NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

TECHNICAL GRADE

SODIUM XYLENESULFONATE

(CAS NO. 1300-72-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

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

June 1998

NTP TR 464 #

NIH Publication No. 98-3380 #

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

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species, and quantitative risk analyses for humans, require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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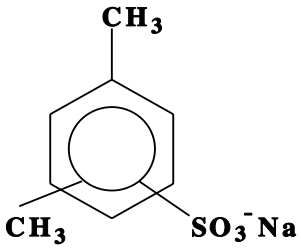
CONTENTS

ABSTRACT



SODIUM XYLENESULFONATE

CAS No. 1300-72-7 #

Chemical Formula: $(CH_3)_2C_6H_3SO_3^-\ Na^+$ Molecular Weight: 208.2

Synonyms: Benzenesulfonic acid, dimethyl-, sodium salt; sodium dimethylbenzenesulfonate; xylenesulfonic acid, sodium salt
Trade names: Conco SXS; Cyclophil; SXS 30; Eletesol SX 30; Naxonate; Naxonate G; Richonate SXS; Stepanate SXS; Stepanate X; SXS 40; # Ultrawet 40SX

Sodium xylenesulfonate is used as a hydrotrope, an organic compound that increases the ability of water to dissolve other molecules. Sodium xylenesulfonate is a component in a variety of widely used shampoos and liquid household detergents where it can constitute up to 10% of the total solution. Because of its widespread use, the potential for human exposure to sodium xylenesulfonate is great. Male and female F344/N rats and B6C3F$_1$ mice were administered sodium xylenesulfonate in water or 50% ethanol dermally for 17 days, 14 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, L5178Y mouse lymphoma cells, and cultured Chinese hamster ovary cells.

17-DAY STUDY IN RATS

Groups of five male and five female rats were administered 300 μL of 0, 5, 15, 44, 133, or 400 mg/mL sodium xylenesulfonate in distilled water by dermal application 5 days per week for 17 days. All rats survived to the end of the study. Final mean body weights and body weight gains of dosed rats were similar to those of the control groups. Dermal applications of 300 μL of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately 10, 30, 90, 260, and 800 mg sodium xylenesulfonate/kg body weight to males and 13, 40, 120, 330, and 1,030 mg/kg to females. Clinical findings generally involved the skin of dosed animals and included tan or brown skin discoloration and crusty white deposits (presumed to be dried chemical) at the site of application. Neither of these observations were considered significant findings. The relative liver weights of 133 and 400 mg/mL male and female rats were significantly greater than those of the control groups, but the absolute liver weights were not increased and the biological significance of the relative differences in liver weight was unclear. In males and females, the few lesions observed grossly and microscopically were generally attributed to repeated clipping and were not considered related to chemical administration.

17-DAY STUDY IN MICE

Groups of five male and five female mice were administered 100 μL of 0, 5, 15, 44, 133, or

400 mg/mL sodium xylenesulfonate in distilled water by dermal application 5 days per week for 17 days. All mice survived to the end of the study. Final mean body weights and body weight gains of dosed mice were similar to those of the controls. Dermal applications of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately, 20, 60, 190, 540, and 1,600 mg sodium xylenesulfonate/kg body weight to males and 26, 80, 220, 680, and 2,000 mg/kg to females. Clinical findings included crusty white deposits (presumed to be dried chemical) at the site of application in two 133 mg/mL males and in all 400 mg/mL males and females. The absolute and relative liver weights of 15 and 44 mg/mL males and 400 mg/mL males and females were significantly greater than those of the control groups, but the biological significance of these differences was unclear. The few skin lesions observed grossly and microscopically in males and females were generally attributed to repeated clipping and were not considered related to chemical administration.

14-Week Study in Rats

Groups of 10 male and 10 female rats were administered 300 μL of 0, 5, 15, 44, 133, or 400 mg/mL sodium xylenesulfonate in 50% ethanol by dermal application for 14 weeks. For special hematology and clinical pathology studies, additional groups of 10 male and 10 female rats were administered 0, 5, 15, 44, 133, or 400 mg/mL sodium xylenesulfonate in 50% ethanol by dermal application for 14 weeks. All rats survived to the end of the study. Final mean body weights and body weight gains of dosed male and female rats were similar to those of the control groups. Dermal applications of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately 6, 20, 60, 170, and 500 mg sodium xylenesulfonate/kg body weight to males and 10, 30, 90, 260, and 800 mg/kg to females. The only notable clinical finding was brown discoloration of the skin at the site of application in dosed animals. Hematology and clinical chemistry parameters of dosed groups of males and females were significantly different from those of the controls in several instances, but these differences were sporadic and did not demonstrate a treatment relationship. The absolute and relative liver weights of males receiving 44, 133, or 400 mg/mL were significantly less than those of the control group, but the biological significance of these differences was unclear, and there were no treatment-related histopathologic effects in the liver. There were no significant differences in liver weights in female rats.

Minimal hyperplasia of the epidermis at the site of application occurred in both male and female rats in the control group as well as most dosed groups. The incidence of epidermal hyperplasia in 400 mg/mL males was possibly chemical related.

14-Week Study in Mice

Groups of 10 male and 10 female mice were administered 100 μL of 0, 5, 15, 44, 133, or 400 mg/mL sodium xylenesulfonate in 50% ethanol by dermal application for 14 weeks. There were no chemical-related deaths. The mean body weight gain of the 400 mg/mL males was significantly greater than that of the control group. Dermal applications of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately 17, 40, 140, 440, and 1,300 mg sodium xylenesulfonate/kg body weight to males and 20, 60, 170, 530, and 1,630 mg/kg to females. There were no clinical findings related to sodium xylenesulfonate administration.

Epidermal hyperplasia occurred in one 44 mg/mL female, two 133 mg/mL males, five 400 mg/mL males, and four 400 mg/kg females. Hyperplasia of the epidermis in 400 mg/mL males and females was probably related to chemical administration.

Chronic inflammation of the skin occurred primarily in the control groups of males and females. These lesions consisted of mononuclear inflammatory cells in the dermis.

2-Year Study in Rats

Groups of 50 male and 50 female rats were dermally administered 0, 60, 120, or 240 mg sodium xylenesulfonate/kg body weight in 50% ethanol for 104 weeks.

Survival, Body Weights, and Clinical Findings

Survival of dosed males and females was similar to that of the control groups. Mean body weights of dosed males and females were similar to those of the

controls throughout the study. In male groups, there were no clinical findings considered treatment related. In females, clinical findings were limited to irritation at the site of application in one control female, four 120 mg/kg females, and two 240 mg/kg females.

Pathology Findings

There were no neoplasms at any site (including the skin) that were considered treatment related. Low incidences of hyperplasia of the epidermis at the site of application occurred in males in the 60, 120, and 240 mg/kg groups. Low incidences of hyperplasia of the epidermis at the site of application also occurred in females in the 120 and 240 mg/kg groups, and they occurred with a significant positive trend. Low incidences of hyperplasia of the sebaceous gland occurred in control and 60 mg/kg males and in control, 120 mg/kg, and 240 mg/kg females.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were dermally administered 0, 182, 364, or 727 mg sodium xylenesulfonate/kg body weight in 50% ethanol for 104 to 105 weeks.

Survival, Body Weights, and Clinical Findings

Survival of dosed males and females was similar to that of the control groups. Mean body weights of dosed males and females were generally similar to those of the controls throughout the study; however, the mean body weights of 727 mg/kg females were greater than those of the control group from week 85 to week 97. With the exception of irritation at the site of application in one 364 mg/kg female, there were no clinical findings related to sodium xylenesulfonate administration.

Pathology Findings

There were no neoplasms at any site (including the skin) that were considered treatment related. Hyperplasia of the epidermis occurred in control, 364 mg/kg, and 727 mg/kg males and in control and dosed females. In male mice, the incidences occurred with a significant positive trend. Focal ulceration occurred in one 727 mg/kg male and in one female in each dose group. In males and females from control and dosed groups, the incidences of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined) were generally higher than those expected by spontaneous occurrence. The incidences of hepatocellular neoplasms in some groups of males and females exceeded the NTP historical control range. Male mice had a pattern of nonneoplastic liver lesions along with silver stained positive helical organisms within the liver which suggests an infection with *Helicobacter hepaticus*. The findings in this study of sodium xylenesulfonate were not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis.

GENETIC TOXICOLOGY

Sodium xylenesulfonate was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537 with or without induced liver S9. Equivocal results were obtained in a mutation assay with mouse lymphoma cells in the presence of induced S9; no evidence of mutagenicity was noted without S9 in this assay. In cytogenetic tests with sodium xylenesulfonate in cultured Chinese hamster ovary cells, significant increases in sister chromatid exchanges were observed in the absence of S9 only, and no increases in chromosomal aberrations were observed with or without S9.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of sodium xylenesulfonate in male or female F344/N rats administered 60, 120, or 240 mg/kg or in male or female B6C3F_1 mice administered 182, 364, or 727 mg/kg.

Increased incidences of epidermal hyperplasia in female rats and male mice may have been related to exposure to sodium xylenesulfonate.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Sodium Xylenesulfonate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 60, 120, or 240 mg/kg in 50% ethanol applied dermally	0, 60, 120, or 240 mg/kg in 50% ethanol applied dermally	0, 182, 364, or 727 mg/kg in 50% ethanol applied dermally	0, 182, 364, or 727 mg/kg in 50% ethanol applied dermally
Body weights	Dosed groups similar to control group	Dosed groups similar to control group	Dosed groups similar to control group	Dosed groups similar to control group
2-Year survival rates	7/50, 17/50, 9/50, 10/50	22/50, 16/50, 17/50, 16/50	32/50, 37/50, 39/50, 35/50	31/50, 32/49, 32/50, 36/50
Nonneoplastic effects	None	None	None	None
Neoplastic effects	None	None	None	None
Uncertain findings	None	Skin (site of application): epidermal hyperplasia (1/50, 0/50, 4/50, 5/50)	Skin (site of application): epidermal hyperplasia (1/50, 0/50, 4/50, 5/50)	None
Level of evidence of carcinogenic activity	No evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative with and without S9 in strains TA98, TA100, TA1535, and TA1537			
Mouse lymphoma mutagenicity	Equivocal with S9; negative without S9			
Sister chromatid exchanges				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with S9; positive without S9 #			
Chromosomal aberrations				
Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9 #			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-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 chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-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. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

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

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on technical grade sodium xylenesulfonate on 5 December 1995 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

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

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 5 December 1995, the draft Technical Report on the toxicology and carcinogenesis studies of sodium xylenesulfonate received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. A. Radovsky, NIEHS, introduced the toxicology and carcinogenesis studies of sodium xylenesulfonate by discussing the uses of the chemical, describing the experimental design, reporting on survival and body weight effects, and commenting on possible chemical-related nonneoplastic lesions in female rats and male mice. Dr. Radovsky reported that the greater than normal incidence of hepatocellular neoplasms in control and treated male mice could be attributed to infection with *Helicobacter* bacteria. Increased incidences of hepatocellular neoplasms in female mice could not be associated with *Helicobacter* with certainty. The proposed conclusions were *no evidence of carcinogenic activity* of sodium xylenesulfonate in male and female F344/N rats and $B6C3F_1$ mice.

Dr. Carlson, a principal reviewer, agreed with the proposed conclusions. He commented that he would not have used ethanol as vehicle for application of the chemical.

Dr. Goldsworthy, the second principal reviewer, agreed in principle with the proposed conclusions provided there were further clarification and documentation on the role of *Helicobacter* in the mouse liver neoplasm responses. He said that the report needed to better address the response in females and the effects observed in males and females in a comprehensive manner to ensure that the responses are properly interpreted as nontreatment related. Dr. Radovsky responded that several other studies with *Helicobacter* infection were completed and would be reviewed at the next review meeting. Hopefully, firmer conclusions could then be drawn about the association of liver neoplasm response and infection in $B6C3F_1$ mice (Appendix L). Dr. Goldsworthy said the report should more clearly state any potential dose or absorption effects that occurred from changing volumes as well as vehicles from the 17-day studies to the 14-week and 2-year studies, and comment on the relevance of these studies to human exposures. Dr. Radovsky said sodium xylenesulfonate was more soluble in water than in ethanol, but ethanol may have enhanced skin penetration more than water. She said that relevance to human exposure would be speculative on her part.

Dr. Tyson, the third principal reviewer, agreed with the proposed conclusions. He also questioned the use of ethanol as the vehicle noting the association of dermally applied ethanol with induction of mononuclear cell leukemia in F344/N rats.

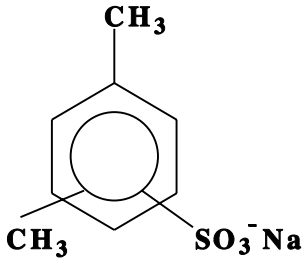
Dr. W.T. Allaben, NCTR, asked for comment on the poor survival in male rats. Dr. J.R. Bucher, NIEHS, said that male rat survival has declined primarily because of increases in nephropathy, body weight, and incidence of pituitary adenoma. Dr. G.N. Rao, NIEHS, commented that survival of rats is lower when they are individually housed as opposed to group-housed. Dr. J.K. Haseman, NIEHS, said that survival in this study was similar to that in other dermal studies using individual housing. Dr. Ryan asked whether there could be a correlation between mice with *Helicobacter* and those with neoplastic lesions. Dr. J.R. Hailey, NIEHS, said that although not all of the animals had been examined, for those that had, there was a good correlation. Dr. Haseman commented that in the previous study with *Helicobacter*, animals with liver neoplasms had the more severe nonneoplastic lesions that were indicative of the infection. Dr. Goldsworthy thought the infection could be a confounding factor in the interpretation of the liver neoplasms in mice. Dr. Haseman said that while total liver neoplasm rates in this study were above expected rates, they were generally similar across groups, yielding no evidence of a chemical-related increase.

Dr. F. Mirer, Health and Safety Department, United Auto Workers Union, had submitted a statement which, at his request, Dr. L.G. Hart, NIEHS, read into the record. Dr. Mirer opined that the studies were *inadequate* to address the carcinogenicity of

sodium xylenesulfonate in humans. He based his assessment on: (1) not high enough a dose to approach a maximum tolerated dose (MTD); (2) likely poor absorption of such an ionic material through intact skin; and (3) wrong route of exposure to estimate human risk, i.e., inhalation exposure should have been used.

Dr. Carlson moved that the Technical Report on sodium xylenesulfonate be accepted with the revisions discussed and with the conclusions as written for male and female rats and mice, *no evidence of carcinogenic activity*. Dr. Tyson seconded the motion. Dr. Goldsworthy offered an amendment that a statement be added to the Abstract that mice were infected with *Helicobacter*. Dr. Carlson agreed to the amendment, and the amended motion was accepted by six yes votes to one no vote (Dr. Russo). Dr. Allaben asked that a short paragraph be added to the discussion regarding individual animal housing and poor survival.

INTRODUCTION



SODIUM XYLENESULFONATE

CAS No. 1300-72-7

Chemical Formula: $(CH_3)_2C_6H_3SO_3^- Na^+$ Molecular Weight: 208.2

Synonyms: Benzenesulfonic acid, dimethyl-, sodium salt; sodium dimethylbenzenesulfonate; xylenesulfonic acid, sodium salt
Trade names: Conco SXS; Cyclophil; SXS 30; Eletesol SX 30; Naxonate; Naxonate G; Richonate SXS; Stepanate SXS; Stepanate X; SXS 40; Ultrawet 40SX

CHEMICAL AND PHYSICAL PROPERTIES

Technical grade sodium xylenesulfonate contains approximately 35% sodium ethylbenzenesulfonate and 11.5%, 38%, and 15.5% of the *ortho*-, *meta*-, and *para*- isomers, respectively, of sodium xylenesulfonate (Mausner and Sosis, 1962). In water at 20° C, the *para*- isomer of sodium xylenesulfonate has a solubility of 170 mg/mL, the *ortho*- isomer has a solubility of 190 mg/mL, and the *meta*- isomer has a solubility of more than 400 mg/mL. Solubility of sodium xylenesulfonate in ethanol is less than that in water. Sodium xylenesulfonate is stable in water under normal laboratory conditions and is incompatible with strong acids and oxidizers (RTECS, 1991).

