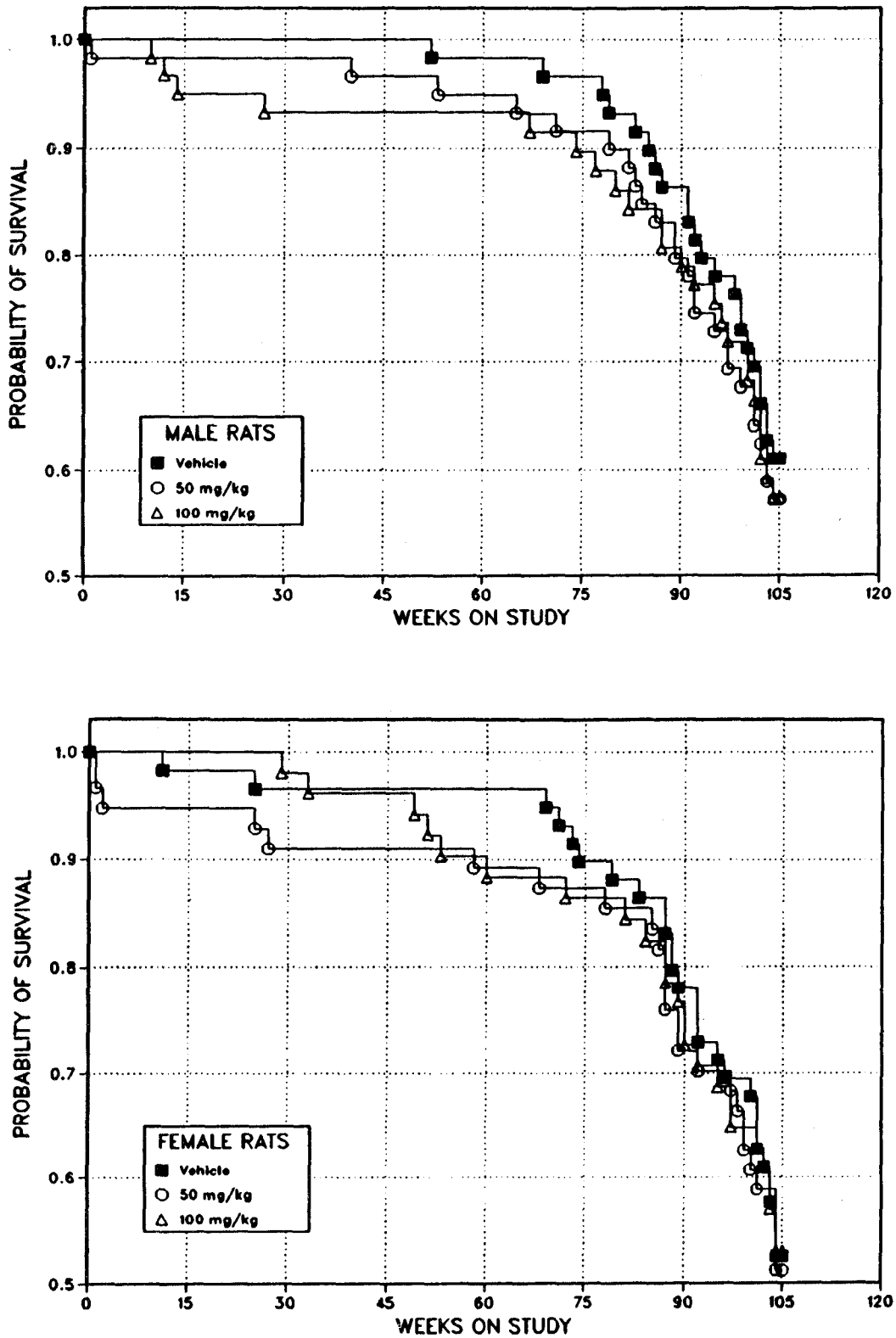


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED SUCCINIC ANHYDRIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

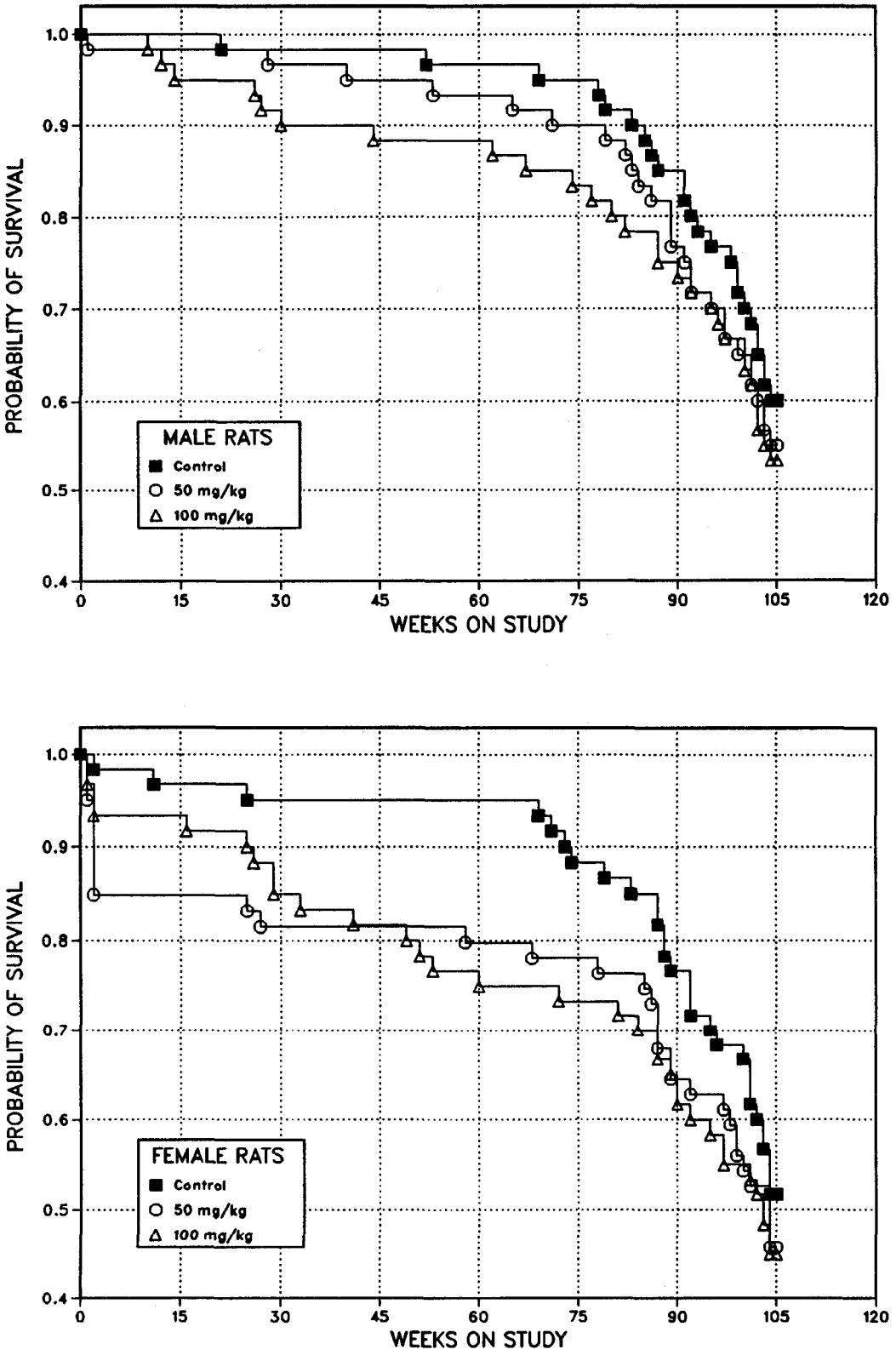


FIGURE 3. STANDARD SURVIVAL CURVES FOR RATS ADMINISTERED SUCCINIC ANHYDRIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the statistically significant changes in the incidences of rats with neoplastic lesions. Marginal increases were seen for the skin and mammary gland. No neoplastic or nonneoplastic lesions appeared to be related to chemical administration.

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

Skin: Keratoacanthomas in male rats occurred with a significant positive trend; however, the incidence in the high dose group was not significantly greater than that in vehicle controls (vehicle control, 2/60; low dose, 0/60; high dose, 6/60) and is lower than the highest historical incidence observed in corn oil gavage vehicle control male F344/N rats (6/50).

Mammary Gland: Fibroadenomas in female rats occurred with a marginally significant negative trend, and the incidence in the high dose group was marginally lower than that in the vehicle controls (Table 7). This decrease was not considered to be chemical related because the difference between the high dose and vehicle control groups was not statistically significant when the incidence of mammary gland fibroadenomas was combined with the incidences of adenomas and adenocarcinomas. Furthermore, the incidence in the high dose group was well within the range of the historical incidences of mammary gland neoplasms in corn oil vehicle control female F344/N rats in recent National Toxicology Program (NTP) 2-year studies (14%-56%; see Table B4).

TABLE 7. MAMMARY GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (a)

	Vehicle Control	50 mg/kg	100 mg/kg
Fibroadenoma (b)			
Overall Rates	25/60 (42%)	23/60 (38%)	12/60 (20%)
Terminal Rates	13/31 (42%)	13/27 (48%)	6/27 (22%)
Day of First Observation	553	603	663
Incidental Tumor Tests	P=0.039N	P=0.422	P=0.038N
Adenoma			
Overall Rates	1/60 (2%)	2/60 (3%)	0/60 (0%)
Adenocarcinoma			
Overall Rates	0/60 (0%)	2/60 (3%)	2/60 (3%)
Adenoma, Fibroadenoma, or Adenocarcinoma (c)			
Overall Rates	26/60 (43%)	25/60 (42%)	14/60 (23%)
Terminal Rates	13/31 (42%)	13/27 (48%)	8/27 (30%)
Day of First Observation	507	603	663
Incidental Tumor Tests	P=0.078N	P=0.322	P=0.079N

(a) For a complete explanation of the entries in this table, see Table B3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence at study laboratory (mean ± SD): 70/150 (47% ± 5%); historical incidence in NTP studies: 615/2,100 (29% ± 9%)
(c) Historical incidence at study laboratory (mean ± SD): 74/150 (49% ± 6%); historical incidence in NTP studies: 647/2,100 (31% ± 10%)

SIXTEEN-DAY STUDIES

All mice that received 875 mg/kg or more died before the end of the studies (Table 8). Because of a malfunction of the weight scales, body weight data could not be interpreted. Compound-related clinical signs included lethargy, distended abdomens, and rough hair coats. No compound-related lesions were seen in the four males and two females examined from the 438 mg/kg groups.

THIRTEEN-WEEK STUDIES

All 10 males and 8/10 females that received 600 mg/kg and 2/10 males and 2/10 females that received 300 mg/kg died before the end of the studies (Table 9). The final mean body weights of mice that received 150 or 300 mg/kg were 13% or 9% lower than that of vehicle controls for males and 8% or 7% lower for females. The final body weights of the two female mice that received 600 mg/kg and lived to the end of the studies were lower than the initial weights. Clinical signs included rough hair coats and lethargy at 600 mg/kg and rough hair coats at 300 mg/kg. The incidence of inflammation of the stomach was increased in male mice that received 150 mg/kg (7/10) or 300 mg/kg (5/10) compared with that in vehicle controls (2/10).

Dose Selection Rationale: Because of the reduced survival of male and female mice that received 300 mg/kg and the lower weight gain for males at 150 mg/kg, doses of succinic anhydride selected for mice for the 2-year studies were 38 and 75 mg/kg for males and 75 and 150 mg/kg for females, administered in corn oil by gavage 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were generally 5%-12% lower than those of vehicle controls after week 11 (Table 10 and Figure 4). Mean body weights of vehicle control and low dose male mice were similar throughout most of the study. Mean body weights of high dose female mice were 10%-32% lower than those of vehicle controls from week 12 to the end of the study. Mean body weights of low dose female mice were 10%-20% lower than those of vehicle controls from week 28 to the end of the study. During months 8 through 12, low and high dose male and female mice assumed arched postures immediately after dosing and became lethargic. The mice had a normal appearance about 15 minutes later. After dosing during this same period, mice were occasionally observed to rub their faces and burrow in bedding. High dose females occasionally wheezed and had rough hair coats.

TABLE 8. SURVIVAL OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF SUCCINIC ANHYDRIDE (a)

Dose (mg/kg)	Survival (b)	
	Male	Female
0	5/5	5/5
219	5/5	5/5
438	4/5	5/5
875	0/5	0/5
1,850	0/5	0/5
3,500	0/5	0/5

(a) Body weight data not usable due to scale malfunction
(b) Number surviving/number initially in group

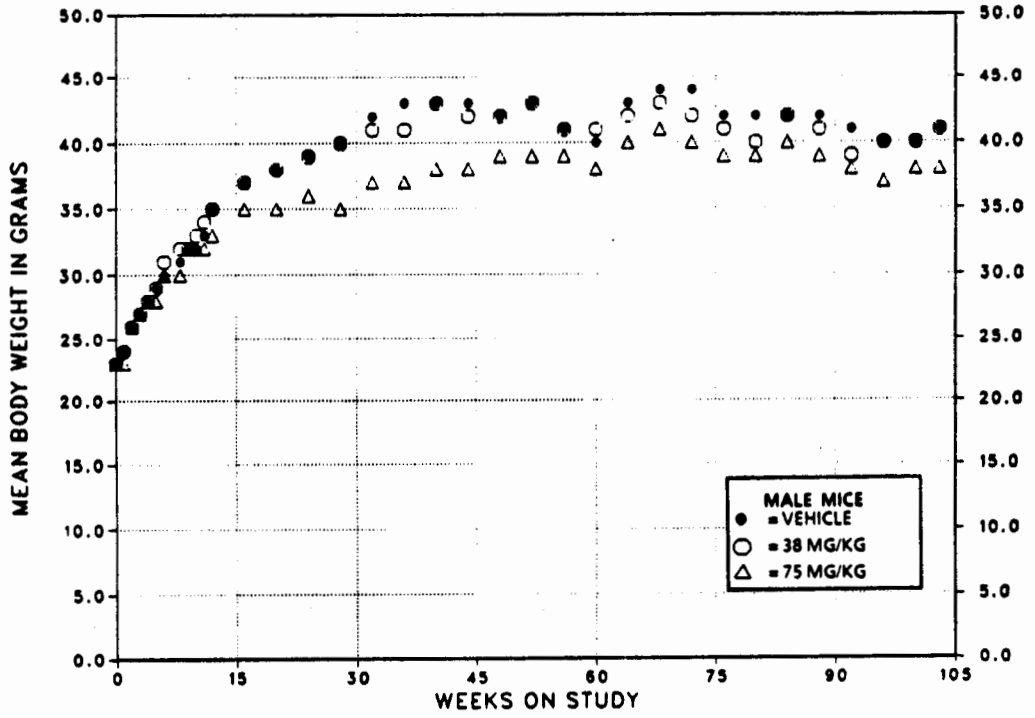
TABLE 9. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	25.5 ± 0.5	34.5 ± 0.9	+9.0 ± 0.7	
37	10/10	25.1 ± 0.5	33.1 ± 1.3	+8.0 ± 1.3	95.9
75	10/10	25.3 ± 0.8	33.7 ± 1.0	+8.4 ± 1.1	97.7
150	10/10	25.3 ± 0.6	30.1 ± 0.5	+4.8 ± 0.6	87.2
300	(d) 8/10	26.3 ± 0.7	31.4 ± 0.5	+5.1 ± 0.8	91.0
600	(e) 0/10	25.3 ± 0.4	(f)	(f)	(f)
FEMALE					
0	10/10	21.6 ± 0.5	25.8 ± 0.5	+4.2 ± 0.6	
37	10/10	21.7 ± 0.4	26.1 ± 0.5	+4.4 ± 0.6	101.2
75	10/10	21.0 ± 0.7	25.6 ± 0.7	+4.6 ± 0.9	99.2
150	10/10	20.9 ± 0.3	23.7 ± 0.2	+2.8 ± 0.3	91.9
300	(g) 8/10	20.3 ± 0.2	24.0 ± 0.7	+3.6 ± 0.7	93.0
600	(h) 2/10	21.3 ± 0.2	17.0 ± 1.0	−3.5 ± 1.5	65.9

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: all 1
(e) Week of death: 1,1,1,1,1,1,5,5,6,7
(f) No data are reported due to 100% mortality in this group.
(g) Week of death: 1,4
(h) Week of death: 1,1,1,2,3,5,5,8

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

Week on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control Number of Survivors	Low Dose Av. Wt. (grams)	Low Dose Wt. (percent of vehicle controls)	Low Dose Number of Survivors	High Dose Av. Wt. (grams)	High Dose Wt. (percent of vehicle controls)	High Dose Number of Survivors
MALE				**38 mg/kg**			**75 mg/kg**	
0	23 6	50	23 5	100	50	23 3	99	50
1	24 4	48	24 3	100	50	23 9	98	50
2	26 2	48	26 2	100	50	26 1	100	50
3	27 4	48	27 8	101	49	27 4	100	50
4	28 6	48	28 4	99	49	28 1	98	50
5	29 3	48	29 3	100	49	28 3	97	50
6	30 8	48	31 0	101	49	30 0	97	50
8	31 7	48	32 1	101	49	30 7	97	50
9	32 1	48	32 8	102	49	32 1	100	50
10	32 5	48	33 2	102	49	32 4	100	50
11	33 5	48	34 0	101	49	32 7	98	50
12	35 1	48	35 4	101	48	33 7	96	50
16	37 4	48	37 5	100	48	35 6	95	50
20	38 3	48	38 4	100	47	35 7	93	48
24	39 4	48	39 1	99	46	36 0	91	48
28	40 5	48	40 1	99	46	35 9	89	48
32	42 1	48	41 2	98	46	37 0	88	47
36	43 2	48	41 8	97	45	37 4	87	47
40	43 9	48	43 3	99	45	38 5	88	46
44	43 6	48	42 5	97	45	38 5	88	46
48	42 5	48	42 2	99	42	39 1	92	46
52	43 2	48	43 1	100	41	39 4	91	46
56	41 3	46	41 7	101	40	39 1	95	45
60	40 1	44	41 0	102	35	38 6	96	45
64	43 0	40	42 7	99	33	40 7	95	44
68	44 6	37	43 7	98	33	41 5	93	44
72	44 1	37	42 5	96	33	40 8	93	44
76	42 3	37	41 2	97	33	39 4	93	44
80	42 3	35	40 8	96	33	39 1	92	44
84	42 8	34	42 2	99	33	40 2	94	44
88	42 4	31	41 6	98	33	39 3	93	44
92	41 3	28	39 9	97	33	38 1	92	44
96	40 9	28	40 2	98	31	37 5	92	44
100	40 4	28	40 7	101	31	38 8	96	42
103	41 3	27	41 1	100	30	38 6	93	42
Mean for weeks								
1 12	30 1		30 4	101		29 6	98	
16 52	41 4		40 9	99		37 3	90	
56 103	42 1		41 5	99		39 4	94	
FEMALE				**75 mg/kg**			**150 mg/kg**	
0	19 3	50	19 1	99	50	18 6	96	50
1	20 1	50	19 6	98	50	19 7	98	50
2	21 7	50	20 9	96	50	20 5	94	50
3	22 6	50	21 7	96	50	21 4	95	50
4	22 9	50	22 4	98	50	22 0	96	50
5	23 7	50	22 9	97	50	22 4	95	50
6	24 2	50	23 3	96	50	23 1	95	50
8	25 0	50	23 9	96	50	23 6	94	50
9	25 5	50	24 7	97	50	23 7	93	50
10	25 7	50	25 0	97	49	24 6	96	50
11	26 6	50	25 2	95	49	24 7	93	50
12	27 7	50	25 6	92	48	25 0	90	49
16	29 8	50	27 8	93	48	25 6	86	49
20	29 3	50	27 8	95	48	25 8	88	49
24	30 7	50	29 1	95	48	25 8	84	49
28	31 8	50	28 2	89	48	25 7	81	49
32	32 1	50	28 6	89	48	24 8	77	49
36	32 7	50	29 3	90	48	24 1	74	49
40	33 2	50	29 1	88	48	26 0	78	49
44	33 5	50	29 0	87	48	26 8	80	49
48	34 5	49	29 8	86	47	27 0	78	49
52	34 3	49	30 8	90	46	28 2	82	48
56	35 4	48	31 8	90	44	28 7	81	47
60	37 4	47	33 5	90	43	29 6	79	44
64	39 7	47	33 8	85	43	31 2	79	44
68	39 0	47	34 1	87	43	30 3	78	44
72	40 3	47	34 6	86	43	31 2	77	44
76	39 9	47	34 5	86	43	31 3	78	44
80	40 8	47	35 5	87	42	31 8	78	44
84	42 4	47	36 5	86	42	32 8	77	44
88	42 0	46	36 6	87	42	32 0	76	43
92	42 9	45	35 5	83	42	31 2	73	43
96	43 5	43	34 9	80	41	31 3	72	42
100	43 0	42	34 9	81	39	30 5	71	41
103	44 1	37	36 3	82	38	29 9	68	41
Mean for weeks								
1 12	24 2		23 2	96		22 8	94	
16 52	32 2		29 0	90		26 0	81	
56 103	40 8		34 8	85		30 9	76	



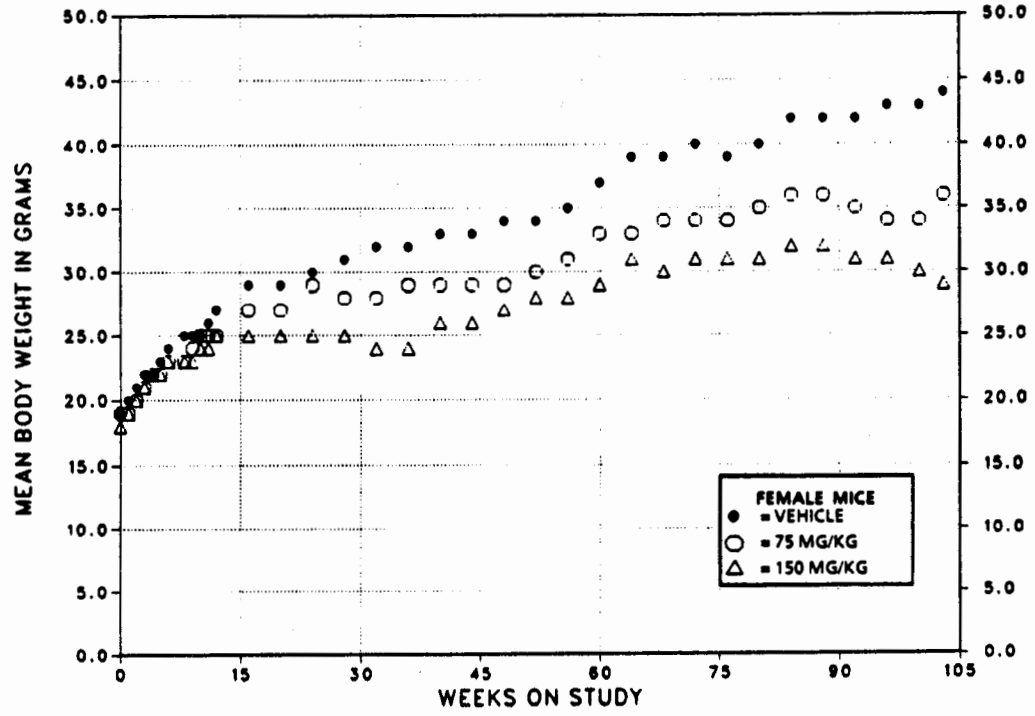


FIGURE 4. GROWTH CURVES FOR MICE ADMINISTERED SUCCINIC ANHYDRIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered succinic anhydride at the doses used in these studies and for vehicle controls are shown in Table 11 and in the Kaplan and Meier curves in Figure 5. Standard (unadjusted) survival curves are presented for comparison in Figure 6. The survival of the vehicle control male mice was significantly lower than that of the high dose group after week 77. No other significant differences in survival were observed between any groups of either sex. To determine whether gavage accidents were the possible cause of early death or the reason for the mice being killed in a moribund condition, a retrospective examination of sections of nose and lung, esophagus and trachea, and heart and mediastinum was performed on all animals that died early. The detection of small oil droplets in the lung of certain animals coded as natural death or moribund kill indicates that some of these deaths may have been related to the dosing (gavage) procedure. A sufficient number of mice in each dose group lived long enough to allow evaluation of the potential carcinogenicity of succinic anhydride.

TABLE 11. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

	Vehicle Control	38 mg/kg	75 mg/kg	150 mg/kg
MALE (a)				
Animals initially in study	50	50	50	
Natural deaths (b)	18	9	(c) 4	
Moribund kills (b)	1	0	1	
Killed accidentally	3	11	3	
Animals missing	1	0	0	
Animals surviving until study termination	27	30	42	
Mean survival (weeks)	87	83	96	
Survival P values (d)	0.001	0.144	0.002	
Survival P values, unadjusted (e)	0.006	0.955	0.004	
FEMALE (a)				
Animals initially in study	50		50	50
Natural deaths (b)	7		4	4
Moribund kills (b)	2		0	0
Killed accidentally	4		8	5
Animals surviving until study termination	37		38	41
Mean survival (weeks)	100		94	97
Survival P values (d)	0.202		0.323	0.286
Survival P values, unadjusted (e)	0.502		1.000	0.562

(a) Termination period: male--week 104; female--weeks 104-105
(b) Some of these early deaths may have been gavage related.
(c) One animal died during the termination period and was combined, for statistical purposes, with those killed at termination.
(d) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns; animals missing or killed accidentally were censored from the analyses.
(e) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns; animals missing or killed accidentally were not censored from the analyses.

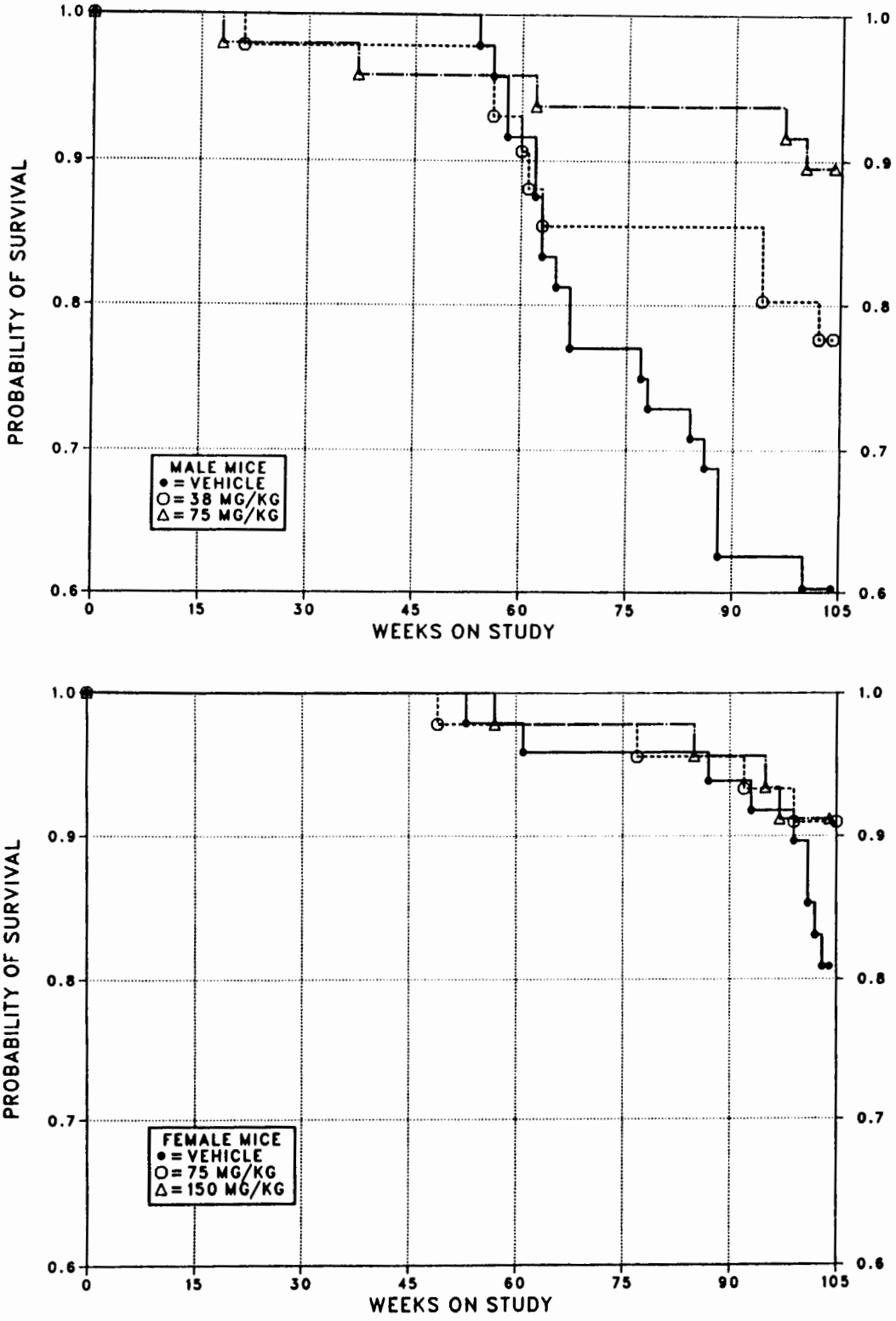


FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED SUCCINIC ANHYDRIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

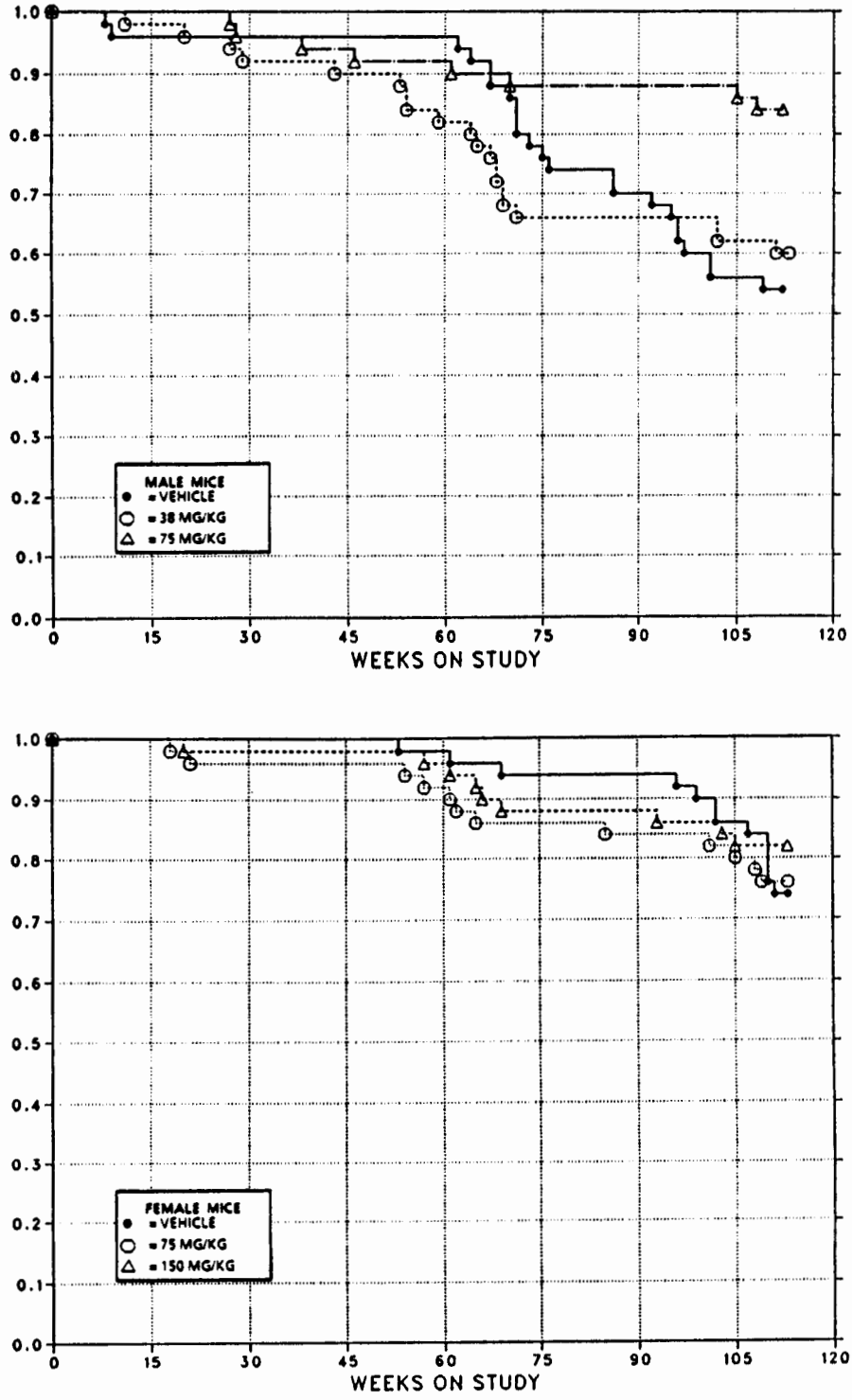


FIGURE 6. STANDARD SURVIVAL CURVES FOR MICE ADMINISTERED SUCCINIC ANHYDRIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with nonneoplastic lesions of the nasal cavity and kidney. No significant increases in the incidences of neoplastic lesions were observed.

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

Nasal Cavity: Acute inflammation and foreign material were seen at increased incidences in dosed male mice (acute inflammation: vehicle control, 1/48; low dose, 9/50; high dose, 9/50; foreign material: 10/48; 24/50; 19/50). The inflammation was considered to be a consequence of the foreign material (corn oil) in the nasal cavity. Squamous metaplasia, secondary to inflammation, was observed in four high dose male mice.

Kidney: Renal mineralization was observed with a decreasing trend in male mice (vehicle control, 16/49; low dose, 6/50; high dose, 0/50).

RESULTS: GENETIC TOXICOLOGY

Succinic anhydride was tested in two laboratories for induction of gene mutations in several strains of *Salmonella typhimurium* by a preincubation protocol with and without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Table H1; Zeiger et al., 1987); no mutagenic activity was observed in any of the strains (TA97, TA98, TA100, TA1535, or TA1537). Succinic anhydride did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells in either the presence or absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Tables H2 and H3). The methods and complete results are presented in Appendix H.

IV. DISCUSSION AND CONCLUSIONS

IV. DISCUSSION AND CONCLUSIONS

Succinic anhydride is a food additive and also has been widely used in the manufacture of polymeric materials, pharmaceuticals, and agricultural chemicals and as a chemical intermediate for a variety of other industrial applications. Toxicology and carcinogenesis studies of 97% pure succinic anhydride (major contaminant was succinic acid) were conducted by administering suspensions in corn oil to male and female F344/N rats and $B6C3F_1$ mice. The gavage route of administration was selected because accurate doses could be given and because human exposure occurs by the oral route. Corn oil was selected as the vehicle because in aqueous media, succinic anhydride readily undergoes hydrolysis to succinic acid, an endogenous metabolic intermediate.

The 13-week studies of succinic anhydride in rats and mice were originally performed after the chemical had been ground with a mortar and pestle before being mixed with corn oil. Because succinic anhydride is not soluble in corn oil, the suspensions were constantly stirred with a magnetic stirrer during the dosing procedures. Before the 2-year studies were begun, a procedure was developed to produce more stable suspensions of succinic anhydride by using a Polytron® homogenizer to reduce particle size. At the start of the 2-year studies, the Polytron®-prepared suspensions were found to be more toxic to rats than those prepared using the mortar and pestle, necessitating a repetition of the short-term studies in this species. The increased toxicity after homogenization with the Polytron® homogenizer may have been due to a decrease in particle size, resulting in increased absorption of succinic anhydride. Dose selection for rats for the 2-year studies presented in this report was based on results of the rat studies in which the Polytron® homogenization procedure was used. Mice did not show similar increased toxic effects in the 2-year studies when dosed with succinic anhydride mixtures prepared by the Polytron® homogenization method; consequently, the 2-year studies in mice were allowed to proceed.

In the 13-week gavage studies, compound-related deaths for male and female rats occurred at doses of 200 mg/kg or higher; these deaths may have arisen from central nervous system depression due to metabolic acidosis resulting from the administration of succinic anhydride. Mean body weights of male rats that received 200 or 400 mg/kg were lower than that of vehicle controls, and these rats were lethargic and had distended abdomens. No clear compound-related histopathologic lesions were detected in the short-term studies in either sex. Thus the doses selected for the 2-year studies in rats were 50 and 100 mg/kg.

In the 13-week studies in mice, compound-related deaths occurred in the 300 and 600 mg/kg groups of males and females. Furthermore, final mean body weights of mice administered 150 or 300 mg/kg succinic anhydride were reduced compared with those of vehicle controls, and the incidence of inflammation of the stomach was increased in males administered 150 or 300 mg/kg. No clear compound-related histopathologic lesions were detected in the short-term studies in either sex. Thus, the highest dose of succinic anhydride selected for the 2-year studies in mice was 75 mg/kg for males and 150 mg/kg for females.

In the 2-year studies, there were no significant decreases in survival between any groups of rats or mice. Male and female rats had an apparent dose-related increase in the number of early deaths attributed to chemical-gavage accidents. Most of the accidental deaths of female rats occurred during the first 2 weeks of the study. Because animals that died from other than natural causes were censored from the survival analyses and because the life table and incidental tumor analyses adjust for intercurrent mortality, these early deaths do not weaken the analyses of the potential carcinogenesis of succinic anhydride. However, to ensure that there would be an adequate number of animals at risk to detect any compound-related neoplastic lesions, the interim evaluation of 10 rats per group scheduled after 15 months of exposure was canceled and all animals surviving to that time were continued on study for the remainder of the exposure period. The design of the studies in mice did not include an interim evaluation. For rats and mice, a sufficient number of animals in each dose group lived long enough to allow evaluation of the potential carcinogenicity of succinic anhydride.

There was a chemical-related effect on body weights for both rats and mice in the 2-year

studies. For rats, mean body weights of high dose males and females were lower than those of vehicle controls during the second year of the studies. For mice, mean body weights of high dose males and dosed females were lower than those of vehicle controls throughout most of the studies.

At no site in rats or mice was there a chemical-related increase in the incidences of nonneoplastic or neoplastic lesions. Squamous metaplasia in the tissues of the nasal cavity was observed in four high dose male mice; however, this effect was considered to be secondary to inflammation resulting from a foreign material (probably the succinic anhydride corn oil mixture) in the nasal cavity. Results of serologic analyses made at three separate intervals during the study were negative for antibodies to murine viruses. The incidence of renal mineralization was decreased in dosed male mice compared with that in vehicle controls; the cause and significance of this change are not known.

Because succinic anhydride is readily hydrolyzed to succinic acid, the most likely site of reactivity of succinic anhydride in a biologic system is its primary site of contact. When applied to the cornea of rabbits, succinic anhydride caused severe eye irritation (Carpenter and Smyth, 1946). In a gavage study, the most likely site of tissue acylation by succinic anhydride is in the gastrointestinal tract. In the 13-week study of succinic anhydride in male mice, the incidences of inflammation of the stomach were increased; however, there were no apparent effects in the stomach of rats or mice after 2 years of exposure to succinic anhydride. Maleic anhydride, an analog of succinic anhydride, caused nasal and ocular irritation but no evidence of systemic toxicity in an inhalation study in which CD® rats, Engle hamsters, or rhesus monkeys were exposed 6 hours per day, 5 days per week for 6 months, at target concentrations of 1, 3, or 10 mg/m^3 (Short et al., 1988). In the only previous extended study of succinic anhydride, Dickens and Jones (1965) observed local transplantable sarcomas in male rats given subcutaneous injections of succinic anhydride for 65 weeks (2 mg per injection, two times per week). Although that study contained too few animals and was too short to evaluate adequately the carcinogenicity of succinic anhydride, it raises concern that direct tissue interaction with succinic anhydride may result in a carcinogenic response. In the current studies, succinic anhydride was not carcinogenic in rats or mice after oral administration.

Phthalic anhydride was the only other anhydride evaluated for carcinogenicity in F344 rats and B6C3F$_1$ mice in 2-year studies (NCI, 1979). In these studies, rats were fed diets containing 0, 7,500, or 15,000 ppm phthalic anhydride for 2 years, and mice were fed diets containing 0, 25,000, or 50,000 ppm. Because of excessive decreases in body weight gain in dosed mice compared with that in controls, doses for males were reduced to 12,500 and 25,000 ppm after week 32 of the study, and doses for females were reduced to 6,250 and 12,500 ppm. There was no evidence of carcinogenicity of phthalic anhydride for rats or mice under the conditions of these studies. In 7-week studies in rats and mice, there were no dose-related histopathologic lesions in either species given diets containing up to 50,000 ppm phthalic anhydride.

Succinic anhydride generally has been negative in assays for mutagenic or clastogenic activity. Succinic anhydride was not mutagenic in *Salmonella typhimurium* (McCann et al., 1975; Kawachi et al., 1978, 1980; Rosenkranz and Poirier, 1979; Simmon 1979a; Ishidate et al., 1981; Zeiger et al., 1987), *Escherichia coli* (Rosenkranz and Poirier, 1979; Rosenkranz and Leifer, 1980; Leifer et al., 1981), *Saccharomyces cerevisiae* (Simmon, 1979b; Simmon et al., 1979), or mouse lymphoma cells (Clive et al., 1979); it was not clastogenic in Chinese hamster lung cells (Ishidate et al., 1981), hamster lung fibroblast or rat bone marrow cells (Kawachi et al., 1978, 1980), or rat hepatocytes (Sina et al., 1983). Succinic anhydride induced morphologically transformed colonies of Syrian golden hamster embryo cells (Pienta et al., 1977; Pienta, 1980) and was positive in the replicative killing test with *E. coli* strain CHY832 (Hayes et al., 1984). Other anhydrides, including acetic anhydride, phthalic anhydride, and maleic anhydride, were also not mutagenic in *S. typhimurium* (Haworth et al., 1983; Zeiger et al., 1985; Mortelmans et al., 1986). In addition, phthalic anhydride did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary

cells (Galloway et al., 1987) but was mutagenic in mouse lymphoma cells (NTP, unpublished).

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

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenic activity** of succinic anhydride for male or female F344/N rats given 50 or 100 mg/kg succinic anhydride. There was *no evidence of carcinogenic activity* for male $B6C3F_1$ mice given 38 or 75 mg/kg succinic anhydride or for female $B6C3F_1$ mice given 75 or 150 mg/kg.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 5.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 8.

V. REFERENCES

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	50 mg/kg	100 mg/kg
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	60	60	60
ALIMENTARY SYSTEM			
Esophagus	(60)	*(60)	(60)
Leiomyosarcoma	1 (2%)		
Intestine large, cecum	(52)	*(60)	(53)
Leukemia mononuclear	1 (2%)		1 (2%)
Lipoma	1 (2%)		
Intestine small, duodenum	(52)	*(60)	(53)
Leiomyosarcoma		1 (2%)	
Intestine small, ileum	(53)	*(60)	(51)
Leiomyosarcoma	1 (2%)		
Intestine small, jejunum	(52)	*(60)	(51)
Leiomyoma			1 (2%)
Liver	(60)	*(60)	(60)
Leukemia mononuclear	13 (22%)	10 (17%)	12 (20%)
Neoplastic nodule	1 (2%)		
Schwannoma malignant, metastatic, peripheral nerve		1 (2%)	
Mesentery	*(60)	*(60)	*(60)
Fibrosarcoma		1 (2%)	
Leukemia mononuclear	1 (2%)		
Mesothelioma malignant		1 (2%)	1 (2%)
Sarcoma		1 (2%)	
Schwannoma malignant, metastatic, peripheral nerve		1 (2%)	
Pancreas	(59)	*(60)	(59)
Leukemia mononuclear	1 (2%)		1 (2%)
Mesothelioma malignant		1 (2%)	1 (2%)
Schwannoma malignant, metastatic, peripheral nerve		1 (2%)	
Salivary glands	(58)	*(60)	(58)
Adenocarcinoma		1 (2%)	
Leukemia mononuclear	1 (2%)		
Sarcoma	1 (2%)	1 (2%)	
Stomach, forestomach	(59)	*(60)	(58)
Leukemia mononuclear	1 (2%)		
Stomach, glandular	(58)	*(60)	(59)
Leukemia mononuclear			1 (2%)
Tooth	*(60)	*(60)	*(60)
Neoplasm, NOS		1 (2%)	
CARDIOVASCULAR SYSTEM			
Heart	(60)	*(60)	(59)
Adenocarcinoma, metastatic, salivary glands		1 (2%)	
Leukemia mononuclear	5 (8%)	1 (2%)	2 (3%)
Osteosarcoma, metastatic, bone	1 (2%)		
Endocardium, schwannoma malignant		1 (2%)	
Epicardium, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(60)	*(60)	(59)
Carcinoma	1 (2%)		
Leukemia mononuclear	5 (8%)	6 (10%)	5 (8%)
Osteosarcoma, metastatic, bone	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
ENDOCRINE SYSTEM (Continued)			
Adrenal gland, medulla	(58)	*(60)	(58)
Leukemia mononuclear	1 (2%)	5 (8%)	1 (2%)
Neuroblastoma malignant		1 (2%)	
Pheochromocytoma malignant	4 (7%)	5 (8%)	2 (3%)
Pheochromocytoma benign	14 (24%)	8 (13%)	9 (16%)
Pheochromocytoma benign, multiple	3 (5%)	1 (2%)	3 (5%)
Bilateral, pheochromocytoma malignant	1 (2%)		
Islets, pancreatic	(59)	*(60)	(60)
Adenoma		2 (3%)	1 (2%)
Adenoma, multiple	1 (2%)		
Carcinoma	1 (2%)		
Parathyroid gland	(51)	*(60)	(51)
Adenoma	1 (2%)		1 (2%)
Pituitary gland	(57)	(59)	(60)
Pars distalis, adenoma	19 (33%)	15 (25%)	13 (22%)
Pars distalis, adenoma, multiple	1 (2%)	1 (2%)	
Pars distalis, carcinoma			1 (2%)
Pars distalis, leukemia mononuclear	1 (2%)	2 (3%)	1 (2%)
Pars intermedia, adenoma	1 (2%)	1 (2%)	
Pars intermedia, leukemia mononuclear	1 (2%)		
Thyroid gland	(60)	(60)	(58)
Leukemia mononuclear	1 (2%)		
C-cell, adenoma	7 (12%)	7 (12%)	5 (9%)
C-cell, carcinoma	6 (10%)	2 (3%)	2 (3%)
Follicular cell, adenoma	1 (2%)		
Follicular cell, adenoma, multiple			1 (2%)
GENERAL BODY SYSTEM			
Tissue, NOS	*(60)	*(60)	*(60)
Schwannoma malignant, metastatic, spinal cord	1 (2%)		
GENITAL SYSTEM			
Epididymis	(60)	*(60)	(59)
Mesothelioma malignant	2 (3%)	2 (3%)	2 (3%)
Preputial gland	(48)	*(60)	(51)
Adenoma		4 (7%)	1 (2%)
Seminal vesicle	(59)	*(60)	(57)
Leukemia mononuclear	1 (2%)		
Mesothelioma malignant		1 (2%)	2 (4%)
Schwannoma malignant, metastatic, peripheral nerve		1 (2%)	
Testes	(60)	*(60)	(60)
Adenoma		1 (2%)	
Leukemia mononuclear	1 (2%)		
Mesothelioma malignant	2 (3%)	3 (5%)	4 (7%)
Interstitial cell, adenoma	8 (13%)	4 (7%)	6 (10%)
Interstitial cell, adenoma, multiple	48 (80%)	43 (72%)	42 (70%)
HEMATOPOIETIC SYSTEM			
Lymph node	(60)	*(60)	(60)
Mediastinal, leukemia mononuclear		1 (2%)	
Mediastinal, mesothelioma malignant, metastatic, mesentery		1 (2%)	
Lymph node, mandibular	(50)	*(60)	(51)
Leukemia mononuclear	1 (2%)	3 (5%)	1 (2%)
Lymph node, mesenteric	(57)	*(60)	(59)
Leukemia mononuclear	2 (4%)	2 (3%)	3 (5%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
HEMATOPOIETIC SYSTEM (Continued)			
Spleen	(59)	*(60)	(60)
Hemangiosarcoma	1 (2%)		
Leukemia mononuclear	13 (22%)	11 (18%)	11 (18%)
Mesothelioma malignant		2 (3%)	1 (2%)
Schwannoma malignant, metastatic, peripheral nerve		1 (2%)	
Thymus	(45)	*(60)	(48)
Leukemia mononuclear	3 (7%)	1 (2%)	1 (2%)
Schwannoma malignant		1 (2%)	
Schwannoma malignant, metastatic, peripheral nerve		1 (2%)	
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	*(60)	(42)
Adenoma	1 (2%)		
Fibroadenoma	1 (2%)	2 (3%)	1 (2%)
Skin	(60)	*(60)	(59)
Basal cell carcinoma	1 (2%)		1 (2%)
Keratoacanthoma	2 (3%)		6 (10%)
Papilloma squamous	2 (3%)	1 (2%)	
Trichoepithelioma	2 (3%)		
Subcutaneous tissue, fibroma	3 (5%)	3 (5%)	2 (3%)
Subcutaneous tissue, myxosarcoma	1 (2%)		
Subcutaneous tissue, neurofibroma		1 (2%)	
Subcutaneous tissue, neurofibrosarcoma			1 (2%)
Subcutaneous tissue, sarcoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(60)	*(60)	(60)
Femur, osteosarcoma	1 (2%)		
Vertebra, osteosarcoma	1 (2%)		
Skeletal muscle	*(60)	*(60)	*(60)
Abdominal, mesothelioma malignant			1 (2%)
Diaphragm, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
NERVOUS SYSTEM			
Brain	(60)	*(60)	(60)
Carcinoma, extension			1 (2%)
Glioma benign	1 (2%)		
Leukemia mononuclear	1 (2%)		1 (2%)
Oligodendroglioma benign		1 (2%)	
Cerebrum, glioma benign	1 (2%)		
Peripheral nerve	*(60)	*(60)	*(60)
Schwannoma malignant		1 (2%)	
Spinal cord	*(60)	*(60)	*(60)
Schwannoma malignant	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(60)	(60)	(60)
Adenocarcinoma, metastatic, salivary glands		1 (2%)	
Alveolar/bronchiolar adenoma	2 (3%)		1 (2%)
Alveolar/bronchiolar carcinoma		1 (2%)	
Leukemia mononuclear	9 (15%)	9 (15%)	10 (17%)
Mesothelioma malignant, metastatic, mesentery		1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)		
Sarcoma, metastatic, salivary glands	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
RESPIRATORY SYSTEM			
Lung (Continued)	(60)	(60)	(60)
Schwannoma malignant, metastatic, peripheral nerve		1 (2%)	
Pleura, mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		1 (2%)	
Pleura, mediastinum, thymoma malignant, metastatic, thymus		1 (2%)	
Nose	(58)	(59)	(59)
Chondroma			1 (2%)
SPECIAL SENSES SYSTEM			
Zymbal gland	*(60)	*(60)	*(60)
Adenoma		1 (2%)	
URINARY SYSTEM			
Kidney	(60)	(60)	(59)
Leukemia mononuclear	2 (3%)	2 (3%)	2 (3%)
Osteosarcoma, metastatic, bone	1 (2%)		
Sarcoma			1 (2%)
Renal tubule, adenoma	1 (2%)		1 (2%)
Urinary bladder	(59)	*(60)	(59)
Leukemia mononuclear	1 (2%)		
Mesothelioma malignant		1 (2%)	2 (3%)
SYSTEMIC LESIONS			
Multiple organs	*(60)	*(60)	*(60)
Leukemia mononuclear	13 (22%)	11 (18%)	12 (20%)
Mesothelioma malignant	2 (3%)	3 (5%)	4 (7%)
Hemangiosarcoma	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	60	60	60
Terminal sacrifice	36	33	32
Moribund (a)	15	16	10
Dead (a)	8	9	14
Gavage death	1	2	4
TUMOR SUMMARY			
Total animals with primary neoplasms **	60	57	52
Total primary neoplasms	159	128	121
Total animals with benign neoplasms	59	56	51
Total benign neoplasms	122	96	95
Total animals with malignant neoplasms	30	28	21
Total malignant neoplasms	37	31	26
Total animals with secondary neoplasms ***	3	5	
Total secondary neoplasms	6	15	
Total animals with neoplasms--uncertain benign or malignant		1	
Total uncertain neoplasms		1	

(a) Some of these early deaths may have been gavage related.
* 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 GAVAGE STUDY OF SUCCINIC ANHYDRIDE: VEHICLE CONTROL

WEEKS ON STUDY	021	052	069	078	079	083	085	086	087	091	091	092	093	095	098	099	099	100	101	102	102	103	103	104	105
CARCASS ID	124	084	035	085	015	025	075	055	155	073	074	065	034	123	064	063	144	133	533	833	014	822	122	092	011
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma												X													
Intestine large	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+
Intestine large, cecum	M	A	A	+	+	+	A	+	A	+	+	M	+	+	+	+	+	+	A	+	+	+	A	+	+
Leukemia mononuclear						X																			
Lipoma																									
Intestine large, colon	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+
Intestine large, rectum	M	A	A	+	+	+	A	+	A	+	+	M	+	+	+	+	+	+	A	+	+	+	A	+	M
Intestine small	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+
Intestine small, duodenum	A	A	A	+	+	+	A	+	A	+	+	M	+	+	+	+	+	+	A	+	+	+	A	+	+
Intestine small, ileum	M	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+
Leiomyosarcoma																				X					
Intestine small, jejunum	M	A	A	+	+	+	A	+	A	+	+	M	+	+	+	+	+	+	A	+	+	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X	X			X					X	X	X								
Neoplastic nodule																									
Mesentery					+	+														+				+	
Leukemia mononuclear						X																			
Pancreas	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X																			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Leukemia mononuclear										X															
Sarcoma															X										
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Stomach, *forestomach*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Leukemia mononuclear							X																		
Stomach, glandular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X	X	X			X							X								
Osteosarcoma, metastatic, bone																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leukemia mononuclear							X									X	X								
Osteosarcoma, metastatic, bone																									
Adrenal gland, medulla	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															
Pheochromocytoma malignant																									
Pheochromocytoma benign							X			X	X			X					X		X				
Pheochromocytoma benign, multiple																								X	X
Bilateral, pheochromocytoma malignant																							X		
Islets, pancreatic	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, multiple																									
Carcinoma															X										
Parathyroid gland	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Pars distalis, adenoma								X			X		X	X						X		X			X
Pars distalis, adenoma, multiple																									
Pars distalis, leukemia mononuclear							X																		
Pars intermedia, adenoma																									
Pars intermedia, leukemia mononuclear					X																				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
C-cell, adenoma																									
C-cell, carcinoma																			X				X		X
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS		+																	+						
Schwannoma malignant, metastatic, spinal cord		X																							
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant									X																
Preputial gland	M	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	M	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
Mesothelioma malignant									X																
Interstitial cell, adenoma		X	X		X		X	X	X											X		X			
Interstitial cell, adenoma, multiple				X		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: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	012	013	021	022	023	024	031	032	033	041	042	043	044	045	051	052	054	055	061	062	071	072	081	091	093
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lipoma																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X			X	X		X	X	X						
Neoplastic nodule															X										
Mesentery						+		+							+			+	+			+			
Leukemia mononuclear																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Salivary glands	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Sarcoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Osteosarcoma, metastatic, bone																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma											X														
Leukemia mononuclear											X						X								
Osteosarcoma, metastatic, bone																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pheochromocytoma malignant		X				X				X															
Pheochromocytoma benign				X			X		X			X			X				X		X				X
Pheochromocytoma benign, multiple																X									
Bilateral, pheochromocytoma malignant																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, multiple																									
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	M
Adenoma							X																		
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X			X						X			X				X						X	
Pars distalis, adenoma, multiple																									
Pars distalis, leukemia mononuclear																									
Pars intermedia, adenoma	X																								
Pars intermedia, leukemia mononuclear																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
C cell, adenoma								X		X						X	X			X				X	X
C cell, carcinoma													X												
Follicular cell, adenoma							X																		
GENERAL BODY SYSTEM																									
Tissue, NOS																									
Schwannoma malignant, metastatic, spinal cord																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant											X														
Preputial gland	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesothelioma malignant											X														
Interstitial cell, adenoma																									
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	X

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	0094	0095	0101	0102	0103	0104	0111	0112	0121	0125	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Leiomyosarcoma											1
Intestine large	+	+	+	+	+	+	+	+	+	+	54
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	52
Leukemia mononuclear											1
Lipoma	X										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	54
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	51
Intestine small	+	+	+	+	+	+	+	+	+	+	54
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	53
Leiomyosarcoma											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	52
Liver	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											13
Neoplastic nodule											1
Mesentery				+			+		+		13
Leukemia mononuclear											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	58
Leukemia mononuclear											1
Sarcoma											1
Stomach	+	+	+	+	+	+	+	+	+	+	59
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	58
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											5
Osteosarcoma, metastatic, bone				X							1
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Carcinoma											1
Leukemia mononuclear											5
Osteosarcoma, metastatic, bone				X							1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	58
Leukemia mononuclear											1
Pheochromocytoma malignant	X										4
Pheochromocytoma benign											14
Pheochromocytoma benign, multiple											3
Bilateral, pheochromocytoma malignant											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	59
Adenoma, multiple				X							1
Carcinoma											1
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	51
Adenoma											1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	57
Pars distalis, adenoma	X	X	X			X			X		19
Pars distalis, adenoma, multiple								X			1
Pars distalis, leukemia mononuclear											1
Pars intermedia, adenoma											1
Pars intermedia leukemia mononuclear											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											1
C cell, adenoma		X									7
C cell, carcinoma								X			6
Follicular cell, adenoma											1
GENERAL BODY SYSTEM											
Tissue, NOS											2
Schwannoma malignant, metastatic, spinal cord											1
GENITAL SYSTEM											
Epididymis	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant											2
Preputial gland	+	+	+	M	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	59
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											1
Testes	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											1
Mesothelioma malignant											2
Interstitial cell, adenoma											8
Interstitial cell, adenoma, multiple	X	X	X	X	X	X	X	X	X	X	48

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

WEEKS ON STUDY	021	052	069	078	079	083	085	086	087	091	091	092	093	095	098	099	099	100	101	102	102	103	103	104	105
CARCASS ID	124	084	035	085	015	025	075	105	115	073	074	065	034	123	064	063	114	113	053	083	014	082	122	092	011
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+
Leukemia mononuclear							X																		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	M	+	+
Leukemia mononuclear						X	X																		
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma	X																								
Leukemia mononuclear					X	X	X			X						X	X	X							
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	M	M	+
Leukemia mononuclear						X	X			X															
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma																					X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																X					X				
Papilloma squamous																									
Trichoepithelioma																								X	
Subcutaneous tissue, fibroma				X													X								
Subcutaneous tissue, myxosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma																									
Vertebra, osteosarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma benign			X																						
Leukemia mononuclear																		X							
Cerebrum, glioma benign																			X						
Spinal cord		+									+				+										
Schwannoma malignant		X																							
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Leukemia mononuclear					X	X				X						X		X							
Osteosarcoma, metastatic, bone																									
Sarcoma, metastatic, salivary glands																X									
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye															+									+	+
Harderian gland																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X	X																		
Osteosarcoma, metastatic, bone																									
Renal tubule, adenoma														X											
Ureter		+																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	012	013	021	022	023	024	031	032	033	041	042	043	044	045	051	052	054	055	061	062	071	072	081	091	093
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	M	+	M	M	+	+	+	+	+
Leukemia mononuclear																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Leukemia mononuclear											X			X	X		X	X	X						
Thymus	+	+	+	+	M	M	M	+	+	M	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+
Leukemia mononuclear																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	M	+	+	M	+	+	+
Adenoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma														X											
Keratoacanthoma																									
Papilloma squamous																		X							
Trichoepithelioma																									
Subcutaneous tissue, fibroma									X																
Subcutaneous tissue, myxosarcoma				X																					
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femur, osteosarcoma																									
Vertebra, osteosarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma benign																									
Leukemia mononuclear																									
Cerebrum, glioma benign																									
Spinal cord																									
Schwannoma malignant																									
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma									X											X					
Leukemia mononuclear											X			X			X		X						
Osteosarcoma, metastatic, bone																									
Sarcoma, metastatic, salivary glands																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye		+					+										+		+						
Harderian gland																	+								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Osteosarcoma, metastatic, bone																									
Renal tubule, adenoma																									
Ureter																									
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL:
CARCASS ID	094	099	101	102	103	104	111	112	121	125	TISSUES TUMORS
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Lymph node	+	+	+	+	+	+	+	+	+	+	60
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	50
Leukemia mononuclear											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	57
Leukemia mononuclear											2
Spleen	+	+	+	+	+	+	+	+	+	+	59
Hemangiosarcoma											1
Leukemia mononuclear											13
Thymus	M	M	+	+	+	M	+	+	M	+	45
Leukemia mononuclear											3
INTEGUMENTARY SYSTEM											
Mammary gland	+	M	+	M	+	+	+	+	+	M	48
Adenoma			X								1
Fibroadenoma											1
Skin	+	+	+	+	+	+	+	+	+	+	60
Basal cell carcinoma											1
Keratoacanthoma											2
Papilloma squamous									X		2
Trichoepithelioma	X										2
Subcutaneous tissue, fibroma											3
Subcutaneous tissue, myxosarcoma											1
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	60
Femur, *osteosarcoma*				X							1
Vertebra, osteosarcoma				X							1
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
Glioma benign											1
Leukemia mononuclear											1
Cerebrum, glioma benign											1
Spinal cord											3
Schwannoma malignant											1
RESPIRATORY SYSTEM											
Larynx	+	+	+	M	+	+	+	+	+	+	59
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma											2
Leukemia mononuclear											9
Osteosarcoma, metastatic, bone				X							1
Sarcoma, metastatic, salivary glands											1
Nose	+	+	+	+	+	+	+	+	+	+	58
Trachea	+	+	+	+	+	+	+	+	+	+	60
SPECIAL SENSES SYSTEM											
Eye					+						8
Harderian gland					+						2
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											2
Osteosarcoma, metastatic, bone				X							1
Renal tubule, adenoma											1
Ureter											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE: 50 mg/kg

WEEKS ON STUDY	001	028	040	053	065	071	079	082	083	084	086	089	089	091	092	092	095	097	097	099	101	101	102	103
CARCASS ID	175	144	145	135	234	225	194	193	165	164	233	224	134	184	133	143	192	205	183	142	132	163	141	245	173
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	A	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	M	A	+	+	+	+	+	+	+	+	+	+	M	+	A	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+
Intestine small, duodenum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+
Leiomyosarcoma									X																
Intestine small, ileum	M	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+
Intestine small, jejunum	M	A	+	+	+	+	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X			X				X		
Schwannoma malignant, metastatic, peripheral nerve							X																		
Mesentery					+		+											+		+				+	
Fibrosarcoma																		X							
Mesothelioma malignant																				X					
Sarcoma																									
Schwannoma malignant, metastatic, peripheral nerve							X																		
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																				X					
Schwannoma malignant, metastatic, peripheral nerve							X																		
Salivary glands		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma				X																					
Sarcoma												X													
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Tooth										+															
Neoplasm, NOS										X															
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, salivary glands				X																					
Leukemia mononuclear																		X							
Endocardium, schwannoma malignant																					X				
Epicardium, alveolar/bronchiolar carcinoma, metastatic, lung																						X			
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X			X							
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X			X							
Neuroblastoma malignant																									
Pheochromocytoma malignant													X				X						X		
Pheochromocytoma benign																X					X	X		X	
Pheochromocytoma benign, multiple																									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+
Adenoma																			X						
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Pars distalis, adenoma					X	X		X											X						
Pars distalis, adenoma, multiple							X																		
Pars distalis, leukemia mononuclear																			X						
Pars intermedia, adenoma																							X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma											X		X		X				X						
C cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant														X					X						
Preputial gland	M	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	M
Adenoma																X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																			X						
Schwannoma malignant, metastatic, peripheral nerve							X																		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Mesothelioma malignant														X					X						
Interstitial cell, adenoma														X				X			X				
Interstitial cell, adenoma, multiple									X	X		X	X	X	X	X	X		X		X	X	X	X	