PRODUCTION, USE, AND HUMAN EXPOSURE

In 1992, over 27.3×10^6 kg of sodium xylenesulfonate was produced in the United States by 10 manufacturers (USITC, 1994). The major use of sodium xylenesulfonate is as a hydrotrope, an organic compound that increases and maintains the solubility of other organic compounds in aqueous solutions. It is used in liquid household detergents and shampoos, in degreasing compounds and printing pastes used in the textile industry, in agents used to extract pentosans and lignin in the paper industry, and as a glue additive in the leather industry.

According to the National Occupational Exposure Survey, approximately 788,092 workers in the United States were potentially exposed to sodium xylenesulfonate during the years 1981 to 1983 (NIOSH, 1990). In shampoos, sodium xylenesulfonate can constitute up to 0.2% of the total solution (Hunting, 1983). Commonly used household products such as disinfectants, floor care products, and kitchen cleaners and degreasers contain sodium xylenesulfonate in concentrations up to 10% (Phil Tham, Reckitt and Colman, Inc., personal communication, 1995). Because many of these shampoos and household products are often used daily, there is widespread potential for human exposure.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

No information on the absorption, distribution, metabolism, and excretion of sodium xylenesulfonate in experimental animals or in humans was found in the literature. Although no information is available about absorption of sodium xylenesulfonate specifically, skin penetration has been shown to be low in compounds that have a polar group, such as the sulfonate group in sodium xylenesulfonate, which can interact with polar groups in the stratum corneum (Grandjean *et al.*, 1988). In general, when absorbed, sulfonates are quickly distributed throughout the body, but are also readily excreted (*Patty's*, 1981).

TOXICITY

No information specific to the toxicity of sodium xylenesulfonate in experimental animals or in humans was found in the literature. In general, the sodium salts of arylsulfonic acids are considered to be of relatively low toxicity (*Patty's*, 1981). The reported minimum lethal gavage dose for sodium toluenesulfonate, a closely related compound, is 12,000 mg/kg in albino rats and 10,000 mg/kg in albino mice (Kondratiuk, 1983).

CARCINOGENICITY

No information specific to the carcinogenicity of sodium xylenesulfonate in experimental animals or in humans was found in the literature.

GENETIC TOXICITY

Sodium xylenesulfonate was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested at concentrations up to 10,000 μg/plate with and without Aroclor 1254-induced male Sprague-Dawley rat or Syrian hamster liver S9 (Zeiger *et al.*, 1987).

STUDY RATIONALE

Sodium xylenesulfonate was nominated by the National Cancer Institute from a soap and detergent class study because of its high annual production and its presence in widely used consumer products.

MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF SODIUM XYLENESULFONATE

Sodium xylenesulfonate was obtained from Ruetgers Nease Chemical Company (State College, PA) in one lot (R092085), which was used for the 17-day, 14-week, and 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO) (Appendix H). Reports on analyses performed in support of the sodium xylenesulfonate studies are on file at the National Institute of Environmental Health Sciences (NIEHS).

The chemical, a white powder, was identified as sodium xylenesulfonate by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The purity was determined by elemental analysis, Karl Fischer water analysis, functional group titration, thin-layer chromatography, and high-performance liquid chromatography.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for sodium xylenesulfonate. Calculated on the basis of 5.15% water and 3.82% sodium sulfate, results for sulfur were slightly higher than theoretical values and results for sodium were slightly lower than theoretical values. Karl Fischer water analysis indicated 5.15% $\pm$ 0.07% water. Functional group titration for ionic sulfate indicated 3.82% $\pm$ 0.04% sodium sulfate. Thin-layer chromatography by one system indicated a major spot and a slight trace impurity; a second system indicated a major spot only. High-performance liquid chromatography by one system indicated a major peak and five impurities with areas totaling 39.2% relative to the major peak; a second system indicated an additional impurity with a peak area of 9.6% relative to the major peak. Under these chromatographic conditions, sodium 2,4- and 2,5-xylenesulfonate coeluted with the major peak. Analysis of nuclear magnetic spectra suggests that one of the impurities may have been ethyl benzenesulfonate.

To ensure stability of the bulk chemical during the 17-day and 14-week studies, sodium xylenesulfonate was stored in glass bottles with Teflon®-lined caps or double bagged in metal drums at room temperature in the dark. During the 2-year studies, the bulk chemical was stored in amber glass bottles at room temperature in the dark.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations for the 17-day studies were prepared twice during the study by stirring the appropriate quantities of sodium xylenesulfonate into deionized water which was then brought to the desired concentration by the further addition of deionized water (Table H1). The dose formulations for the 14-week studies were prepared every 2 weeks by mixing the appropriate amount of sodium xylenesulfonate with 50% ethanol (in deionized water) which was then brought to the desired concentration by the further addition of 50% ethanol (Table H1). The 5 and 15 mg/mL doses were stirred to solution; the 44, 133, and 400 mg/mL doses were stirred to suspension. Dose formulations in the 2-year studies of sodium xylenesulfonate were prepared every 2 to 3 weeks by mixing the appropriate weight of sodium xylenesulfonate in deionized water (Table H1). A suspension was formed by shaking, and then the mixture was brought to the desired concentrations of ethanol and sodium xylenesulfonate by the addition of 95% ethanol. The resulting suspension was the required dose in 50% ethanol. Dose formulations in the 17-day, 14-week, and 2-year studies were stored at room temperature in glass bottles with Teflon®-lined lids in the dark for up to 3 weeks (17-day and 14-week studies) or for 3 to 4 weeks (2-year studies).

Stability studies of 4 mg/mL dose formulations (in deionized water and in 50% ethanol) were conducted by the analytical chemistry laboratory using high-performance liquid chromatography. Stability was

confirmed for at least 3 weeks when stored in the dark at room temperature in sealed glass vials and for 3 hours at room temperature open to air and light. Homogeneity studies of the doses used in the 2-year studies and a limited stability study of the 75 mg/mL dose formulation used in the 2-year studies were performed by the study laboratory. Homogeneity was confirmed and the stability of the 75 mg/mL dose formulation was confirmed for 29 days when stored at room temperature, and protected from light.

Periodic analyses of the dose formulations of sodium xylenesulfonate were conducted by the study laboratory with high-performance liquid chromatography. During the 17-day studies, doses were analyzed at the beginning of the study (Table H2). During the 14-week studies, doses were analyzed at the beginning, midpoint, and end of the studies (Table H3). During the 2-year studies, dose formulations were analyzed at the beginning of the studies and every 7 to 10 weeks thereafter (Table H4). Although the results of a preliminary mixing trial for the 5 and 400 mg/mL concentrations used in the 17-day studies were within 10% of the target concentrations, the first set of dose formulations were 12% to 14% greater than the target concentrations due to a mixing error. These formulations were remixed and were all within 10% of the target concentrations (Table H2). Animal-room samples for the 17-day studies were also within 10% of the target concentrations. During the 14-week studies, all 15 of the dose formulations and all three of the animal room samples were within 10% of the target concentrations. In the 2-year studies, all 42 of the dose formulations and seven of the nine animal room samples were within 10% of the target concentrations. For the 14-week studies, two referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results of the study laboratory (Table H5).

17-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY). On receipt, rats were 22 days old, and mice were 31 days old. Animals were quarantined for 12 (rats) or 11 (mice) days and were 5 (rats) or 6 (mice) weeks old on the first day of the studies. Groups of five male and five female rats and mice received dermal applications of sodium xylenesulfonate in distilled water at dose concentrations of 0, 5, 15, 44, 133, or 400 mg/mL. Doses were applied 5 days per week for 17 days to the clipped interscapular skin at a volume of 300 μL for rats and 100 μL for mice (Appendix I). Feed and water were available *ad libitum*. Rats and mice were housed individually. Clinical findings for rats and mice were recorded twice daily and at the end of the studies. Animals were weighed on days 1 and 8 and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

A necropsy was performed on all animals. The heart, right kidney, liver, lungs, right testis, and thymus were weighed. Histopathologic examination was restricted to skin from the site of application, skin from an untreated site, and gross lesions. Table 1 lists the tissues and organs examined.

14-WEEK STUDIES

The 14-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to sodium xylenesulfonate and to determine the appropriate doses to be used in the 2-year studies. Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Farms (Germantown, NY). On receipt rats and mice were 31 days old. Animals were quarantined for 12 (rats) or 19 (mice) days and were 6 (rats) or 7 (mice) weeks old on the first day of the studies. Before the studies began, five male and five female rats and mice were randomly selected for parasite evaluation and gross observation for evidence of disease. At the end of the studies, serologic analyses were performed on five male and five female rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix K).

Groups of 10 male and 10 female rats and mice received dermal applications of sodium xylenesulfonate in 50% ethanol at dose concentrations of 0, 5, 15, 44, 133, or 400 mg/mL (Appendix I). A 50% solution of ethanol in water was chosen as the vehicle in the 14-week studies because solutions of sodium xylenesulfonate in water alone were observed to bead up rather than to spread out on rodent skin. Doses were applied 5 days per week for 14 weeks to the clipped interscapular skin at a volume of 300 μL for rats and 100 μL for mice. Feed and water were available *ad libitum*. Rats and mice were housed

individually. Clinical findings for rats and mice were recorded weekly and at the end of the studies. Animals were weighed initially, weekly, and at the end of the studies. Details of the study design and animal maintenance are summarized in Table 1.

For special hematology and clinical chemistry studies, additional groups of 10 male and 10 female rats received dermal applications of sodium xylenesulfonate in 50% ethanol at doses of 0, 5, 15, 44, 133, or 400 mg/mL.

Blood was collected from special study rats under carbon dioxide anesthesia on days 5 and 21 via the retroorbital sinus. Using the same method, blood was also collected from core study rats at the end of the study. For hematology analyses, samples were placed in containers containing EDTA as an anticoagulant. For clinical chemistry analyses, samples were collected in plastic centrifuge tubes. Hemoglobin concentrations, hematocrit values, and erythrocyte, platelet, and leukocyte counts were measured on an Ortho ELT-8 analyzer (Ortho Instruments, Westwood, MA). Differential leukocyte counts, reticulocyte counts, and leukocyte, erythrocyte, and platelet morphologies were determined by light microscopy of blood films. Mean cell volume, mean cell hemoglobin, and mean cell hemoglobin concentrations were calculated from the results of analyses for hemoglobin concentration, hematocrit, and erythrocyte counts. The hematology parameters measured are listed in Table 1. Clinical chemistry parameters were measured on a Roche Cobas FARA chemistry analyzer (Roche Diagnostic Systems, Inc., Montclair, NJ). The clinical chemistry parameters measured are listed in Table 1.

A necropsy was performed on all core study rats and on all mice. The heart, right kidney, liver, lungs, right testis, and thymus were weighed. Tissues for microscopic examination were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin. Complete histopathologic examinations were performed on all control rats (core) and mice and rats (core) and mice from the 400 mg/mL groups. Table 1 lists the tissues and organs routinely examined. Skin from the site of application was examined microscopically in progressively lower dose groups until no skin lesions were observed in a dose group.

2-YEAR STUDIES

Groups of 50 male and 50 female rats were administered dermal applications of 0, 60, 120, or 240 mg sodium xylenesulfonate/kg body weight in 50% ethanol. Groups of 50 male and 50 female mice were administered dermal applications of 0, 182, 364, or 727 mg sodium xylenesulfonate/kg body weight. Doses were applied five days per week for 104 (rats and male mice) or 105 (female mice) weeks to the clipped interscapular skin at volumes of 85 to 357 μL for rats and of 46 to 128 μL for mice. Volumes were adjusted for the weights of the animals throughout the study (Appendix I).

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Simonsen Laboratories (Gilroy, CA) for use in the 2-year studies. Rats and mice were quarantined for 14 days prior to the start of the studies. Five male and five female rats and mice were selected for parasite evaluation and gross observation of disease. Serology samples were collected for viral screening. Rats and mice were approximately 6 weeks old at the beginning of the studies. The health of the animals was monitored during the studies according to the protocols of the NTP Sentinel Animal Program (Appendix K).

Animal Maintenance

Rats and mice were housed individually. Feed and water were available *ad libitum*. Cages were changed weekly and racks were rotated once every 2 weeks. Further details of animal maintenance are given in Table 1.

Clinical Examinations and Pathology

All animals were observed twice daily and clinical findings were recorded monthly. Body weights were recorded weekly through week 13, monthly thereafter, and at the end of the studies.

All animals were necropsied. A complete histopathologic examination was performed on all rats and mice that died prior to study termination, and on control rats and mice, and on 240 mg/kg rats and 727 mg/kg

mice at the end of the studies. Skin from the site of application was examined for all dose groups. At necropsy, all organs and tissues were examined for grossly visible lesions. Major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 5 to 6 μm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (i.e., adrenal gland, kidney, ovary), samples from each organ were examined. Tissues examined microscopically are listed in Table 1.

Microscopic evaluations were completed by the study laboratory pathologist, and the pathology data were entered into the Toxicology Data Management System. The slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were evaluated by an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, the slide and tissue counts were verified, and the histotechnique was evaluated. For the 2-year studies, a quality assessment pathologist reviewed the skin of rats and mice and the liver of mice for all lesions; the liver and spleen of male rats for mononuclear cell leukemia; and the clitoral gland of female rats for proliferative lesions (hyperplasia, adenoma, and carcinoma).

The quality assessment report and the reviewed slides were submitted to the NTP Pathology Working Group (PWG) chairperson, who reviewed the selected tissues and addressed any inconsistencies in the diagnoses made by the laboratory and quality assessment pathologists. Representative histopathology slides containing examples of lesions related to chemical administration, examples of disagreements in diagnoses between the laboratory and quality assessment pathologist, or lesions of general interest were presented by the chairperson to the PWG for review. The PWG consisted of the quality assessment pathologist and other pathologists experienced in rodent toxicologic pathology. This group examined the tissues without any knowledge of dose groups or previously rendered diagnoses. When the PWG consensus differed from the opinion of the laboratory pathologist, the diagnosis was changed. Final diagnoses for reviewed lesions represent a consensus between the laboratory pathologist, reviewing pathologist(s), and the PWG. The PWG reviewed the following: proliferative lesions of the thyroid gland in all female mice and in control and 727 mg/kg male mice; all control male rat testes for interstitial cell neoplasms; clitoral glands in female rats and preputial glands in control and 240 mg/kg male rats for proliferative lesions; thyroid, adrenal (medulla), and pituitary glands in control and 240 mg/kg groups of male and female rats. Details of these review procedures have been described, in part, by Maronpot and Boorman (1982) and Boorman *et al*. (1985). For subsequent analyses of the pathology data, the decision of whether to evaluate the diagnosed lesions for each tissue type separately or combined was generally based on 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 found dead of other than natural causes or missing were censored from the survival analyses; animals dying from natural causes were not censored. Statistical analyses for possible dose-related effects on survival used Cox's (1972) method for testing two groups for equality and Tarone's (1975) life table test to identify dose-related trends. All reported P values for the survival analyses are two sided.

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions as presented in Tables A1, A4, B1, B4, C1, C5, D1, and D5 are given as the number of animals bearing such lesions at a specific anatomic site and the number of animals with that site examined microscopically. For calculation of statistical significance, the incidences of most neoplasms (Tables A3, B3, C3, and D3) and all nonneoplastic lesions are given as the numbers of animals affected at each site examined microscopically. However, when macroscopic examination was required to detect neoplasms in certain tissues (e.g., skin, intestine, harderian gland, and mammary gland) before microscopic evaluation, or when neoplasms had multiple potential sites of occurrence (e.g., leukemia or lymphoma), the denominators consist of the number of animals on

which a necropsy was performed. Tables A3, B3, C3, and D3 also give the survival-adjusted neoplasm rate for each group and each site-specific neoplasm, i.e., the Kaplan-Meier estimate of the neoplasm incidence that would have been observed at the end of the study in the absence of mortality from all competing risks (Kaplan and Meier, 1958)

Analysis of Neoplasm Incidences

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

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

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-related trend. Continuity-corrected tests were used in the analysis of neoplasm incidence, and reported P values are one sided. The procedures described in the preceding paragraphs were also used to evaluate selected nonneoplastic lesions. For further discussion of these statistical methods, refer to Haseman (1984).