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 50 mg/kg (Continued)

WEEKS ON STUDY	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	182	231	131	151	152	153	154	155	161	162	171	172	174	181	185	191	195	201	202	203	204	211	212	213	214
ALIMENTARY SYSTEM																									
Esophagus	+	+																							
Intestine large	+	+																							
Intestine large, cecum	+	+																							
Intestine large, colon	+	+																							
Intestine large, rectum	+	+																							
Intestine small	+	+																							
Intestine small, duodenum	+	+																							
Leiomyosarcoma																									
Intestine small, ileum	+	+																							
Intestine small, jejunum	+	+																							
Liver	+	+			+	+	+		+			+	+	+	+	+	+	+			+	+	+	+	+
Leukemia mononuclear		X													X	X								X	
Schwannoma malignant, metastatic, peripheral nerve																									
Mesentery							+				+	+			+					+				+	+
Fibrosarcoma																									
Mesothelioma malignant																									
Sarcoma							X																		
Schwannoma malignant, metastatic, peripheral nerve																									
Pancreas	+	+																							
Mesothelioma malignant																									
Schwannoma malignant, metastatic, peripheral nerve																									
Salivary glands	+	+																							
Adenocarcinoma																									
Sarcoma																									
Stomach	+	+																				+			+
Stomach, forestomach	+	+																							+
Stomach, glandular	+	+																				+			+
Tooth																									
Neoplasm, NOS																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+				+																			
Adenocarcinoma, metastatic, salivary glands																									
Leukemia mononuclear																									
Endocardium, schwannoma malignant																									
Epicardium, alveolar/bronchiolar carcinoma, metastatic, lung																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X												X	X									
Adrenal gland, medulla	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Leukemia mononuclear			X																					X	
Neuroblastoma malignant																		X							
Pheochromocytoma malignant											X														
Pheochromocytoma benign		X				X																			
Pheochromocytoma benign, multiple	X																								
Islets, pancreatic	+	+						+																	
Adenoma								X																	
Parathyroid gland	+	+																							
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X						X	X	X						X		X	X						
Pars distalis, adenoma, multiple																									
Pars distalis, leukemia mononuclear																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma													X	X			X								
C cell, carcinoma		X																							
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+																				+			
Mesothelioma malignant																									
Preputial gland	+	+								+			+					+							
Adenoma	X												X					X							
Prostate	+	+																					+		
Seminal vesicle	+	+												+											
Mesothelioma malignant																									
Schwannoma malignant, metastatic, peripheral nerve																									
Testes	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+
Adenoma																									
Mesothelioma malignant										X															
Interstitial cell, adenoma									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	X	X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 50 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	215	221	222	223	232	235	241	242	243	244	
ALIMENTARY SYSTEM											
Esophagus			+								28
Intestine large			+					+			27
Intestine large, cecum			+					+			24
Intestine large, colon			+								25
Intestine large, rectum			+								25
Intestine small			+								25
Intestine small, duodenum			+								24
Leiomyosarcoma											1
Intestine small, ileum			+								24
Intestine small, jejunum			+								23
Liver		+	+				+		+		47
Leukemia mononuclear							X		X		10
Schwannoma malignant, metastatic, peripheral nerve											1
Mesentery				+	+						14
Fibrosarcoma											1
Mesothelioma malignant											1
Sarcoma											1
Schwannoma malignant, metastatic, peripheral nerve											1
Pancreas			+								26
Mesothelioma malignant											1
Schwannoma malignant, metastatic, peripheral nerve											1
Salivary glands			+								27
Adenocarcinoma											1
Sarcoma											1
Stomach	+		+	+							31
Stomach, forestomach	+		+								29
Stomach, glandular	+		+	+							31
Tooth											1
Neoplasm, NOS											1
CARDIOVASCULAR SYSTEM											
Heart			+								29
Adenocarcinoma, metastatic, salivary glands											1
Leukemia mononuclear											1
Endocardium, schwannoma malignant											1
Epicardium, alveolar/bronchiolar carcinoma, metastatic, lung											1
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear							X				6
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	58
Leukemia mononuclear									X		5
Neuroblastoma malignant											1
Pheochromocytoma malignant								X			5
Pheochromocytoma benign			X			X					8
Pheochromocytoma benign, multiple											1
Islets, pancreatic			+								27
Adenoma											2
Parathyroid gland			+								26
Pituitary gland	+	+	+	+	+	+	+	+	+	+	59
Pars distalis, adenoma	X		X	X							15
Pars distalis, adenoma, multiple											1
Pars distalis, leukemia mononuclear									X		2
Pars intermedia, adenoma											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C cell, adenoma											7
C cell, carcinoma				X							2
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Epididymis			+								29
Mesothelioma malignant											2
Preputial gland			+								23
Adenoma											4
Prostate			+								29
Seminal vesicle	+	+	+								30
Mesothelioma malignant											1
Schwannoma malignant, metastatic, peripheral nerve											1
Testes	+	+	+	+	+	+	+	+	+	+	58
Adenoma								X			1
Mesothelioma malignant											3
Interstitial cell, adenoma											4
Interstitial cell, adenoma, multiple		X	X	X	X	X	X		X	X	43

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 50 mg/kg (Continued)

WEEKS ON STUDY	001	028	040	053	065	071	079	082	083	084	086	089	089	089	091	092	092	095	097	097	099	101	101	102	103
CARCASS ID	175	144	145	135	234	225	194	193	165	164	233	224	134	184	133	143	192	205	183	142	132	163	141	245	173
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear																					X				
Mediastinal, mesothelioma malignant, metastatic, mesentery																				X					
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X					X				
Lymph node, mesenteric	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X			X		X		X		
Mesothelioma malignant															X					X					
Schwannoma malignant, metastatic, peripheral nerve							X																		
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Schwannoma malignant											X														
Schwannoma malignant, metastatic, peripheral nerve							X																		
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Subcutaneous tissue, fibroma					X																				X
Subcutaneous tissue, neurofibroma						X																			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																							+		
Diaphragm, alveolar/bronchiolar carcinoma, metastatic, lung																							X		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma benign																							X		
Peripheral nerve							+																		
Schwannoma malignant							X																		
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, salivary glands				X																					
Alveolar/bronchiolar carcinoma																							X		
Leukemia mononuclear																X			X		X				
Mesothelioma malignant, metastatic, mesentery																				X					
Schwannoma malignant, metastatic, peripheral nerve							X																		
Pleura, mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																							X		
Pleura, mediastinum, thymoma malignant, metastatic, thymus											X														
Nose	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye							+														+	+	+		
Harderian gland																						+			
Zymbal gland																	+								
Adenoma																	X								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X									
Urinary bladder	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant															X										

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 50 mg/kg (Continued)

WEEKS ON STUDY	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	182	231	131	151	152	153	154	155	161	162	171	172	174	181	185	191	195	201	202	203	204	211	212	213	214
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+																							
Lymph node	+	+																							
Mediastinal, leukemia mononuclear																									
Mediastinal, mesothelioma malignant, metastatic, mesentery																									
Lymph node, mandibular	+	+																							
Leukemia mononuclear																									
Lymph node, mesenteric	+	+																							
Leukemia mononuclear																									
Spleen	+	+	+		+								+		+	+	+				+			+	
Leukemia mononuclear		X	X												X	X								X	
Mesothelioma malignant																									
Schwannoma malignant, metastatic, peripheral nerve																									
Thymus	+	+																							
Leukemia mononuclear																									
Schwannoma malignant																									
Schwannoma malignant, metastatic, peripheral nerve																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+											+												
Fibroadenoma													X												
Skin	+	+															+								
Papilloma squamous																	X								
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, neurofibroma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+																							
Skeletal muscle																									
Diaphragm, alveolar/bronchiolar carcinoma, metastatic, lung																									
NERVOUS SYSTEM																									
Brain		+																							
Oligodendroglioma benign																									
Peripheral nerve																									
Schwannoma malignant																									
RESPIRATORY SYSTEM																									
Larynx	+	+																							
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, salivary glands																									
Alveolar/bronchiolar carcinoma																									
Leukemia mononuclear		X	X												X	X									
Mesothelioma malignant, metastatic, mesentery																									
Schwannoma malignant, metastatic, peripheral nerve																									
Pleura, mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																									
Pleura, mediastinum, thymoma malignant, metastatic, thymus																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+																							
SPECIAL SENSES SYSTEM																									
Eye								+														+	+	+	
Harderian gland																									
Zymbal gland																									
Adenoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X									
Urinary bladder	+	+																							
Mesothelioma malignant																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 50 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	215	221	222	223	232	235	241	242	243	244	
HEMATOPOIETIC SYSTEM											
Bone marrow			+								28
Lymph node			+						+		29
Mediastinal, leukemia mononuclear											1
Mediastinal, mesothelioma malignant, *metastatic, mesentery*											1
Lymph node, mandibular			+						+		28
Leukemia mononuclear									X		3
Lymph node, mesenteric			+						+		28
Leukemia mononuclear									X		2
Spleen			+		+		+		+		39
Leukemia mononuclear							X		X		11
Mesothelioma malignant											2
Schwannoma malignant, metastatic, peripheral nerve											1
Thymus			+						+		28
Leukemia mononuclear									X		1
Schwannoma malignant											1
Schwannoma malignant, metastatic, peripheral nerve											1
INTEGUMENTARY SYSTEM											
Mammary gland		+	M								25
Fibroadenoma		X									2
Skin			+						+		29
Papilloma squamous											1
Subcutaneous tissue, fibroma									X		3
Subcutaneous tissue, neurofibroma											1
MUSCULOSKELETAL SYSTEM											
Bone			+								28
Skeletal muscle											1
Diaphragm, alveolar/bronchiolar carcinoma, metastatic, lung											1
NERVOUS SYSTEM											
Brain			+								27
Oligodendroglioma benign											1
Peripheral nerve											1
Schwannoma malignant											1
RESPIRATORY SYSTEM											
Larynx			+								27
Lung	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma, metastatic, salivary glands											1
Alveolar/bronchiolar carcinoma											1
Leukemia mononuclear							X		X		9
Mesothelioma malignant, metastatic, mesentery											1
Schwannoma malignant, metastatic, peripheral nerve											1
Pleura, mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung											1
Pleura, mediastinum, thymoma malignant, metastatic, thymus											1
Nose	+	+	+	+	+	+	+	+	+	+	59
Trachea			+								28
SPECIAL SENSES SYSTEM											
Eye											8
Harderian gland											1
Zymbal gland											1
Adenoma											1
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											2
Urinary bladder			+								27
Mesothelioma malignant											1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE: 100 mg/kg

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 100 mg/kg (Continued)

WEEKS ON STUDY	102	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	263	312	341	251	252	254	261	262	271	272	273	281	282	291	292	293	301	302	303	311	321	322	323	331	334
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Mesentery						+						+	+								+			+	+
Mesothelioma malignant																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesothelioma malignant																						X			
Pharynx										+															
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Tooth																		+							
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pheochromocytoma malignant								X																	
Pheochromocytoma benign		X	X		X			X		X				X				X			X				
Pheochromocytoma benign, multiple													X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	M	M	M
Adenoma			X																						
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X		X		X					X	X						X			X				
Pars distalis, carcinoma																									
Pars distalis, leukemia mononuclear																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma		X					X	X	X											X					
C cell, carcinoma								X		X															
Follicular cell, adenoma, multiple		X																							
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Mesothelioma malignant																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																X						X			
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																X						X			
Interstitial cell, adenoma	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	X	X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 100 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	342	343	345	351	352	353	354	355	361	362	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large	+	+	+	+	+	+	+	+	+	+	54
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	53
Leukemia mononuclear											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	51
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	54
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	53
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	51
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	51
Leiomyoma								X			1
Liver	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X		X	X		X					12
Mesentery						+			+		12
Mesothelioma malignant											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											1
Mesothelioma malignant											1
Pharynx											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	58
Stomach	+	+	+	+	+	+	+	+	+	+	59
Stomach, forestomach	+	+	+	+	+	+	+	+	+	M	58
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											1
Tooth											1
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											2
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	59
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear	X										5
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	58
Leukemia mononuclear						X					1
Pheochromocytoma malignant										X	2
Pheochromocytoma benign											9
Pheochromocytoma benign, multiple											3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Adenoma	X										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	51
Adenoma											1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma				X					X		13
Pars distalis, carcinoma											1
Pars distalis, leukemia mononuclear											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	58
C cell, adenoma											5
C cell, carcinoma											2
Follicular cell, adenoma, multiple											1
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Epididymis	+	+	+	+	+	+	+	+	+	+	59
Mesothelioma malignant											2
Preputial gland	M	+	+	+	+	+	+	+	+	M	51
Adenoma											1
Prostate	+	+	+	+	+	+	+	+	+	+	58
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	57
Mesothelioma malignant											2
Testes	+	+	+	+	+	+	+	+	+	+	60
Mesothelioma malignant											4
Interstitial cell, adenoma											6
Interstitial cell, adenoma, multiple	X	X	X	X	X	X	X	X	X	X	42

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 100 mg/kg (Continued)

WEEKS ON STUDY	010	012	014	026	027	030	044	062	067	074	077	080	082	087	087	090	092	095	096	097	100	100	101	102	102
CARCASS ID	335	344	305	255	325	365	285	265	364	315	333	253	264	314	284	304	332	313	283	324	295	294	274	275	363
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	M	M	+	+	M	+	M
Leukemia mononuclear																								X	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X		X				X	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X								X	X		X	X		X	X	
Mesothelioma malignant																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	A	+	+	+	+	+
Leukemia mononuclear																								X	
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	M	+	M	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Basal cell carcinoma																									
Keratoacanthoma																							X		
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, neurofibrosarcoma																									
Subcutaneous tissue, sarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle													+												
Abdominal, mesothelioma malignant													X												
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, extension														X											
Leukemia mononuclear										X															
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Leukemia mononuclear										X							X	X		X	X		X	X	
Nose	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondroma																			X						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye											+										+				
Harderian gland																					+				
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Leukemia mononuclear										X										X					
Sarcoma																									
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Mesothelioma malignant																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 100 mg/kg (Continued)

WEEKS ON STUDY	102	103	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	263	312	341	251	252	254	261	262	271	272	273	281	282	291	292	293	301	302	303	311	321	322	323	331	334
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	
Leukemia mononuclear																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear																	X								
Mesothelioma malignant																						X			
Thymus	+	+	+	M	+	+	+	+	+	+	+	M	M	M	M	+	M	+	+	+	+	M	+	+	
Leukemia mononuclear																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	M	M	M	M	+	+	+	+	+	+	M	+	M	+	M	M
Fibroadenoma																	X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Basal cell carcinoma																		X							
Keratoacanthoma										X	X									X		X			
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, neurofibrosarcoma																									
Subcutaneous tissue, sarcoma														X											
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle												+													
Abdominal, mesothelioma malignant																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, extension																									
Leukemia mononuclear																									
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma								X																	
Leukemia mononuclear																	X								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chondroma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye		+				+		+										+							
Harderian gland						+																			
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Sarcoma																X									
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																X						X			

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 100 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	342	343	345	351	352	353	354	355	361	362	
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+	+	+	+	+	+	59
Lymph node	+	+	+	+	+	+	+	+	+	+	60
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear											1
Lymph node, mesenteric	M	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											3
Spleen	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X		X	X							11
Mesothelioma malignant											1
Thymus	M	+	+	+	+	+	+	+	M	+	48
Leukemia mononuclear											1
INTEGUMENTARY SYSTEM											
Mammary gland	+	+	M	+	M	+	+	+	M	+	42
Fibroadenoma											1
Skin	+	+	+	+	+	+	+	+	+	+	59
Basal cell carcinoma											1
Keratoacanthoma	X										6
Subcutaneous tissue, fibroma							X		X		2
Subcutaneous tissue, neurofibrosarcoma			X								1
Subcutaneous tissue, sarcoma											1
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											2
Abdominal, mesothelioma malignant											1
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
Carcinoma, extension											1
Leukemia mononuclear											1
RESPIRATORY SYSTEM											
Larynx	+	+	+	+	+	+	+	+	+	+	59
Lung	+	+	+	+	+	+	+	+	+	+	60
Alveolar/bronchiolar adenoma											1
Leukemia mononuclear	X					X					10
Nose	+	+	+	+	+	+	+	+	+	+	59
Chondroma											1
Trachea	+	+	+	+	+	+	+	+	+	+	59
SPECIAL SENSES SYSTEM											
Eye				+						+	8
Harderian gland										+	3
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											2
Sarcoma											1
Renal tubule, adenoma		X									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	59
Mesothelioma malignant											2

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	50 mg/kg	100 mg/kg
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	17/58 (29%)	9/58 (16%)	12/58 (21%)
Adjusted Rates (b)	38.3%	23.2%	31.9%
Terminal Rates (c)	10/36 (28%)	3/31 (10%)	7/32 (22%)
Day of First Observation	590	641	625
Life Table Tests (d)	P=0.266N	P=0.129N	P=0.321N
Incidental Tumor Tests (d)	P=0.318N	P=0.092N	P=0.390N
Cochran-Armitage Trend Test (d)	P=0.156N		
Fisher Exact Test (d)		P=0.059N	P=0.196N
Adrenal Medulla: Malignant Pheochromocytoma			
Overall Rates (a)	5/58 (9%)	5/58 (9%)	2/58 (3%)
Adjusted Rates (b)	13.5%	12.9%	6.3%
Terminal Rates (c)	4/36 (11%)	2/31 (6%)	2/32 (6%)
Day of First Observation	716	620	729
Life Table Tests (d)	P=0.233N	P=0.556	P=0.267N
Incidental Tumor Tests (d)	P=0.255N	P=0.557	P=0.278N
Cochran-Armitage Trend Test (d)	P=0.180N		
Fisher Exact Test (d)		P=0.629	P=0.219N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	22/58 (38%)	14/58 (24%)	13/58 (22%)
Adjusted Rates (b)	49.1%	33.6%	34.6%
Terminal Rates (c)	14/36 (39%)	5/31 (16%)	8/32 (25%)
Day of First Observation	590	620	625
Life Table Tests (d)	P=0.108N	P=0.187N	P=0.130N
Incidental Tumor Tests (d)	P=0.123N	P=0.136N	P=0.158N
Cochran-Armitage Trend Test (d)	P=0.040N		
Fisher Exact Test (d)		P=0.080N	P=0.052N
Preputial Gland: Adenoma			
Overall Rates (a)	0/48 (0%)	(e) 4/23 (17%)	1/51 (2%)
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	20/57 (35%)	16/59 (27%)	13/60 (22%)
Adjusted Rates (b)	48.5%	37.8%	34.0%
Terminal Rates (c)	14/34 (41%)	9/33 (27%)	8/32 (25%)
Day of First Observation	599	451	533
Life Table Tests (d)	P=0.156N	P=0.340N	P=0.177N
Incidental Tumor Tests (d)	P=0.098N	P=0.301N	P=0.139N
Cochran-Armitage Trend Test (d)	P=0.065N		
Fisher Exact Test (d)		P=0.234N	P=0.080N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	20/57 (35%)	16/59 (27%)	14/60 (23%)
Adjusted Rates (b)	48.5%	37.8%	35.4%
Terminal Rates (c)	14/34 (41%)	9/33 (27%)	8/32 (25%)
Day of First Observation	599	451	533
Life Table Tests (d)	P=0.213N	P=0.340N	P=0.240N
Incidental Tumor Tests (d)	P=0.144N	P=0.301N	P=0.201N
Cochran-Armitage Trend Test (d)	P=0.096N		
Fisher Exact Test (d)		P=0.234N	P=0.116N
Skin: Keratoacanthoma			
Overall Rates (f)	2/60 (3%)	0/60 (0%)	6/60 (10%)
Adjusted Rates (b)	4.7%	0.0%	17.8%
Terminal Rates (c)	0/36 (0%)	0/33 (0%)	5/32 (16%)
Day of First Observation	691		703
Life Table Tests (d)	P=0.049	P=0.264N	P=0.107
Incidental Tumor Tests (d)	P=0.048	P=0.276N	P=0.104
Cochran-Armitage Trend Test (d)	P=0.061		
Fisher Exact Test (d)		P=0.248N	P=0.136

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Skin: Trichoepithelioma or Basal Cell Carcinoma			
Overall Rates (f)	3/60 (5%)	0/60 (0%)	1/60 (2%)
Adjusted Rates (b)	8.1%	0.0%	3.1%
Terminal Rates (c)	2/36 (6%)	0/33 (0%)	1/32 (3%)
Day of First Observation	723		729
Life Table Tests (d)	P=0.205N	P=0.139N	P=0.349N
Incidental Tumor Tests (d)	P=0.204N	P=0.145N	P=0.346N
Cochran-Armitage Trend Test (d)	P=0.176N		
Fisher Exact Test (d)		P=0.122N	P=0.309N
Subcutaneous Tissue: Fibroma			
Overall Rates (f)	3/60 (5%)	3/60 (5%)	2/60 (3%)
Adjusted Rates (b)	6.6%	7.4%	6.3%
Terminal Rates (c)	1/36 (3%)	1/33 (3%)	2/32 (6%)
Day of First Observation	542	451	729
Life Table Tests (d)	P=0.469N	P=0.624	P=0.556N
Incidental Tumor Tests (d)	P=0.365N	P=0.626	P=0.479N
Cochran-Armitage Trend Test (d)	P=0.412N		
Fisher Exact Test (d)		P=0.660	P=0.500N
Subcutaneous Tissue: Fibroma or Neurofibroma			
Overall Rates (f)	3/60 (5%)	4/60 (7%)	2/60 (3%)
Adjusted Rates (b)	6.6%	9.1%	6.3%
Terminal Rates (c)	1/36 (3%)	1/33 (3%)	2/32 (6%)
Day of First Observation	542	451	729
Life Table Tests (d)	P=0.477N	P=0.463	P=0.556N
Incidental Tumor Tests (d)	P=0.329N	P=0.451	P=0.479N
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Subcutaneous Tissue: Fibroma, Neurofibroma, Sarcoma, Neurofibrosarcoma, or Myxosarcoma			
Overall Rates (f)	4/60 (7%)	4/60 (7%)	4/60 (7%)
Adjusted Rates (b)	9.3%	9.1%	12.5%
Terminal Rates (c)	2/36 (6%)	1/33 (3%)	4/32 (13%)
Day of First Observation	542	451	729
Life Table Tests (d)	P=0.503	P=0.600	P=0.574
Incidental Tumor Tests (d)	P=0.513N	P=0.612	P=0.635
Cochran-Armitage Trend Test (d)	P=0.573		
Fisher Exact Test (d)		P=0.641	P=0.641
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	56/60 (93%)	48/58 (83%)	48/60 (80%)
Adjusted Rates (b)	100.0%	97.9%	97.9%
Terminal Rates (c)	36/36 (100%)	30/31 (97%)	31/32 (97%)
Day of First Observation	364	575	431
Life Table Tests (d)	P=0.406N	P=0.465N	P=0.436N
Incidental Tumor Tests (d)	P=0.189N	P=0.153N	P=0.196N
Cochran-Armitage Trend Test (d)	P=0.026N		
Fisher Exact Test (d)		P=0.067N	P=0.029N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	7/60 (12%)	7/60 (12%)	5/58 (9%)
Adjusted Rates (b)	19.4%	16.7%	15.1%
Terminal Rates (c)	7/36 (19%)	3/33 (9%)	4/32 (13%)
Day of First Observation	729	598	719
Life Table Tests (d)	P=0.411N	P=0.548	P=0.461N
Incidental Tumor Tests (d)	P=0.439N	P=0.607	P=0.474N
Cochran-Armitage Trend Test (d)	P=0.351N		
Fisher Exact Test (d)		P=0.611N	P=0.405N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	6/60 (10%)	2/60 (3%)	2/58 (3%)
Adjusted Rates (b)	15.5%	5.9%	6.3%
Terminal Rates (c)	4/36 (11%)	1/33 (3%)	2/32 (6%)
Day of First Observation	706	723	729
Life Table Tests (d)	P=0.111N	P=0.170N	P=0.178N
Incidental Tumor Tests (d)	P=0.121N	P=0.178N	P=0.193N
Cochran-Armitage Trend Test (d)	P=0.088N		
Fisher Exact Test (d)		P=0.136N	P=0.147N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	13/60 (22%)	9/60 (15%)	6/58 (10%)
Adjusted Rates (b)	34.0%	21.8%	18.1%
Terminal Rates (c)	11/36 (31%)	4/33 (12%)	5/32 (16%)
Day of First Observation	706	598	719
Life Table Tests (d)	P=0.090N	P=0.316N	P=0.106N
Incidental Tumor Tests (d)	P=0.101N	P=0.281N	P=0.116N
Cochran-Armitage Trend Test (d)	P=0.059N		
Fisher Exact Test (d)		P=0.240N	P=0.077N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (f)	13/60 (22%)	11/60 (18%)	12/60 (20%)
Adjusted Rates (b)	27.8%	28.1%	28.8%
Terminal Rates (c)	6/36 (17%)	6/33 (18%)	5/32 (16%)
Day of First Observation	549	641	515
Life Table Tests (d)	P=0.508	P=0.506N	P=0.547
Incidental Tumor Tests (d)	P=0.522	P=0.442N	P=0.557
Cochran-Armitage Trend Test (d)	P=0.455N		
Fisher Exact Test (d)		P=0.410N	P=0.500N
All Sites: Mesothelioma			
Overall Rates (f)	2/60 (3%)	3/60 (5%)	4/60 (7%)
Adjusted Rates (b)	4.6%	7.5%	10.5%
Terminal Rates (c)	1/36 (3%)	1/33 (3%)	2/32 (6%)
Day of First Observation	603	634	570
Life Table Tests (d)	P=0.226	P=0.463	P=0.292
Incidental Tumor Tests (d)	P=0.201	P=0.525	P=0.264
Cochran-Armitage Trend Test (d)	P=0.265		
Fisher Exact Test (d)		P=0.500	P=0.340

(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 vehicle 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 vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Incomplete sampling of tissues
(f) Number of tumor-bearing animals/number of animals examined grossly at the site

TABLE A4. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence of Keratoacanthomas in Vehicle Controls
Historical Incidence at Microbiological Associates, Inc.	
d-Limonene	2/50
Benzyl alcohol	3/50
α-Methylbenzyl alcohol	1/50
TOTAL	6/150 (4.0%)
SD (b)	2.00%
Range (c)	
High	3/50
Low	1/50
Overall Historical Incidence	
TOTAL	61/2,099 (2.9%)
SD (b)	2.94%
Range (c)	
High	6/50
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	50 mg/kg	100 mg/kg
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	60	60	60
ALIMENTARY SYSTEM			
Esophagus	(60)	(28)	(60)
Fibrosis, focal	1 (2%)		
Inflammation, acute			1 (2%)
Necrosis		1 (4%)	
Muscularis, regeneration			1 (2%)
Intestine large	(54)	(27)	(54)
Circumanal gland, hyperplasia			2 (4%)
Intestine large, cecum	(52)	(24)	(53)
Inflammation, acute		1 (4%)	
Parasite protozoan		1 (4%)	1 (2%)
Intestine small, ileum	(53)	(24)	(51)
Foreign body	1 (2%)		
Inflammation, chronic	1 (2%)		
Liver	(60)	(47)	(60)
Angiectasis	3 (5%)	3 (6%)	1 (2%)
Basophilic focus	4 (7%)	7 (15%)	2 (3%)
Basophilic focus, multiple	15 (25%)	5 (11%)	19 (32%)
Congestion		4 (9%)	3 (5%)
Cytologic alterations	2 (3%)	4 (9%)	1 (2%)
Cytologic alterations, multiple	5 (8%)		1 (2%)
Fibrosis, focal	5 (8%)	4 (9%)	4 (7%)
Hemorrhage	1 (2%)		
Hepatodiaphragmatic nodule	6 (10%)	9 (19%)	6 (10%)
Hyperplasia, focal	2 (3%)	4 (9%)	
Hyperplasia, nodular	1 (2%)	1 (2%)	
Inflammation, chronic	6 (10%)	1 (2%)	4 (7%)
Necrosis, focal	1 (2%)	1 (2%)	
Necrosis, multifocal	1 (2%)		
Vacuolization cytoplasmic	6 (10%)	7 (15%)	4 (7%)
Bile duct, cyst	1 (2%)		
Bile duct, hyperplasia	42 (70%)	28 (60%)	46 (77%)
Centrilobular, congestion		1 (2%)	
Centrilobular, necrosis	1 (2%)	2 (4%)	3 (5%)
Centrilobular, vacuolization cytoplasmic	2 (3%)		3 (5%)
Mesentery	(13)	(14)	(12)
Inflammation, chronic	2 (15%)		
Artery, inflammation, multifocal			1 (8%)
Fat, necrosis	12 (92%)	10 (71%)	11 (92%)
Pancreas	(59)	(26)	(59)
Cyst		2 (8%)	
Inflammation, chronic	1 (2%)		
Acinus, atrophy, diffuse	1 (2%)	1 (4%)	
Acinus, atrophy, focal	22 (37%)	2 (8%)	17 (29%)
Acinus, hyperplasia, focal	1 (2%)		
Artery, inflammation, chronic	1 (2%)		1 (2%)
Artery, inflammation, chronic active	1 (2%)		
Pharynx			(1)
Developmental malformation			1 (100%)
Salivary glands	(58)	(27)	(58)
Cyst	1 (2%)		
Hemorrhage	1 (2%)		
Inflammation, chronic	2 (3%)		1 (2%)
Vacuolization cytoplasmic		1 (4%)	

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
ALIMENTARY SYSTEM (Continued)			
Stomach, forestomach	(59)	(29)	(58)
Edema		1 (3%)	
Fungus		1 (3%)	
Inflammation, acute			1 (2%)
Inflammation, chronic	2 (3%)		1 (2%)
Inflammation, chronic active	1 (2%)		
Ulcer	2 (3%)	2 (7%)	1 (2%)
Stomach, glandular	(58)	(31)	(59)
Atrophy		1 (3%)	
Dilatation		1 (3%)	
Edema	1 (2%)	1 (3%)	
Erosion		1 (3%)	
Tooth		(1)	(1)
Peridontal tissue, inflammation, acute			1 (100%)
CARDIOVASCULAR SYSTEM			
Heart	(60)	(29)	(59)
Cardiomyopathy	47 (78%)	22 (76%)	43 (73%)
Atrium, thrombus	3 (5%)	1 (3%)	2 (3%)
Endocardium, fibrosis			1 (2%)
Epicardium, fibrosis		1 (3%)	
Epicardium, inflammation, chronic		1 (3%)	2 (3%)
Epicardium, inflammation, chronic active	1 (2%)		
Myocardium, inflammation, acute			1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(60)	(60)	(59)
Angiectasis			1 (2%)
Hematopoietic cell proliferation			1 (2%)
Hyperplasia	6 (10%)	3 (5%)	4 (7%)
Hypertrophy, focal	1 (2%)	1 (2%)	
Necrosis, focal	1 (2%)	1 (2%)	1 (2%)
Vacuolization cytoplasmic, focal	4 (7%)	8 (13%)	3 (5%)
Adrenal gland, medulla	(58)	(58)	(58)
Hyperplasia	21 (36%)	9 (16%)	14 (24%)
Necrosis		1 (2%)	
Islets, pancreatic	(59)	(27)	(60)
Hyperplasia	2 (3%)		3 (5%)
Parathyroid gland	(51)	(26)	(51)
Hyperplasia	1 (2%)		
Pituitary gland	(57)	(59)	(60)
Hemorrhage	1 (2%)		
Pars distalis, angiectasis	2 (4%)	3 (5%)	5 (8%)
Pars distalis, cyst		2 (3%)	2 (3%)
Pars distalis, hyperplasia	8 (14%)	11 (19%)	11 (18%)
Pars distalis, inflammation, chronic		1 (2%)	
Pars distalis, thrombus		1 (2%)	
Pars distalis, vacuolization cytoplasmic			1 (2%)
Thyroid gland	(60)	(60)	(58)
Cyst	2 (3%)		2 (3%)
Fibrosis		1 (2%)	
Inflammation, chronic	2 (3%)		
C-cell, hyperplasia	11 (18%)	6 (10%)	4 (7%)
Follicular cell, hyperplasia		1 (2%)	1 (2%)
GENERAL BODY SYSTEM			
None			

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
GENITAL SYSTEM			
Epididymis	(60)	(29)	(59)
Inflammation, acute		1 (3%)	
Inflammation, chronic			1 (2%)
Serosa, hyperplasia, focal	1 (2%)		
Preputial gland	(48)	(23)	(51)
Dilatation	1 (2%)		1 (2%)
Hyperplasia	1 (2%)		1 (2%)
Inflammation, acute	5 (10%)		3 (6%)
Inflammation, chronic	1 (2%)		1 (2%)
Metaplasia, osseous			1 (2%)
Prostate	(59)	(29)	(58)
Hemorrhage			1 (2%)
Hyperplasia	7 (12%)	3 (10%)	1 (2%)
Inflammation, acute	3 (5%)	1 (3%)	1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)
Pigmentation		1 (3%)	
Testes	(60)	(58)	(60)
Atrophy		3 (5%)	2 (3%)
Interstitial cell, hyperplasia		1 (2%)	4 (7%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(60)	(28)	(59)
Fibrosis	1 (2%)		
Hyperplasia			1 (2%)
Hyperplasia, reticulum cell	1 (2%)		
Lymph node	(60)	(29)	(60)
Mediastinal, giant cell, multiple	1 (2%)		
Mediastinal, hemorrhage	3 (5%)	1 (3%)	
Mediastinal, hyperplasia	1 (2%)		1 (2%)
Lymph node, mandibular	(50)	(28)	(51)
Cyst	5 (10%)	2 (7%)	
Hemorrhage	1 (2%)	1 (4%)	3 (6%)
Hyperplasia, lymphoid	4 (8%)		3 (6%)
Spleen	(59)	(39)	(60)
Congestion		1 (3%)	1 (2%)
Fibrosis, focal	2 (3%)	5 (13%)	3 (5%)
Hematopoietic cell proliferation	1 (2%)	1 (3%)	2 (3%)
Hemorrhage	1 (2%)	1 (3%)	
Hyperplasia, nodular	1 (2%)		
Necrosis			1 (2%)
Pigmentation	4 (7%)	1 (3%)	
Thymus	(45)	(28)	(48)
Congestion			1 (2%)
Hemorrhage		1 (4%)	2 (4%)
INTEGUMENTARY SYSTEM			
Mammary gland	(48)	(25)	(42)
Dilatation	5 (10%)	1 (4%)	1 (2%)
Pigmentation			1 (2%)
Skin	(60)	(29)	(59)
Cyst epithelial inclusion		1 (3%)	2 (3%)
Inflammation, chronic active	1 (2%)		
Epithelium, hyperplasia		1 (3%)	
Subcutaneous tissue, edema			1 (2%)
Subcutaneous tissue, inflammation, acute			1 (2%)
Subcutaneous tissue, thrombus			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
MUSCULOSKELETAL SYSTEM			
Bone	(60)	(28)	(60)
Sternum, hemorrhage	1 (2%)		
Skeletal muscle		(1)	(2)
Cyst			1 (50%)
Inflammation, chronic			1 (50%)
NERVOUS SYSTEM			
Brain	(60)	(27)	(60)
Congestion		1 (4%)	
Thrombus, multifocal	2 (3%)		
Cerebrum, inflammation, chronic			1 (2%)
Meninges, hemorrhage			1 (2%)
Meninges, inflammation, chronic			1 (2%)
Thalamus, compression			1 (2%)
Spinal cord	(3)		
Nerve, demyelination	1 (33%)		
RESPIRATORY SYSTEM			
Larynx	(59)	(27)	(59)
Necrosis			1 (2%)
Lung	(60)	(60)	(60)
Congestion	5 (8%)	10 (17%)	12 (20%)
Fibrosis, focal	1 (2%)	2 (3%)	
Foreign body		3 (5%)	7 (12%)
Hemorrhage		2 (3%)	1 (2%)
Hyperplasia		1 (2%)	
Hyperplasia, adenomatous	10 (17%)	4 (7%)	2 (3%)
Infiltration cellular, histiocytic	12 (20%)	18 (30%)	11 (18%)
Inflammation, granulomatous			1 (2%)
Leukocytosis		1 (2%)	
Metaplasia, osseous	2 (3%)		
Necrosis, focal			1 (2%)
Necrosis, multifocal		1 (2%)	2 (3%)
Pigmentation	1 (2%)		
Thrombus		3 (5%)	
Alveolar epithelium, hyperplasia	2 (3%)		1 (2%)
Alveolus, fibrosis, focal			1 (2%)
Interstitium, edema		1 (2%)	
Interstitium, inflammation, chronic		1 (2%)	2 (3%)
Mediastinum, hemorrhage			1 (2%)
Nose	(58)	(59)	(59)
Inflammation, chronic active	1 (2%)		
Nasolacrimal duct, inflammation, acute	2 (3%)	1 (2%)	1 (2%)
Olfactory epithelium, inflammation, chronic			1 (2%)
Sinus, foreign body	1 (2%)	2 (3%)	3 (5%)
Sinus, fungus	1 (2%)	7 (12%)	5 (8%)
Sinus, hemorrhage		1 (2%)	
Sinus, inflammation, acute	7 (12%)	11 (19%)	11 (19%)
Turbinate, foreign body	1 (2%)		
Turbinate, inflammation, acute	1 (2%)		1 (2%)
Turbinate, inflammation, chronic	1 (2%)		3 (5%)
Turbinate, metaplasia, squamous			1 (2%)
Trachea	(60)	(28)	(59)
Inflammation, acute	1 (2%)		
Inflammation, chronic			1 (2%)
Necrosis		1 (4%)	3 (5%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
SPECIAL SENSES SYSTEM			
Eye	(8)	(8)	(8)
Hemorrhage		1 (13%)	
Capsule, lens, cataract		1 (13%)	
Lens capsule, cataract	4 (50%)	4 (50%)	2 (25%)
Retina, atrophy	8 (100%)	8 (100%)	5 (63%)
Sclera, metaplasia, osseous	4 (50%)	4 (50%)	4 (50%)
Harderian gland	(2)	(1)	(3)
Inflammation, chronic		1 (100%)	
Inflammation, chronic, focal	2 (100%)		2 (67%)
URINARY SYSTEM			
Kidney	(60)	(60)	(59)
Abscess	1 (2%)		
Congestion			1 (2%)
Cyst	4 (7%)	2 (3%)	1 (2%)
Hydronephrosis	1 (2%)	1 (2%)	
Inflammation, chronic	1 (2%)		
Inflammation, suppurative		1 (2%)	
Mineralization	1 (2%)		2 (3%)
Nephropathy	52 (87%)	40 (67%)	26 (44%)
Papilla, necrosis	1 (2%)		
Pelvis, dilatation	1 (2%)		
Pelvis, inflammation, acute	1 (2%)		
Pelvis, mineralization			1 (2%)
Renal tubule, atrophy, diffuse		1 (2%)	
Renal tubule, pigmentation	1 (2%)		2 (3%)
Ureter	(1)		
Inflammation, acute	1 (100%)		
Urinary bladder	(59)	(27)	(59)
Hemorrhage	2 (3%)		1 (2%)
Inflammation, acute	1 (2%)		

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	50 mg/kg	100 mg/kg
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	60	60	60
ALIMENTARY SYSTEM			
Intestine large, cecum	(54)	*(60)	(53)
Adenocarcinoma, extension	1 (2%)		
Intestine large, colon	(55)	*(60)	(55)
Adenocarcinoma, extension	1 (2%)		
Sarcoma stromal, metastatic, uterus		1 (2%)	
Intestine small, duodenum	(55)	*(60)	(52)
Adenocarcinoma, extension	1 (2%)		
Intestine small, ileum	(53)	*(60)	(51)
Leukemia mononuclear			1 (2%)
Liver	(60)	*(60)	(60)
Adenocarcinoma, extension	1 (2%)		
Leukemia mononuclear	11 (18%)	5 (8%)	8 (13%)
Neoplastic nodule	2 (3%)	1 (2%)	2 (3%)
Neoplastic nodule, multiple			1 (2%)
Mesentery	*(60)	*(60)	*(60)
Adenocarcinoma, extension	1 (2%)		
Leukemia mononuclear	1 (2%)		
Sarcoma, metastatic, skeletal muscle	1 (2%)		
Pancreas	(59)	*(60)	(59)
Adenocarcinoma, extension	1 (2%)		
Leukemia mononuclear	1 (2%)		3 (5%)
Salivary glands	(60)	*(60)	(59)
Leukemia mononuclear			1 (2%)
Stomach, forestomach	(58)	*(60)	(57)
Leukemia mononuclear			3 (5%)
Papilloma squamous		1 (2%)	
Stomach, glandular	(58)	*(60)	(54)
Leukemia mononuclear			1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(60)	*(60)	(60)
Leukemia mononuclear	2 (3%)		1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(60)	*(60)	(59)
Adenocarcinoma, extension	1 (2%)		
Adenoma, multiple	1 (2%)		
Carcinoma		1 (2%)	
Leukemia mononuclear	2 (3%)	3 (5%)	4 (7%)
Adrenal gland, medulla	(59)	*(60)	(54)
Leukemia mononuclear	2 (3%)		
Pheochromocytoma malignant	1 (2%)		
Pheochromocytoma benign	2 (3%)	1 (2%)	3 (6%)
Pheochromocytoma benign, multiple	1 (2%)		
Pituitary gland	(60)	*(60)	(60)
Pars distalis, adenoma	27 (45%)	25 (42%)	18 (30%)
Pars distalis, adenoma, multiple	3 (5%)	1 (2%)	2 (3%)
Pars distalis, carcinoma	1 (2%)		1 (2%)
Pars distalis, leukemia mononuclear	2 (3%)	1 (2%)	2 (3%)
Thyroid gland	(59)	*(60)	(60)
C-cell, adenoma	5 (8%)	2 (3%)	5 (8%)
C-cell, carcinoma	4 (7%)	2 (3%)	3 (5%)
Follicular cell, adenoma			1 (2%)
Follicular cell, carcinoma	1 (2%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(39)	*(60)	(53)
Adenoma	2 (5%)	2 (3%)	3 (6%)
Papilloma squamous, multiple	1 (3%)		
Ovary	(59)	*(60)	(60)
Adenocarcinoma, metastatic, uterus	1 (2%)		
Leukemia mononuclear	3 (5%)		3 (5%)
Luteoma		1 (2%)	
Squamous cell carcinoma, metastatic, skin			1 (2%)
Uterus	(59)	*(60)	(60)
Adenocarcinoma	1 (2%)		
Hemangiosarcoma		1 (2%)	
Leiomyosarcoma		1 (2%)	
Leukemia mononuclear	1 (2%)	1 (2%)	
Sarcoma	1 (2%)		
Sarcoma stromal			1 (2%)
Squamous cell carcinoma, metastatic, skin			1 (2%)
Endometrium, polyp stromal	11 (19%)	8 (13%)	6 (10%)
Endometrium, polyp stromal, multiple			3 (5%)
Endometrium, sarcoma stromal		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(60)	*(60)	(60)
Leukemia mononuclear	1 (2%)		1 (2%)
Lymph node	(59)	*(60)	(60)
Adenocarcinoma, metastatic, uterus	1 (2%)		
Mediastinal, leukemia mononuclear	2 (3%)		1 (2%)
Lymph node, mandibular	(54)	*(60)	(55)
Leukemia mononuclear	2 (4%)	1 (2%)	3 (5%)
Lymph node, mesenteric	(59)	*(60)	(59)
Leukemia mononuclear	4 (7%)	1 (2%)	3 (5%)
Spleen	(59)	*(60)	(60)
Leukemia mononuclear	11 (19%)	6 (10%)	8 (13%)
Thymus	(48)	*(60)	(52)
Leukemia mononuclear	1 (2%)		2 (4%)
Squamous cell carcinoma, metastatic, skin			1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(59)	(55)	(59)
Adenocarcinoma		2 (4%)	2 (3%)
Adenoma	1 (2%)	2 (4%)	
Fibroadenoma	17 (29%)	17 (31%)	12 (20%)
Fibroadenoma, multiple	8 (14%)	6 (11%)	
Skin	(60)	*(60)	(60)
Sarcoma		1 (2%)	
Squamous cell carcinoma			1 (2%)
Head, sebaceous gland, adenoma	1 (2%)		
Subcutaneous tissue, fibroma			1 (2%)
Subcutaneous tissue, fibrosarcoma			1 (2%)
Subcutaneous tissue, lipoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(60)	*(60)	*(60)
Sarcoma	1 (2%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
NERVOUS SYSTEM			
Brain	(60)	*(60)	(60)
Astrocytoma benign			1 (2%)
Carcinoma	1 (2%)		
Ependymoma benign			1 (2%)
Leukemia mononuclear	1 (2%)		2 (3%)
Oligodendroglioma benign	1 (2%)		
Spinal cord	*(60)	*(60)	*(60)
Leukemia mononuclear	1 (2%)		
RESPIRATORY SYSTEM			
Lung	(60)	*(60)	(60)
Adenocarcinoma, metastatic, uterus	1 (2%)		
Alveolar/bronchiolar adenoma	3 (5%)	1 (2%)	
Leukemia mononuclear	7 (12%)	4 (7%)	7 (12%)
Sarcoma, metastatic, skeletal muscle	1 (2%)		
Squamous cell carcinoma, metastatic, skin			1 (2%)
SPECIAL SENSES SYSTEM			
Zymbal gland	*(60)	*(60)	*(60)
Squamous cell carcinoma	1 (2%)		
URINARY SYSTEM			
Kidney	(60)	(59)	(60)
Leukemia mononuclear	4 (7%)	2 (3%)	3 (5%)
Nephroblastoma		2 (3%)	
Squamous cell carcinoma, metastatic, skin			1 (2%)
Urinary bladder	(56)	*(60)	(60)
Leiomyosarcoma		1 (2%)	
Leukemia mononuclear			3 (5%)
SYSTEMIC LESIONS			
Multiple organs	*(60)	*(60)	*(60)
Leukemia mononuclear	11 (18%)	6 (10%)	8 (13%)
Hemangiosarcoma		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	60	60	60
Terminal sacrifice	30	27	26
Dead (a)	10	11	11
Moribund (a)	19	15	14
Gavage death	1	6	9
Accident		1	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
TUMOR SUMMARY			
Total animals with primary neoplasms **	55	47	39
Total primary neoplasms	117	86	77
Total animals with benign neoplasms	52	42	34
Total benign neoplasms	87	68	59
Total animals with malignant neoplasms	21	15	18
Total malignant neoplasms	30	18	18
Total animals with secondary neoplasms ***	2	1	1
Total secondary neoplasms	5	1	5

(a) Some of these early deaths may have been gavage related.
* 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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE: VEHICLE CONTROL

WEEKS ON STUDY	0 0 2	0 1 5	0 2 5	0 6 9	0 7 1	0 7 3	0 7 4	0 7 9	0 8 3	0 8 7	0 8 7	0 8 8	0 8 8	0 8 9	0 9 2	0 9 2	0 9 5	0 9 6	1 0 0	1 0 1	1 0 1	1 0 1	1 0 2	1 0 3
CARCASS ID	4 7 5	4 5 5	3 9 5	4 7 4	4 6 5	3 8 5	3 9 4	4 5 4	3 7 5	3 8 1	4 5 3	4 3 5	4 2 5	4 4 5	3 8 4	4 1 5	4 6 4	4 7 3	4 3 1	3 7 4	4 1 4	4 6 3	4 8 5	3 8 2	4 2 4
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	
Intestine large, cecum	A	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	A	+	
Adenocarcinoma, extension									X																
Intestine large, colon	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	A	+	
Adenocarcinoma, extension									X																
Intestine large, rectum	A	M	A	+	+	+	+	+	+	M	+	+	+	+	+	+	A	+	+	+	+	A	A	+	
Intestine small	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	
Intestine small, duodenum	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	A	+	
Adenocarcinoma, extension									X																
Intestine small, ileum	A	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	A	+	
Intestine small, jejunum	A	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	A	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, extension									X																
Leukemia mononuclear					X						X		X						X	X	X				
Neoplastic nodule																									
Mesentery									+		+									+	+				+
Adenocarcinoma, extension									X																
Leukemia mononuclear											X														
Sarcoma, metastatic, skeletal muscle																									X
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, extension									X																
Leukemia mononuclear																					X				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
CARDIOVASCULAR SYSTEM																									
Blood vessel			+																						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Leukemia mononuclear					X														X						
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, extension									X																
Adenoma, multiple																									
Leukemia mononuclear																					X				
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	
Leukemia mononuclear											X									X					
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Pheochromocytoma benign, multiple																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Parathyroid gland	A	+	+	M	M	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X		X		X	X		X		X		X		X	X		X	X
Pars distalis, adenoma, multiple																									
Pars distalis, carcinoma																									
Pars distalis, leukemia mononuclear													X						X						
Thyroid gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma					X																				
C cell, carcinoma																									
Follicular cell, carcinoma																						X			
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	A	M	+	+	M	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	M
Adenoma																X									
Papilloma squamous, multiple				X																					
Ovary	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma, metastatic, uterus									X																
Leukemia mononuclear																			X	X					
Uterus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenocarcinoma									X																
Leukemia mononuclear											X														
Sarcoma										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 B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	103	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	434	372	481	421	371	373	383	391	392	393	401	402	403	404	405	411	412	413	422	423	432	433	441	442	443
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, extension																									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, extension																									
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, extension																									
Intestine small, ileum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, extension																									
Leukemia mononuclear								X			X	X													
Neoplastic nodule																									X
Mesentery					+																				
Adenocarcinoma, extension																									
Leukemia mononuclear																									
Sarcoma, metastatic, skeletal muscle																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, extension																									
Leukemia mononuclear																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, extension																									
Adenoma, multiple																						X			
Leukemia mononuclear												X													
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pheochromocytoma malignant																									
Pheochromocytoma benign				X														X							
Pheochromocytoma benign, multiple							X																		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	M	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X	X		X	X		X	X				X		X	X		X	X	X	X				
Pars distalis, adenoma, multiple																	X						X		
Pars distalis, carcinoma																									
Pars distalis, leukemia mononuclear																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma							X					X													
C-cell, carcinoma																			X			X			
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	M	M	+	+	+	+	+	M	M	+	+	M	+	M	M	M	+	+	+	+	+	+	M	+	M
Adenoma																								X	
Papilloma squamous, multiple																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																									
Leukemia mononuclear												X													
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Leukemia mononuclear																									
Sarcoma																									
Endometrium, polyp stromal				X	X				X	X	X			X			X				X	X		X	

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

WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL TISSUES TUMORS
CARCASS ID	4 4 4	4 5 1	4 5 2	4 6 1	4 6 2	4 7 1	4 7 2	4 8 2	4 8 3	4 8 4	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large	+	+	+	+	+	+	+	+	+	+	56
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	54
Adenocarcinoma, extension											1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	55
Adenocarcinoma, extension											1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	53
Intestine small	+	+	+	+	+	+	+	+	+	+	56
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	55
Adenocarcinoma, extension											1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	53
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	53
Liver	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma, extension											1
Leukemia mononuclear							X	X			11
Neoplastic nodule								X			2
Mesentery											6
Adenocarcinoma, extension											1
Leukemia mononuclear											1
Sarcoma, metastatic, skeletal muscle											1
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma, extension											1
Leukemia mononuclear											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	60
Stomach	+	+	+	+	+	+	+	+	+	+	59
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	58
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	58
CARDIOVASCULAR SYSTEM											
Blood vessel											1
Heart	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											2
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma, extension											1
Adenoma, multiple											1
Leukemia mononuclear											2
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											2
Pheochromocytoma malignant										X	1
Pheochromocytoma benign											2
Pheochromocytoma benign, multiple											1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma		X	X								27
Pars distalis, adenoma, multiple	X										3
Pars distalis, carcinoma						X					1
Pars distalis, leukemia mononuclear											2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	59
C cell, adenoma						X	X				5
C cell, carcinoma					X					X	4
Follicular cell, carcinoma											1
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Clitoral gland	M	+	M	+	+	M	+	+	+	+	39
Adenoma											2
Papilloma squamous, multiple											1
Ovary	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma, metastatic, uterus											1
Leukemia mononuclear											3
Uterus	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma											1
Leukemia mononuclear											1
Sarcoma											1
Endometrium, polyp stromal											11

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

WEEKS ON STUDY	002	011	025	069	071	073	074	079	083	087	087	088	088	089	092	092	092	095	096	100	101	101	101	102	103
CARCASS ID	47 5	45 5	39 5	47 4	46 5	38 5	39 4	45 4	37 5	38 1	45 3	43 5	42 5	44 5	38 4	41 5	46 4	47 3	43 1	37 4	41 4	46 3	48 5	38 2	42 4
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X												
Lymph node	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus									X																
Mediastinal, leukemia mononuclear																				X	X				
Lymph node, mandibular	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Leukemia mononuclear													X						X						
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X		X						X		X				
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X						X		X						X	X	X				
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	M	M	+	M	M	+	+	+	+
Leukemia mononuclear																			X						
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Fibroadenoma								X		X					X						X		X	X	X
Fibroadenoma, multiple									X								X								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Head, sebaceous gland, adenoma																									
Subcutaneous tissue, lipoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									+
Sarcoma																									X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leukemia mononuclear																									
Oligodendroglioma benign																								X	
Spinal cord																									
Leukemia mononuclear																									
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus									X																
Alveolar/bronchiolar adenoma																									
Leukemia mononuclear					X						X		X						X	X	X				
Sarcoma, metastatic, skeletal muscle																									X
Nose	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear	+																								
Eye		+		+																					
Zymbal gland														+											
Squamous cell carcinoma														X											
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X								X		X				
Urinary bladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+

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

WEEKS ON STUDY	103	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	434	372	481	421	371	737	383	391	392	393	401	402	403	404	405	411	412	413	422	423	432	433	441	442	443
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																									
Mediastinal, leukemia mononuclear																									
Lymph node, mandibular	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X	X													
Thymus	+	+	M	M	M	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+
Leukemia mononuclear																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Fibroadenoma			X	X											X		X	X			X		X		
Fibroadenoma, multiple	X													X											X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Head, sebaceous gland, adenoma										X															
Subcutaneous tissue, lipoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Sarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Leukemia mononuclear												X													
Oligodendroglioma benign																									
Spinal cord												+													
Leukemia mononuclear												X													
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, uterus																									
Alveolar/bronchiolar adenoma	X																					X			
Leukemia mononuclear												X													
Sarcoma, metastatic, skeletal muscle																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Ear																									
Eye		A										+						+							
Zymbal gland																									
Squamous cell carcinoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

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

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	444	451	452	461	462	471	472	482	483	484	
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											1
Lymph node	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma, metastatic, uterus											1
Mediastinal, leukemia mononuclear											2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	54
Leukemia mononuclear											2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											4
Spleen	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear							X	X			11
Thymus	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear											1
INTEGUMENTARY SYSTEM											
Mammary gland	+	+	+	+	+	+	+	+	+	+	59
Adenoma											1
Fibroadenoma		X			X	X					17
Fibroadenoma, multiple	X			X			X				8
Skin	+	+	+	+	+	+	+	+	+	+	60
Head, sebaceous gland, adenoma											1
Subcutaneous tissue, lipoma			X								1
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											1
Sarcoma											1
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
Carcinoma						X					1
Leukemia mononuclear											1
Oligodendroglioma benign											1
Spinal cord											1
Leukemia mononuclear											1
RESPIRATORY SYSTEM											
Larynx	+	+	+	+	+	+	+	+	+	M	58
Lung	+	+	+	+	+	+	+	+	+	+	60
Adenocarcinoma, metastatic, uterus											1
Alveolar/bronchiolar adenoma										X	3
Leukemia mononuclear											7
Sarcoma, metastatic, skeletal muscle											1
Nose	+	+	+	+	+	+	+	+	+	+	59
Trachea	+	+	+	+	+	+	+	+	+	+	60
SPECIAL SENSES SYSTEM											
Ear											1
Eye											4
Zymbal gland											1
Squamous cell carcinoma											1
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											4
Urinary bladder	+	+	+	+	+	+	+	M	+	+	56

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE: 50 mg/kg

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 50 mg/kg (Continued)

WEEKS ON STUDY	099	099	100	101	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	544	522	584	514	551	571	591	594	491	501	511	512	513	521	531	532	533	534	535	542	543	552	562	563	564			
ALIMENTARY SYSTEM																												
Esophagus	+	+	+	+	+	+	+	+						+								+	+	+			
Intestine large	+	+	+	+	+	+	+	+						+								+	+	+			
Intestine large, cecum	+	+	+	+	+	+	+	+						+								+	+	+			
Intestine large, colon	+	+	+	+	+	+	+	+						+								+	+	+			
Sarcoma stromal, metastatic, uterus			X																									
Intestine large, rectum	+	+	+	+	+	+	+	+						+								+	+	+			
Intestine small	+	+	+	+	+	+	+	+						+								+	+	+			
Intestine small, duodenum	+	+	+	+	+	+	+	+						+								+	+	+			
Intestine small, ileum	+	+	+	+	+	+	+	+						+								+	+	+			
Intestine small, jejunum	+	+	+	+	+	+	+	+						+								+	+	+			
Liver	+	+	+	+	+	+	+	+			+	+		+	+		+			+		+	+	+		+	
Leukemia mononuclear				X																							X	
Neoplastic nodule															X													
Mesentery								+	+																			
Pancreas	+	+	+	+	+	+	+	+						+								+	+	+			
Salivary glands	+	+	+	+	+	+	+	+						+								+	+	+			
Stomach	+	+	+	+	+	+	+	+						+								+	+	+			
Stomach, forestomach	+	+	+	+	+	+	+	+						+								+	+	+			
Papilloma squamous														X														
Stomach, glandular	+	+	+	+	+	+	+	+						+								+	+	+			
CARDIOVASCULAR SYSTEM																												
Heart	+	+	+	+	+	+	+	+						+								+	+	+			
ENDOCRINE SYSTEM																												
Adrenal gland	+	+	+	+	+	+	+	+	+					+								+	+	+			
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+					+								+	+	+			
Carcinoma									X																			
Leukemia mononuclear				X																								
Adrenal gland, medulla	+	+	+	+	+	+		+						+								+	+	+			
Pheochromocytoma benign																						X						
Islets, pancreatic	+	+	+	+	+	+	+	+						+								+	+	+			
Parathyroid gland	+	+	+	+	+	+	+	M						+								+	+	+			
Pituitary gland	+	+	+	+	+	+	+	+		+	+	+	+	+		+	+	+	+	+		+	+	+		+	
Pars distalis, adenoma	X	X		X	X	X	X	X		X		X	X			X					X	X		X		X	
Pars distalis, adenoma, multiple																												
Pars distalis, leukemia mononuclear																											X	
Thyroid gland	+	+	+	+	+	+	+	+			+			+								+	+	+			
C cell, adenoma								X																				
C cell, carcinoma								X			X																	
GENERAL BODY SYSTEM																												
None																												
GENITAL SYSTEM																												
Clitoral gland	M	+	+	+	+	+	+	+						M				+		+		+	+	+			
Adenoma		X																										
Ovary	+	+	+	+	+	+		+						+								+	+	+			
Luteoma																												
Uterus	+	+	+	+	+	+	+	+	+		+			+								+	+	+	+		
Hemangiosarcoma																												
Leiomyosarcoma																											X	
Leukemia mononuclear																											X	
Endometrium, polyp stromal						X	X																X					
Endometrium, sarcoma stromal			X																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 50 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	572	573	581	582	583	592	593	601	603	604	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+		+		+	+	45
Intestine large	+	+	+	+	+		+		+	+	45
Intestine large, cecum	+	+	+	+	+		+		+	+	35
Intestine large, colon	+	+	+	+	+		+		+	+	44
Sarcoma stromal, metastatic, uterus											1
Intestine large, rectum	+	+	+	+	+		+		+	+	35
Intestine small	+	+	+	+	+		+		+	+	45
Intestine small, duodenum	+	+	+	+	+		+		+	+	44
Intestine small, ileum	+	+	+	+	+		+		+	+	35
Intestine small, jejunum	+	+	+	+	+		+		+	+	35
Liver	+	+	+	+	+	+	+		+	+	52
Leukemia mononuclear		X			X						5
Neoplastic nodule											1
Mesentery				+							6
Pancreas	+	+	+	+	+		+		+	+	44
Salivary glands	+	+	+	+	+		+		+	+	45
Stomach	+	+	+	+	+		+		+	+	45
Stomach, forestomach	+	+	+	+	+		+		+	+	44
Papilloma squamous											1
Stomach, glandular	+	+	+	+	+		+		+	+	45
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+		+		+	+	45
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+		+		+	+	46
Adrenal gland, cortex	+	+	+	+	+		+		+	+	45
Carcinoma											1
Leukemia mononuclear		X			X						3
Adrenal gland, medulla	+	+	+	+	+		+		+	+	43
Pheochromocytoma benign											1
Islets, pancreatic	+	+	+	+	+		+		+	+	44
Parathyroid gland	+	+	+	+	+		+		+	+	38
Pituitary gland	+	+	+	+	+		+	+	+	+	55
Pars distalis, adenoma	X		X	X	X					X	25
Pars distalis, adenoma, multiple									X		1
Pars distalis, leukemia mononuclear											1
Thyroid gland	+	+	+	+	+		+		+	+	45
C cell, adenoma									X		2
C-cell, carcinoma											2
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Clitoral gland	+	+	+	M	+		M		+	+	27
Adenoma											2
Ovary	+	+	+	+	+		+		+	+	44
Luteoma											1
Uterus	+	+	+	+	+		+		+	+	48
Hemangiosarcoma											1
Leiomyosarcoma											1
Leukemia mononuclear											1
Endometrium, polyp stromal					X					X	8
Endometrium, sarcoma stromal											1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 50 mg/kg (Continued)

WEEKS ON STUDY	0 0 1	0 0 1	0 0 1	0 0 2	0 0 2	0 0 2	0 0 2	0 0 2	0 0 2	0 0 2	0 2 5	0 2 7	0 5 8	0 6 8	0 7 8	0 8 5	0 8 6	0 8 7	0 8 7	0 8 7	0 8 9	0 8 9	0 9 2	0 9 7	0 9 8
CARCASS ID	4 9 5	5 2 5	4 9 4	5 0 4	5 0 5	6 0 5	5 0 3	5 7 5	5 1 5	5 0 2	5 2 4	5 9 5	4 9 3	5 6 1	5 5 5	4 9 2	5 4 5	5 7 4	5 5 4	5 8 5	5 4 1	5 6 5	6 0 2	5 5 3	5 2 3
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Adenocarcinoma																						X			
Adenoma																				X			X		
Fibroadenoma																		X	X		X	X		X	X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Sarcoma																								X	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Leukemia mononuclear																									
Nose	M	M	M	M	M	M	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye							+							+	+										
Harderian gland										+															
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
Nephroblastoma											X		X												
Urinary bladder	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Leiomyosarcoma																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 50 mg/kg (Continued)