Analysis of Nonneoplastic Lesion Incidences

Because all nonneoplastic lesions in this study were considered to be incidental to the cause of death or not rapidly lethal, the primary statistical analysis used was a logistic regression analysis in which nonneoplastic lesion prevalence was modeled as a logistic function of chemical exposure and time. For lesions detected at the interim evaluation, the Fisher exact test, a procedure based on the overall proportion of affected animals, was used.

Analysis of Continuous Variables

Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data, which have approximately normal distributions, were analyzed using the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Clinical chemistry and hematology data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) and Dunn (1964). Jonckheere's test (Jonckheere, 1954) was used to assess the significance of the dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to analysis, extreme values identified by the outlier test of Dixon and Massey (1951) were examined by NTP personnel, and implausible values were eliminated from the analysis. Average severity values were analyzed for significance using the Mann-Whitney U test (Hollander and Wolfe, 1973).

Historical Control Data

Although the concurrent control group is always the first and most appropriate control group used for evaluation, historical control data can be helpful in the overall assessment of neoplasm incidence in certain instances. Consequently, neoplasm incidences from the NTP historical control database, which is updated yearly, are included in the NTP reports for neoplasms appearing to show compound-related effects.

QUALITY ASSURANCE METHODS

The 14-week and 2-year studies were conducted in compliance with Food and Drug Administration Good Laboratory Practice Regulations (21 CFR, Part 58). In addition, as records from the 2-year studies were submitted to the NTP Archives, these studies were audited retrospectively by an independent quality assurance contractor. Separate audits covering completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report were conducted. Audit procedures and findings are presented in the reports and are on file at NIEHS. The audit findings were reviewed and assessed by NTP staff, so all comments had been resolved or were otherwise addressed during the preparation of this Technical Report.

GENETIC TOXICOLOGY

The genetic toxicity of sodium xylenesulfonate was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and mutations in L5178Y mouse lymphoma cells. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies of sodium xylenesulfonate are part of a larger effort by the NTP to develop a database that would permit the evaluation of carcinogenicity in experimental animals from the structure and responses of the chemical in short-term *in vitro* and *in vivo* genetic toxicity tests. These genetic toxicity tests were originally developed to study mechanisms of chemically induced DNA damage and to predict carcinogenicity in animals, based on the electrophilic theory of chemical carcinogenesis and the somatic mutation theory (Miller and Miller, 1977; Straus, 1981; Crawford, 1985).

There is a strong correlation between a chemical's potential electrophilicity (structural alert to DNA reactivity), mutagenicity in *Salmonella*, and carcinogenicity in rodents. The combination of electrophilicity and *Salmonella* mutagenicity is highly correlated with the induction of carcinogenicity in rats and mice and/or at multiple tissue sites (Ashby and Tennant, 1991). Other *in vitro* genetic toxicity tests do not correlate well with rodent carcinogenicity (Tennant *et al.*, 1987; Zeiger *et al.*, 1990), although these other tests can provide information on the types of DNA and chromosome effects that can be induced by the chemical being investigated. Data from NTP studies show that a positive response in *Salmonella* is currently the most predictive *in vitro* test for rodent carcinogenicity (89% of the *Salmonella* mutagens were rodent carcinogens), and that there is no complementarity among the *in vitro* genetic toxicity tests. That is, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone.

TABLE 1
Experimental Design and Materials and Methods in the Dermal Studies of Sodium Xylenesulfonate

17-Day Studies	14-Week Studies	2-Year Studies
Study Laboratory		
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)	Battelle Columbus Laboratories (Columbus, OH)
Strain and Species		
Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$	Rats: F344/N Mice: $B6C3F_1$
Animal Source		
Taconic Farms (Germantown, NY)	Taconic Farms (Germantown, NY)	Simonsen Laboratories, Inc. (Gilroy, CA)
Time Held Before Studies		
Rats: 12 days Mice: 11 days	Rats: 12 days Mice: 19 days	14 days
Average Age When Studies Began		
Rats: 5 weeks Mice: 6 weeks	Rats: 6 weeks Mice: 7 weeks	7 weeks
Date of First Dose		
Rats: 20 July 1987 Mice: 27 July 1987	Rats: 16 February 1988 Mice: 23 February 1988	Rats: 29 November 1990 Mice: 20 December 1990
Duration of Dosing		
5 days per week for 17 days	5 days per week for 14 weeks	5 days per week for 104 weeks (rats and male mice) or 105 weeks (female mice)
Date of Last Dose		
Rats: 5-6 August 1987 Mice: 11-12 August 1987	Rats: 17-19 May 1988 (core) 16-17 May 1988 (special study) Mice: 24-26 May 1988	Rats: 20 November 1992 Mice: 11 December 1992 (males) 18 December 1992 (females)
Necropsy Dates		
Rats: 5-6 August 1987 Mice: 12-13 August 1987	Rats: 18-20 May 1988 Mice: 25-27 May 1988	Rats: 2-3 December 1992 Mice: 21-23 December 1992 (males) 28-30 December 1992 (females)
Average Age at Necropsy		
Rats: 7 weeks Mice: 8 weeks	Rats: 19-20 weeks Mice: 20-21 weeks	Rats: 111-112 weeks Mice: 111-112 weeks

TABLE 1 #
Experimental Design and Materials and Methods in the Dermal Studies of Sodium Xylenesulfonate (continued) #

17-Day Studies	14-Week Studies	2-Year Studies
Size of Study Groups		
5 males and 5 females	10 males and 10 females (rats and mice; core study) 10 male and 10 female rats (special study)	50 males and 50 females
Method of Distribution		
Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 17-day studies	Same as 17-day studies
Animals per Cage		
1	1	1
Method of Animal Identification		
Toe clip	Toe clip	Tail tattoo
Diet		
NIH-07 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*	Same as 17-day studies	Same as 17-day studies
Water Distribution		
Tap water (City of Birmingham municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 17-day studies	Tap water (Columbus municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*
Cages		
Polycarbonate (Lab Products Inc., Maywood, NJ), changed once weekly	Same as 17-day studies	Same as 17-day studies
Bedding		
Heat-treated hardwood chips (P.J. Murphy Forest Products Co., Montville, NJ)	Same as 17-day studies	Sani-Chip® hardwood chips (P.J. Murphy Forest Products Corp., Montville, NJ)
Cage Filters		
Reemay® spun-bonded polyester (Andico, Birmingham, AL)	Same as 17-day studies	DuPont 2024 spun-bonded polyester (Snow Filtration Co., Cincinnati, OH)

TABLE 1 #
Experimental Design and Materials and Methods in the Dermal Studies of Sodium Xylenesulfonate (continued) #

17-Day Studies	14-Week Studies	2-Year Studies
Racks		
Stainless steel (Lab Products Inc., Maywood, NJ), not rotated	Stainless steel (Lab Products Inc., Maywood, NJ), rotated once every 2 weeks	Stainless steel (Lab Products Inc., Maywood, NJ), rotated once every 2 weeks
Animal Room Environment		
Temperature: 22.5° to 25.6° C (rats); 15.8° to 23.9° C (mice) Relative humidity: 51% to 68% (rats); 31% to 50% (mice) Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour	Temperature: 20.1° to 24.5° C (rats); 21.5° to 23.9° C (mice) Relative humidity: 20% to 67% (rats); 15% to 63% (mice) Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour	Temperature: 20.0° to 24.4° C (rats); 16.7° to 25.6° C (mice) Relative humidity: 35% to 70% (rats); 34% to 69% (mice) Fluorescent light: 12 hours/day Room air: minimum of 10 changes/hour
Doses		
0, 5, 15, 44, 133, or 400 mg/mL (dose volumes of 300 μL for rats and 100 μL for mice)	0, 5, 15, 44, 133, or 400 mg/mL (dose volumes of 300 μL for rats and 100 μL for mice)	Rats: 0, 60, 120, or 240 mg/kg (dose volumes of 85 to 357 μL) Mice: 0, 182, 364, or 727 mg/kg (dose volumes of 46 to 128 μL)
Type and Frequency of Observation		
Observed twice daily; animals were weighed on days 1 and 8, and at the end of the studies. Clinical findings were recorded twice daily and at the end of the studies.	Observed twice daily; animals were weighed initially, weekly, and at the end of the studies. Clinical findings were recorded weekly and at the end of the studies. Feed consumption was measured weekly for each animal.	Observed twice daily; clinical findings were recorded monthly, body weights were recorded weekly through week 13, monthly thereafter, and at the end of the studies.
Method of Sacrifice		
CO_2 asphyxiation	CO_2 asphyxiation	CO_2 asphyxiation
Necropsy		
Necropsy performed on all animals. Organs weighed included the heart, right kidney, liver, lungs, right testis, and thymus.	Necropsy performed on all core study rats and on all mice. Organs weighed included the heart, right kidney, liver, lungs, right testis, and thymus.	Necropsy performed on all animals.

TABLE 1 #
Experimental Design and Materials and Methods in the Dermal Studies of Sodium Xylenesulfonate (continued) #

17-Day Studies	14-Week Studies	2-Year Studies
Clinical Pathology		
None	Blood was collected from special study rats on day 5 and on day 21 and from core study rats at the end of the study. Blood was collected from the retroorbital sinus. ***Hematology:*** hematocrit, hemoglobin concentration, erythrocyte and reticulocyte counts, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, platelet count, and leukocyte count and differentials. ***Clinical Chemistry:*** urea nitrogen, creatinine, total protein, albumin, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, and bile acids.	None
Histopathology		
Histopathologic examination was limited to the skin (site of application and untreated skin) and gross lesions.	Complete histopathologic examinations were performed on control rats (core) and mice, and rats (core study) and mice from the 400 mg/mL groups. In addition to gross lesions, tissue masses, and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. Skin samples were examined in lower dose groups until a no-effect level was reached.	Complete histopathologic examinations were performed on all control, on all 240 mg/kg rats and 727 mg/kg mice, and on all animals that died early. In these animals, in addition to gross lesions, tissue masses, and associated lymph nodes, the tissues examined included: adrenal gland, bone and marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, kidney, large intestine (cecum, colon, and rectum), small intestine (duodenum, jejunum, and ileum), liver, lung, lymph nodes (mandibular and mesenteric), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular stomach), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. In 60 and 120 mg/kg rats and in 182 and 364 mg/kg mice, tissues examined microscopically included skin from the site of application and control skin. Additional review was made of the liver and spleen of 60 and 120 mg/kg male rats for mononuclear cell leukemia; the clitoral gland of female rats and the preputial gland of control and high-dose male rats for proliferative lesions; the liver of 182 and 364 mg/kg male and female mice; and the thyroid gland of 182 and 364 mg/kg female mice.

RESULTS

RATS

17-DAY STUDY

All rats survived to the end of the study (Table 2). Final mean body weights and body weight gains of dosed rats were similar to those of the control groups. Dermal applications of 300 μL of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately 10, 30, 90, 260, and 800 mg sodium xylenesulfonate/kg body weight to males and 13, 40, 120, 330, and 1,030 mg/kg to females. Clinical findings generally involved the skin of dosed animals and included tan or brown skin discoloration and crusty white deposits (presumed to be dried chemical) at the site of application. Neither of these observations were considered significant findings. The relative liver weights of 133 and 400 mg/mL male and female rats were significantly greater than those of the control groups, but the absolute weights were similar. The biological significance of the differences in relative liver weights was unclear (Table F1). In males and females, the few skin lesions observed grossly and microscopically were generally attributed to repeated clipping and were not considered related to chemical administration.

TABLE 2
Survival and Body Weights of Rats in the 17-Day Dermal Study of Sodium Xylenesulfonate

Dose (mg/mL)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	110 ± 5	181 ± 7	71 ± 1	
5	5/5	111 ± 6	188 ± 6	78 ± 1	104
15	5/5	112 ± 5	187 ± 8	75 ± 3	103
44	5/5	106 ± 4	174 ± 7	68 ± 4	96
133	5/5	114 ± 6	188 ± 12	74 ± 7	104
400	5/5	111 ± 5	186 ± 8	75 ± 4	102
Female					
0	5/5	92 ± 6	136 ± 5	44 ± 3	
5	5/5	97 ± 5	137 ± 5	40 ± 1	101
15	5/5	98 ± 5	137 ± 5	39 ± 2	101
44	5/5	93 ± 2	133 ± 4	40 ± 3	98
133	5/5	100 ± 3	139 ± 5	40 ± 4	103
400	5/5	98 ± 3	134 ± 5	36 ± 3	99

[a] Number of animals surviving at 17 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the control group were not significant by Dunnett's test.

14-WEEK STUDY

All rats survived to the end of the study (Table 3). Final mean body weights and body weight gains of dosed male and female rats were similar to those of the control groups. Dermal applications of 300 μL of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately 6, 20, 60, 170, and 500 mg sodium xylenesulfonate/kg body weight to males and 10, 30, 90, 260, and 800 mg/kg to females. The only notable clinical finding was brown discoloration of the skin at the site of application in dosed animals.

Hematology and clinical chemistry parameters of dosed groups of males and females were significantly different from those of the controls in several instances, but these differences were sporadic and did not demonstrate a treatment relationship (Appendix G).

The absolute and relative liver weights of males receiving 44, 133, or 400 mg/mL were significantly less than those of the control group (Table F2). There were no treatment-related histopathologic alterations in the livers of dosed male and female rats; thus, the biological significance of the decreased liver weights was unclear.

Minimal hyperplasia of the epidermis at the site of application occurred in male and female rats from the control groups as well as most dosed groups. The incidence of epidermal hyperplasia in 400 mg/mL males was considered to be possibly chemical-related (Table 4). Lesions in rats from lower dose groups were attributed to vehicle application and weekly clipping. Epidermal hyperplasia typically consisted of a minimal multifocal increase in the thickness of the epidermis.

TABLE 3
Survival and Body Weights of Rats in the 14-Week Dermal Study of Sodium Xylenesulfonate

Dose (mg/mL)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	147 ± 5	350 ± 8	203 ± 8	
5	10/10	145 ± 6	346 ± 5	202 ± 4	99
15	10/10	136 ± 5	346 ± 6	209 ± 5	99
44	10/10	133 ± 7	328 ± 6	195 ± 9	94
133	10/10	141 ± 4	339 ± 8	199 ± 8	97
400	10/10	144 ± 7	344 ± 5	200 ± 6	98
Female					
0	10/10	110 ± 3	195 ± 4	85 ± 3	
5	10/10	103 ± 3	189 ± 3	86 ± 3	97
15	10/10	102 ± 3	188 ± 2	86 ± 3	96
44	10/10	99 ± 3*	190 ± 2	90 ± 3	98
133	10/10	107 ± 2	197 ± 4	90 ± 3	101
400	10/10	107 ± 2	195 ± 3	88 ± 3	100

* Significantly different ($P \leq 0.05$) from the control group by Dunnett's test
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

TABLE 4
Incidences of Epidermal Hyperplasia in Rats in the 14-Week Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	5 mg/mL	15 mg/mL	44 mg/mL	133 mg/mL	400 mg/mL
Male						
Skin, Site of Application[a]	10	10	10	10	10	10
Epidermal Hyperplasia[b]	1 (1.0)[c]	3 (1.0)	6* (1.0)	0	0	8** (1.0)
Female						
Skin, Site of Application	10	10	10	10	10	10
Epidermal Hyperplasia	5 (1.0)	3 (1.0)	1 (1.0)	6 (1.0)	6 (1.0)	3 (1.0)

* Significantly different ($P \leq 0.05$) from the vehicle control by the Fisher exact test
** $P \leq 0.01$
[a] Number of rats with skin examined microscopically
[b] Number of rats with lesion
[c] Average severity grade of lesion in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Dose Selection Rationale: In the 17-day and 14-week studies, dose concentrations of up to 400 mg/mL were well tolerated. The only limitation to the concentration used in dermal dosing in the 2-year study was the difficulty of getting a uniform suspension of sodium xylenesulfonate in the vehicle. To obtain uniform suspensions, the highest dose concentration was decreased to 300 mg/mL (used to deliver the 240 mg/kg dose) in the 2-year study. Fixed volumes and concentrations were used in the 17-day and 14-week studies which resulted in decreasing dose concentrations (mg/kg body weight) as the animals grew (Appendix I). Constant dose concentrations were achieved in the 2-year study by adjusting the applied dose volumes to the mean body weights throughout the study.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 5 and in the Kaplan-Meier survival curves (Figure 1). Survival of dosed males and females was similar to that of the control groups and consistent with survival of control groups in other NTP studies in which rats were individually housed (Rao, 1995).