WEEKS ON STUDY	099	099	100	101	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	54 4	52 2	58 4	51 4	55 1	57 1	59 1	59 4	49 1	50 1	51 1	51 2	51 3	52 1	53 1	53 2	53 3	53 4	53 5	54 2	54 3	55 2	56 2	56 3	56 4
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+						+								+	+	+	
Lymph node	+	+	+	+	+	+	+	+						+								+	+	+	
Lymph node, mandibular	+	+	+	+	+	+	+	+						+								+	+	+	
Leukemia mononuclear																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+						+								+	+	+	
Leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+						+								+	+	+	+
Leukemia mononuclear				X																					X
Thymus	+	+	+	+	+	+	+	+						+								M	+	+	
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma								X																	
Adenoma																									
Fibroadenoma						X	X	X			X				X		X	X	X	X	X				
Fibroadenoma, multiple	X												X	X								X			X
Skin	+	+	+	+	+	+	+	+						+								+	+	+	
Sarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+						+								+	+	+	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+						+								+	+	+	
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+						+								+	+	+	
Lung	+	+	+	+	+	+	+	+	+					+	+							+	+	+	+
Alveolar/bronchiolar adenoma									X																
Leukemia mononuclear				X																					X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+						+								+	+	+	
SPECIAL SENSES SYSTEM																									
Eye					+			+		+							+								
Harderian gland																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									X
Nephroblastoma																									
Urinary bladder	M	+	+	+	+	+		+						+							+	+	+	+	
Leiomyosarcoma																					X				

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 50 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	572	573	581	582	583	592	593	601	603	604	
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+		+		+	+	45
Lymph node	+	+	+	+	+		+		+	+	45
Lymph node, mandibular	+	+	+	+	+		+		+	+	43
Leukemia mononuclear					X						1
Lymph node, mesenteric	+	+	+	+	+		+		+	+	43
Leukemia mononuclear		X									1
Spleen	+	+	+	+	+		+	+	+	+	46
Leukemia mononuclear		X			X			X			6
Thymus	+	+	+	+	M		+		+	+	41
INTEGUMENTARY SYSTEM											
Mammary gland	+	+	+	+	+	+	+	+	+	+	55
Adenocarcinoma											2
Adenoma											2
Fibroadenoma	X										17
Fibroadenoma, multiple					X						6
Skin	+	+	+	+	+		+		+	+	44
Sarcoma											1
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+		+		+	+	45
NERVOUS SYSTEM											
Brain	+	+	+	+	+		+		+	+	45
RESPIRATORY SYSTEM											
Larynx	+	+	+	+	+		+		+	+	44
Lung	+	+	+	+	+		+	+	+	+	49
Alveolar/bronchiolar adenoma											1
Leukemia mononuclear		X			X						4
Nose	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+		+		+	+	44
SPECIAL SENSES SYSTEM											
Eye						+					8
Harderian gland											1
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											2
Nephroblastoma											2
Urinary bladder	+	+	+	+	+		+		+	+	41
Leiomyosarcoma											1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE: 100 mg/kg

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 100 mg/kg (Continued)

WEEKS ON STUDY	097	097	101	102	103	103	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	66 62	66 93	61 15	62 33	62 22	64 42	68 83	68 84	61 11	61 14	62 21	63 11	63 32	63 33	63 34	64 41	65 51	66 61	67 11	67 72	67 73	67 74	68 81	68 82	68 85
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																				X					
Intestine small, jejunum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X											X	X			X		
Neoplastic nodule																			X						
Neoplastic nodule, multiple																	X								
Mesentery														+											
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X												X					
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X												X					
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Leukemia mononuclear																				X					
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X																	
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X												X					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	M	+	M	+	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X	X	X			X		X	X	X	X			X			X	X	X			X		X	
Pars distalis, adenoma, multiple													X								X				
Pars distalis, carcinoma				X																					
Pars distalis, leukemia mononuclear								X												X					
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma												X							X				X		
C cell, carcinoma																								X	
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Adenoma							X																		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X												X					
Squamous cell carcinoma, metastatic, skin																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma stromal																									
Squamous cell carcinoma, metastatic, skin																									
Endometrium, polyp stromal					X																	X			X
Endometrium, polyp stromal, multiple		X												X											
Endometrium, sarcoma stromal										X															
Vagina																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 100 mg/kg (Continued)

WEEKS ON STUDY	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	10 5	TOTAL TISSUES TUMORS
CARCASS ID	69 1	69 2	70 1	70 2	71 1	71 2	71 4	71 5	72 1	72 2	
ALIMENTARY SYSTEM											
Esophagus	+	+	+	+	+	+	+	+	+	+	60
Intestine large	+	+	+	+	+	+	+	+	+	+	55
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	53
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	55
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	53
Intestine small	+	+	+	+	+	+	+	+	+	+	52
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	52
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	51
Leukemia mononuclear											1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	51
Liver	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X										8
Neoplastic nodule									X		2
Neoplastic nodule, multiple											1
Mesentery					+						3
Pancreas	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											3
Salivary glands	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											1
Stomach	+	+	+	+	+	+	+	+	+	+	58
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	57
Leukemia mononuclear											3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	54
Leukemia mononuclear											1
CARDIOVASCULAR SYSTEM											
Heart	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											1
ENDOCRINE SYSTEM											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	60
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											4
Adrenal gland, medulla	+	M	+	+	+	+	+	+	+	+	54
Pheochromocytoma benign							X	X		X	3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	60
Parathyroid gland	+	+	+	+	+	+	+	M	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	60
Pars distalis, adenoma										X	18
Pars distalis, adenoma, multiple											2
Pars distalis, carcinoma											1
Pars distalis, leukemia mononuclear											2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	60
C cell, adenoma									X		5
C cell, carcinoma								X		X	3
Follicular cell, adenoma											1
GENERAL BODY SYSTEM											
None											
GENITAL SYSTEM											
Clitoral gland	+	+	+	M	+	+	+	+	+	+	53
Adenoma									X		3
Ovary	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											3
Squamous cell carcinoma, metastatic, skin											1
Uterus	+	+	+	+	+	+	+	+	+	+	60
Sarcoma stromal						X					1
Squamous cell carcinoma, metastatic, skin											1
Endometrium, polyp stromal				X	X						6
Endometrium, polyp stromal, multiple										X	3
Endometrium, sarcoma stromal											1
Vagina											1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 100 mg/kg (Continued)

WEEKS ON STUDY	0 0 1	0 0 1	0 0 2	0 0 2	0 1 6	0 2 5	0 2 6	0 2 9	0 2 9	0 3 3	0 4 1	0 4 9	0 5 1	0 5 3	0 6 0	0 7 2	0 8 1	0 8 4	0 8 7	0 8 7	0 8 9	0 9 0	0 9 0	0 9 2	0 9 5
CARCASS ID	6 6 5	7 2 5	6 3 5	6 6 4	6 6 3	6 5 3	6 5 2	6 4 5	7 0 5	6 2 5	6 9 5	6 5 4	6 4 4	6 5 5	7 2 4	6 7 5	6 2 4	6 9 4	6 1 3	7 0 4	6 1 2	6 4 3	7 1 3	7 2 3	7 0 3
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia *mononuclear*																			X						
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear																			X						
Lymph node, mandibular	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Leukemia mononuclear																			X						
Lymph node, mesenteric	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X		X				
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+
Leukemia mononuclear																									
Squamous cell carcinoma, metastatic, skin																				X					
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma																									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																				X					
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+																	
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign																									X
Ependymoma benign												X													
Leukemia mononuclear																			X						
Spinal cord															+										
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																			X		X				
Squamous cell carcinoma, metastatic, skin																				X					
Nose	+	+	A	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia *mononuclear*																			X						
Squamous cell carcinoma, metastatic, skin																				X					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 100 mg/kg (Continued)

WEEKS ON STUDY	097	097	101	102	103	103	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	662	693	615	623	622	642	683	684	611	614	621	631	632	633	634	641	651	661	671	672	673	674	681	682	685
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X													X					
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X												X					
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X											X	X			X		
Thymus	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+
Leukemia mononuclear							X													X					
Squamous cell carcinoma, metastatic, skin																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma									X									X							
Fibroadenoma			X	X	X	X	X					X					X						X	X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Subcutaneous tissue, fibroma		X																							
Subcutaneous tissue, fibrosarcoma						X																			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma benign																									
Ependymoma benign																									
Leukemia mononuclear								X																	
Spinal cord																									
RESPIRATORY SYSTEM																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X											X	X					
Squamous cell carcinoma, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye							+				+			+											
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X												X					
Squamous cell carcinoma, metastatic, skin																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X	X												X					

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 100 mg/kg (Continued)

WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	691	692	701	702	711	712	714	715	721	722	
HEMATOPOIETIC SYSTEM											
Bone marrow	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											1
Lymph node	+	+	+	+	+	+	+	+	+	+	60
Mediastinal, leukemia mononuclear											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	55
Leukemia mononuclear											3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	59
Leukemia mononuclear											3
Spleen	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X										8
Thymus	+	+	M	+	+	+	+	+	+	+	52
Leukemia mononuclear											2
Squamous cell carcinoma, metastatic, skin											1
INTEGUMENTARY SYSTEM											
Mammary gland	+	+	+	+	+	+	+	+	+	+	59
Adenocarcinoma											2
Fibroadenoma								X		X	12
Skin	+	+	+	+	+	+	+	+	+	+	60
Squamous cell carcinoma											1
Subcutaneous tissue, fibroma											1
Subcutaneous tissue, fibrosarcoma											1
MUSCULOSKELETAL SYSTEM											
Bone	+	+	+	+	+	+	+	+	+	+	60
Skeletal muscle											1
NERVOUS SYSTEM											
Brain	+	+	+	+	+	+	+	+	+	+	60
Astrocytoma benign											1
Ependymoma benign											1
Leukemia mononuclear											2
Spinal cord											1
RESPIRATORY SYSTEM											
Larynx	+	+	+	+	+	+	+	+	+	+	60
Lung	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear	X										7
Squamous cell carcinoma, metastatic, skin											1
Nose	+	+	+	+	+	+	+	+	+	+	57
Trachea	+	+	+	+	+	+	+	+	+	+	60
SPECIAL SENSES SYSTEM											
Eye									+		4
URINARY SYSTEM											
Kidney	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											3
Squamous cell carcinoma, metastatic, skin											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	60
Leukemia mononuclear											3

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	50 mg/kg	100 mg/kg
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	3/59 (5%)	(b) 1/43 (2%)	3/54 (6%)
Adjusted Rates (c)	9.4%		11.5%
Terminal Rates (d)	2/31 (6%)		3/26 (12%)
Day of First Observation	726		729
Life Table Test (e)			P=0.586
Incidental Tumor Test (e)			P=0.577
Fisher Exact Test (e)			P=0.617
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	4/59 (7%)	(b) 1/43 (2%)	3/54 (6%)
Adjusted Rates (c)	12.5%		11.5%
Terminal Rates (d)	3/31 (10%)		3/26 (12%)
Day of First Observation	726		729
Life Table Test (e)			P=0.590N
Incidental Tumor Test (e)			P=0.598N
Fisher Exact Test (e)			P=0.550N
Clitoral Gland: Adenoma			
Overall Rates (a)	2/39 (5%)	(b) 2/27 (7%)	3/53 (6%)
Adjusted Rates (c)	7.1%		10.0%
Terminal Rates (d)	1/20 (5%)		1/24 (4%)
Day of First Observation	641		642
Life Table Test (e)			P=0.493
Incidental Tumor Test (e)			P=0.521
Fisher Exact Test (e)			P=0.644
Liver: Neoplastic Nodule			
Overall Rates (a)	2/60 (3%)	1/52 (2%)	3/60 (5%)
Adjusted Rates (c)	6.5%	5.3%	11.1%
Terminal Rates (d)	2/31 (6%)	1/19 (5%)	3/27 (11%)
Day of First Observation	729	729	729
Life Table Tests (e)	P=0.346	P=0.669N	P=0.436
Incidental Tumor Tests (e)	P=0.346	P=0.669N	P=0.436
Cochran-Armitage Trend Test (e)	P=0.402		
Fisher Exact Test (e)		P=0.554N	P=0.500
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/60 (5%)	(b) 1/49 (2%)	0/60 (0%)
Adjusted Rates (c)	9.1%		0.0%
Terminal Rates (d)	2/31 (6%)		0/27 (0%)
Day of First Observation	719		
Life Table Test (e)			P=0.147N
Incidental Tumor Test (e)			P=0.158N
Fisher Exact Test (e)			P=0.122N
Mammary Gland: Fibroadenoma			
Overall Rates (f)	25/60 (42%)	23/60 (38%)	12/60 (20%)
Adjusted Rates (c)	57.0%	61.0%	35.8%
Terminal Rates (d)	13/31 (42%)	13/27 (48%)	6/27 (22%)
Day of First Observation	553	603	663
Life Table Tests (e)	P=0.049N	P=0.470	P=0.047N
Incidental Tumor Tests (e)	P=0.039N	P=0.422	P=0.038N
Cochran-Armitage Trend Test (e)	P=0.008N		
Fisher Exact Test (e)		P=0.426N	P=0.009N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (f)	26/60 (43%)	25/60 (42%)	12/60 (20%)
Adjusted Rates (c)	57.8%	63.0%	35.8%
Terminal Rates (d)	13/31 (42%)	13/27 (48%)	6/27 (22%)
Day of First Observation	507	603	663
Life Table Tests (e)	P=0.041N	P=0.392	P=0.035N
Incidental Tumor Tests (e)	P=0.032N	P=0.322	P=0.030N
Cochran-Armitage Trend Test (e)	P=0.005N		
Fisher Exact Test (e)		P=0.500N	P=0.005N
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma			
Overall Rates (f)	26/60 (43%)	25/60 (42%)	14/60 (23%)
Adjusted Rates (c)	57.8%	63.0%	42.0%
Terminal Rates (d)	13/31 (42%)	13/27 (48%)	8/27 (30%)
Day of First Observation	507	603	663
Life Table Tests (e)	P=0.084N	P=0.392	P=0.079N
Incidental Tumor Tests (e)	P=0.078N	P=0.322	P=0.079N
Cochran-Armitage Trend Test (e)	P=0.014N		
Fisher Exact Test (e)		P=0.500N	P=0.016N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	30/60 (50%)	26/55 (47%)	20/60 (33%)
Adjusted Rates (c)	65.8%	72.6%	55.8%
Terminal Rates (d)	16/31 (52%)	14/23 (61%)	12/27 (44%)
Day of First Observation	553	471	337
Life Table Tests (e)	P=0.188N	P=0.407	P=0.193N
Incidental Tumor Tests (e)	P=0.175N	P=0.292	P=0.160N
Cochran-Armitage Trend Test (e)	P=0.040N		
Fisher Exact Test (e)		P=0.458N	P=0.048N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	31/60 (52%)	26/55 (47%)	21/60 (35%)
Adjusted Rates (c)	68.0%	72.6%	57.1%
Terminal Rates (d)	17/31 (55%)	14/23 (61%)	12/27 (44%)
Day of First Observation	553	471	337
Life Table Tests (e)	P=0.195N	P=0.460	P=0.202N
Incidental Tumor Tests (e)	P=0.181N	P=0.355	P=0.169N
Cochran-Armitage Trend Test (e)	P=0.041N		
Fisher Exact Test (e)		P=0.388N	P=0.048N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	5/59 (8%)	(b) 2/45 (4%)	5/60 (8%)
Adjusted Rates (c)	14.5%		17.2%
Terminal Rates (d)	4/31 (13%)		4/27 (15%)
Day of First Observation	494		663
Life Table Test (e)			P=0.533
Incidental Tumor Test (e)			P=0.496
Fisher Exact Test (e)			P=0.618N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	4/59 (7%)	(b) 2/45 (4%)	3/60 (5%)
Adjusted Rates (c)	12.9%		11.1%
Terminal Rates (d)	4/31 (13%)		3/27 (11%)
Day of First Observation	729		729
Life Table Test (e)			P=0.577N
Incidental Tumor Test (e)			P=0.577N
Fisher Exact Test (e)			P=0.491N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	9/59 (15%)	(b) 3/45 (7%)	8/60 (13%)
Adjusted Rates (c)	27.1%		28.0%
Terminal Rates (d)	8/31 (26%)		7/27 (26%)
Day of First Observation	494		663
Life Table Test (e)			P=0.584
Incidental Tumor Test (e)			P=0.554
Fisher Exact Test (e)			P=0.485N
Uterus: Stromal Polyp			
Overall Rates (f)	11/60 (18%)	8/60 (13%)	9/60 (15%)
Adjusted Rates (c)	0.0%	22.7%	28.7%
Terminal Rates (d)	9/31 (29%)	3/27 (11%)	6/27 (22%)
Day of First Observation	663		606
Life Table Tests (e)	P=0.489N	P=0.429N	P=0.539N
Incidental Tumor Tests (e)	P=0.541N	P=0.453N	P=0.572N
Cochran-Armitage Trend Test (e)	P=0.353N		
Fisher Exact Test (e)		P=0.309N	P=0.404N
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (f)	11/60 (18%)	6/60 (10%)	8/60 (13%)
Adjusted Rates (c)	26.6%	19.4%	24.5%
Terminal Rates (d)	5/31 (16%)	4/27 (15%)	4/27 (15%)
Day of First Observation	494	599	606
Life Table Tests (e)	P=0.384N	P=0.252N	P=0.450N
Incidental Tumor Tests (e)	P=0.427N	P=0.254N	P=0.511N
Cochran-Armitage Trend Test (e)	P=0.255N		
Fisher Exact Test (e)		P=0.148N	P=0.309N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence in animals killed at the end of the study
(e) Beneath the vehicle 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 vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in vehicle controls is indicated by (N).
(f) Number of tumor-bearing animals/number of animals examined grossly at the site

TABLE B4. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Fibroadenoma	Adenocarcinoma	Fibroadenoma or Adenocarcinoma
Historical Incidence at Microbiological Associates, Inc.			
d-Limonene	(b) 23/50	1/50	(b) 23/50
Benzyl alcohol	(c) 26/50	2/50	(c) 28/50
α-Methylbenzyl alcohol	21/50	2/50	23/50
TOTAL	70/150 (46.7%)	5/150 (3.3%)	74/150 (49.3%)
SD (d)	5.03%	1.15%	5.77%
Range (e)			
High	26/50	2/50	28/50
Low	21/50	1/50	23/50
Overall Historical Incidence			
TOTAL	(f) 615/2,100 (29.3%)	(g) 48/2,100 (2.3%)	(f,g) 647/2,100 (30.8%)
SD (d)	9.21%	1.95%	9.87%
Range (e)			
High	26/50	5/50	28/50
Low	7/50	0/50	7/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes one adenoma, NOS, and one cystadenoma, NOS
(c) Includes two adenomas, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes 17 adenomas, NOS, 1 papillary adenoma, 5 cystadenomas, NOS, and 1 papillary cystadenoma, NOS
(g) Includes two carcinomas, NOS, and one papillary cystadenocarcinoma, NOS

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	50 mg/kg	100 mg/kg
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	60	60	60
ALIMENTARY SYSTEM			
Esophagus	(60)	(45)	(60)
Hemorrhage		1 (2%)	
Inflammation, chronic			3 (5%)
Adventitia, fibrosis			1 (2%)
Muscularis, regeneration	1 (2%)		2 (3%)
Intestine large, colon	(55)	(44)	(55)
Inflammation, acute	1 (2%)		
Intestine large, rectum	(53)	(35)	(53)
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)		
Liver	(60)	(52)	(60)
Angiectasis	1 (2%)		
Basophilic focus		3 (6%)	
Basophilic focus, multiple	27 (45%)	16 (31%)	25 (42%)
Congestion		2 (4%)	3 (5%)
Cytologic alterations	1 (2%)	1 (2%)	6 (10%)
Cytologic alterations, multiple	1 (2%)	1 (2%)	
Fibrosis, focal	6 (10%)	12 (23%)	10 (17%)
Hematopoietic cell proliferation	1 (2%)		
Hepatodiaphragmatic nodule	5 (8%)	12 (23%)	14 (23%)
Hyperplasia, nodular		3 (6%)	1 (2%)
Inflammation, acute			1 (2%)
Inflammation, chronic	16 (27%)	15 (29%)	15 (25%)
Necrosis, focal	1 (2%)	1 (2%)	
Necrosis, multifocal		3 (6%)	2 (3%)
Vacuolization cytoplasmic	6 (10%)	3 (6%)	4 (7%)
Bile duct, hyperplasia	19 (32%)	6 (12%)	9 (15%)
Centrilobular, congestion			1 (2%)
Centrilobular, fibrosis, multifocal		1 (2%)	
Centrilobular, necrosis		3 (6%)	
Centrilobular, vacuolization cytoplasmic	5 (8%)	1 (2%)	1 (2%)
Hepatocyte, inclusion body intranuclear			1 (2%)
Mesentery	(6)	(6)	(3)
Hemorrhage		1 (17%)	1 (33%)
Inflammation, chronic		1 (17%)	1 (33%)
Fat, necrosis	3 (50%)	4 (67%)	2 (67%)
Pancreas	(59)	(44)	(59)
Cyst			1 (2%)
Ectopic tissue	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, acute		1 (2%)	
Inflammation, chronic	1 (2%)		1 (2%)
Acinus, atrophy, diffuse	2 (3%)		
Acinus, atrophy, focal	10 (17%)	5 (11%)	5 (8%)
Acinus, hyperplasia	1 (2%)		
Stomach	(59)	(45)	(58)
Hyperplasia, focal			1 (2%)
Stomach, forestomach	(58)	(44)	(57)
Edema		1 (2%)	
Erosion, acute			1 (2%)
Foreign body	1 (2%)		
Inflammation, acute		2 (5%)	
Inflammation, chronic	3 (5%)	1 (2%)	1 (2%)
Epithelium, hyperplasia	1 (2%)	1 (2%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
ALIMENTARY SYSTEM (Continued)			
Stomach, glandular	(58)	(45)	(54)
Inflammation, acute		1 (2%)	
Inflammation, chronic	1 (2%)		
Epithelium, cyst			1 (2%)
CARDIOVASCULAR SYSTEM			
Blood vessel	(1)		
Foreign body	1 (100%)		
Aorta, inflammation, chronic active	1 (100%)		
Heart	(60)	(45)	(60)
Cardiomyopathy	38 (63%)	18 (40%)	21 (35%)
Foreign body		1 (2%)	
Atrium, thrombus		1 (2%)	1 (2%)
Coronary artery, inflammation, chronic			1 (2%)
Epicardium, foreign body			2 (3%)
Epicardium, inflammation, acute			2 (3%)
Epicardium, inflammation, chronic		2 (4%)	
Epicardium, inflammation, chronic active	1 (2%)		3 (5%)
Epicardium, necrosis		2 (4%)	2 (3%)
Pericardium, inflammation, acute		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(60)	(45)	(59)
Angiectasis	1 (2%)		
Congestion		1 (2%)	2 (3%)
Hematopoietic cell proliferation	1 (2%)		
Hyperplasia	4 (7%)		2 (3%)
Hypertrophy			1 (2%)
Hypertrophy, focal		1 (2%)	
Metaplasia, osseous		1 (2%)	
Necrosis, focal	2 (3%)	5 (11%)	1 (2%)
Vacuolization cytoplasmic, focal	1 (2%)		6 (10%)
Adrenal gland, medulla	(59)	(43)	(54)
Hyperplasia	11 (19%)	3 (7%)	9 (17%)
Pituitary gland	(60)	(55)	(60)
Hemorrhage			1 (2%)
Pars distalis, angiectasis	9 (15%)	9 (16%)	8 (13%)
Pars distalis, concretion	1 (2%)		
Pars distalis, cyst	4 (7%)		3 (5%)
Pars distalis, degeneration, focal	1 (2%)		1 (2%)
Pars distalis, hyperplasia	2 (3%)	2 (4%)	7 (12%)
Pars distalis, pigmentation		1 (2%)	
Thyroid gland	(59)	(45)	(60)
C-cell, hyperplasia	8 (14%)	4 (9%)	5 (8%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(39)	(27)	(53)
Dilatation	2 (5%)	1 (4%)	1 (2%)
Hyperplasia	1 (3%)		
Inflammation, acute	1 (3%)	1 (4%)	1 (2%)
Ovary	(59)	(44)	(60)
Atrophy			2 (3%)
Congestion			2 (3%)
Cyst	4 (7%)	4 (9%)	2 (3%)
Hemorrhage		1 (2%)	

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
GENITAL SYSTEM (Continued)			
Uterus	(59)	(48)	(60)
Congestion			1 (2%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Endometrium, hyperplasia, cystic	4 (7%)	3 (6%)	
Vagina			(1)
Inflammation, acute			1 (100%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(60)	(45)	(60)
Hyperplasia	3 (5%)		1 (2%)
Hyperplasia, reticulum cell	1 (2%)	2 (4%)	1 (2%)
Hypoplasia		1 (2%)	
Lymph node	(59)	(45)	(60)
Mediastinal, foreign body			2 (3%)
Mediastinal, giant cell, multiple		1 (2%)	
Mediastinal, hemorrhage			1 (2%)
Lymph node, mandibular	(54)	(43)	(55)
Congestion			1 (2%)
Cyst			1 (2%)
Hemorrhage	1 (2%)	2 (5%)	
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Lymph node, mesenteric	(59)	(43)	(59)
Edema	1 (2%)	2 (5%)	
Hemorrhage			3 (5%)
Pigmentation		1 (2%)	
Spleen	(59)	(46)	(60)
Congestion		1 (2%)	
Fibrosis, focal			1 (2%)
Hematopoietic cell proliferation	6 (10%)	3 (7%)	1 (2%)
Infarct		1 (2%)	
Inflammation, chronic			1 (2%)
Pigmentation	10 (17%)	7 (15%)	9 (15%)
Thymus	(48)	(41)	(52)
Hemorrhage			2 (4%)
Necrosis		2 (5%)	2 (4%)
INTEGUMENTARY SYSTEM			
Mammary gland	(59)	(55)	(59)
Dilatation	8 (14%)	4 (7%)	1 (2%)
Hyperplasia	2 (3%)	3 (5%)	2 (3%)
Skin	(60)	(44)	(60)
Subcutaneous tissue, inflammation, acute			1 (2%)
MUSCULOSKELETAL SYSTEM			
Bone	(60)	(45)	(60)
Cranium, hemorrhage		1 (2%)	
Cranium, femur, hyperostosis	2 (3%)		
Skeletal muscle	(1)		(1)
Inflammation, chronic active			1 (100%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
NERVOUS SYSTEM			
Brain	(60)	(45)	(60)
Abscess	1 (2%)		
Hemorrhage		3 (7%)	
Thrombus, focal	1 (2%)		
Thrombus, multifocal			1 (2%)
Meninges, infiltration cellular, lymphocytic			1 (2%)
Pons, vacuolization cytoplasmic			1 (2%)
Thalamus, compression	1 (2%)		
RESPIRATORY SYSTEM			
Larynx	(58)	(44)	(60)
Inflammation, chronic			1 (2%)
Necrosis		1 (2%)	
Lung	(60)	(49)	(60)
Congestion	2 (3%)	5 (10%)	9 (15%)
Edema		1 (2%)	2 (3%)
Fibrosis, focal			1 (2%)
Foreign body	2 (3%)	7 (14%)	8 (13%)
Hemorrhage	3 (5%)	3 (6%)	3 (5%)
Hyperplasia, adenomatous	4 (7%)	4 (8%)	4 (7%)
Infiltration cellular, histiocytic	23 (38%)	13 (27%)	24 (40%)
Inflammation, acute	2 (3%)	3 (6%)	3 (5%)
Inflammation, chronic		1 (2%)	2 (3%)
Inflammation, granulomatous		1 (2%)	
Pigmentation		1 (2%)	2 (3%)
Alveolar epithelium, hyperplasia	1 (2%)		
Bronchiole, foreign body			1 (2%)
Bronchiole, inflammation, acute			2 (3%)
Bronchiole, inflammation, subacute			1 (2%)
Mediastinum, foreign body	1 (2%)		1 (2%)
Mediastinum, hemorrhage			1 (2%)
Mediastinum, inflammation, acute	1 (2%)		
Mediastinum, inflammation, chronic active	1 (2%)		3 (5%)
Mediastinum, necrosis			1 (2%)
Pleura, fibrosis			3 (5%)
Pleura, foreign body		1 (2%)	
Pleura, inflammation, acute		1 (2%)	
Pleura, inflammation, chronic	2 (3%)		
Pleura, inflammation, chronic active			2 (3%)
Pleura, necrosis		5 (10%)	4 (7%)
Nose	(59)	(50)	(57)
Foreign body		1 (2%)	
Sinus, foreign body	1 (2%)	2 (4%)	5 (9%)
Sinus, fungus	1 (2%)		2 (4%)
Sinus, hemorrhage			1 (2%)
Sinus, inflammation, acute	2 (3%)	7 (14%)	9 (16%)
Turbinate, inflammation, chronic	2 (3%)	1 (2%)	
Turbinate, inflammation, subacute			2 (4%)
Turbinate, necrosis			1 (2%)
Trachea	(60)	(44)	(60)
Hemorrhage			1 (2%)
Inflammation, chronic			1 (2%)
Necrosis		1 (2%)	5 (8%)
SPECIAL SENSES SYSTEM			
Eye	(4)	(8)	(4)
Abscess	1 (25%)		
Lens capsule, cataract	1 (25%)	4 (50%)	4 (100%)
Retina, atrophy	3 (75%)	5 (63%)	4 (100%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	50 mg/kg	100 mg/kg
URINARY SYSTEM			
Kidney	(60)	(59)	(60)
Congestion		1 (2%)	
Cyst	1 (2%)		1 (2%)
Hemorrhage		1 (2%)	
Mineralization	1 (2%)		
Nephropathy	20 (33%)	15 (25%)	9 (15%)
Pigmentation		2 (3%)	1 (2%)
Papilla, necrosis	1 (2%)		
Pelvis, dilatation	1 (2%)		
Pelvis, mineralization	5 (8%)	3 (5%)	3 (5%)
Renal tubule, atrophy		1 (2%)	
Renal tubule, vacuolization cytoplasmic	1 (2%)		
Urinary bladder	(56)	(41)	(60)
Angiectasis	1 (2%)		
Hyperplasia	1 (2%)		

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	38 mg/kg	75 mg/kg
Animals initially in study	50	50	50
Animals missing	1		
Animals necropsied	49	50	50
Animals examined histopathologically	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Keratoacanthoma			1 (2%)
*Subcutaneous tissue	(49)	(50)	(50)
Sarcoma, NOS			1 (2%)
Fibroma	1 (2%)		
Lipoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(49)	(23)	(49)
Hepatocellular carcinoma, metastatic	2 (4%)	1 (4%)	1 (2%)
Alveolar/bronchiolar adenoma	4 (8%)	4 (17%)	6 (12%)
Alveolar/bronchiolar carcinoma	1 (2%)	1 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Malignant lymphoma, lymphocytic type	2 (4%)		1 (2%)
Malignant lymphoma, histiocytic type		1 (2%)	
Malignant lymphoma, mixed type			3 (6%)
#Lymph node	(44)	(18)	(49)
Squamous cell carcinoma, metastatic	1 (2%)		
#Mesenteric lymph node	(44)	(18)	(49)
Mucinous adenocarcinoma, metastatic			1 (2%)
CIRCULATORY SYSTEM			
#Spleen	(48)	(18)	(50)
Hemangiosarcoma	1 (2%)	1 (6%)	
#Liver	(49)	(50)	(50)
Hemangiosarcoma	1 (2%)		
*Preputial gland	(49)	(50)	(50)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(50)
Islet cell carcinoma, metastatic	1 (2%)		
Hepatocellular adenoma	9 (18%)	2 (4%)	2 (4%)
Hepatocellular carcinoma	5 (10%)	5 (10%)	5 (10%)
#Forestomach	(48)	(17)	(50)
Squamous cell papilloma	1 (2%)	2 (12%)	2 (4%)
#Jejunum	(39)	(8)	(49)
Adenocarcinoma, NOS			1 (2%)
#Cecum	(46)	(15)	(49)
Mucinous adenocarcinoma			1 (2%)
URINARY SYSTEM			
None			

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	38 mg/kg	75 mg/kg
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(15)	(45)
Adenoma, NOS	1 (2%)		
#Adrenal	(45)	(16)	(47)
Cortical adenoma	1 (2%)		
#Thyroid	(48)	(17)	(50)
Follicular cell adenoma			1 (2%)
#Pancreatic islets	(45)	(15)	(49)
Islet cell carcinoma	1 (2%)		
REPRODUCTIVE SYSTEM			
#Testis	(48)	(17)	(50)
Interstitial cell tumor	2 (4%)		1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(49)	(50)	(50)
Papillary adenoma	5 (10%)	2 (4%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
Tail			
Sarcoma, NOS			1
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death (a)	18	9	5
Moribund sacrifice (a)	1		1
Terminal sacrifice	27	30	41
Dosing accident	3	11	3
Animal missing	1		
TUMOR SUMMARY			
Total animals with primary tumors**	28	13	24
Total primary tumors	35	18	31
Total animals with benign tumors	19	8	15
Total benign tumors	24	10	16
Total animals with malignant tumors	10	8	14
Total malignant tumors	11	8	15
Total animals with secondary tumors##	4	1	2
Total secondary tumors	4	1	2

(a) Some of these early deaths may have been gavage related.
* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE: VEHICLE CONTROL

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

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed

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

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

ANIMAL NUMBER	C 0 8	C 0 9	C 1 4	C 1 8	C 1 9	C 2 2	C 2 4	C 2 6	C 2 7	C 2 8	C 2 9	C 3 0	C 3 2	C 3 3	C 3 6	C 3 8	C 3 9	C 4 0	C 4 3	C 4 4	C 4 5	C 4 6	C 4 7	C 4 8	C 4 9	TOTAL:
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibroma	X																									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic									X		X															2
Alveolar/bronchiolar adenoma	X												X			X										4
Alveolar/bronchiolar carcinoma																					X					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																	X									1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	44
Squamous cell carcinoma, metastatic								X																		1
Thymus	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell carcinoma, metastatic																		X								1
Hepatocellular adenoma		X	X					X															X			9
Hepatocellular carcinoma			X						X		X															5
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma							X																			1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Large intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS																X										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	45
Cortical adenoma							X																			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	+	+	−	+	+	+	+	−	−	−	+	−	−	+	+	+	+	+	−	+	+	+	+	+	+	31
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Islet cell carcinoma																		X								1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Interstitial cell tumor					X																					2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Papillary adenoma				X											X	X								X		5
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malignant lymphoma, lymphocytic type														X				X								2

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE: 38 mg/kg

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 38 mg/kg (Continued)

ANIMAL NUMBER	C 1 1 1	C 1 1 2	C 1 1 3	C 1 1 4	C 1 1 5	C 1 1 8	C 1 1 9	C 2 2 4	C 2 2 5	C 2 2 7	C 2 2 8	C 2 2 9	C 3 3 1	C 3 3 2	C 3 3 3	C 3 3 4	C 3 3 7	C 4 4 0	C 4 4 2	C 4 4 3	C 4 4 4	C 4 4 6	C 4 4 8	C 4 4 9	C 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	+		23
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma			X																					X		4
Alveolar/bronchiolar carcinoma																								X		1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		17
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		17
Spleen	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		18
Hemangiosarcoma																										1
Lymph nodes	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		18
Thymus	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		13
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		17
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		17
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular adenoma									X							X										2
Hepatocellular carcinoma									X													X				5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder & common bile duct	N	+	N	N	+	+	+	+	N	N	+	+	N	+	+	+	N	+	+	+	+	+	+	N		*50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		15
Esophagus	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		15
Stomach	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–		17
Squamous cell papilloma												X														2
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		8
Large intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		15
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		17
ENDOCRINE SYSTEM																										
Pituitary	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		15
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		16
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		17
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		6
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Testis	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		17
Prostate	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		17
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–		17
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Papillary adenoma																X										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Malignant lymphoma, histiocytic type			X																							1

* Animals necropsied

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE: 75 mg/kg

ANIMAL NUMBER	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041	C041
WEEKS ON STUDY	018	020	029	037	053	062	097	100	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																							X	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																								X
Lipoma																								
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																								
Alveolar/bronchiolar adenoma																X				X	X			
Alveolar/bronchiolar carcinoma																				X			X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucinous adenocarcinoma, metastatic																								
Thymus	+	–	+	–	–	–	+	–	–	+	+	–	+	+	+	+	+	+	+	+	–	+	–	
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								
Hepatocellular carcinoma						X																X	X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	N
Pancreas	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								
Small intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																								
Large intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mucinous adenocarcinoma																								
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																								
Parathyroid	–	+	–	+	+	–	–	+	+	+	+	–	+	–	+	–	+	+	–	+	–	+	+	–
REPRODUCTIVE SYSTEM																								
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangioma																								
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																								
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																					X			
ALL OTHER SYSTEMS																								
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, lymphocytic type																								
Malignant lymphoma, mixed type							X																	
Tail																								
Sarcoma, NOS																								

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 75 mg/kg (Continued)

ANIMAL NUMBER	C 2 4	C 2 6	C 2 7	C 2 8	C 2 9	C 3 0	C 3 1	C 3 2	C 3 3	C 3 4	C 3 5	C 3 6	C 3 7	C 3 8	C 3 9	C 4 0	C 4 2	C 4 3	C 4 4	C 4 5	C 4 6	C 4 7	C 4 8	C 4 9	C 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Lipoma											X															1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic						X																				1
Alveolar/bronchiolar adenoma					X			X														X				6
Alveolar/bronchiolar carcinoma																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mucinous adenocarcinoma, metastatic																					X					1
Thymus	+	+	–	–	+	–	+	+	+	–	+	+	+	+	–	+	+	+	–	+	+	+	–	+	+	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X																X									2
Hepatocellular carcinoma						X									X											5
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma															X										X	2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS		X																								1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mucinous adenocarcinoma																					X					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	45
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																		X								1
Parathyroid	–	+	+	+	+	–	–	+	–	–	+	+	+	–	–	–	+	+	+	+	+	+	+	–	–	30
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor													X													1
Prostate	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangioma						X																				1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, lymphocytic type														X												1
Malignant lymphoma, mixed type												X				X										3
Tail																										
Sarcoma, NOS																									X	1

* Animals necropsied

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	38 mg/kg	75 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/49 (8%)	(b) 4/23 (17%)	6/49 (12%)
Adjusted Rates (c)	13.8%		14.6%
Terminal Rates (d)	3/27 (11%)		6/41 (15%)
Week of First Observation	88		104
Life Table Test (e)			P=0.633
Incidental Tumor Test (e)			P=0.479
Fisher Exact Test (e)			P=0.370
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	(b) 4/23 (17%)	7/49 (14%)
Adjusted Rates (c)	17.4%		17.1%
Terminal Rates (d)	4/27 (15%)		7/41 (17%)
Week of First Observation	88		104
Life Table Test (e)			P=0.575N
Incidental Tumor Test (e)			P=0.535
Fisher Exact Test (e)			P=0.380
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (f)	0/49 (0%)	(g) 0/50 (0%)	3/50 (6%)
Adjusted Rates (c)	0.0%	0.0%	6.9%
Terminal Rates (d)	0/27 (0%)	0/30 (0%)	2/42 (5%)
Week of First Observation			97
Life Table Tests (e)	P=0.077	(h)	P=0.212
Incidental Tumor Tests (e)	P=0.067	(h)	P=0.229
Cochran-Armitage Trend Test (e)	P=0.039		
Fisher Exact Test (e)		(h)	P=0.125
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (f)	2/49 (4%)	(g) 1/50 (2%)	4/50 (8%)
Adjusted Rates (c)	7.4%	3.3%	9.3%
Terminal Rates (d)	2/27 (7%)	1/30 (3%)	3/42 (7%)
Week of First Observation	104	104	97
Life Table Tests (e)	P=0.423	P=0.463N	P=0.553
Incidental Tumor Tests (e)	P=0.424	P=0.463N	P=0.572
Cochran-Armitage Trend Test (e)	P=0.249		
Fisher Exact Test (e)		P=0.492N	P=0.348
Liver: Hepatocellular Adenoma			
Overall Rates (a)	9/49 (18%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (c)	27.9%	6.7%	4.8%
Terminal Rates (d)	6/27 (22%)	2/30 (7%)	2/42 (5%)
Week of First Observation	58	104	104
Life Table Tests (e)	P=0.002N	P=0.025N	P=0.006N
Incidental Tumor Tests (e)	P=0.007N	P=0.032N	P=0.025N
Cochran-Armitage Trend Test (e)	P=0.009N		
Fisher Exact Test (e)		P=0.023N	P=0.023N
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	5/49 (10%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (c)	16.3%	15.5%	11.5%
Terminal Rates (d)	3/27 (11%)	3/30 (10%)	4/42 (10%)
Week of First Observation	86	94	62
Life Table Tests (e)	P=0.313N	P=0.569N	P=0.395N
Incidental Tumor Tests (e)	P=0.481	P=0.549	P=0.467
Cochran-Armitage Trend Test (e)	P=0.554N		
Fisher Exact Test (e)		P=0.617N	P=0.617N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	38 mg/kg	75 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	13/49 (27%)	6/50 (12%)	7/50 (14%)
Adjusted Rates (c)	38.6%	18.6%	16.2%
Terminal Rates (d)	8/27 (30%)	4/30 (13%)	6/42 (14%)
Week of First Observation	58	94	62
Life Table Tests (e)	P=0.012N	P=0.053N	P=0.019N
Incidental Tumor Tests (e)	P=0.091N	P=0.088N	P=0.187N
Cochran-Armitage Trend Test (e)	P=0.065N		
Fisher Exact Test (e)		P=0.056N	P=0.096N
Harderian Gland: Papillary Adenoma			
Overall Rates (f)	5/49 (10%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (c)	16.8%	6.7%	2.4%
Terminal Rates (d)	4/27 (15%)	2/30 (7%)	1/42 (2%)
Week of First Observation	63	104	104
Life Table Tests (e)	P=0.022N	P=0.192N	P=0.040N
Incidental Tumor Tests (e)	P=0.032N	P=0.206N	P=0.066N
Cochran-Armitage Trend Test (e)	P=0.056N		
Fisher Exact Test (e)		P=0.210N	P=0.098N
All Sites: Benign Tumors			
Overall Rates (f)	19/49 (39%)	8/50 (16%)	15/50 (30%)
Adjusted Rates (c)	57.7%	26.7%	35.7%
Terminal Rates (d)	14/27 (52%)	8/30 (27%)	15/42 (36%)
Week of First Observation	58	104	104
Life Table Tests (e)	P=0.016N	P=0.006N	P=0.019N
Incidental Tumor Tests (e)	P=0.066N	P=0.013N	P=0.101N
Cochran-Armitage Trend Test (e)	P=0.194N		
Fisher Exact Test (e)		P=0.010N	P=0.240N
All Sites: Malignant Tumors			
Overall Rates (f)	10/49 (20%)	8/50 (16%)	14/50 (28%)
Adjusted Rates (c)	32.5%	24.2%	31.7%
Terminal Rates (d)	7/27 (26%)	5/30 (17%)	12/42 (29%)
Week of First Observation	86	94	62
Life Table Tests (e)	P=0.494N	P=0.319N	P=0.521N
Incidental Tumor Tests (e)	P=0.236	P=0.484N	P=0.277
Cochran-Armitage Trend Test (e)	P=0.214		
Fisher Exact Test (e)		P=0.380N	P=0.259
All Sites: All Tumors			
Overall Rates (f)	28/49 (57%)	13/50 (26%)	24/50 (48%)
Adjusted Rates (c)	79.3%	39.4%	54.5%
Terminal Rates (d)	20/27 (74%)	10/30 (33%)	22/42 (52%)
Week of First Observation	58	94	62
Life Table Tests (e)	P=0.007N	P=0.001N	P=0.005N
Incidental Tumor Tests (e)	P=0.096N	P=0.002N	P=0.132N
Cochran-Armitage Trend Test (e)	P=0.206N		
Fisher Exact Test (e)		P=0.002N	P=0.239N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence in animals killed at the end of the study
(e) Beneath the vehicle 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 vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in vehicle controls is indicated by (N).
(f) Number of tumor-bearing animals/number of animals examined grossly at the site
(g) Eighteen spleens were examined microscopically.
(h) No P value is reported because no tumors were observed in the vehicle control and 38 mg/kg groups.

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	38 mg/kg	75 mg/kg
Animals initially in study	50	50	50
Animals missing	1		
Animals necropsied	49	50	50
Animals examined histopathologically	49	50	50
INTEGUMENTARY SYSTEM			
*Skin	(49)	(50)	(50)
Inflammation, acute			1 (2%)
Fibrosis	1 (2%)		
Hyperplasia, epithelial	1 (2%)		
*Subcutaneous tissue	(49)	(50)	(50)
Inflammation, acute		2 (4%)	
Abscess, NOS	1 (2%)		2 (4%)
Inflammation, granulomatous		1 (2%)	
RESPIRATORY SYSTEM			
#Nasal cavity	(48)	(50)	(50)
Congestion, NOS		1 (2%)	
Inflammation, acute	1 (2%)	9 (18%)	9 (18%)
Foreign material, NOS	10 (21%)	24 (48%)	19 (38%)
Hyperplasia, epithelial		1 (2%)	
Metaplasia, NOS			4 (8%)
#Lung/bronchiole	(49)	(23)	(49)
Necrosis, NOS		1 (4%)	
#Lung	(49)	(23)	(49)
Congestion, NOS	10 (20%)	10 (43%)	1 (2%)
Hemorrhage	2 (4%)	2 (9%)	2 (4%)
Lymphocytic inflammatory infiltrate		3 (13%)	1 (2%)
Necrosis, NOS		3 (13%)	
Foreign material, NOS	14 (29%)	10 (43%)	4 (8%)
Hyperplasia, alveolar epithelium	4 (8%)	4 (17%)	5 (10%)
Histiocytosis	4 (8%)	3 (13%)	3 (6%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(49)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)		2 (4%)
*Subcutaneous tissue	(49)	(50)	(50)
Mastocytosis	1 (2%)		
#Spleen	(48)	(18)	(50)
Necrosis, NOS		1 (6%)	
Hyperplasia, lymphoid			1 (2%)
Hematopoiesis	3 (6%)		4 (8%)
#Lymph node	(44)	(18)	(49)
Hyperplasia, lymphoid			2 (4%)
#Mandibular lymph node	(44)	(18)	(49)
Necrosis, NOS		1 (6%)	
Hyperplasia, lymphoid			1 (2%)
Mastocytosis	1 (2%)		
#Mesenteric lymph node	(44)	(18)	(49)
Hemorrhage	21 (48%)	1 (6%)	15 (31%)
Hyperplasia, lymphoid		1 (6%)	
#Lung	(49)	(23)	(49)
Leukocytosis, NOS	1 (2%)		
#Thymus	(40)	(13)	(34)
Cyst, NOS	7 (18%)		5 (15%)
Necrosis, NOS	5 (13%)		
Atrophy, NOS	1 (3%)		
Depletion, lymphoid	1 (3%)		
Hyperplasia, epithelial	1 (3%)		

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	38 mg/kg	75 mg/kg
CIRCULATORY SYSTEM			
*Multiple organs	(49)	(50)	(50)
Thrombosis, NOS			1 (2%)
Polyangiitis	1 (2%)		
*Subcutaneous tissue	(49)	(50)	(50)
Lymphangiectasis		1 (2%)	1 (2%)
#Heart	(49)	(17)	(50)
Mineralization			1 (2%)
#Heart/ventricle	(49)	(17)	(50)
Necrosis, hemorrhagic	1 (2%)		
#Cardiac valve	(49)	(17)	(50)
Degeneration, cystic		1 (6%)	
Pigmentation, NOS	4 (8%)	1 (6%)	8 (16%)
Hemosiderosis	1 (2%)		
*Blood vessel	(49)	(50)	(50)
Mineralization	1 (2%)		
Inflammation, granulomatous	1 (2%)		
*Aorta	(49)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, chronic			1 (2%)
*Renal artery	(49)	(50)	(50)
Inflammation, chronic			1 (2%)
DIGESTIVE SYSTEM			
*Hard palate	(49)	(50)	(50)
Inflammation, acute	1 (2%)		
*Lip	(49)	(50)	(50)
Inflammation, acute	1 (2%)		
*Tooth	(49)	(50)	(50)
Inflammation, acute		1 (2%)	
#Salivary gland	(49)	(17)	(49)
Lymphocytic inflammatory infiltrate	5 (10%)	1 (6%)	8 (16%)
Inflammation, granulomatous			1 (2%)
Necrosis, fat			1 (2%)
Amyloidosis	1 (2%)		
Atrophy, NOS			1 (2%)
#Liver	(49)	(50)	(50)
Abnormal curvature			1 (2%)
Necrosis, NOS	4 (8%)	1 (2%)	1 (2%)
Pigmentation, NOS	1 (2%)		
Cytoplasmic vacuolization	1 (2%)	9 (18%)	3 (6%)
Basophilic cyto change	2 (4%)		1 (2%)
Clear cell change	7 (14%)	2 (4%)	4 (8%)
Hepatocytomegaly	1 (2%)		
Angiectasis		1 (2%)	
#Pancreas	(45)	(15)	(49)
Dilatation/ducts			3 (6%)
Cyst, NOS	1 (2%)		
Lymphocytic inflammatory infiltrate			1 (2%)
Inflammation, acute	1 (2%)		
Granuloma, NOS			1 (2%)
#Pancreatic duct	(45)	(15)	(49)
Inflammation, acute/chronic			1 (2%)
#Pancreatic acinus	(45)	(15)	(49)
Focal cellular change	3 (7%)		1 (2%)
Atrophy, NOS	6 (13%)	2 (13%)	10 (20%)
Hyperplasia, nodular			1 (2%)
*Esophageal lumen	(49)	(50)	(50)
Hemorrhage			1 (2%)
#Esophagus	(48)	(15)	(50)
Cyst, NOS			1 (2%)
Inflammation, acute		1 (7%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	38 mg/kg	75 mg/kg
DIGESTIVE SYSTEM (Continued)			
#Periesophageal tissue	(48)	(15)	(50)
Inflammation, acute	2 (4%)	1 (7%)	
#Forestomach	(48)	(17)	(50)
Inflammation, acute			1 (2%)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic	1 (2%)		
Hyperplasia, epithelial	1 (2%)		
#Ileum	(39)	(8)	(49)
Amyloidosis	1 (3%)		
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Mineralization	16 (33%)	6 (12%)	
Hydronephrosis	2 (4%)		
Cyst, NOS	3 (6%)	1 (2%)	3 (6%)
Multiple cysts	1 (2%)		
Hemorrhage	1 (2%)	2 (4%)	1 (2%)
Glomerulonephritis, NOS			1 (2%)
Lymphocytic inflammatory infiltrate		2 (4%)	
Pyelonephritis, acute	1 (2%)	1 (2%)	
Infection, bacterial		1 (2%)	
Nephrosis, NOS	5 (10%)	10 (20%)	5 (10%)
Infarct, NOS	1 (2%)		1 (2%)
Metaplasia, osseous			1 (2%)
#Urinary bladder	(49)	(17)	(49)
Dilatation, NOS	2 (4%)	3 (18%)	
Hemorrhage	1 (2%)		
Inflammation, acute	4 (8%)	2 (12%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(46)	(15)	(45)
Cyst, NOS			2 (4%)
Hyperplasia, chromophobe cell			1 (2%)
#Adrenal/capsule	(45)	(16)	(47)
Hyperplasia, NOS	8 (18%)	1 (6%)	9 (19%)
#Adrenal cortex	(45)	(16)	(47)
Clear cell change	2 (4%)		1 (2%)
Atrophy, brown	4 (9%)		7 (15%)
Hypertrophy, focal	3 (7%)	1 (6%)	3 (6%)
Hyperplasia, NOS	1 (2%)		2 (4%)
#Adrenal medulla	(45)	(16)	(47)
Hyperplasia, NOS	1 (2%)		
#Thyroid	(48)	(17)	(50)
Cystic follicles		1 (6%)	
Follicular cyst, NOS	4 (8%)		6 (12%)
Crystals, NOS	2 (4%)		3 (6%)
Hyperplasia, follicular cell	2 (4%)	1 (6%)	1 (2%)
#Parathyroid	(31)	(6)	(30)
Cyst, NOS			1 (3%)
REPRODUCTIVE SYSTEM			
*Penis	(49)	(50)	(50)
Inflammation, acute	1 (2%)		
*Preputial gland	(49)	(50)	(50)
Dilatation, NOS			1 (2%)
Impaction, NOS		1 (2%)	2 (4%)
Lymphocytic inflammatory infiltrate			1 (2%)
Abscess, NOS	2 (4%)		4 (8%)
Inflammation, acute/chronic		2 (4%)	3 (6%)

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	38 mg/kg	75 mg/kg
REPRODUCTIVE SYSTEM (Continued)			
#Prostate	(47)	(17)	(48)
Hemorrhage	1 (2%)	1 (6%)	1 (2%)
Inflammation, acute	6 (13%)	1 (6%)	
*Seminal vesicle	(49)	(50)	(50)
Dilatation, NOS	4 (8%)	1 (2%)	
Inflammation, acute	4 (8%)	1 (2%)	
Atrophy, NOS	1 (2%)		
#Testis	(48)	(17)	(50)
Mineralization	2 (4%)		
Spermatocele	1 (2%)		
Edema, NOS	1 (2%)		
Syncytial alteration		1 (6%)	
Atrophy, NOS	1 (2%)		3 (6%)
#Tunica albuginea	(48)	(17)	(50)
Inflammation, granulomatous			1 (2%)
*Epididymis	(49)	(50)	(50)
Mineralization	1 (2%)		1 (2%)
Granuloma, spermatic			1 (2%)
NERVOUS SYSTEM			
#Brain	(49)	(17)	(50)
Mineralization	22 (45%)	4 (24%)	23 (46%)
Cytoplasmic vacuolization	5 (10%)	1 (6%)	2 (4%)
SPECIAL SENSE ORGANS			
*Eye	(49)	(50)	(50)
Cataract	1 (2%)	1 (2%)	1 (2%)
*Eyelid	(49)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
*Eye/conjunctiva	(49)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
*Nasolacrimal duct	(49)	(50)	(50)
Hyperplasia, papillary			1 (2%)
*Middle ear	(49)	(50)	(50)
Inflammation, acute			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(49)	(50)	(50)
Foreign material, NOS	1 (2%)		
*Abdominal cavity	(49)	(50)	(50)
Necrosis, fat	1 (2%)		
Foreign material, NOS			1 (2%)
*Pleura	(49)	(50)	(50)
Inflammation, acute	1 (2%)	1 (2%)	

TABLE C4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	38 mg/kg	75 mg/kg
ALL OTHER SYSTEMS			
*Multiple organs	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
Hemorrhage		1 (2%)	
Lymphocytic inflammatory infiltrate	3 (6%)		6 (12%)
Inflammation, granulomatous	1 (2%)		
Necrosis, NOS	1 (2%)	1 (2%)	
Amyloidosis			1 (2%)
Adipose tissue			
Inflammation, chronic	1		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		6	
Animal missing/no necropsy	1		

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

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	75 mg/kg	150 mg/kg
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
None			
RESPIRATORY SYSTEM			
#Lung	(50)	(12)	(49)
Alveolar/bronchiolar adenoma	3 (6%)		4 (8%)
Alveolar/bronchiolar carcinoma		1 (8%)	
Osteosarcoma, metastatic	2 (4%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	2 (4%)	1 (2%)	
Malignant lymphoma, lymphocytic type		1 (2%)	
Malignant lymphoma, histiocytic type			2 (4%)
Malignant lymphoma, mixed type	5 (10%)	3 (6%)	4 (8%)
#Pancreatic lymph node	(49)	(13)	(45)
Malignant lymphoma, mixed type	1 (2%)		
CIRCULATORY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	
Hemangiosarcoma, metastatic	1 (2%)		
#Spleen	(49)	(17)	(49)
Hemangiosarcoma	2 (4%)		
#Lung	(50)	(12)	(49)
Hemangiosarcoma, metastatic		1 (8%)	
#Liver	(50)	(13)	(50)
Hemangiosarcoma, metastatic	1 (2%)		
#Uterus	(49)	(40)	(50)
Hemangioma	1 (2%)		1 (2%)
Hemangiosarcoma		1 (3%)	
DIGESTIVE SYSTEM			
#Liver	(50)	(13)	(50)
Hepatocellular adenoma	1 (2%)		1 (2%)
Hepatocellular carcinoma	1 (2%)	1 (8%)	
Endometrial stromal sarcoma, metastatic	1 (2%)		
#Pancreas	(48)	(11)	(48)
Islet cell adenoma	1 (2%)		
#Forestomach	(47)	(8)	(47)
Squamous cell carcinoma	2 (4%)		
#Cecum	(48)	(11)	(47)
Leiomyosarcoma			1 (2%)
URINARY SYSTEM			
None			
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(47)	(49)
Adenoma, NOS		3 (6%)	
#Anterior pituitary	(48)	(47)	(49)
Adenoma, NOS	9 (19%)	5 (11%)	3 (6%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	75 mg/kg	150 mg/kg
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(10)	(50)
Follicular cell adenoma	1 (2%)	1 (10%)	2 (4%)
Follicular cell carcinoma	1 (2%)		
#Pancreatic islets	(48)	(11)	(48)
Islet cell adenoma	1 (2%)		2 (4%)
REPRODUCTIVE SYSTEM			
#Uterus	(49)	(40)	(50)
Endometrial stromal polyp	1 (2%)	2 (5%)	
Endometrial stromal sarcoma	2 (4%)		
#Ovary	(48)	(16)	(48)
Tubular adenoma	1 (2%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Vertebra	(50)	(50)	(50)
Osteosarcoma	1 (2%)		
*Tibia	(50)	(50)	(50)
Osteosarcoma	1 (2%)		
BODY CAVITIES			
*Mesentery	(50)	(50)	(50)
Endometrial stromal sarcoma, metastatic	1 (2%)		
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death (a)	7	4	4
Moribund sacrifice (a)	2		
Terminal sacrifice	37	38	41
Dosing accident	4	8	5
TUMOR SUMMARY			
Total animals with primary tumors**	27	14	16
Total primary tumors	37	20	20
Total animals with benign tumors	17	9	11
Total benign tumors	19	11	13
Total animals with malignant tumors	15	9	7
Total malignant tumors	18	9	7
Total animals with secondary tumors##	4	1	
Total secondary tumors	6	1	

(a) Some of these early deaths may have been gavage related.
* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE: VEHICLE CONTROL

ANIMAL NUMBER	C 2 7	C 5 0	C 1 6	C 1 7	C 3 8	C 4 2	C 4 3	C 4 7	C 1 2	C 2 6	C 4 5	C 3 3	C 2 8	C 0 1	C 0 2	C 0 3	C 0 4	C 0 5	C 0 6	C 0 7	C 0 8	C 0 9	C 1 0	C 1 1	C 1 3
WEEKS ON STUDY	0 4 4	0 5 3	0 6 1	0 8 7	0 9 0	0 9 3	0 9 4	0 9 9	1 0 1	1 0 1	1 0 1	1 0 2	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Hemangiosarcoma, metastatic						X																			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Osteosarcoma, metastatic			X			X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X				X															
Lymph nodes	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Thymus	+	+	−	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma				X																					
Endometrial stromal sarcoma, metastatic																									
Hemangiosarcoma, metastatic										X															
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	N	N	N	N	+	N	N	+	N	+	+	+	+	+	+	+	+	N	+	+	+
Pancreas	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Small intestine	−	+	+	−	+	+	−	−	+	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS					X						X		X			X									X
Adrenal	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																								X	
Follicular cell carcinoma																						X			
Parathyroid	+	+	−	−	+	+	+	+	+	+	−	−	+	+	+	−	+	−	+	−	+	+	+	+	+
Pancreatic islets	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+
Uterus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									
Endometrial stromal sarcoma																									
Hemangioma																									
Ovary	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular adenoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma			X			X																			
BODY CAVITIES																									
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Endometrial stromal sarcoma, metastatic																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS				X					X																
Malignant lymphoma, mixed type								X			X		X												

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

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

ANIMAL NUMBER	C 1 1 4	C 1 1 5	C 1 1 8	C 1 1 9	C 2 2 0	C 2 2 1	C 2 2 2	C 2 2 3	C 2 2 4	C 2 2 5	C 2 2 9	C 3 3 0	C 3 3 1	C 3 3 2	C 3 3 4	C 3 3 5	C 3 3 6	C 3 3 7	C 3 3 9	C 4 4 0	C 4 4 1	C 4 4 4	C 4 4 6	C 4 4 8	C 4 4 9	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Hemangiosarcoma, metastatic																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma											X												X		X	3
Osteosarcoma, metastatic																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type													X													1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X																		1
Hepatocellular carcinoma																										1
Endometrial stromal sarcoma, metastatic						X																				1
Hemangiosarcoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma				X																						1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma										X															X	2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS															X	X						X			X	9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Follicular cell carcinoma																										1
Parathyroid	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	–	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma															X											1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	N	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp						X																				1
Endometrial stromal sarcoma						X														X						2
Hemangioma																								X		1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tubular adenoma																				X						1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										2
BODY CAVITIES																										
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Endometrial stromal sarcoma, metastatic						X																				1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS																										2
Malignant lymphoma, mixed type		X																							X	5

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE: 75 mg/kg

ANIMAL NUMBER	C 0 4	C 1 9	C 2 4	C 2 1	C 0 1	C 2 7	C 1 2	C 4 5	C 3 1	C 1 8	C 3 3	C 1 0	C 0 2	C 0 3	C 0 5	C 0 6	C 0 7	C 0 8	C 0 9	C 1 1	C 1 3	C 1 4	C 1 5	C 1 6	C 1 7
WEEKS ON STUDY	0 0 9	0 1 2	0 4 5	0 4 9	0 5 3	0 5 3	0 5 6	0 7 7	0 9 2	0 9 6	0 9 9	1 0 1	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N
Hemangiosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	−	+	+	+	+	−	+	+	+	−	−	+	−	−	−	−	−	−	−	−	−	−
Alveolar/bronchiolar carcinoma																									
Hemangiosarcoma, metastatic								X																	
Trachea	+	+	+	−	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Nasal cavity	+	+	+	+	+	+	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	−	+	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Spleen	+	+	+	+	+	+	+	+	+	−	+	+	−	−	+	+	−	−	−	−	−	−	−	−	+
Lymph nodes	+	+	−	−	+	+	+	+	−	+	−	+	−	+	−	−	−	−	−	−	−	−	−	−	+
Thymus	+	+	+	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	−	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
DIGESTIVE SYSTEM																									
Salivary gland	+	+	−	−	+	+	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+
Liver	+	+	+	+	+	+	+	+	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Gallbladder & common bile duct	+	+	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	−	+	+	+	−	−	−	+	−	+	−	−	−	+	−	−	−	−	−	−	−
Esophagus	+	+	+	−	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Stomach	−	+	+	+	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Small intestine	+	+	−	+	+	−	−	+	+	−	−	+	−	−	−	−	−	−	−	−	−	+	−	−	+
Large intestine	+	+	+	+	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	−	−	+	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Urinary bladder	+	+	+	+	+	+	+	+	−	−	−	+	−	+	−	−	−	−	−	−	−	−	−	−	−
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	−	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																@X	X			X				X	
Adrenal	+	+	+	+	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Thyroid	+	+	+	−	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
Follicular cell adenoma																									
Parathyroid	+	+	−	−	+	+	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N
Uterus	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	−
Endometrial stromal polyp																									
Hemangiosarcoma								X																	
Ovary	+	+	+	+	+	+	+	+	−	−	+	+	−	−	−	−	−	−	−	−	+	−	+	−	−
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	−	−	−	+	−	−	−	−	−	−	−	−	−	−	−	−	−
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																									
Malignant lymphoma, lymphocytic type											X														
Malignant lymphoma, mixed type																									X