Body Weights and Clinical Findings

Mean body weights of dosed males and females were similar to those of the controls throughout the study. (Tables 6 and 7, Figure 2). In males, there were no clinical findings considered treatment related. In females, clinical findings were limited to irritation at the site of application in one control female, four 120 mg/kg females, and two 240 mg/kg females.

TABLE 5
Survival of Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Male				
Animals initially in study	50	50	50	50
Moribund	28	25	22	30
Natural deaths	15	8	19	10
Animals surviving to study termination	7	17	9	10
Percent probability of survival at end of study[a]	14	34	18	20
Mean survival (days)[b]	638	634	632	635
Survival analysis[c]	P=1.000N	P=0.115N	P=0.927N	P=0.580N
Female				
Animals initially in study	50	50	50	50
Accidental death[d]	1	0	0	0
Moribund	14	10	15	12
Natural deaths	13	24	18	22
Animals surviving to study termination	22	16[e]	17	16
Percent probability of survival at end of study	46	32	34	32
Mean survival (days)	647	610	641	621
Survival analysis	P=0.309	P=0.156	P=0.329	P=0.193

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.
[d] Censored from survival analyses
[e] Includes one animal that died during the last week of the study

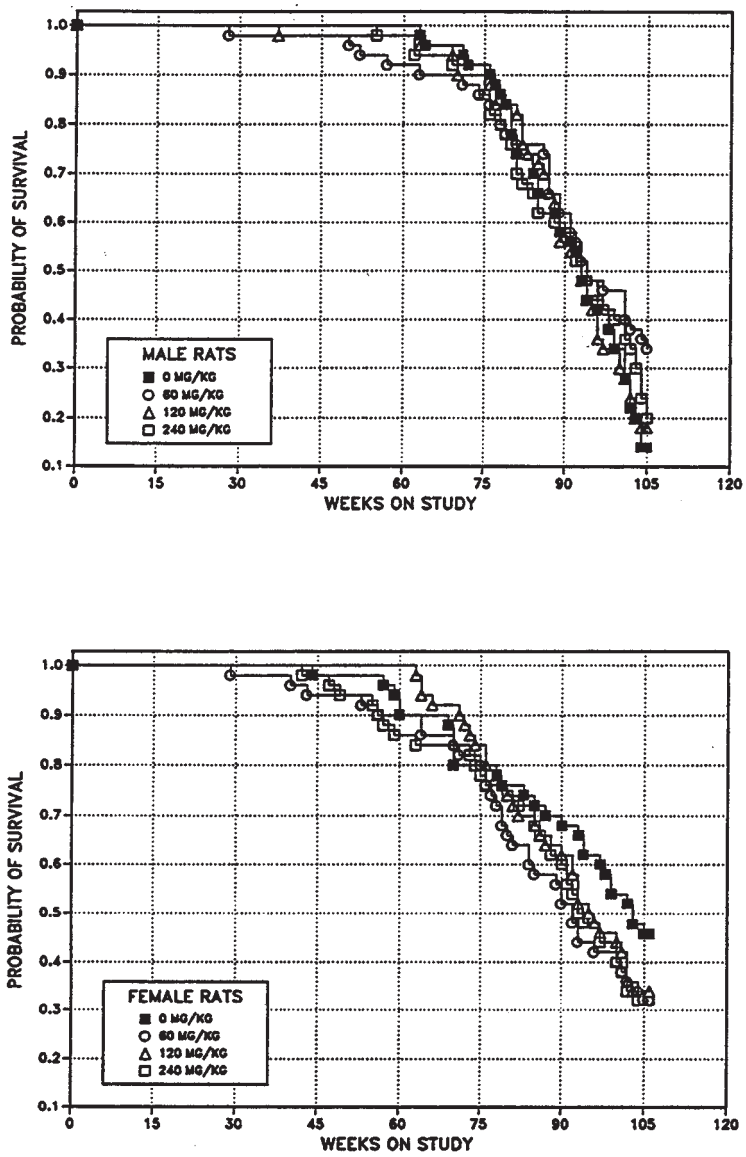


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Administered Sodium Xylenesulfonate Dermally for 2 Years

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate

Weeks on Study	Vehicle Control		60 mg/kg			120 mg/kg			240 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	127	50	127	100	50	128	100	50	127	100	50
2	155	50	154	100	50	154	99	50	154	100	50
3	187	50	188	101	50	185	99	50	187	100	50
4	206	50	208	101	50	206	100	50	206	100	50
5	228	50	231	101	50	228	100	50	227	99	50
6	245	50	245	100	50	243	99	50	241	99	50
7	259	50	261	101	50	259	100	50	256	99	50
8	271	50	271	100	50	270	100	50	265	98	50
9	282	50	282	100	50	280	99	50	277	98	50
10	292	50	293	100	50	290	99	50	287	98	50
11	298	50	298	100	50	295	99	50	292	98	50
12	305	50	307	101	50	304	100	50	299	98	50
13	311	50	312	100	50	309	99	50	305	98	50
17	336	50	335	100	50	329	98	50	327	97	50
21	356	50	352	99	50	347	97	50	341	96	50
25	369	50	364	99	50	360	98	50	354	96	50
29	382	50	380	99	49	374	98	50	368	96	50
33	393	50	391	100	49	384	98	50	382	97	50
37	399	50	397	100	49	389	97	50	387	97	50
41	407	50	405	100	49	400	98	49	392	96	50
45	414	50	414	100	49	411	99	49	402	97	50
49	414	50	415	100	49	412	99	49	407	98	50
52	421	50	420	100	47	415	99	49	412	98	50
57	432	50	428	99	47	427	99	49	422	98	49
61	433	50	436	101	46	433	100	49	426	98	49
65	429	48	437	102	45	431	101	48	429	100	47
69	433	48	442	102	45	432	100	47	432	100	47
73	439	46	437	99	44	434	99	45	429	98	46
77	434	45	440	102	42	436	101	44	432	100	41
81	438	39	446	102	39	432	99	42	427	98	37
85	431	35	444	103	38	426	99	37	424	98	33
89	427	30	438	103	33	423	99	32	417	98	30
93	416	26	424	102	27	413	99	27	416	100	26
97	410	21	414	101	24	419	102	18	409	100	22
101	376	16	390	104	23	373	99	15	397	106	20
104	376	9	372	99	18	358	95	9	366	97	13
Mean for weeks											
1-13	244		244	100		242	99		240	98	
14-52	389		387	99		382	98		377	97	
53-104	421		427	101		418	99		417	99	

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate

Weeks on Study	Vehicle Control		60 mg/kg			120 mg/kg			240 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	108	50	107	100	50	107	99	50	107	100	50
2	124	50	124	100	50	124	100	50	124	100	50
3	136	50	136	100	50	137	101	50	135	100	50
4	144	50	143	99	50	144	100	50	142	99	50
5	149	50	149	100	50	150	100	50	147	98	50
6	158	50	156	99	50	159	101	50	155	98	50
7	163	50	162	100	50	164	101	50	161	99	50
8	165	50	164	100	50	167	101	50	162	98	50
9	171	50	170	99	50	172	100	50	167	98	50
10	174	50	173	99	50	174	100	50	170	98	50
11	177	50	176	99	50	177	100	50	174	98	50
12	179	50	179	100	50	180	100	50	176	98	50
13	182	50	181	99	50	182	100	50	179	98	50
17	189	50	188	100	50	190	101	50	186	98	50
21	196	50	195	100	50	197	100	50	191	98	50
25	201	50	200	100	50	202	101	50	196	98	50
29	210	50	208	99	50	210	100	50	205	98	50
33	216	50	215	100	49	217	100	50	211	98	50
37	220	50	219	99	49	221	101	50	213	97	50
41	227	50	226	100	48	226	99	50	218	96	50
45	234	49	232	99	47	233	100	50	225	96	49
49	240	49	238	99	47	239	100	50	228	95	48
52	246	49	246	100	47	244	99	50	235	96	47
57	255	48	256	100	45	253	99	50	246	96	45
61	262	45	261	99	45	259	99	50	252	96	43
65	263	45	263	100	43	260	99	47	253	96	42
69	264	45	266	101	43	264	100	46	255	97	42
73	266	40	266	100	41	266	100	44	254	95	42
77	271	40	268	99	38	272	100	40	262	97	38
81	273	38	275	101	33	273	100	37	266	98	37
85	274	37	277	101	29	272	99	35	266	97	35
89	279	35	276	99	29	273	98	32	268	96	31
93	282	33	288	102	22	281	100	28	271	96	27
97	282	31	283	100	21	290	103	23	268	95	24
101	289	26	278	96	19	285	98	22	270	93	20
104	277	23	278	101	17	282	102	17	271	98	16
Mean for weeks											
1-13	156		155	99		157	101		154	99	
14-52	218		217	100		218	100		211	97	
53-104	272		272	100		272	100		262	96	

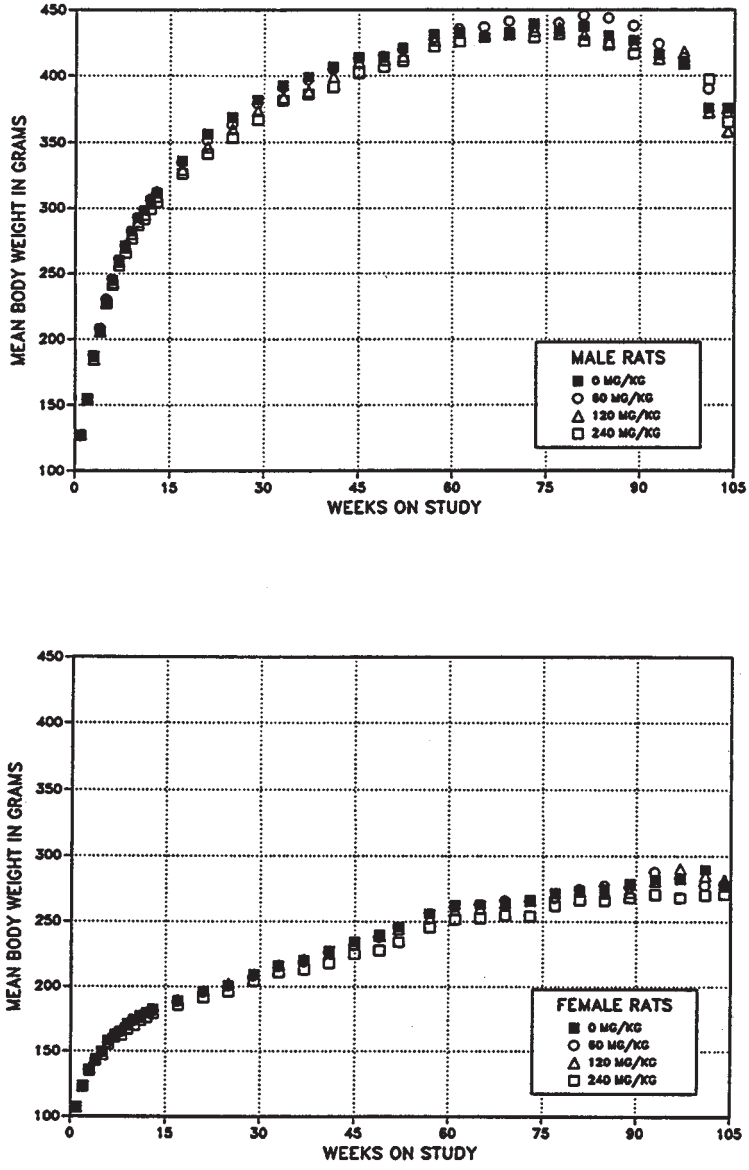


FIGURE 2
Growth Curves for Male and Female Rats Administered Sodium Xylenesulfonate Dermally for 2 Years

Pathology and Statistical Analysis

This section describes the statistically significant and biologically noteworthy changes in the incidences of mononuclear cell leukemia and neoplasms and nonneoplastic lesions of the skin and other organs. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, and statistical analyses of primary neoplasms that occurred with incidences of at least 5% in at least one animal group are presented in Appendix A for male rats and Appendix B for female rats.

Skin: Incidences of neoplasms in the skin and subcutaneous tissues of male rats are given in Tables 8, A1, and A3. The incidences and morphologies of these neoplasms were typical of spontaneous neoplasms in F344/N rats and, therefore, were not considered related to treatment. There were no skin neoplasms observed at the site of application in female rats.

Hyperplasia of the epidermis at the site of application occurred at low incidences in males in the 60, 120, and 240 mg/kg groups (Tables 8 and A4). Hyperplasia of the epidermis at the site of application occurred at low incidences in females in the 120 and 240 mg/kg groups and occurred with a significant positive trend ($P \leq 0.05$; Tables 8 and B4). Incidences of hyperplasia of the epidermis might have been related to chemical administration. These multifocal lesions were minimal to mild in severity and consisted of extensive increased numbers of cell layers of the epidermal epithelium.

Other nonneoplastic lesions of the skin did not appear related to chemical administration, but more probably were a result of repeated hair clipping and vehicle application. Focal ulceration of the epidermis occurred in control, 120 mg/kg, and 240 mg/kg females (Tables 8 and B4). Ulceration through the layers of the epidermal epithelium was typically accompanied by inflammatory cells in the exposed dermis and an effluxing of protein and necrotic cells which were diagnosed as exudate. Hyperplasia of the sebaceous glands occurred at low incidences in control and 60 mg/kg males and in control, 120 mg/kg, and 240 mg/kg females (Tables 8, A4, and B4) and consisted of numerous large sebaceous glands in the dermis. Inflammation of the dermis or subcutaneous tissues consisted of accumulations of both mononuclear and neutrophil inflammatory cells.

TABLE 8
Incidences of Neoplasms and Nonneoplastic Lesions of the Skin in Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control		60 mg/kg		120 mg/kg		240 mg/kg	
Male								
Skin, Site of Application[a]	50		50		50		50	
Epidermis, Hyperplasia[b]	0		1	(1.0)[c]	1	(1.0)	2	(1.5)
Sebaceous Gland, Hyperplasia	1	(2.0)	1	(1.0)	0		0	
Inflammation, Chronic Active	0		1	(1.0)	0		0	
Sebaceous Gland Carcinoma	1		0		0		0	
Basal Cell Adenoma	0		1		1		0	
Subcutaneous Tissue, Fibroma, Multiple	1		0		0		0	
Subcutaneous Tissue, Fibrous Histiocytoma	0		1		0		0	
Female								
Skin, Site of Application	50		50		50		50	
Epidermis, Exudate	0		0		0		2	(1.0)
Epidermis, Hyperplasia	1	(2.0)	0		4	(1.8)	5	(1.4)
Epidermis, Inflammation, Chronic Active	0		0		0		1	(1.0)
Epidermis, Ulcer	1	(3.0)	0		2	(3.0)	2	(3.0)
Sebaceous Gland, Hyperplasia	2	(1.5)	0		2	(2.5)	2	(2.0)
Inflammation, Chronic Active	1	(2.0)	0		2	(3.0)	2	(2.5)

[a] Number of rats with skin examined microscopically
[b] Number of rats with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Other Organs: There was no relation to dose in the incidences of pituitary gland adenoma in male rats (44/50, 27/33, 34/41, 36/50; Table A3). The control incidence was unusually high compared to historical control incidences from some dermal and feed studies [dermal acetone: 59/100 (59.0% ± 15.6%); range, 48%-70%; dermal ethanol: 31/52; feed: 377/1,284 (29.4% ± 10.6%); range, 14%-60%]; however, it was similar to controls in a "neat" dermal study (39/44). Likewise, the incidences of testicular interstitial cell adenoma were not treatment related (13/50, 6/33, 8/41, 13/50; Table A1), but the control incidences were lower than historical control incidences from dermal and feed studies [dermal acetone: 75/100 (75.0% ± 18.4%); range, 62%-88%; dermal ethanol: 42/52; feed: 1,169/1,302 (89.8% ± 5.9%); range, 74%-98%] yet higher than controls in a "neat" dermal study (4/50). The biological significance of increased incidences of pituitary gland adenoma and decreased incidences of testicular interstitial cell adenoma in controls was unclear.