@ Multiple occurrence of morphology

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 75 mg/kg (Continued)

ANIMAL NUMBER	C 2 2 0	C 2 2 2	C 2 2 3	C 2 2 5	C 2 2 6	C 2 2 8	C 2 2 9	C 3 3 0	C 3 3 2	C 3 3 4	C 3 3 5	C 3 3 6	C 3 3 7	C 3 3 8	C 3 3 9	C 4 4 0	C 4 4 1	C 4 4 2	C 4 4 3	C 4 4 4	C 4 4 6	C 4 4 7	C 4 4 8	C 4 4 9	C 5 5 0	TOTAL. TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Hemangiosarcoma														X												1
RESPIRATORY SYSTEM																										
Lungs and bronchi	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	12
Alveolar/bronchiolar carcinoma									X																	1
Hemangiosarcoma, metastatic																										1
Trachea	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+	–	–	–	–	–	10
Nasal cavity	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
HEMATOPOIETIC SYSTEM																										
Bone marrow	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Spleen	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	–	–	17
Lymph nodes	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	–	–	13
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5
CIRCULATORY SYSTEM																										
Heart	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
DIGESTIVE SYSTEM																										
Salivary gland	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	9
Liver	–	–	–	–	+	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	+	–	–	13
Hepatocellular carcinoma					X																					1
Bile duct	–	–	–	–	+	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	+	–	–	13
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	11
Esophagus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Stomach	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	8
Small intestine	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Large intestine	–	–	–	–	–	–	–	–	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	11
URINARY SYSTEM																										
Kidney	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	11
Urinary bladder	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	10
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS					X				X											X						7
Adrenal	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
Thyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	+	–	–	–	–	–	10
Follicular cell adenoma														X												1
Parathyroid	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	7
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	+	N	N	N	N	N	N	N	N	N	*50
Uterus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	–	+	–	+	+	–	+	+	+	–	40
Endometrial stromal polyp					X		X																			2
Hemangiosarcoma																										1
Ovary	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	+	–	–	–	–	+	–	+	–	16
NERVOUS SYSTEM																										
Brain	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	9
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, NOS							X																			1
Malignant lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type																X		X								3

* Animals necropsied

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE: 150 mg/kg

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 150 mg/kg (Continued)

ANIMAL NUMBER	C 1 9	C 2 0	C 2 1	C 2 2	C 2 3	C 2 4	C 2 5	C 2 6	C 2 7	C 2 8	C 2 9	C 3 1	C 3 3	C 3 6	C 3 7	C 3 9	C 4 0	C 4 1	C 4 4	C 4 5	C 4 6	C 4 7	C 4 8	C 4 9	C 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	49
Alveolar/bronchiolar adenoma																				X						4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	45
Thymus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyosarcoma			X																							1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS										X			X	X												3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										2
Parathyroid	+	−	+	−	+	−	+	−	+	+	+	−	+	+	+	+	+	−	+	−	−	−	+	+	+	35
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																		X								2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma						X																				1
Ovary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malignant lymphoma, histiocytic type																									X	2
Malignant lymphoma, mixed type																			X							4

* Animals necropsied

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	75 mg/kg	150 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	(b) 0/12 (0%)	4/49 (8%)
Adjusted Rates (c)	8.1%		9.7%
Terminal Rates (d)	3/37 (8%)		3/40 (7%)
Week of First Observation	104		97
Life Table Test (e)			P=0.534
Incidental Tumor Test (e)			P=0.442
Fisher Exact Test (e)			P=0.488
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (f)	6/50 (12%)	(g) 3/50 (6%)	4/50 (8%)
Adjusted Rates (c)	14.7%	7.9%	9.5%
Terminal Rates (d)	3/37 (8%)	3/38 (8%)	3/41 (7%)
Week of First Observation	99	104	97
Life Table Tests (e)	P=0.266N	P=0.247N	P=0.338N
Incidental Tumor Tests (e)	P=0.505N	P=0.397N	P=0.632
Cochran-Armitage Trend Test (e)	P=0.297N		
Fisher Exact Test (e)		P=0.244N	P=0.371N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (f)	8/50 (16%)	(g) 5/50 (10%)	6/50 (12%)
Adjusted Rates (c)	18.5%	12.8%	14.3%
Terminal Rates (d)	3/37 (8%)	4/38 (11%)	5/41 (12%)
Week of First Observation	87	99	97
Life Table Tests (e)	P=0.297N	P=0.295N	P=0.356N
Incidental Tumor Tests (e)	P=0.487	P=0.565N	P=0.510
Cochran-Armitage Trend Test (e)	P=0.326N		
Fisher Exact Test (e)		P=0.277N	P=0.387N
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (f)	3/50 (6%)	(g) 2/50 (4%)	1/50 (2%)
Adjusted Rates (c)	7.1%	4.9%	2.4%
Terminal Rates (d)	1/37 (3%)	1/38 (3%)	1/41 (2%)
Week of First Observation	93	77	104
Life Table Tests (e)	P=0.219N	P=0.518N	P=0.296N
Incidental Tumor Tests (e)	P=0.320N	P=0.605N	P=0.522N
Cochran-Armitage Trend Test (e)	P=0.222N		
Fisher Exact Test (e)		P=0.500N	P=0.309N
Intermedia Pituitary Gland: Adenoma			
Overall Rates (a)	0/48 (0%)	3/47 (6%)	0/49 (0%)
Adjusted Rates (c)	0.0%	7.9%	0.0%
Terminal Rates (d)	0/37 (0%)	3/38 (8%)	0/41 (0%)
Week of First Observation		104	
Life Table Tests (e)	P=0.611N	P=0.126	(h)
Incidental Tumor Tests (e)	P=0.611N	P=0.126	(h)
Cochran-Armitage Trend Test (e)	P=0.633N		
Fisher Exact Test (e)		P=0.117	(h)
Anterior Pituitary Gland: Adenoma			
Overall Rates (a)	9/48 (19%)	5/47 (11%)	3/49 (6%)
Adjusted Rates (c)	22.1%	13.2%	7.3%
Terminal Rates (d)	6/37 (16%)	5/38 (13%)	3/41 (7%)
Week of First Observation	90	104	104
Life Table Tests (e)	P=0.032N	P=0.194N	P=0.050N
Incidental Tumor Tests (e)	P=0.065N	P=0.309N	P=0.104N
Cochran-Armitage Trend Test (e)	P=0.039N		
Fisher Exact Test (e)		P=0.205N	P=0.056N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	75 mg/kg	150 mg/kg
All Sites: Benign Tumors			
Overall Rates (f)	17/50 (34%)	9/50 (18%)	11/50 (22%)
Adjusted Rates (c)	42.2%	23.7%	26.2%
Terminal Rates (d)	14/37 (38%)	9/38 (24%)	10/41 (24%)
Week of First Observation	90	104	97
Life Table Tests (e)	P=0.063N	P=0.049N	P=0.087N
Incidental Tumor Tests (e)	P=0.120N	P=0.079N	P=0.175N
Cochran-Armitage Trend Test (e)	P=0.101N		
Fisher Exact Test (e)		P=0.055N	P=0.133N
All Sites: Malignant Tumors			
Overall Rates (f)	15/50 (30%)	9/50 (18%)	7/50 (14%)
Adjusted Rates (c)	32.9%	22.3%	16.7%
Terminal Rates (d)	7/37 (19%)	7/38 (18%)	6/41 (15%)
Week of First Observation	61	77	97
Life Table Tests (e)	P=0.031N	P=0.150N	P=0.046N
Incidental Tumor Tests (e)	P=0.113N	P=0.280N	P=0.179N
Cochran-Armitage Trend Test (e)	P=0.032N		
Fisher Exact Test (e)		P=0.121N	P=0.045N
All Sites: All Tumors			
Overall Rates (f)	27/50 (54%)	14/50 (28%)	16/50 (32%)
Adjusted Rates (c)	58.4%	34.8%	38.1%
Terminal Rates (d)	18/37 (49%)	12/38 (32%)	15/41 (37%)
Week of First Observation	61	77	97
Life Table Tests (e)	P=0.011N	P=0.013N	P=0.016N
Incidental Tumor Tests (e)	P=0.041N	P=0.027N	P=0.066N
Cochran-Armitage Trend Test (e)	P=0.015N		
Fisher Exact Test (e)		P=0.007N	P=0.022N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Incomplete sampling of tissues
(c) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence in animals killed at the end of the study
(e) Beneath the vehicle 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 vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group than in vehicle controls is indicated by (N).
(f) Number of tumor-bearing animals/number of animals examined grossly at the site
(g) Thirteen livers and 17 spleens were examined microscopically.
(h) No P value is reported because no tumors were observed in the vehicle control and 150 mg/kg groups.

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE

	Vehicle Control	75 mg/kg	150 mg/kg
Animals initially in study	50	50	50
Animals necropsied	50	50	50
Animals examined histopathologically	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Vegetable foreign body	1 (2%)		
Edema, NOS	1 (2%)		
Inflammation, acute	1 (2%)		
Necrosis, fat	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal cavity	(49)	(8)	(50)
Inflammation, acute	27 (55%)	4 (50%)	20 (40%)
Foreign material, NOS	33 (67%)	7 (88%)	22 (44%)
Metaplasia, NOS	1 (2%)		3 (6%)
#Lung	(50)	(12)	(49)
Congestion, NOS	3 (6%)	4 (33%)	4 (8%)
Hemorrhage	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)	1 (8%)	
Necrosis, NOS		1 (8%)	2 (4%)
Foreign material, NOS	7 (14%)	6 (50%)	5 (10%)
Hyperplasia, alveolar epithelium	5 (10%)		1 (2%)
Histiocytosis		2 (17%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hyperplasia, lymphoid	2 (4%)	1 (2%)	1 (2%)
Hematopoiesis	2 (4%)		
#Bone marrow	(50)	(8)	(50)
Atrophy, NOS	1 (2%)		
Myelosclerosis	6 (12%)		9 (18%)
#Spleen	(49)	(17)	(49)
Inflammation, granulomatous	1 (2%)		
Hemosiderosis	3 (6%)		2 (4%)
Angiectasis			1 (2%)
Hyperplasia, lymphoid	4 (8%)	1 (6%)	
Hematopoiesis	1 (2%)	2 (12%)	1 (2%)
#Mandibular lymph node	(49)	(13)	(45)
Cyst, NOS	1 (2%)		
#Mediastinal lymph node	(49)	(13)	(45)
Hemorrhage	1 (2%)		1 (2%)
Hyperplasia, lymphoid	1 (2%)		
#Mesenteric lymph node	(49)	(13)	(45)
Hemorrhage	3 (6%)	2 (15%)	2 (4%)
Hyperplasia, lymphoid	1 (2%)		1 (2%)
#Liver	(50)	(13)	(50)
Leukemoid reaction	1 (2%)		
Hematopoiesis	1 (2%)		
#Jejunum	(43)	(9)	(45)
Hyperplasia, lymphoid		1 (11%)	
#Ileum	(43)	(9)	(45)
Hyperplasia, lymphoid	1 (2%)		
#Thymus	(45)	(5)	(43)
Cyst, NOS	11 (24%)		2 (5%)
Multiple cysts	1 (2%)		
Depletion, lymphoid			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	75 mg/kg	150 mg/kg
CIRCULATORY SYSTEM			
#Cardiac valve	(50)	(8)	(48)
Mineralization	1 (2%)		
Hemorrhagic cyst	1 (2%)		
Pigmentation, NOS	12 (24%)		13 (27%)
#Ovary	(48)	(16)	(48)
Thrombosis, NOS		1 (6%)	1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(9)	(45)
Lymphocytic inflammatory infiltrate			3 (7%)
Necrosis, fat			1 (2%)
Atrophy, NOS	4 (8%)	1 (11%)	1 (2%)
#Liver	(50)	(13)	(50)
Cyst, NOS		1 (8%)	
Lymphocytic inflammatory infiltrate	1 (2%)	1 (8%)	1 (2%)
Inflammation, acute	1 (2%)	1 (8%)	4 (8%)
Necrosis, NOS	1 (2%)		
Cytoplasmic vacuolization	5 (10%)		1 (2%)
Basophilic cyto change			2 (4%)
Focal cellular change	1 (2%)		
Clear cell change	4 (8%)		6 (12%)
Angiectasis	1 (2%)	1 (8%)	1 (2%)
#Pancreatic acinus	(48)	(11)	(48)
Focal cellular change	1 (2%)		1 (2%)
Atrophy, NOS	7 (15%)	1 (9%)	6 (13%)
Hypertrophy, focal	1 (2%)		
Hyperplasia, NOS	1 (2%)		
#Esophagus	(50)	(8)	(50)
Inflammation, acute	1 (2%)		2 (4%)
Inflammation, chronic			1 (2%)
#Glandular stomach	(47)	(8)	(47)
Inflammation, acute	1 (2%)	1 (13%)	
#Forestomach	(47)	(8)	(47)
Cyst, NOS			1 (2%)
Inflammation, acute	3 (6%)		1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(11)	(50)
Cyst, NOS	1 (2%)		
Hemorrhage		1 (9%)	
Glomerulonephritis, NOS	1 (2%)	1 (9%)	
Lymphocytic inflammatory infiltrate	1 (2%)		
Glomerulonephritis, acute			1 (2%)
Nephrosis, NOS	1 (2%)		4 (8%)
Necrosis, NOS			1 (2%)
Pigmentation, NOS			1 (2%)
#Perirenal tissue	(50)	(11)	(50)
Hemorrhagic cyst	1 (2%)		
#Kidney/tubule	(50)	(11)	(50)
Dilatation, NOS	1 (2%)		
#Urinary bladder	(47)	(10)	(48)
Lymphocytic inflammatory infiltrate			3 (6%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	75 mg/kg	150 mg/kg
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(47)	(49)
Hemorrhage			1 (2%)
Hyperplasia, chromophobe cell	7 (15%)	12 (26%)	9 (18%)
Angiectasis	3 (6%)	2 (4%)	1 (2%)
#Adrenal	(49)	(9)	(50)
Hemorrhage		1 (11%)	
#Adrenal/capsule	(49)	(9)	(50)
Hyperplasia, NOS	5 (10%)		5 (10%)
#Adrenal cortex	(49)	(9)	(50)
Congestion, NOS	1 (2%)		
Cytoplasmic vacuolization	2 (4%)		
Atrophy, NOS	1 (2%)		
Atrophy, brown	32 (65%)		29 (58%)
Hypertrophy, focal	1 (2%)		
#Adrenal medulla	(49)	(9)	(50)
Hyperplasia, NOS			1 (2%)
#Thyroid	(50)	(10)	(50)
Follicular cyst, NOS	7 (14%)	1 (10%)	11 (22%)
Hyperplasia, follicular cell	4 (8%)	1 (10%)	2 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	1 (2%)		1 (2%)
Lactation	4 (8%)		1 (2%)
*Vagina	(50)	(50)	(50)
Inflammation, acute			1 (2%)
#Uterus	(49)	(40)	(50)
Dilatation, NOS	1 (2%)		
Inflammation, acute	2 (4%)	2 (5%)	
Angiectasis	1 (2%)		
#Uterus/endometrium	(49)	(40)	(50)
Cyst, NOS	10 (20%)	3 (8%)	6 (12%)
Inflammation, acute	1 (2%)		1 (2%)
Fibrosis	1 (2%)		
Hyperplasia, epithelial			1 (2%)
Hyperplasia, cystic	31 (63%)	31 (78%)	35 (70%)
Angiectasis	1 (2%)		
#Uterus/myometrium	(49)	(40)	(50)
Fibrosis			1 (2%)
#Ovary	(48)	(16)	(48)
Mineralization		1 (6%)	
Cyst, NOS	15 (31%)	8 (50%)	14 (29%)
Hemorrhage	1 (2%)	1 (6%)	
Hemorrhagic cyst	2 (4%)		3 (6%)
Inflammation, granulomatous		1 (6%)	
Angiectasis	1 (2%)	1 (6%)	1 (2%)
NERVOUS SYSTEM			
#Brain	(50)	(9)	(50)
Mineralization	24 (48%)		23 (46%)
Cytoplasmic vacuolization			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Collapse			1 (2%)
Cataract	2 (4%)		3 (6%)
*Harderian gland	(50)	(50)	(50)
Hyperplasia, epithelial			1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF SUCCINIC ANHYDRIDE (Continued)

	Vehicle Control	75 mg/kg	150 mg/kg
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Necrosis, fat	2 (4%)		
*Inguinal region	(50)	(50)	(50)
Necrosis, fat		1 (2%)	
*Pleura	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
*Mesentery	(50)	(50)	(50)
Necrosis, fat	2 (4%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Congestion, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	26 (52%)		26 (52%)
Adhesion, fibrous			1 (2%)
Amyloidosis	1 (2%)		
Adipose tissue			
Inflammation, granulomatous			1
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		3	

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

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. SENTINEL ANIMAL PROGRAM

Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via 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 rats surviving 24 months were collected from 5/50 or 5/60 randomly selected vehicle control animals of each sex. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

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

Results

No positive results were seen in rat serum at 6, 12, 18, and 24 months. No positive results were seen in mouse serum at 6, 12, and 18 months.

APPENDIX F

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

Pelleted Diet: April 1981 to July 1984

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

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

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

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

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

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

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

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

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.48 ± 1.11	21.3-26.3	39
Crude fat (percent by weight)	5.06 ± 0.53	3.3-6.3	39
Crude fiber (percent by weight)	3.43 ± 0.45	2.8-5.6	39
Ash (percent by weight)	6.53 ± 0.39	5.7-7.3	39
Amino Acids (percent of total diet)			
Arginine	1.320 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.05	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	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	11,787 ± 4,078	3,600-24,000	39
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	17.61 ± 3.24	12.0-27.0	(a) 38
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	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	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 ± 0.15	0.72-1.54	39
Phosphorus (percent)	0.97 ± 0.52	0.87-1.10	39
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	81.7-99.4	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

(a) One lot (7/22/81) was not analyzed for thiamine.

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

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.48 ± 0.14	0.17-0.77	39
Cadmium (ppm) (a)	0.10		39
Lead (ppm)	0.82 ± 0.63	0.33-3.37	39
Mercury (ppm) (a)	< 0.05		39
Selenium (ppm)	0.31 ± 0.07	0.13-0.42	39
Aflatoxins (ppb) (b)	<10.0	<5.0-<10.0	39
Nitrate nitrogen (ppm) (c)	9.14 ± 3.97	0.10-22.0	39
Nitrite nitrogen (ppm) (c)	1.71 ± 1.78	0.10-7.20	39
BHA (ppm) (d)	4.50 ± 4.30	0.40-17.0	39
BHT (ppm) (d)	2.84 ± 2.24	0.90-12.0	39
Aerobic plate count (CFU/g) (e)	43,956 ± 32,729	4,900-130,000	39
Coliform (MPN/g) (f)	37.44 ± 101.47	3.00-460	39
E. coli (MPN/g) (f)	3.00		39
Total nitrosamines (ppb) (g,h)	3.49 ± 4.93	0.80-30.00	39
Total nitrosamines (ppb) (g,i)	11.28 ± 42.18	1.17-266.2	39
N-Nitrosodimethylamine (ppb) (g,j)	1.08 ± 0.41	0.5-2.90	39
N-Nitrosodimethylamine (ppb) (g,k)	10.20 ± 42.16	0.80-265.0	39
N-Nitrosopyrrolidine (ppb) (g)	1.09 ± 0.40	0.50-2.90	39
Pesticides (ppm)			
α-BHC (a,l)	<0.01		39
β-BHC (a)	<0.02		39
γ-BHC-Lindane (a)	<0.01		39
δ-BHC (a)	<0.01		39
Heptachlor (a)	<0.01		39
Aldrin (a)	<0.01		39
Heptachlor epoxide (a)	<0.01		39
DDE (a)	<0.01		39
DDD (a)	<0.01		39
DDT (a)	<0.01		39
HCB (a)	<0.01		39
Mirex (a)	<0.01		39
Methoxychlor (a)	<0.05		39
Dieldrin (a)	<0.01		39
Endrin (a)	<0.01		39
Telodrin (a)	<0.01		39
Chlordane (a)	<0.05		39
Toxaphene (a)	<0.1		39
Estimated PCB's (a)	<0.2		39
Ronnel (a)	<0.01		39
Ethion (a)	<0.02		39
Trithion (a)	<0.05		39
Diazinon (a)	<0.1		39
Methyl parathion (a)	<0.02		39
Ethyl parathion (a)	<0.02		39
Malathion (m)	0.11 ± 0.09	0.05-0.45	39
Endosulfan I (a)	<0.01		39
Endosulfan II (a)	<0.01		39
Endosulfan sulfate (a)	<0.03		39

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

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: alfalfa, grains, and fish meal
(d) Source of contamination: soy oil and fish meal
(e) CFU = colony-forming unit
(f) MPN = most probable number
(g) All values were corrected for percent recovery.
(h) Mean, standard deviation, and range exclude the high value of 266.2 ppm obtained for the lot produced on 4/21/81.
(i) Mean, standard deviation, and range include the high value given in footnote h.
(j) Mean, standard deviation, and range exclude the high value of 265.0 ppm obtained for the lot produced on 4/21/81.
(j) Mean, standard deviation, and range include the high value given in footnote j.
(l) BHC = hexachlorocyclohexane or benzene hexachloride
(m) Twenty lots contained more than 0.05 ppm.

APPENDIX G

CHEMICAL CHARACTERIZATION, ANALYSIS, AND DOSE PREPARATION OF SUCCINIC ANHYDRIDE FOR THE TOXICOLOGY STUDIES

APPENDIX G. CHEMICAL CHARACTERIZATION

Procurement and Characterization of Succinic Anhydride

Succinic anhydride was obtained as a white, flaky solid in two lots from Aldrich Chemical Company (Table G1), with purity indicated on the label as 99%. Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the succinic anhydride studies are on file at the National Institute of Environmental Health Sciences.

Both lots of the study chemical were identified as succinic anhydride by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared and nuclear magnetic resonance spectra (Figures G1-G4) were consistent with those expected for the structure and with the literature spectra (Sadtler Standard Spectra). The ultraviolet/visible spectra were consistent with that expected for the structure of succinic anhydride.

The purity of both lots studied was determined by elemental analysis, Karl Fischer water analysis, gas chromatography, potentiometric titration with 0.1 N sodium methoxide to determine total acid and anhydride, and back-titration of excess aniline with 0.5 N perchloric acid in dioxane (lot no. LC081487) or of excess morpholine with 0.5 N methanolic hydrochloric acid (lot no. PE072797) to determine total acid anhydride. Gas chromatographic analysis was performed with flame ionization detection, a nitrogen carrier, and either a 3% OV-225 column and a carrier flow rate of 32 ml/minute (system 1) or a 20% SP2100/0.1% Carbowax 1500 column and a carrier flow rate of 50 ml/minute (system 2).

The results of elemental analysis of lot no. LC081487 for carbon and hydrogen were in agreement with the theoretical values. Lot no. LC081487 contained 0.41% water. Titration for total acid and anhydride indicated 100.7% purity; back-titration of excess aniline indicated an acid anhydride content of 100.9%. Gas chromatography detected one impurity with an area 0.19% of the major peak area by system 1 and one impurity with an area 0.18% of the major peak area by system 2.

The results of elemental analysis of lot no. PE072797 for carbon and hydrogen were in agreement with the theoretical values. Lot no. PE072797 contained 0.027% water. Titration indicated a total acid and anhydride content of 102.2%. Back-titration of excess morpholine indicated 96.6% acid anhydride; combining the results of the two titration methods indicated the presence of 3.3% succinic acid. Concurrent analysis of lot no. LC081487 using back-titration of excess morpholine indicated 98.0% succinic anhydride and 2.2% succinic acid. Gas chromatography detected no impurities having areas 0.01% or greater relative to the area of the major peak by system 1 and one impurity with an area 0.02% relative to the major peak area by system 2.

TABLE G1. IDENTITY AND SOURCE OF SUCCINIC ANHYDRIDE USED IN THE GAVAGE STUDIES

Sixteen-Day Studies in Mice	Twenty-Day Studies in Rats	Thirteen-Week Studies in Mice	Thirteen-Week Studies in Rats	Two-Year Studies
Lot Numbers				
LC081487	PE072797	LC081487	PE072797	PE072797
Supplier				
Aldrich Chemical Company (Milwaukee, WI)	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies	Same as 16-d studies

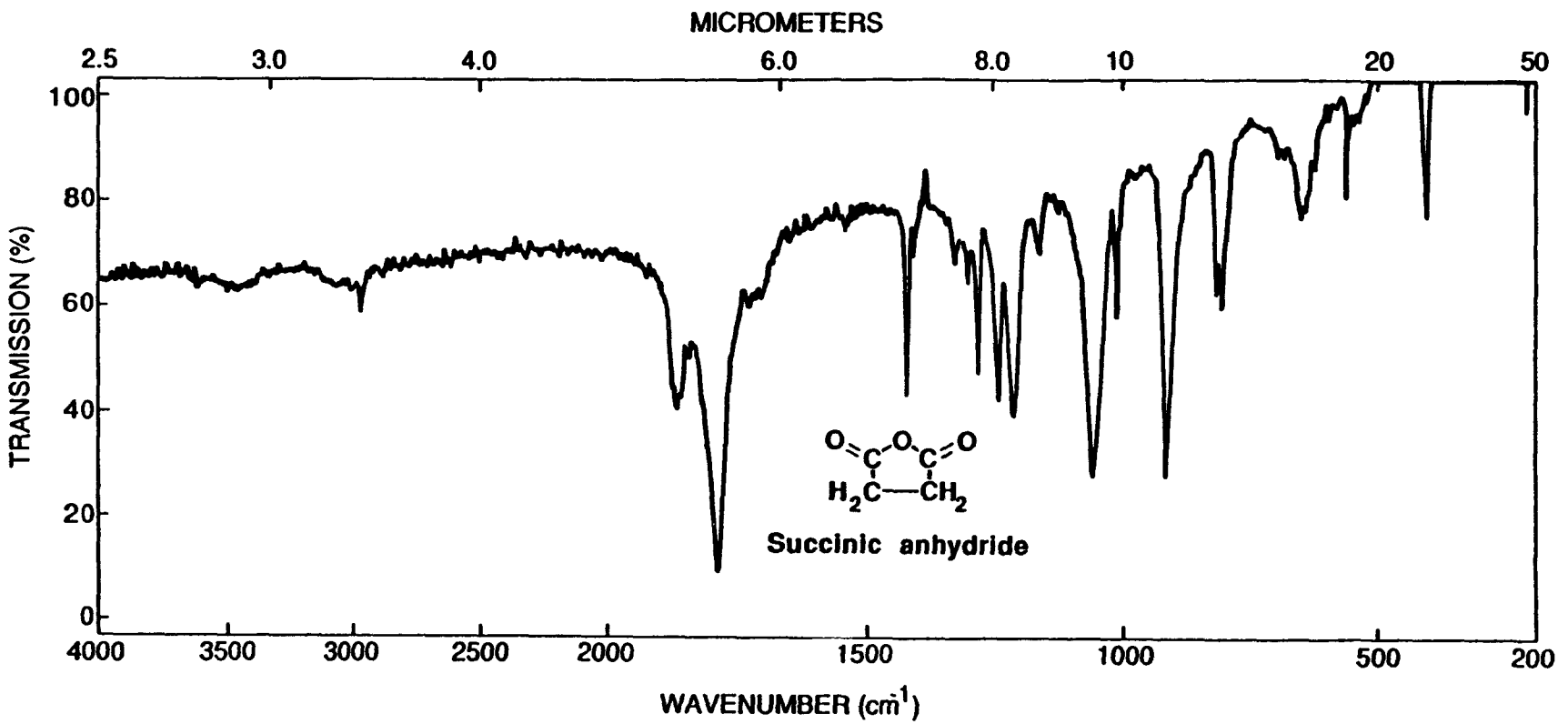

FIGURE G1. INFRARED ABSORPTION SPECTRUM OF SUCCINIC ANHYDRIDE (LOT NO. PE072797)

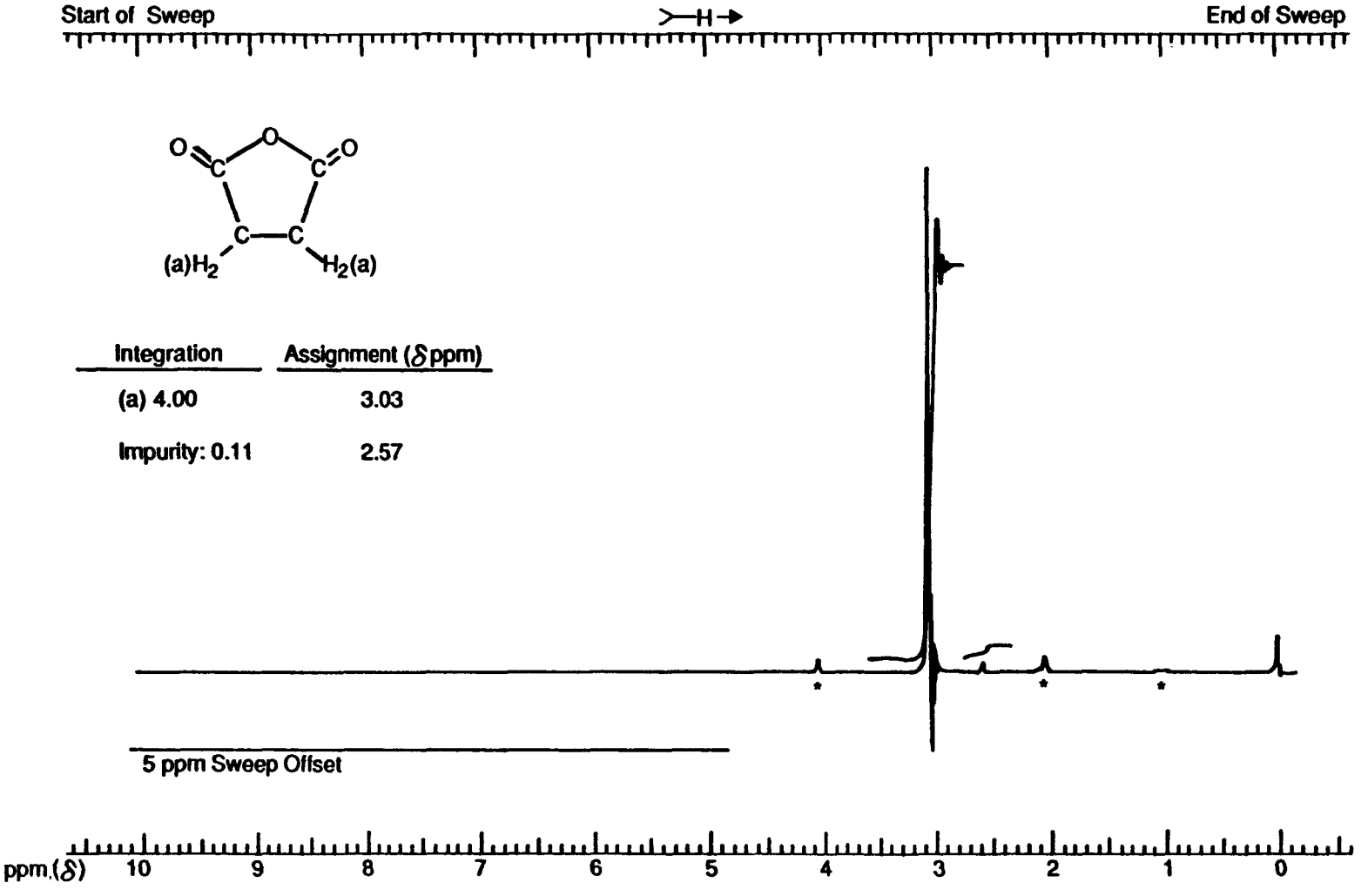

FIGURE G2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF SUCCINIC ANHYDRIDE (LOT NO. PE072797)

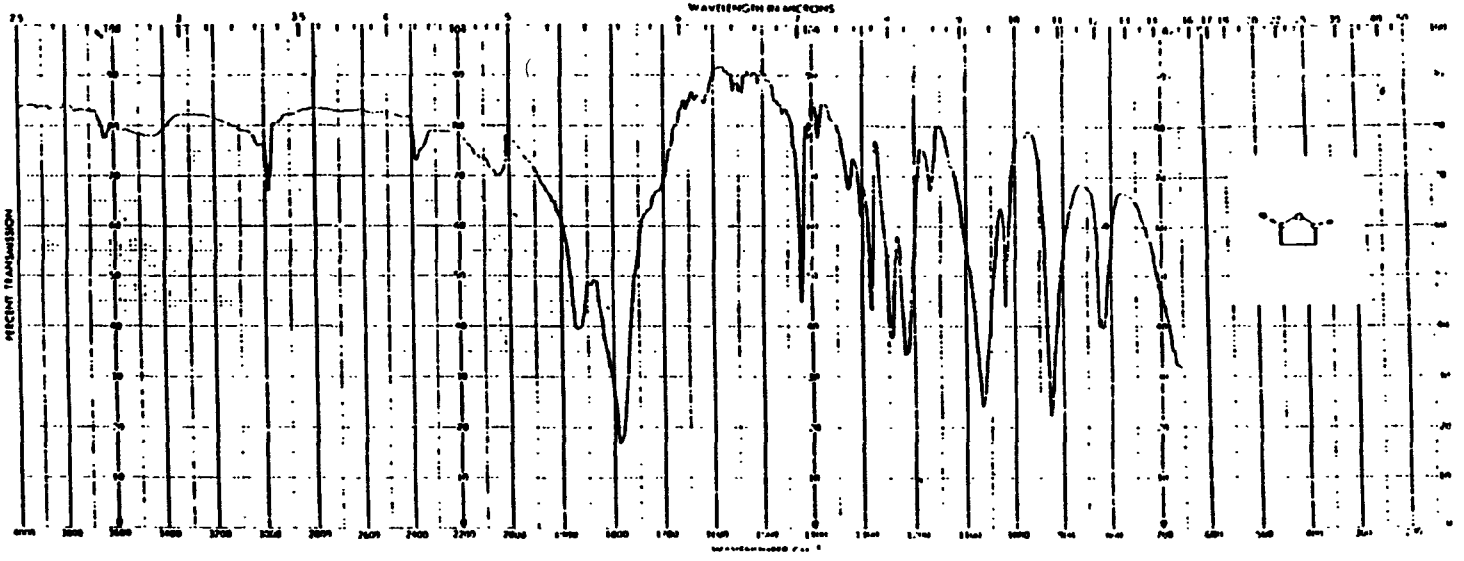

FIGURE G3. INFRARED ABSORPTION SPECTRUM OF SUCCINIC ANHYDRIDE (LOT NO. LC081487)

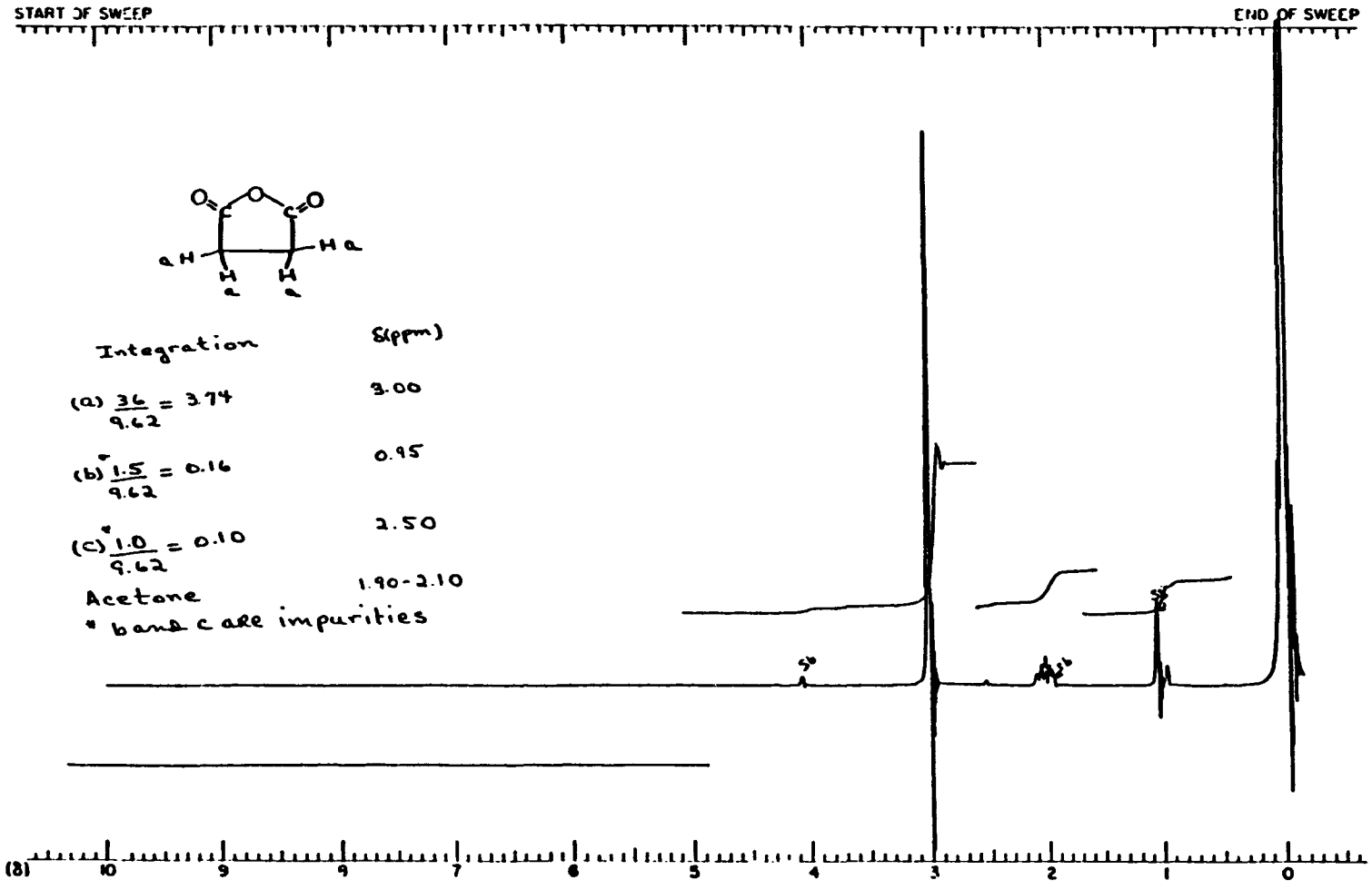

FIGURE G4. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF SUCCINIC ANHYDRIDE (LOT NO. LC081487)

Stability studies performed by back-titration of excess aniline with 0.5 N perchloric acid in dioxane indicated that succinic anhydride was stable as a bulk chemical when stored at temperatures up to 60° C for 2 weeks. During the 2-year studies, succinic anhydride was stored at 4° C. Confirmation of the stability of the bulk chemical during the studies was obtained by gas chromatography and analysis of total anhydride. No deterioration of succinic anhydride was observed throughout the studies. The identity of the chemical at the study laboratory was confirmed by infrared analysis.

Preparation and Characterization of Dose Formulations

During the 16-day and 13-week studies in mice, succinic anhydride was ground with a mortar and pestle before being mixed with the appropriate volume of corn oil to produce dose formulations of the desired concentrations (Table G2). Since succinic anhydride is not soluble in corn oil, the formulations were constantly stirred during dosing with a magnetic stirrer to produce uniform suspensions. Before the beginning of the 2-year studies, a procedure was developed to produce more stable suspensions by using a Polytron® homogenizer to reduce particle size. The smaller particles, however, proved to be more toxic to rats than those prepared with the mortar and pestle, necessitating a repetition of the short-term studies in rats to select new doses for the 2-year studies.

The stability of succinic anhydride in corn oil at concentrations of 15 or 25 mg/ml at the study laboratory was determined, after extraction of the formulation with methanol, and quantitation by gas chromatography with flame ionization detection, a nitrogen carrier, and a 10% DEGS-PS column with isobutyl phthalate as an internal standard. The chemical was found to be stable as a suspension in corn oil for at least 18 days when stored at room temperature.

TABLE G2. PREPARATION AND STORAGE OF DOSE FORMULATIONS IN THE GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

Sixteen-Day Studies in Mice	Twenty-Day Studies in Rats	Thirteen-Week Studies in Mice	Thirteen-Week Studies in Rats	Two-Year Studies
Preparation				
Chemical was ground with mortar and pestle, passed through a mesh, and weighed into volumetric flask. Corn oil was added, and contents were mixed by shaking	Chemical in corn oil was homogenized with a Polytron® homogenizer for 6 min and stirred for 3 min	Chemical was ground with mortar and pestle, passed through a mesh, and weighed into volumetric flask. Corn oil was added to volume. Mixture was stirred by magnetic stirrer	Chemical in corn oil was homogenized with a Polytron® homogenizer	Appropriate amount of chemical and corn oil were homogenized with a Polytron® PT 10-ST probe at setting 7 for 2 min, followed by setting 9 for 1 min
Maximum Storage Time				
8 d	1 wk	15 d	2 wk	3 wk
Storage Conditions				
Room temperature	Refrigerator	4° C	4°-8° C	5° C

APPENDIX G. CHARACTERIZATION

Periodic analysis of succinic anhydride/corn oil dose formulations was conducted at the study laboratory and the analytical chemistry laboratory. Dose formulations were analyzed once before the 13-week studies in mice and once before and once during the 13-week studies in rats. During the 13-week studies, succinic anhydride in corn oil was determined by gas chromatography with the same system as described above. During the 13-week studies in mice, the concentration of all dose formulations was found to be 20%-39% high. During the 13-week studies in rats, all dose formulations except one were found to be within ±10% of the target concentrations by the study laboratory (Table G3). The analytical chemistry (referee) laboratory analyzed one dose formulation and found that, although it was not within specifications, their result was within 10% of the study laboratory result.

During the 2-year studies, the dose formulations were analyzed at intervals of approximately 8 weeks. The formulations were prepared within ±10% of the target concentrations approximately 98% (61/62) of the time throughout the studies (Table G4). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated agreement with the results from the study laboratory (Table G5).

TABLE G3. RESULTS OF ANALYSIS OF DOSE FORMULATIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

Preparation Date	Concentration of Succinic Anhydride in Corn Oil (mg/ml)		Determined as a Percent of Target
	Target	Determined	
13-week studies in mice			
03/28/80	(a) 4.04	5.36	(b) 133
	(a) 8.19	11.4	(b) 139
	(a) 16.4	22.4	(b) 137
	(a) 20.5	26.7	(b) 130
	(a) 32.8	41.6	(b) 127
	(a) 40.9	54.9	(b) 134
	(a) 65.5	86.8	(b) 133
	(a) 81.9	98.5	(b) 120
	(a) 164	221	(b) 135
	(a) 328	398	(b) 121
13-week studies in rats			
10/02/81	2.5	2.54	102
	5.0	5.22	104
	10	9.37	93.7
	20	19.2	96.0
	40	42.3	106
	80	74.0	92.5
	80	(c) 69.8	(b) 87.3
11/17/81	2.5	2.55	102.0
	5.0	4.98	99.6
	10	10.4	104
	20	20.1	100
	40	38.8	97.0
	80	71.6	(b) 89.5

(a) Expressed as milligrams per gram
(b) Out of specifications
(c) Results of referee analysis

TABLE G4. RESULTS OF ANALYSIS OF DOSE FORMULATIONS IN THE TWO-YEAR GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

Preparation Date	Concentration of Succinic Anhydride in Corn Oil for Target Concentration (mg/ml) (a)				
	3.8	7.5	10	15	20
05/14/81	3.70	7.79		15.1	
09/07/81	3.83	(b) 8.43		14.5	
11/04/81		7.93		14.2	
11/18/81	3.78				
12/30/81	3.68	7.28		14.3	
03/08/82	4.10	7.92		14.3	
04/21/82	3.50	7.98		13.5	
06/16/82	3.85	8.07		16.0	
08/25/82	3.74	7.77	10.6	16.0	20.0
10/06/82	3.65	6.84	10.5	14.8	19.2
12/01/82	3.78	6.81	10.4	14.2	20.6
01/26/83	3.80	7.51	9.2	14.9	20.3
03/23/83	3.76	7.69	10.1	15.8	19.0
05/18/83			10.2		18.7
07/13/83			10.3		18.7
09/07/83			9.8		20.0
11/02/83			9.9		21.4
12/14/83			10.5		19.0
02/08/84			10.6		18.5
04/18/84			9.9		18.2
06/13/84			9.8		19.1
08/08/84			10.3		19.5
Mean (mg/ml)	3.76	7.67	10.2	14.8	19.4
Standard deviation	0.142	0.486	0.40	0.80	0.90
Coefficient of variation (percent)	3.8	6.3	3.9	5.4	4.6
Range (mg/ml)	3.50-4.10	6.81-8.43	9.2-10.6	13.5-16.0	18.2-21.4
Number of samples	12	12	14	12	14

(a) Results of duplicate analysis
(b) Out of specifications

TABLE G5. RESULTS OF REFEREE ANALYSIS OF DOSE FORMULATIONS IN THE TWO-YEAR GAVAGE STUDIES OF SUCCINIC ANHYDRIDE

Preparation Date	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
05/14/81	3.8	3.70	3.64
04/21/82	3.8	3.50	2.38
06/16/82	3.8	3.85	3.63
08/25/82	10	10.6	9.27
01/26/83	10	9.18	9.09
11/02/83	20	21.4	17.4
12/14/83	20	19.0	19.0
06/13/84	10	9.79	9.52

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

APPENDIX H

GENETIC TOXICOLOGY OF SUCCINIC ANHYDRIDE

APPENDIX H. 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 (TA97, 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) in each of two different laboratories. If all results were negative, the chemical was retested in all strains; in the second testing laboratory, repeat trials were performed with a different concentration of S9.

Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate.

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

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985) 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 0.5 mg/ml.

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

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

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

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

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

RESULTS

Succinic anhydride was tested in two laboratories for induction of gene mutations in several strains of *S. typhimurium* using a preincubation protocol with and without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9 (Table H1; Zeiger et al., 1987); no mutagenic activity was observed in any of the strains (TA97, TA98, TA100, TA1535, or TA1537). Succinic anhydride did not induce SCEs or chromosomal aberrations in cultured CHO cells in either the presence or absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Tables H2 and H3).

TABLE H1. MUTAGENICITY OF SUCCINIC ANHYDRIDE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) Trial 1	+S9 (hamster) Trial 2	+S9 (rat) Trial 1	+S9 (rat) Trial 2
Study performed at SRI International							
TA100	0	94 ± 4.4	123 ± 7.5	131 ± 8.5	111 ± 9.9	111 ± 6.1	115 ± 5.2
	3	118 ± 16.5	--	--	--	--	--
	10	--	99 ± 12.3	--	--	--	--
	33	114 ± 6.1	120 ± 3.7	--	--	--	--
	100	101 ± 1.5	103 ± 6.0	124 ± 8.2	93 ± 4.0	129 ± 1.2	110 ± 7.5
	333	113 ± 6.1	93 ± 9.3	116 ± 11.5	104 ± 6.6	127 ± 7.3	120 ± 5.0
	666	87 ± 12.0	41 ± 2.3	--	--	--	--
	1,000	--	--	111 ± 9.6	107 ± 5.0	114 ± 8.3	103 ± 6.4
	3,333	--	--	107 ± 9.3	81 ± 7.0	97 ± 6.1	105 ± 4.4
	10,000	--	--	105 ± 16.7	71 ± 8.5	99 ± 9.2	77 ± 9.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		431 ± 13.3	411 ± 28.4	1,500 ± 142.6	1,358 ±108.2	481 ± 28.2	721 ± 14.5
TA1535	0	19 ± 2.5	30 ± 2.2	9 ± 2.0	7 ± 1.2	9 ± 2.3	11 ± 2.7
	3	27 ± 0.6	--	--	--	--	--
	10	--	32 ± 2.1	--	--	--	--
	33	20 ± 0.3	25 ± 3.0	--	--	--	--
	100	25 ± 2.1	30 ± 4.9	10 ± 2.6	6 ± 0.6	9 ± 2.2	10 ± 2.6
	333	22 ± 1.7	19 ± 3.5	8 ± 2.1	6 ± 0.6	9 ± 1.5	7 ± 0.3
	666	7 ± 3.1	6 ± 4.3	--	--	--	--
	1,000	--	--	11 ± 2.5	7 ± 1.2	11 ± 1.2	6 ± 0.6
	3,333	--	--	6 ± 1.2	6 ± 1.3	5 ± 0.3	9 ± 0.0
	10,000	--	--	4 ± 0.7	6 ± 0.0	4 ± 0.9	6 ± 0.0
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		511 ± 11.6	436 ± 10.7	503 ± 14.7	389 ± 3.5	186 ± 15.3	167 ± 3.2
TA1537	0	5 ± 1.2	7 ± 2.0	6 ± 1.5	9 ± 1.7	8 ± 2.3	9 ± 2.0
	3	5 ± 0.9	--	--	--	--	--
	10	--	5 ± 1.0	--	--	--	--
	33	4 ± 0.9	7 ± 2.5	--	--	--	--
	100	6 ± 1.2	5 ± 1.2	8 ± 2.0	10 ± 2.9	9 ± 2.1	5 ± 0.6
	333	5 ± 1.8	5 ± 2.0	8 ± 0.6	7 ± 0.3	11 ± 1.2	6 ± 1.5
	666	3 ± 0.9	2 ± 0.7	--	--	--	--
	1,000	--	--	7 ± 1.7	8 ± 0.0	5 ± 1.5	5 ± 1.2
	3,333	--	--	6 ± 2.8	5 ± 1.5	6 ± 0.9	7 ± 1.2
	10,000	--	--	5 ± 2.2	6 ± 1.0	8 ± 2.2	7 ± 0.9
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		248 ± 86.7	166 ± 31.4	462 ± 22.6	321 ± 25.6	147 ± 16.6	179 ± 19.8
TA98	0	22 ± 5.0	16 ± 2.1	25 ± 2.3	23 ± 3.3	24 ± 3.2	26 ± 2.0
	3	16 ± 1.5	--	--	--	--	--
	10	--	15 ± 0.3	--	--	--	--
	33	19 ± 3.4	14 ± 0.9	--	--	--	--
	100	16 ± 1.2	16 ± 0.9	33 ± 2.9	23 ± 3.3	24 ± 4.9	26 ± 0.3
	333	12 ± 1.8	11 ± 1.9	27 ± 2.1	23 ± 3.7	24 ± 2.5	19 ± 0.3
	666	7 ± 0.9	4 ± 0.3	--	--	--	--
	1,000	--	--	23 ± 2.5	20 ± 0.6	29 ± 2.0	27 ± 2.8
	3,333	--	--	18 ± 0.3	22 ± 4.5	25 ± 5.1	23 ± 3.0
	10,000	--	--	19 ± 1.5	15 ± 1.7	24 ± 2.1	19 ± 3.8
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		757 ± 11.3	793 ± 19.0	1,287 ± 249.6	1,229 ± 84.4	355 ± 43.6	474 ± 45.7

TABLE H1. MUTAGENICITY OF SUCCINIC ANHYDRIDE IN *SALMONELLA TYPHIMURIUM* (Continued)

Strain	Dose (µg/plate)	Revertants/Plate (b) −S9 Trial 1	−S9 Trial 2	+S9 (hamster) 10%	+S9 (hamster) 30%	+S9 (rat) 10%	+S9 (rat) 30%
Study performed at Microbiological Associates, Inc.							
TA100	0	100 ± 4.3	128 ± 9.5	94 ± 8.4	118 ± 6.6	96 ± 1.0	103 ± 2.3
	3.3	--	141 ± 9.4	--	--	--	--
	10	--	124 ± 8.5	--	--	--	--
	33	--	126 ± 15.3	--	119 ± 8.4	--	108 ± 8.1
	100	88 ± 8.1	130 ± 3.0	90 ± 1.7	106 ± 7.8	100 ± 4.8	108 ± 4.3
	333	74 ± 3.5	(d) 112 ± 10.4	94 ± 7.2	103 ± 2.7	101 ± 4.9	107 ± 11.6
	1,000	(d) 52 ± 16.5	--	104 ± 5.2	104 ± 3.8	83 ± 2.6	120 ± 2.1
	3,333	Toxic	--	(d) 88 ± 5.6	87 ± 2.3	(d) 80 ± 10.5	88 ± 10.0
	6,666	(d) 74 ± 0.0	--	(d) 89 ± 6.2	--	Toxic	--
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		1,096 ± 18.8	1,130 ± 47.3	890 ± 31.9	385 ± 31.2	1,408 ± 48.0	806 ± 19.3
TA1535	0	29 ± 2.0	27 ± 5.9	12 ± 0.3	13 ± 3.3	13 ± 0.3	12 ± 1.8
	3.3	29 ± 0.3	25 ± 4.7	--	--	--	--
	10	20 ± 3.0	24 ± 2.2	--	--	--	--
	33	25 ± 2.5	19 ± 1.8	--	10 ± 0.9	--	14 ± 0.9
	100	22 ± 3.4	23 ± 4.5	9 ± 1.7	13 ± 1.5	7 ± 2.5	13 ± 1.9
	333	(d) 20 ± 2.1	(d) 21 ± 1.2	8 ± 2.4	16 ± 1.7	8 ± 1.3	13 ± 0.6
	1,000	--	--	9 ± 1.5	15 ± 0.9	12 ± 2.3	11 ± 0.6
	3,333	--	--	(d) 8 ± 0.9	11 ± 2.0	(d) 9 ± 2.7	11 ± 1.8
	6,666	--	--	(d) 5 ± 0.9	--	Toxic	--
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		849 ± 29.3	53 ± 2.2	61 ± 3.2	91 ± 4.0	85 ± 1.0	74 ± 0.6
TA97	0	90 ± 2.5	98 ± 11.3	101 ± 2.7	118 ± 4.9	92 ± 4.3	188 ± 6.8
	3.3	92 ± 3.1	106 ± 3.0	--	--	--	--
	10	91 ± 3.5	90 ± 3.7	--	--	--	--
	33	86 ± 7.4	100 ± 3.7	--	118 ± 5.3	--	185 ± 6.9
	100	88 ± 4.6	89 ± 9.6	111 ± 1.2	155 ± 9.9	88 ± 10.7	184 ± 5.8
	333	(d) 79 ± 4.7	(d) 77 ± 5.6	97 ± 10.1	143 ± 11.6	72 ± 7.5	185 ± 8.8
	1,000	--	--	99 ± 7.4	131 ± 4.5	106 ± 1.8	186 ± 9.4
	3,333	--	--	(d) 80 ± 2.0	115 ± 1.2	(d) 82 ± 1.0	97 ± 6.4
	6,666	--	--	Toxic	--	(d) 49 ± 6.6	--
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		611 ± 67.2	414 ± 22.9	538 ± 8.4	317 ± 15.6	883 ± 43.6	438 ± 11.3
TA98	0	19 ± 1.9	17 ± 1.5	29 ± 5.4	26 ± 3.6	29 ± 1.5	38 ± 4.8
	3.3	15 ± 1.2	18 ± 3.8	--	--	--	--
	10	14 ± 3.2	23 ± 5.2	--	--	--	--
	33	18 ± 2.6	25 ± 2.3	--	23 ± 2.7	--	29 ± 4.0
	100	20 ± 1.7	18 ± 1.5	25 ± 2.0	28 ± 2.1	24 ± 0.7	37 ± 3.2
	333	(d) 12 ± 3.0	16 ± 4.9	21 ± 3.4	31 ± 3.6	28 ± 3.8	30 ± 1.3
	1,000	--	--	28 ± 3.0	29 ± 4.1	24 ± 4.9	32 ± 4.5
	3,333	--	--	(d) 23 ± 3.4	30 ± 2.6	(d) 14 ± 1.0	(d) 24 ± 1.3
	6,666	--	--	(d) 46 ± 37.5	--	(d) 7 ± 0.3	--
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control (c)		168 ± 8.9	170 ± 17.2	480 ± 20.3	80 ± 5.8	993 ± 26.8	202 ± 11.9

TABLE H1. MUTAGENICITY OF SUCCINIC ANHYDRIDE IN *SALMONELLA TYPHIMURIUM* (Continued)

(a) The detailed protocol is presented by Zeiger et al. (1987). Cells and study compound or solvent (dimethyl sulfoxide) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility but did not exceed 10 mg/plate; 0 μg/plate dose is the solvent control.
(b) Revertants are presented as mean ± standard error from three plates.
(c) Positive control; 2-aminoanthracene was used on all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-*o*-phenylenediamine was used with TA98, sodium azide was used with TA100 and TA1535, and 9-aminoacridine was used with TA1537 and TA97.
(d) Slight toxicity

TABLE H2. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY SUCCINIC ANHYDRIDE (a)

Compound	Dose (µg/ml)	Total Cells	Number of Chromosomes	Number of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c)--Summary: Negative								
Dimethyl sulfoxide		50	1,033	411	0.4	8.2	25.5	
Succinic anhydride	50	50	1,033	362	0.35	7.2	25.5	87.8
	166.5	50	1,039	392	0.38	7.8	25.5	95.1
	500	50	1,040	369	0.35	7.4	25.5	90.2
Mitomycin C	0.001	50	1,017	509	0.50	10.2	25.5	124.4
	0.01	5	105	200	1.90	40.0	25.5	487.8
+S9 (d)--Summary: Negative								
Dimethyl sulfoxide		50	1,045	384	0.37	7.7	25.5	
Succinic anhydride	50	50	1,041	424	0.41	8.5	25.5	110.4
	166.5	50	1,040	401	0.39	8.0	25.5	103.9
	500	50	1,039	372	0.36	7.4	25.5	96.1
Cyclophosphamide	0.4	50	1,035	711	0.69	14.2	25.5	184.4
	2	5	104	181	1.74	36.2	25.5	470.1

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

TABLE H3. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY SUCCINIC ANHYDRIDE (a)

−S9 (b)					+S9 (c)				
Dose (µg/ml)	Total Cells	Number of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	Number of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time: 10.5 hours					Harvest time: 12.5 hours				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	1	0.01	1.0		100	2	0.02	2.0
Succinic anhydride					Succinic anhydride				
500	100	1	0.01	1.0	500	100	4	0.04	4.0
750	100	3	0.03	3.0	750	100	4	0.04	3.0
1,000	100	2	0.02	1.0	1,000	100	4	0.04	3.0
Summary: Negative					Summary: Negative				
Mitomycin C					Cyclophosphamide				
0.5	100	6	0.06	5.0	7.5	100	10	0.10	9.0
1	25	8	0.32	28.0	37.5	25	15	0.60	40.0

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

APPENDIX I

AUDIT SUMMARY

APPENDIX I. AUDIT SUMMARY

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

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

Procedures and events for the exposure phase of the studies were documented adequately, with the exception that archival records to document part or all of the following were not at the Archives: disposition of surplus animals prior to study start; room air change rate; room light cycle; type of lighting system, cages, filters, racks, feeders, bedding, and water system; original chemistry data for stability studies, dosage analyses, and determination of succinic anhydride and succinic dimethyl ester content in dosing solutions; method of animal kill; and maximum storage time for feed. Review of the available records indicated that protocol-specified procedures for animal care were followed adequately. Records that documented the administration of doses to animals were complete and accurate. Recalculation of approximately 35% of the group mean body weight values in the Technical Report showed 45/51 to be correct; three of the six errors detected were corrected and the remaining three were of small magnitude. The observation of external masses recorded during the last few months of life was thorough, and their correlation with observations recorded at necropsy was good. (All inlife masses correlated, except for 1/146 in rats and 6/22 in mice.) The date of death recorded at necropsy for early-death animals was supported by the inlife records for 153/174 rats and 81/85 mice; the discrepancies appeared to be due to data entry errors and all but one (31 days) involved differences of 1-4 days. The mode of death recorded at necropsy was in agreement with the inlife records for all mice and for 341/360 rats; the discrepancies (11 of which were suggestive of dosing accident) were resolved as described in the survival section of the Results chapter of the Technical Report.

Individual animal identifiers (ear tags) were present and correct in the residual tissue bags for 85/85 rats and 59/69 mice examined. Review of the entire data trail for the 10 mice with less than complete

and correct identifiers indicated that the integrity of individual animal identity had been maintained. A total of 17 untrimmed potential lesions (3 involved the liver, 1 involved the nasal cavity) were found in the wet tissues of 85 rats examined and 8 (1 liver, 1 nasal cavity) were found in those of 69 mice examined. Intestinal segments were incompletely opened for 32/85 rats (7-45 cm in length) and for 6/69 mice (up to 15 cm in length) examined; no untrimmed potential lesions were evident by external examination of mucosal surfaces, but the presence of ingesta in about half of the unopened intestinal segments made thorough examination difficult. Organs in low dose mice groups were incised or opened inconsistently. Each gross observation made at necropsy had a corresponding microscopic diagnosis for all but three in rats and four in mice. Tissue sections in blocks and on slides matched each other properly. All post-Pathology Working Group changes in diagnoses had been incorporated into the final pathology tables. Rates for the incidence of tumors given in the Technical Report were the same as those in the final pathology tables at the Archives.

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

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NATIONAL TOXICOLOGY PROGRAM TECHNICAL REPORTS
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TR No.	CHEMICAL
201	2,3,7,8-Tetrachlorodibenzo-p-dioxin (Dermal)
206	Dibromochloropropane
207	Cytembena
208	FD & C Yellow No. 6
209	2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (Gavage)
210	1,2-Dibromoethane (Inhalation)
211	C.I. Acid Orange 10
212	Di(2-ethylhexyl)adipate
213	Butylbenzyl 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
229	Guar Gum
230	Agar
231	Stannous Chloride
233	2-Biphenylamine Hydrochloride
234	Allyl Isothiocyanate
235	Zearalenone
236	D-Mannitol
238	Ziram
239	Bis(2-chloro-1-methylethyl)ether
240	Propyl Gallate
242	Diallyl Phthalate (Mice)
244	Polybrominated Biphenyl Mixture
245	Melamine
247	L-Ascorbic Acid
248	4,4'-Methylenedianiline Dihydrochloride
249	Amosite Asbestos
250	Benzyl Acetate
251	Toluene Diisocyanate
252	Geranyl Acetate
253	Allyl Isovalerate
255	1,2-Dichlorobenzene
257	Diglycidyl Resorcinol Ether
259	Ethyl Acrylate
261	Chlorobenzene
263	1,2-Dichloropropane
266	Monuron
267	Propylene Oxide
269	Telone II®
271	HC Blue No. 1
272	Propylene
273	Trichloroethylene (Four strains of rats)
274	Tris(2-ethylhexyl)phosphate
275	2-Chloroethanol
276	8-Hydroxyquinoline
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 and 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
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
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	Mercaptobenzothiazole
333	*N*-Phenyl-2-naphthylamine
334	2-Amino-5-nitrophenol
335	C.I. Acid Orange 3
336	Penicillin VK
337	Nitrofurazone
338	Erythromycin Stearate
339	2-Amino-4-nitrophenol
343	Benzyl Alcohol
344	Tetracycline Hydrochloride
345	Roxarsone
348	α-Methyldopa Sesquihydrate
349	Pentachlorophenol
350	Tribromomethane
353	2,4-Dichlorophenol
356	Furosemide
357	Hydrochlorothiazide
358	Ochratoxin A
359	8-Methoxypsoralen
361	Hexachloroethane

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