All Organs: Mononuclear cell leukemia is a common neoplasm in F344/N rats in 2-year studies. The incidences of mononuclear cell leukemia in 60 and 240 mg/kg males were significantly greater than in the control group by the logistic regression test (0 mg/kg, 12/50; 60 mg/kg, 24/50; 120 mg/kg, 15/50; 240 mg/kg, 25/50; Table A3) but not by the life table test (a more appropriate statistic for this generally fatal neoplasm). The incidence in the male control group was low compared to the mean incidences in NTP historical controls for two dermal studies [dermal acetone: 40/100 (40.0% ± 11.3%); range, 32%-48%; dermal ethanol: 23/52] although higher than that of the control group in a "neat" dermal study (9/50). The marginal increases in mononuclear cell leukemia in rats were considered unrelated to chemical administration because of the lack of statistical significance by the life table analysis and the lack of a clear dose-response relationship.

MICE

17-DAY STUDY

All mice survived to the end of the study (Table 9). Final mean body weights and body weight gains of dosed mice were similar to those of the controls. Dermal applications of 100 μL of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately 20, 60, 190, 540, and 1,600 mg sodium xylenesulfonate/kg body weight to males and 26, 80, 220, 680, and 2,000 mg/kg to females. Clinical findings included crusty white deposits (presumed to be dried chemical) at the site of application in two 133 mg/mL males and in all 400 mg/mL males and females. The absolute and relative liver weights of 15 and 44 mg/mL males and 400 mg/mL males and females were significantly greater than those of the control groups, but the biological significance of these differences was unclear (Table F3). The few skin lesions observed grossly and microscopically in males and females were generally attributed to repeated clipping and were not considered related to chemical administration.

TABLE 9
Survival and Body Weights of Mice in the 17-Day Dermal Study of Sodium Xylenesulfonate

Dose (mg/mL)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	23.7 ± 0.9	25.4 ± 0.8	1.7 ± 0.3	
5	5/5	24.0 ± 0.5	24.8 ± 1.8	0.8 ± 1.6	98
15	5/5	23.2 ± 0.6	26.1 ± 0.7	2.9 ± 0.2	103
44	5/5	22.3 ± 0.3	25.0 ± 0.3	2.6 ± 0.2	98
133	5/5	23.7 ± 0.4	25.6 ± 0.4	1.9 ± 0.3	101
400	5/5	23.3 ± 0.4	26.4 ± 0.3	3.1 ± 0.2	104
Female					
0	5/5	18.4 ± 0.2	20.9 ± 0.4	2.5 ± 0.3	
5	5/5	17.9 ± 0.5	20.2 ± 0.3	2.4 ± 0.4	97
15	5/5	18.2 ± 0.3	20.8 ± 0.5	2.6 ± 0.4	100
44	5/5	18.8 ± 0.5	20.8 ± 0.5	2.0 ± 0.3	99
133	5/5	18.2 ± 0.3	21.0 ± 0.3	2.8 ± 0.4	100
400	5/5	18.1 ± 0.4	21.3 ± 0.2	3.2 ± 0.4	102

[a] Number of animals surviving at 17 days/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the control group were not significant by Dunnett's test.

14-WEEK STUDY

There were no chemical-related deaths (Table 10). The mean body weight gain of 400 mg/mL males was significantly greater than that of the control group. Dermal applications of 100 μL of 5, 15, 44, 133, and 400 mg/mL delivered average daily doses of approximately 17, 40, 140, 440, and 1,300 mg sodium xylenesulfonate/kg body weight to males and 20, 60, 170, 530, and 1,630 mg/kg to females. There were no clinical findings related to sodium xylenesulfonate administration.

Epidermal hyperplasia occurred in 44 mg/mL females, 133 mg/mL males, and 400 mg/mL males and females (Table 11). Hyperplasia of the epidermis in 400 mg/mL males and females was considered related to chemical administration. Epidermal hyperplasia was most pronounced in male mice where it typically developed as a mild multifocal nodular to papillary thickening of the epidermis. The involved epidermis was somewhat disorganized, and cells tended to be elongated (oval or columnar) rather than normal cuboidal epidermal epithelium.

Chronic inflammation of the skin occurred primarily in three control and one dosed animal of each gender. These lesions consisted of mononuclear inflammatory cells in the dermis. Chronic inflammation was frequently accompanied by a minimal epidermal hyperplasia which was clearly a reaction to the inflammation and not diagnosed separately.

TABLE 10
Survival and Body Weights of Mice in the 14-Week Dermal Study of Sodium Xylenesulfonate

Dose (mg/mL)	Survival[a]	Mean Body Weight[b] (g) #			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	25.9 ± 0.5	35.7 ± 0.5	9.8 ± 0.5	
5	10/10	25.5 ± 0.5	34.5 ± 0.6	9.0 ± 0.5	96
15	10/10	25.9 ± 0.4	35.5 ± 0.7	9.6 ± 0.4	100
44	10/10	25.9 ± 0.5	36.6 ± 0.7	10.7 ± 0.4	102
133	10/10	25.2 ± 0.4	35.7 ± 0.7	10.5 ± 0.6	100
400	10/10	25.5 ± 0.6	37.4 ± 0.7	11.9 ± 1.0*	105
Female					
0	10/10	19.0 ± 0.3	30.8 ± 0.7	11.9 ± 0.6	
5	9/10[c]	19.0 ± 0.3	29.6 ± 0.6	10.6 ± 0.6	96
15	9/10[c]	19.1 ± 0.3	31.0 ± 0.8	12.2 ± 0.7	101
44	10/10	19.5 ± 0.2	32.6 ± 0.5	13.2 ± 0.6	106
133	9/10[c]	19.4 ± 0.4	30.4 ± 0.6	11.4 ± 0.6	99
400	10/10	19.1 ± 0.3	30.0 ± 0.5	10.9 ± 0.4	97

* #Significantly different ($P \leq 0.05$) from the control group by Williams' test
[a] Number of animals surviving at 14 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Subsequent calculations are based on animals surviving to the end of the study.
[c] One mouse was removed from study on day 8 due to pregnancy.

TABLE 11
Incidences of Epidermal Hyperplasia in Mice in the 14-Week Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	5 mg/mL	15 mg/mL	44 mg/mL	133 mg/mL	400 mg/mL
Male						
Skin, Site of Application[a]	10	10	10	10	10	10
Epidermal Hyperplasia[b]	0	0	0	0	2 (1.0)[c]	5* (1.8)
Female						
Skin, Site of Application	10	9	9	10	9	10
Epidermal Hyperplasia	0	0	0	1 (1.0)	0	4* (1.0)

* Significantly different ($P \leq 0.05$) from the vehicle control by the Fisher exact test
[a] Number of mice with skin examined microscopically
[b] Number of mice with lesion
[c] Average severity grade of lesion in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Dose Selection Rationale: In the 17-day and 14-week studies, dose concentrations of up to 400 mg/mL were well tolerated. The only limitation to the concentration tration used in dermal dosing in the 2-year study was the difficulty of obtaining a uniform suspension of sodium xylenesulfonate in the vehicle. To obtain uniform suspensions, the highest dose concentration was decreased to 300 mg/mL (used to deliver the 727 mg/kg dose) in the 2-year study. Fixed volumes and concentrations were used in the 17-day and 14-week studies which resulted in decreasing dose concentrations (mg/kg body weight) as the animals grew (Appendix I). Constant dose concentrations were achieved in the 2-year study by adjusting the applied dose volumes to the body weights throughout the study.

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 12 and in the Kaplan-Meier survival curves (Figure 3). Survival of dosed males and females was similar to that of the control groups.

Body Weights and Clinical Findings

Mean body weights of dosed males and females were generally similar to those of the controls throughout the study; however, the mean body weight of 727 mg/kg females was greater than that of the control group from week 85 to week 97 (Tables 13 and 14, Figure 4). With the exception of irritation at the site of application in one 364 mg/kg female, there were no clinical findings related to sodium xylenesulfonate administration.

TABLE 12
Survival of Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Male				
Animals initially in study	50	50	50	50
Moribund	7	3	8	6
Natural deaths	11	10	3	9
Animals surviving to study termination	32	37	39	35
Percent probability of survival at end of study[a]	64	74	78	70
Mean survival (days)[b]	704	704	710	705
Survival analysis[c]	P=0.681N	P=0.440N	P=0.218N	P=0.635N
Female				
Animals initially in study	50	50	50	50
Missing[d]	0	1	0	0
Moribund	12	7	9	6
Natural deaths	7	10	9	8
Animals surviving to study termination	31	32	32	36
Percent probability of survival at end of study	62	66	64	72
Mean survival (days)	690	679	704	703
Survival analysis	P=0.305N	P=0.896N	P=0.967N	P=0.335N

[a] Kaplan-Meier determinations
[b] Mean of all deaths (uncensored, censored, and terminal sacrifice)
[c] The result of the life table trend test (Tarone, 1975) is in the vehicle control column, and the results of the life table pairwise comparisons (Cox, 1972) with the vehicle controls are in the dosed columns. A negative trend or lower mortality in a dose group is indicated by N.
[d] Censored from survival analyses

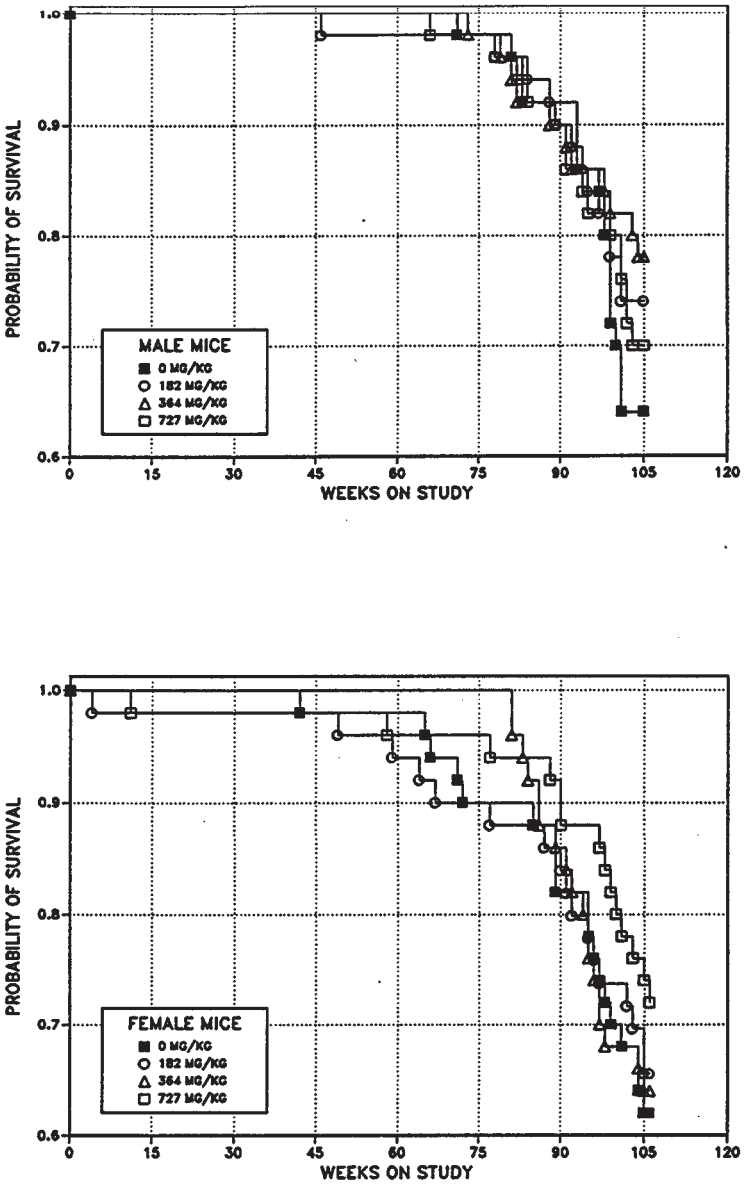


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Administered Sodium Xylenesulfonate Dermally for 2 Years

TABLE 13
Mean Body Weights and Survival of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate

Weeks on Study	Vehicle Control		182 mg/kg			364 mg/kg			727 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.5	50	23.5	100	50	23.8	101	50	23.6	100	50
2	23.7	50	24.3	103	50	24.2	102	50	24.5	103	50
3	25.8	50	26.0	101	50	25.9	100	50	26.4	102	50
4	26.0	50	26.3	101	50	26.5	102	50	26.6	102	50
5	27.0	50	27.0	100	50	27.5	102	50	27.4	102	50
6	28.4	50	28.5	100	50	28.6	101	50	28.7	101	50
7	28.3	50	28.4	100	50	28.6	101	50	28.9	102	50
8	29.0	50	29.3	101	50	29.3	101	50	29.4	101	50
9	30.2	50	30.4	101	50	30.4	101	50	30.6	101	50
10	30.2	50	30.7	102	50	30.3	100	50	31.1	103	50
11	31.2	50	31.9	102	50	31.6	101	50	32.1	103	50
12	32.3	50	32.6	101	50	32.2	100	50	32.5	101	50
13	33.3	50	33.7	101	50	33.2	100	50	33.8	102	50
17	35.7	50	36.1	101	50	35.8	100	50	36.2	101	50
21	37.7	50	38.3	102	50	37.5	100	50	38.6	102	50
25	38.6	50	39.5	102	50	38.9	101	50	40.1	104	50
28	41.3	50	41.8	101	50	41.0	99	50	42.5	103	50
33	41.9	50	42.1	101	50	41.6	99	50	42.3	101	50
37	43.2	50	43.9	102	50	43.1	100	50	43.6	101	50
41	43.4	50	44.1	102	50	43.4	100	50	43.9	101	50
45	44.8	50	44.9	100	50	44.5	99	50	45.3	101	50
49	45.1	50	45.8	102	49	44.6	99	50	46.0	102	50
53	46.1	50	46.0	100	49	45.3	98	50	46.5	101	50
57	45.6	50	46.9	103	49	45.9	101	50	47.1	103	50
61	46.6	50	46.9	101	49	46.5	100	50	46.9	101	50
65	46.5	50	47.1	101	49	46.7	100	50	46.8	101	50
69	47.2	50	47.1	100	49	46.7	99	50	47.6	101	49
73	46.9	49	47.0	100	49	46.4	99	50	47.5	101	49
77	46.8	49	46.9	100	49	46.6	100	49	47.8	102	49
80	45.8	49	46.2	101	48	46.1	101	48	47.1	103	48
85	46.0	46	45.3	99	47	46.1	100	46	46.9	102	46
89	44.7	46	44.3	99	46	45.6	102	45	46.1	103	46
93	42.8	46	42.9	100	44	44.4	104	43	44.3	104	43
97	42.6	43	42.6	100	42	43.8	103	43	44.3	104	41
101	42.5	35	42.0	99	39	43.6	103	41	43.2	102	40
105	41.5	32	40.0	96	37	42.0	101	39	42.2	102	35
Mean for weeks											
1-13	28.4		28.7	101		28.6	101		28.9	102	
14-52	41.3		41.8	101		41.2	100		42.1	102	
53-105	45.1		45.1	100		45.4	101		46.0	102	

TABLE 14
Mean Body Weights and Survival of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate

Weeks on Study	Vehicle Control		182 mg/kg			364 mg/kg			727 mg/kg		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	18.7	50	18.9	101	50	18.8	101	50	18.9	101	50
2	19.6	50	20.4	104	50	20.0	102	50	20.1	103	50
3	22.0	50	22.2	101	50	22.3	101	50	22.0	100	50
4	22.4	50	22.6	101	50	22.5	100	50	22.7	101	50
5	22.9	50	23.5	103	49	23.4	102	50	23.5	103	50
6	24.1	50	24.9	103	49	24.9	103	50	25.2	105	50
7	24.7	50	25.0	101	49	25.1	102	50	25.1	102	50
8	25.3	50	25.6	101	49	25.7	102	50	25.7	102	50
9	26.2	50	26.6	102	49	26.5	101	50	26.5	101	50
10	26.9	50	27.3	102	49	27.1	101	50	27.2	101	50
11	27.0	50	27.5	102	49	27.7	103	50	27.5	102	50
12	27.9	50	28.2	101	49	27.7	99	50	28.0	100	49
13	28.8	50	29.6	103	49	29.2	101	50	29.1	101	49
17	30.6	50	31.3	102	49	30.8	101	50	30.6	100	49
21	33.0	50	33.7	102	49	32.8	99	50	32.9	100	49
25	34.0	50	35.4	104	49	34.2	101	50	34.1	100	49
28	37.3	50	38.2	102	49	37.4	100	50	36.9	99	49
33	38.0	50	38.8	102	49	37.9	100	50	37.4	98	49
37	40.2	50	40.9	102	49	40.0	100	50	39.6	99	49
41	41.0	50	41.6	102	49	40.6	99	50	40.8	100	49
45	42.4	49	43.2	102	49	41.9	99	50	42.3	100	49
49	43.0	49	44.4	103	48	42.7	99	50	42.9	100	49
53	45.0	49	45.6	101	48	44.1	98	50	44.7	99	49
57	45.0	49	46.9	104	48	45.0	100	50	46.2	103	49
61	46.2	49	47.4	103	47	46.1	100	50	47.2	102	48
65	47.6	49	48.4	102	46	46.8	98	50	48.8	103	48
69	49.0	47	50.1	102	45	48.1	98	50	50.1	102	48
73	49.1	45	50.8	104	45	49.1	100	50	51.2	104	48
77	50.1	45	51.6	103	45	49.3	98	50	51.7	103	48
81	50.6	45	52.3	103	44	49.3	97	50	52.7	104	47
85	50.1	44	52.7	105	44	50.3	100	46	53.0	106	47
89	48.8	44	51.0	105	43	49.8	102	44	51.9	106	46
93	47.9	41	48.8	102	39	49.0	102	41	51.3	107	44
97	47.3	38	49.4	104	37	49.0	104	37	50.9	108	44
101	47.2	34	47.5	101	36	48.9	104	34	49.2	104	40
105	45.8	31	44.9	98	33	46.5	102	32	46.6	102	37
Mean for weeks											
1-13	24.3		24.8	102		24.7	102		24.7	102	
14-52	37.7		38.6	102		37.6	100		37.5	99	
53-105	47.8		49.1	103		48.0	100		49.7	104	

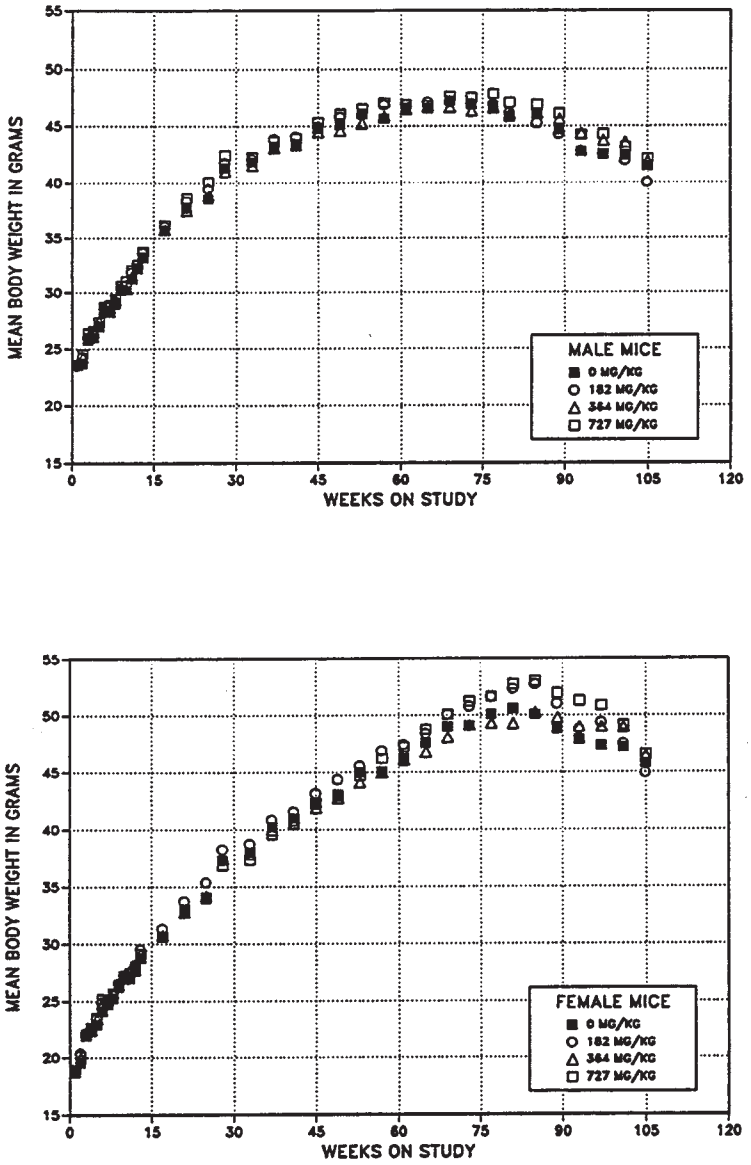


FIGURE 4
Growth Curves for Male and Female Mice Administered Sodium Xylenesulfonate Dermally for 2 Years

Pathology and Statistical Analysis

This section describes the statistically significant and biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the skin and liver. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses and statistical analyses of primary neoplasms that occurred with incidences of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix C for male mice and Appendix D for female mice.

Skin: The incidences and morphologies of the neoplasms that occurred in males and females were typical of spontaneous neoplasms in $B6C3F_1$ mice and were not considered related to treatment (Tables 15, C1, and D1).

Hyperplasia of the epidermis occurred in control and 364 and 727 mg/kg males and in control and dosed females (Tables 15, C5, and D5). These lesions consisted of minimal to mild multifocally extensive thickening of the layers of epidermal epithelium. In males, there was a possible treatment-related effect in the incidences of epidermal hyperplasia as the incidences occurred with a positive ($P \leq 0.05$) trend; however, other nonneoplastic lesions of the skin at the site of application were not considered related to chemical administration. Focal ulceration occurred in one 727 mg/kg male and in one female in each dose group (Tables 15 and D5). Typically, sites of ulceration had superficial accumulations of protein and necrotic cell debris, and the exposed dermis had infiltrates of both neutrophils and mononuclear inflammatory cells. Exudates of cell debris and protein on the surface of the epidermis without evidence of ulceration were diagnosed separately, as was inflammation in the dermis or subcutaneous tissues.

TABLE 15
Incidences of Neoplasms and Nonneoplastic Lesions of the Skin of Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control		182 mg/kg		364 mg/kg		727 mg/kg	
Male								
Skin, Site of Application[a]	50		50		50		50	
Epidermis, Exudate[b]	0		1	(1.0)[c]	1	(1.0)	1	(3.0)
Epidermis, Hyperkeratosis	0		0		1	(2.0)	0	
Epidermis, Hyperplasia	1	(1.0)	0		4	(1.3)	5	(1.4)
Epidermis, Ulcer	0		0		0		1	(3.0)
Subcutaneous Tissue, Hemangioma	0		0		1		0	
Subcutaneous Tissue, Hemangiosarcoma	0		0		1		0	
Subcutaneous Tissue, Histiocytic Sarcoma	0		2		0		0	
Subcutaneous Tissue, Malignant Lymphoma	0		0		1		0	
Female								
Skin, Site of Application	50		49		50		50	
Epidermis, Exudate	1	(2.0)	4	(1.0)	4	(1.5)	1	(4.0)
Epidermis, Hyperplasia	4	(1.3)	1	(2.0)	4	(1.5)	4	(1.5)
Epidermis, Ulcer	0		1	(2.0)	1	(2.0)	1	(3.0)
Inflammation, Chronic	4	(1.0)	1	(2.0)	1	(1.0)	1	(1.0)
Parakeratosis	0		0		1	(1.0)	0	
Subcutaneous Tissue, Fibrosarcoma	0		1		1		0	

[a] Number of mice with skin examined microscopically
[b] Number of mice with lesion
[c] Average severity grade of lesions in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked

Inflammation in the skin of female mice was subclassified according to the inflammatory cells present: suppurative (composed of neutrophils); chronic active (neutrophils and inflammatory cells); and chronic (mononuclear inflammatory cells). Hyperkeratosis occurred in a single 364 mg/kg male and consisted of focally thickened layers of keratin overlying the epidermis (Tables 15 and C5). Parakeratosis in a single 364 mg/kg female was a superficial accumulation of desquamated epidermal cells that retained obvious nuclei (Tables 15 and D5).

Liver: In males and females from control and dosed groups, incidences of hepatocellular adenoma, hepatocellular carcinoma, hepatocellular adenoma or carcinoma (combined), chronic active inflammation (hepatitis), and hyperplasia of bile ductular epithelium (males only) were generally greater than those expected by spontaneous occurrence (Tables 16, C1, C5, D1, and D5). The hepatocellular neoplasm incidences exceeded those in historical controls from 2-year NTP dermal and feed studies (Tables 16, C4, and D4). Chronic active inflammation in the liver consisted of mononuclear cells and sometimes lesser numbers of neutrophils centered around bile ducts but also focally in the parenchyma. Primarily in male mice, this diagnosis also included various degrees of hepatocytomegaly, hepatocyte degeneration, fibrosis and/or regenerative hyperplasia of hepatocytes. Bile duct hyperplasia included oval (bile ductule) cell proliferation as well as increased numbers of bile ducts. Chronic active inflammation and bile duct hyperplasia, typically graded as mild to moderate, were both noted in more than 80% of control and dosed male mice (Table 16). In female mice, reviewing pathologists identified minimal severity chronic active inflammation in approximately half of both control and dosed groups, whereas bile duct hyperplasia, typically minimal, was identified in only two or four animals in each group. Steiner's modification of the Warthin-Starry stain was applied to the livers of 10 male and 10 female mice with lesions of chronic-active inflammation and bile duct hyperplasia. Organisms consistent with *Helicobacter hepaticus* bacteria were identified in the livers of six males, but in none of the females (Appendix L).

TABLE 16
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Male				
Number Examined Microscopically	50	50	50	50
Inflammation, Chronic Active[a]	46 (2.5)[b]	44 (2.8)	41 (2.5)	43 (2.4)
Bile Duct Hyperplasia	43 (2.5)	41 (2.8)	36 (2.6)	37 (2.6)
Hepatocellular Adenoma (includes multiple)	37	32	21**	29
Hepatocellular Carcinoma (includes multiple)	35	31	22**	26
Hepatocellular Adenoma or Carcinoma[c]	46	41	31	45
Hepatoblastoma	0	4	0	2
Female				
Number Examined Microscopically	50	49	50	50
Inflammation, Chronic Active	22 (1.0)	28 (1.1)	24 (1.1)	21 (1.1)
Bile Duct Hyperplasia	4 (1.8)	2 (1.0)	4 (1.0)	2 (1.5)
Hepatocellular Adenoma (includes multiple)	18	17	18	28
Hepatocellular Carcinoma (includes multiple)	10	13	7	10
Hepatocellular Adenoma or Carcinoma[d]	27	23	23	33

** Significantly different ($P \leq 0.01$) from the vehicle control by the logistic regression test
[a] Number of mice with lesion
[b] Average severity grade of lesion in affected animals: 1 = minimal; 2 = mild; 3 = moderate; 4 = marked
[c] Historical incidence for 2-year NTP dermal (acetone or ethanol vehicle) or feed studies with undosed control groups (mean ± standard deviation): acetone: 63/150 (42.0% ± 22.3%); range, 18%-62%; ethanol: 29/50 (58.0%); feed: 596/1,465 (40.7% ± 14.5%); range, 10%-68%
[d] Historical incidence: acetone: 40/150 (26.7% ± 17.0%); range, 14%-46%; ethanol: 27/52 (51.9%); feed: 313/1,464 (21.4% ± 13.0%); range, 3%-56%

GENETIC TOXICOLOGY

Sodium xylenesulfonate (100 to 10,000 μg/plate) was not mutagenic in *Salmonella typhimurium* strain TA98, TA100, TA1535, or TA1537, with or without induced S9 (Table E1). Results obtained with sodium xylenesulfonate in a mammalian gene mutation assay with cultured L5178Y mouse lymphoma cells in the presence of S9 (Table E2) were concluded to be equivocal because the significant increase in mutant colonies noted in the first trial with S9 was not convincingly demonstrated in the second trial. Without S9, no significant increase in mutations was noted. Sodium xylenesulfonate induced dose-related increases in sister chromatid exchanges in cultured Chinese hamster ovary cells at concentrations that produced cell cycle delay (2,513 to 5,000 μg/mL) in the absence of S9; with S9, no increases in sister chromatid exchanges were noted (Table E3). Finally, no induction of chromosomal aberrations was observed in cultured Chinese hamster ovary cells treated with sodium xylenesulfonate (2,513 to 5,000 μg/mL) with or without S9 (Table E4).

DISCUSSION AND CONCLUSIONS

Sodium xylenesulfonate is used as a hydrotrope in liquid household detergents and in shampoos; thus, dermal exposure to human skin is widespread. Consumers may be exposed to solutions containing up to 10% (100 mg/mL) sodium xylenesulfonate (Phil Tham, Reckitt and Colman, Inc., personal communication, 1995). In 1992, United States production of sodium xylenesulfonate was approximately 30,000 tons (USITC, 1994). The present studies are the first to address the possible dermal toxicity and carcinogenicity of sodium xylenesulfonate.

Technical grade sodium xylenesulfonate contains approximately 35% sodium ethylbenzenesulfonate and 11.5% *ortho*-, 38% *meta*-, and 15.5% *para*-sodium xylenesulfonate (Mausner and Sosis, 1962). Although sodium xylenesulfonate is sometimes classified with surface-active agents, its alkyl chain is too short to confer surface active properties (*Kirk-Othmer*, 1994). As a hydrotrope, sodium xylenesulfonate increases the solvent capacity of water toward other molecules, unlike surfactants that solubilize by enclosing solutes in micelles (Hunting, 1983). Because of the polar sulfonate group, dermal absorption of sodium xylenesulfonate is probably poor (Grandjean *et al.,* 1988). Because ethanol has a higher permeability constant for the skin than water (Scheuplein and Blank, 1971), the use of a 50% ethanol vehicle in the 14-week and 2-year studies may have enhanced absorption over that in the 17-day studies, in which the vehicle was water. As in all dermal studies, there was potential for some ingestion as animals groomed themselves.

Modifications were made to the dosing regimens between the different duration studies. Water was used as a vehicle for sodium xylenesulfonate for the 17-day studies, but this vehicle was changed to 50% ethanol for the longer duration studies because the suspensions in water were noted to bead up on the skin and were easily shaken off by the animals. Dose concentrations of up to 400 mg/mL technical grade sodium xylenesulfonate in 50% alcohol were applied in the 14-week studies, but because the solubility of sodium xylenesulfonate is less in ethanol than in water, the 400 mg/mL concentration was found to require constant agitation during dosing in order to avoid settling of the chemical. Therefore, to obtain more uniform suspensions, the highest concentration used in the 2-year studies was 300 mg/mL. Constant volumes were applied during the 17-day and 14-week studies, and because the animals gained weight during the studies, the dose concentrations (mg/kg body weight) decreased as the animals grew (Appendix I). To maintain constant dose concentrations throughout the 2-year studies, dose volumes were adjusted according to body weight as the animals aged. These modifications resulted in less chemical treatment in the 2-year studies than in the shorter duration studies. The actual amount of chemical treatment in the shorter duration studies, however, was probably less than the calculated amount because of the problems of rapid removal in the 17-day studies and of non-uniform suspensions in the 14-week studies.

Use of 50% ethanol as a vehicle rather than water increased the probability of skin penetration (Grandjean, 1988). However, the low dermal toxicity of sodium xylenesulfonate in 50% ethanol in the present studies does not rule out dermal toxicity of more complex mixtures which might further affect penetration or reactivity of the skin, nor do the present studies address the toxicity of complex mixtures containing sodium xylenesulfonate by other routes of exposure, such as occupational inhalation of aerosolized compound.

Dermal application of 400 mg/mL sodium xylenesulfonate did not significantly affect survival or mean body weights of rats or mice dosed for 17 days or 14 weeks. Similarly, dermal applications of 300 mg/mL sodium xylenesulfonate did not significantly affect the survival or mean body weights of rats and mice dosed for 2 years. Survival of male rats to termination of the 2-year study was 18% in the control and 120 mg/kg groups and 36% and 26% in the 60 and 240 mg/kg groups. Survival was low in comparison to studies in the NTP database in which

rats were not housed individually, but survival was consistent with other studies utilizing individual housing (Rao, 1995). It has been postulated that the social interaction afforded by multiple housing enhances the well-being of rats (Rao, 1995), whereas individual housing is detrimental to survival, particularly of males.

In rats in the 17-day and 14-week studies, the only treatment-related clinical finding was brownish discoloration at the site of application. The sebaceous gland hyperplasia noted in both control and dosed rats in the 2-year study suggests that fur-clipping and vehicle application may stimulate sebaceous glands and the production of sebum in this species. The brownish discoloration of the skin may have resulted from the combinations of sebum and sodium xylenesulfonate.

There was some indication that the incidences, but not the severities, of epidermal hyperplasia were related to chemical administration in male and female rats and mice in the 14-week studies and in female rats and male mice in the 2-year studies. In the 14-week studies, epidermal hyperplasia occurred in control and dosed groups and was less apparent in rats than in mice. In the 2-year study, rats with epidermal hyperplasia had slightly more extensive and thicker lesions than in the 14-week study, but the lesions were typically minimal in severity.

Some male mice in the 14-week study had papillary thickening of the epidermis. Based on results of the 2-year study, there was no evidence that these lesions would have progressed to skin neoplasms in time. Further, there was less focally exuberant epidermal hyperplasia in male mice in the 2-year study than in male mice in the 14-week study. Because epidermal hyperplasia occurred in control groups as well as dosed groups in the 14-week study, these lesions may have been due to irritation from weekly fur clipping and vehicle application. Comparatively lower incidences of hyperplasia in the 2-year study may reflect physiologic adaptation to treatment, resolution of lesions during the 10 days between the last dose and necropsy, or the lower dosing concentration used in the 2-year study.

Ten percent or less of the rats and mice in the 2-year studies developed epidermal hyperplasia. These lesions were typically minimal to mild in severity. In male and female rats and in male mice, there was a suggestion that sodium xylenesulfonate exacerbated epidermal hyperplasia; however, the incidences in dosed groups did not differ significantly from each other or from those in the control groups. In female mice, the incidences and severities of epidermal hyperplasia in dosed and control groups of mice were similar. In addition to epidermal hyperplasia, pinpoint ulcers of the epidermis occurred in up to two animals per group in dosed female rats and dosed male and female mice and in one control female rat. The low incidences and severities of these lesions lead to the conclusion that sodium xylenesulfonate is not dermally toxic. Most lesions were also observed in control animals receiving only the vehicle, which suggests that the occurrence of these lesions was related to weekly fur clipping and vehicle application rather than to the application of sodium xylenesulfonate. In both rats and mice, neoplasms that occurred in the skin at the site of application in the 2-year studies were typical in morphology and incidence to spontaneously occurring lesions in F344/N rats and B6C3F$_1$ mice. None were considered related to chemical administration.

The only neoplasm showing a possible chemical-related effect in the 2-year study was mononuclear cell leukemia, of which the incidences were marginally increased in the 60 and 240 mg/kg male rat groups. The lack of statistical significance by the life table analysis (an appropriate test for this generally fatal neoplasm) and the lack of a clear dose-response relationship suggest that these increases were unrelated to chemical administration.

Incidences of hepatocellular carcinoma and hepatocellular adenoma and carcinoma (combined) in all groups of male mice exceeded the NTP historical control ranges. Female mice in the control and 727 mg/kg groups had incidences of hepatocellular carcinoma that matched the highest control incidence, and the combined incidence of hepatocellular adenoma and carcinoma in 727 mg/kg females exceeded the historical control range. Chronic active inflammation, bile duct hyperplasia, and organisms consistent with the recently discovered bacteria *Helicobacter hepaticus* were observed in the livers of male mice in these studies.

Based on retrospective analyses, *H. hepaticus* was determined to have infected mice in 12 recent NTP 2-year studies (Appendix L). Of the 12 studies, mice (primarily males) from nine studies (including this study of sodium xylenesulfonate) had *H. hepaticus*-associated hepatitis. Qualitatively, the hepatitis and silver-staining organisms within the liver were similar among the nine studies. With assays based on polymerase chain reaction, *H. hepaticus* was identified in studies from which adequately preserved (frozen) liver tissue was available. In general, efforts to identify *H. hepaticus* from tissue fixed in formalin for over a week were not successful (Malarkey *et al.*, 1997), which was the case for this study of sodium xylenesulfonate. However, because of the presence of the typical liver lesions and silver-positive helical organisms, mice from this study were presumed to be infected with *H. hepaticus*.

Increases in the incidence of hepatocellular neoplasms in male mice have been shown to be associated with *H. hepaticus* infection when hepatitis is also present (Ward *et al.*, 1994; Fox *et al.*, 1996; Appendix L). Additionally, within NTP studies with *H. hepaticus*-associated hepatitis, increased incidences of hemangiosarcoma were seen in the livers of male mice (Appendix L.)

Because of these associations, interpretation of a treatment-related increase, but not a lack of response, in the incidences of these two neoplasm types in the liver of male mice is considered confounded. Chemical-related responses (or lack thereof) at other sites in male mice and in female mice are not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis (Appendix L). In the present studies of sodium xylenesulfonate, the incidences of hepatocellular neoplasms were not increased with dose; thus it is concluded that the presence of *H. hepaticus* did not obscure any potential chemical-related neoplasia.

CONCLUSIONS

Under the conditions of these 2-year dermal studies, there was *no evidence of carcinogenic activity** of sodium xylenesulfonate in male or female F344/N rats administered 60, 120, or 240 mg/kg or in male or female $B6C3F_1$ mice administered 182, 364, or 727 mg/kg.

Increased incidences of epidermal hyperplasia in female rats and male mice may have been related to exposure to sodium xylenesulfonate.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

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APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR DERMAL STUDY OF SODIUM XYLENESULFONATE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	28	25	22	30
Natural deaths	15	8	19	10
Survivors				
Terminal sacrifice	7	17	9	10
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(33)	(41)	(50)
Intestine large, cecum	(50)	(33)	(41)	(50)
Intestine small, duodenum	(50)	(33)	(41)	(50)
Carcinoma, metastatic, kidney			1 (2%)	
Leiomyosarcoma, metastatic, stomach, forestomach			1 (2%)	
Sarcoma, metastatic, mesentery			1 (2%)	
Intestine small, jejunum	(50)	(33)	(41)	(50)
Carcinoma	1 (2%)			1 (2%)
Leiomyosarcoma		1 (3%)		
Leiomyosarcoma, metastatic, stomach, forestomach			1 (2%)	
Intestine small, ileum	(50)	(33)	(41)	(50)
Liver	(50)	(45)	(47)	(50)
Carcinoma, metastatic, kidney		1 (2%)		
Hepatocellular carcinoma		1 (2%)		
Histiocytic sarcoma			1 (2%)	1 (2%)
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (2%)		
Leiomyosarcoma, metastatic, stomach, forestomach			1 (2%)	
Mesentery	(8)	(7)	(9)	(8)
Carcinoma, metastatic, kidney		1 (14%)	1 (11%)	
Histiocytic sarcoma				1 (13%)
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (14%)		
Leiomyosarcoma, metastatic, stomach, forestomach			1 (11%)	
Sarcoma			1 (11%)	
Oral mucosa	(2)	(1)	(3)	(6)
Gingival, squamous cell carcinoma	1 (50%)			1 (17%)
Pharyngeal, squamous cell carcinoma				1 (17%)
Pancreas	(50)	(33)	(41)	(50)
Carcinoma, metastatic, kidney		1 (3%)	1 (2%)	
Histiocytic sarcoma			1 (2%)	1 (2%)
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (3%)		
Leiomyosarcoma, metastatic, stomach, forestomach			1 (2%)	
Mixed tumor benign			1 (2%)	

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Alimentary System (continued)				
Stomach, forestomach	(50)	(33)	(41)	(50)
Leiomyosarcoma			1 (2%)	
Stomach, glandular	(50)	(33)	(41)	(50)
Leiomyosarcoma			1 (2%)	
Sarcoma, metastatic, mesentery			1 (2%)	
Cardiovascular System				
Heart	(50)	(33)	(41)	(50)
Endocrine System				
Adrenal cortex	(50)	(33)	(41)	(50)
Adenoma	1 (2%)			
Histiocytic sarcoma				1 (2%)
Leiomyosarcoma, metastatic, stomach, forestomach			1 (2%)	
Adrenal medulla	(50)	(33)	(41)	(50)
Pheochromocytoma malignant				1 (2%)
Pheochromocytoma benign	8 (16%)	5 (15%)	3 (7%)	9 (18%)
Islets, pancreatic	(50)	(33)	(41)	(50)
Adenoma	5 (10%)			3 (6%)
Carcinoma		1 (3%)		1 (2%)
Carcinoma, metastatic, kidney		1 (3%)	1 (2%)	
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (3%)		
Pituitary gland	(50)	(33)	(41)	(50)
Adenoma, multiple	1 (2%)			
Pars distalis, adenoma	34 (68%)	26 (79%)	30 (73%)	31 (62%)
Pars distalis, adenoma, multiple	9 (18%)	1 (3%)	4 (10%)	5 (10%)
Pars distalis, carcinoma	1 (2%)			
Pars distalis, craniopharyngioma				1 (2%)
Thyroid gland	(50)	(33)	(41)	(50)
Bilateral, C-cell, adenoma	1 (2%)			1 (2%)
Bilateral, C-cell, carcinoma				1 (2%)
C-cell, adenoma	8 (16%)	3 (9%)	1 (2%)	5 (10%)
Follicular cell, carcinoma	1 (2%)		1 (2%)	1 (2%)
General Body System				
Peritoneum	(3)	(1)		(2)
Genital System				
Epididymis	(50)	(33)	(41)	(50)
Preputial gland	(50)	(33)	(40)	(50)
Adenoma	1 (2%)		1 (3%)	
Carcinoma			1 (3%)	
Prostate	(50)	(33)	(41)	(50)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Genital System (continued)				
Seminal vesicle	(50)	(33)	(41)	(50)
Carcinoma, metastatic, kidney		1 (3%)	1 (2%)	
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (3%)		
Leiomyosarcoma, metastatic, stomach, forestomach			1 (2%)	
Testes	(50)	(33)	(41)	(50)
Bilateral, interstitial cell, adenoma	11 (22%)	2 (6%)	5 (12%)	17 (34%)
Interstitial cell, adenoma	13 (26%)	6 (18%)	8 (20%)	13 (26%)
Hematopoietic System				
Bone marrow	(50)	(32)	(41)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Lymph node	(41)	(25)	(31)	(41)
Mediastinal, carcinoma, metastatic, kidney		1 (4%)	1 (3%)	
Mediastinal, histiocytic sarcoma			1 (3%)	1 (2%)
Renal, carcinoma, metastatic, kidney			1 (3%)	
Lymph node, mandibular	(50)	(33)	(40)	(49)
Histiocytic sarcoma			1 (3%)	
Lymph node, mesenteric	(50)	(33)	(41)	(50)
Carcinoma, metastatic, kidney		1 (3%)	1 (2%)	
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (3%)		
Spleen	(50)	(46)	(47)	(50)
Fibroma		1 (2%)		
Histiocytic sarcoma			1 (2%)	1 (2%)
Leiomyosarcoma, metastatic, stomach, forestomach			1 (2%)	
Thymus	(46)	(31)	(41)	(50)
Thymoma benign				1 (2%)
Integumentary System				
Mammary gland	(50)	(32)	(40)	(50)
Carcinoma		1 (3%)		
Fibroadenoma	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma				1 (2%)
Keratoacanthoma		1 (2%)	1 (2%)	
Squamous cell papilloma			1 (2%)	1 (2%)
Sebaceous gland, skin, site of application, carcinoma	1 (2%)			
Skin, site of application, basal cell adenoma		1 (2%)	1 (2%)	
Subcutaneous tissue, fibroma		1 (2%)	1 (2%)	3 (6%)
Subcutaneous tissue, histiocytic sarcoma				1 (2%)
Subcutaneous tissue, schwannoma malignant			1 (2%)	
Subcutaneous tissue, pinna, melanoma malignant	1 (2%)			
Subcutaneous tissue, skin, site of application, fibroma, multiple	1 (2%)			
Subcutaneous tissue, skin, site of application, fibrous histiocytoma		1 (2%)		

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Musculoskeletal System				
Bone	(50)	(32)	(41)	(50)
Osteosarcoma			1 (2%)	
Rib, osteosarcoma		1 (3%)		
Skeletal muscle		(3)	(2)	
Carcinoma, metastatic, kidney		1 (33%)	1 (50%)	
Histiocytic sarcoma			1 (50%)	
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (33%)		
Osteosarcoma, metastatic, bone		1 (33%)		
Nervous System				
Brain	(50)	(33)	(41)	(50)
Astrocytoma malignant	1 (2%)	1 (3%)		
Carcinoma, metastatic, pituitary gland	1 (2%)			
Oligodendroglioma malignant			1 (2%)	
Respiratory System				
Lung	(50)	(33)	(41)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			
Alveolar/bronchiolar carcinoma	2 (4%)			
Carcinoma, metastatic, kidney		1 (3%)	1 (2%)	
Carcinoma, metastatic, skin	1 (2%)			
Histiocytic sarcoma			1 (2%)	1 (2%)
Leiomyosarcoma, metastatic, intestine small, jejunum		1 (3%)		
Osteosarcoma, metastatic, bone			1 (2%)	
Mediastinum, osteosarcoma, metastatic, bone		1 (3%)		
Special Senses System				
Harderian gland	(1)	(1)		(1)
Squamous cell carcinoma, metastatic, oral mucosa				1 (100%)
Zymbal's gland			(2)	(2)
Adenoma			1 (50%)	
Carcinoma			1 (50%)	2 (100%)
Urinary System				
Kidney	(50)	(33)	(41)	(50)
Adenoma, tubular	1 (2%)			
Carcinoma, metastatic, kidney		1 (3%)		
Sarcoma		1 (3%)		
Renal tubule, adenoma	1 (2%)			1 (2%)
Renal tubule, carcinoma		1 (3%)	1 (2%)	
Urinary bladder	(50)	(33)	(41)	(50)
Transitional epithelium, carcinoma			1 (2%)	
Transitional epithelium, papilloma	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	1 (2%)
Leukemia mononuclear	12 (24%)	24 (48%)	15 (30%)	25 (50%)
Mesothelioma malignant	1 (2%)			
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	45	46	49
Total primary neoplasms	120	80	85	127
Total animals with benign neoplasms	49	29	39	49
Total benign neoplasms	98	47	58	92
Total animals with malignant neoplasms	18	28	25	30
Total malignant neoplasms	22	33	27	35
Total animals with metastatic neoplasms	7	4	4	3
Total metastatic neoplasms	42	33	21	22
Total animals with malignant neoplasms-uncertain primary site	5	1		2

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: Vehicle Control

Number of Days on Study	4 4 1	4 4 7	4 9 2	4 9 9	5 2 7	5 3 4	5 4 6	5 4 7	5 5 4	5 5 7	5 6 0	5 6 5	5 6 7	5 8 2	5 8 3	5 9 0	5 9 5	6 1 6	6 1 6	6 1 7	6 1 8	6 3 6	6 3 9	6 4 5	6 4 8
Carcass ID Number	0 0 8	0 0 5	0 1 0	0 3 4	0 3 8	0 4 4	0 2 9	0 1 3	0 0 7	0 4 9	0 3 1	0 0 2	0 0 6	0 4 0	0 0 1	0 3 9	0 2 4	0 1 6	0 3 5	0 3 7	0 3 6	0 1 5	0 4 3	0 2 0	0 2 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site												X													X
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site												X													
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site												X													X
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma					X																				
Mesothelioma malignant, metastatic, uncertain primary site																									X
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site												X													X
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery											+	+						+							+
Mesothelioma malignant, metastatic, uncertain primary site												X													X
Oral mucosa							+																		
Gingival, squamous cell carcinoma							X																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site												X													X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site												X													X
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site												X													X
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X																
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X	X																					X
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: Vehicle Control (continued)

Number of Days on Study	650	652	658	672	681	682	687	687	701	702	707	708	712	713	715	724	728	728	735	735	735	735	735	735	735	
Carcass ID Number	027	009	004	033	011	017	046	048	018	014	022	030	026	047	023	032	025	042	003	012	019	028	041	045	050	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site																										2
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site																										2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Mesothelioma malignant, metastatic, uncertain primary site										X																2
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery			+				+			+	+															8
Mesothelioma malignant, metastatic, uncertain primary site										X																3
Oral mucosa													+													2
Gingival, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site										X																3
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site																										2
Tooth																+										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X			X				X			X			X				X		X						8
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X								X											5
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46

TABLE A2 #
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	4 4 1	4 4 7	4 9 2	4 9 9	5 2 7	5 3 4	5 4 6	5 4 7	5 5 4	5 5 7	5 6 0	5 6 5	5 6 7	5 8 2	5 8 3	5 9 0	5 9 5	6 1 6	6 1 6	6 1 7	6 1 8	6 3 6	6 3 9	6 4 5	6 4 8
Carcass ID Number	0 0 8	0 0 5	0 1 0	0 3 4	0 3 8	0 4 4	0 2 9	0 1 3	0 0 7	0 4 9	0 3 1	0 0 2	0 0 6	0 4 0	0 0 1	0 3 9	0 2 4	0 1 6	0 3 5	0 3 7	0 3 6	0 1 5	0 4 3	0 2 0	0 2 1
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, multiple		X																							
Pars distalis, adenoma	X		X	X	X	X				X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Pars distalis, adenoma, multiple									X																
Pars distalis, carcinoma							X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma								X						X											
Follicular cell, carcinoma																									
General Body System																									
Peritoneum												+						+							+
Mesothelioma malignant, metastatic, uncertain primary site												X						X							X
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site												X						X							X
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site																									X
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site												X													X
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site												X						X							X
Bilateral, interstitial cell, adenoma								X														X			X
Interstitial cell, adenoma						X						X	X						X					X	
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+		+		+	+	+	+	+	+	+	+	+	+	+	+	+		+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: Vehicle Control (continued)

	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	
Number of Days on Study	5	5	5	7	8	8	8	8	0	0	0	0	1	1	1	2	2	2	3	3	3	3	3	3	3	
	0	2	8	2	1	2	7	7	1	2	7	8	2	3	5	4	8	8	5	5	5	5	5	5	5	
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	Total
Carcass ID Number	2	0	0	3	1	1	4	4	1	1	2	3	2	4	2	3	2	4	0	1	1	2	4	4	5	Tissues/
	7	9	4	3	1	7	6	8	8	4	2	0	6	7	3	2	5	2	3	2	9	8	1	5	0	Tumors
Endocrine System (continued)																										
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, multiple																										1
Pars distalis, adenoma		X	X		X	X			X	X		X	X		X	X	X	X					X	X		34
Pars distalis, adenoma, multiple	X			X			X	X											X	X	X				X	9
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma										X																1
C-cell, adenoma						X	X									X		X					X	X		8
Follicular cell, carcinoma												X														1
General Body System																										
Peritoneum																										3
Mesothelioma malignant, metastatic, uncertain primary site																										3
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site										X	X															5
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X															1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site											X															2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site																										2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site										X	X															5
Bilateral, interstitial cell, adenoma								X		X	X			X					X	X		X		X		11
Interstitial cell, adenoma				X					X			X			X	X	X				X				X	13
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+		+	+	+		+	+	+	+	+	+	+			+		+	+		+	+	+	41
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	M	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	46

TABLE A2 #
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	4 4 1	4 4 7	4 9 2	4 9 9	5 2 7	5 3 4	5 4 6	5 4 7	5 5 4	5 5 7	5 6 0	5 6 5	5 6 7	5 8 2	5 8 3	5 9 0	5 9 5	6 1 6	6 1 6	6 1 7	6 1 8	6 3 6	6 3 9	6 4 5	6 4 8
Carcass ID Number	0 0 8	0 0 5	0 1 0	0 3 4	0 3 8	0 4 4	0 2 9	0 1 3	0 0 7	0 4 9	0 3 1	0 0 2	0 0 6	0 4 0	0 0 1	0 3 9	0 2 4	0 1 6	0 3 5	0 3 7	0 3 6	0 1 5	0 4 3	0 2 0	0 2 1
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																								X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, skin, site of application, carcinoma													X												
Subcutaneous tissue, pinna, melanoma malignant																									
Subcutaneous tissue, skin, site of application, fibroma, multiple																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Carcinoma, metastatic, pituitary gland							X																		
Peripheral nerve																						+			
Spinal cord																						+			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					
Alveolar/bronchiolar carcinoma																						X			
Carcinoma, metastatic, skin													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye							+			+															
Harderian gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, tubular																									
Mesothelioma malignant, metastatic, uncertain primary site												X													
Renal tubule, adenoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site												X													X
Transitional epithelium, papilloma																						X			
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X			X							X	X					
Mesothelioma malignant									X																

TABLE A2 #
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	650	652	658	672	681	682	687	687	701	702	707	708	712	711	713	715	724	728	728	735	735	735	735	735	735	735	
Carcass ID Number	00227	00209	00044	00333	00111	00117	00446	00448	00118	00114	00222	00330	00226	00447	00323	00325	00425	00428	00423	00103	00121	00199	00288	00411	00455	00550	Total Tissues/ Tumors
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sebaceous gland, skin, site of application, carcinoma																											1
Subcutaneous tissue, pinna, melanoma malignant																	X										1
Subcutaneous tissue, skin, site of application, fibroma, multiple				X																							1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										X	1
Carcinoma, metastatic, pituitary gland																											1
Peripheral nerve																											1
Spinal cord																											1
Respiratory System																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																											1
Alveolar/bronchiolar carcinoma													X														2
Carcinoma, metastatic, skin																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye		+																									3
Harderian gland																									+		1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, tubular			X																								1
Mesothelioma malignant, metastatic, uncertain primary site																											1
Renal tubule, adenoma																									X		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site										X																	3
Transitional epithelium, papilloma																											1
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X			X	X			X	X	X	X													X	12
Mesothelioma malignant																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg

Number of Days on Study	1 9 6	3 4 9	3 6 2	3 9 3	4 4 1	4 9 1	5 1 6	5 2 7	5 4 0	5 4 1	5 4 7	5 6 5	6 0 1	6 0 3	6 0 3	6 0 9	6 0 9	6 1 9	6 2 3	6 3 1	6 3 1	6 4 3	6 4 5	6 4 5	6 5 6
Carcass ID Number	0 6 9	0 9 9	0 8 6	0 9 6	0 7 2	0 5 6	0 7 0	0 8 7	0 9 1	0 5 7	0 5 4	0 6 6	0 9 3	0 8 4	0 9 8	0 5 1	0 8 8	0 6 1	0 8 5	0 5 5	0 7 8	0 6 5	0 5 3	0 8 3	0 7 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site																									
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma										X															
Mesothelioma malignant, metastatic, uncertain primary site																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																									X
Hepatocellular carcinoma																									
Leiomyosarcoma, metastatic, intestine small, jejunum										X															
Mesentery								+		+							+			+				+
Carcinoma, metastatic, kidney																									X
Leiomyosarcoma, metastatic, intestine small, jejunum										X															
Mesothelioma malignant, metastatic, uncertain primary site																									
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																									X
Leiomyosarcoma, metastatic, intestine small, jejunum										X															
Mesothelioma malignant, metastatic, uncertain primary site																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site																									
Tongue																							+		
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg
(continued)

Number of Days on Study	658	674	702	700	702	710	726	732	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	00881	00897	00958	00990	01000	00880	00860	00871	00552	00559	00562	00663	00664	00667	00668	00673	00774	00776	00779	00882	00892	00992	00994	00995		Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+																			33
Intestine large, colon	+	+	+	+	+	+	+	+																			33
Intestine large, rectum	+	+	+	+	+	+	+	+																			33
Intestine large, cecum	+	+	+	+	+	+	+	+																			33
Intestine small, duodenum	+	+	+	+	+	+	+	+																			33
Mesothelioma malignant, metastatic, uncertain primary site		X																									1
Intestine small, jejunum	+	+	+	+	+	+	+	+																			33
Leiomyosarcoma																											1
Mesothelioma malignant, metastatic, uncertain primary site		X																									1
Intestine small, ileum	+	+	+	+	+	+	+	+																			33
Mesothelioma malignant, metastatic, uncertain primary site		X																									1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+	+			+	+	+	+	+		45
Carcinoma, metastatic, kidney																											1
Hepatocellular carcinoma			X																								1
Leiomyosarcoma, metastatic, intestine small, jejunum																											1
Mesentery		+					+																				7
Carcinoma, metastatic, kidney																											1
Leiomyosarcoma, metastatic, intestine small, jejunum																											1
Mesothelioma malignant, metastatic, uncertain primary site		X																									1
Oral mucosa		+																									1
Pancreas	+	+	+	+	+	+	+	+																			33
Carcinoma, metastatic, kidney																											1
Leiomyosarcoma, metastatic, intestine small, jejunum																											1
Mesothelioma malignant, metastatic, uncertain primary site		X																									1
Salivary glands	+	+	+	+	+	+	+	+																			33
Stomach, forestomach	+	+	+	+	+	+	+	+																			33
Mesothelioma malignant, metastatic, uncertain primary site		X																									1
Stomach, glandular	+	+	+	+	+	+	+	+																			33
Mesothelioma malignant, metastatic, uncertain primary site		X																									1
Tongue																											1
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+																			33
Heart	+	+	+	+	+	+	+	+																			33

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg
(continued)

Number of Days on Study	1 9 6	3 4 9	3 6 2	3 9 3	4 4 1	4 9 1	5 1 6	5 2 7	5 4 0	5 4 1	5 4 7	5 6 5	6 0 1	6 0 3	6 0 3	6 0 9	6 0 9	6 1 9	6 2 3	6 3 1	6 3 1	6 4 3	6 4 5	6 4 5	6 5 6
Carcass ID Number	0 6 9	0 9 9	0 8 6	0 9 6	0 7 2	0 5 6	0 7 0	0 8 7	0 9 1	0 5 7	0 5 4	0 6 6	0 9 3	0 8 4	0 9 8	0 5 1	0 8 8	0 6 1	0 8 5	0 5 5	0 7 8	0 6 5	0 5 3	0 8 3	0 7 5
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Carcinoma, metastatic, kidney																									X
Leiomyosarcoma, metastatic, intestine small, jejunum										X															
Parathyroid gland	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X	X	X		X		X	X	X	X		X	X	X	X	X	X	X		X	X	X	
Pars distalis, adenoma, multiple																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X										X		X			
General Body System																									
Peritoneum																									
Mesothelioma malignant, metastatic, uncertain primary site																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																									X
Leiomyosarcoma, metastatic, intestine small, jejunum										X															
Mesothelioma malignant, metastatic, uncertain primary site																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site																									
Bilateral, interstitial cell, adenoma																						X			
Interstitial cell, adenoma										X							X						X	X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node	+		+		+			+	+	+	+	+		+	+	+	+	+	+	+	+		+		+
Mediastinal, carcinoma, metastatic, kidney																									X
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg
(continued)

Number of Days on Study	658	674	702	700	702	710	726	732	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	0081	0097	0058	0090	1000	0080	0660	0771	0552	0559	0662	0663	0664	0667	0668	0673	0774	0776	0777	0779	0782	0889	0992	0994	0995	Total Tissues/ Tumors
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+																		33
Adrenal medulla	+	+	+	+	+	+	+	+																		33
Pheochromocytoma benign		X	X			X		X																		5
Islets, pancreatic	+	+	+	+	+	+	+	+																		33
Carcinoma							X																			1
Carcinoma, metastatic, kidney																										1
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Parathyroid gland	+	+	+	+	M	+	+	+																		29
Pituitary gland	+	+	+	+	+	+	+	+																		33
Pars distalis, adenoma	X	X	X		X	X	X	X																		26
Pars distalis, adenoma, multiple				X																						1
Thyroid gland	+	+	+	+	+	+	+	+																		33
C-cell, adenoma																										3
General Body System																											
Peritoneum		+																								1
Mesothelioma malignant, metastatic, uncertain primary site		X																								1
Genital System																											
Epididymis	+	+	+	+	+	+	+	+																		33
Mesothelioma malignant, metastatic, uncertain primary site		X																								1
Preputial gland	+	+	+	+	+	+	+	+																		33
Prostate	+	+	+	+	+	+	+	+																		33
Mesothelioma malignant, metastatic, uncertain primary site		X																								1
Seminal vesicle	+	+	+	+	+	+	+	+																		33
Carcinoma, metastatic, kidney																										1
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Mesothelioma malignant, metastatic, uncertain primary site		X																								1
Testes	+	+	+	+	+	+	+	+																		33
Mesothelioma malignant, metastatic, uncertain primary site		X																								1
Bilateral, interstitial cell, adenoma							X																			2
Interstitial cell, adenoma						X		X																		6
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+																		32
Lymph node	+	+	+	+	+	+	+																			25
Mediastinal, carcinoma, metastatic, kidney																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+																		33

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg
(continued)

Number of Days on Study	1 3 3 3 4 4 5 5 5 5 5 6 6 6 6 6 6 6 6 6 6 6 6 6 6 6 9 4 6 9 4 9 1 2 4 4 4 6 0 0 0 0 0 1 2 3 3 4 4 4 5 6 9 2 3 1 1 6 7 0 1 7 5 1 3 3 9 9 9 3 1 1 3 5 5 6
Carcass ID Number	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 9 8 9 7 5 7 8 9 5 5 6 9 8 9 5 8 6 8 5 5 7 6 5 8 7 9 9 6 6 2 6 0 7 1 7 4 6 3 4 8 1 8 1 5 5 8 5 3 3 5
Hematopoietic System (continued)	
Lymph node, mesenteric	+ +
Carcinoma, metastatic, kidney	X
Leiomyosarcoma, metastatic, intestine small, jejunum	X
Spleen	+ +
Fibroma	
Thymus	+ + + + + M + + + + + + M + + + + + + + + + + + +
Integumentary System	
Mammary gland	+ + + + + + + + + M + + + + + + + + + + + + + + +
Carcinoma	
Skin	+ +
Keratoacanthoma	
Skin, site of application, basal cell adenoma	
Subcutaneous tissue, fibroma	X
Subcutaneous tissue, skin, site of application, fibrous histiocytoma	
Musculoskeletal System	
Bone	+ + + + + + + + + + + + + + + + M + + + + + + + + +
Rib, osteosarcoma	
Skeletal muscle	+ +
Carcinoma, metastatic, kidney	X
Leiomyosarcoma, metastatic, intestine small, jejunum	X
Osteosarcoma, metastatic, bone	
Nervous System	
Brain	+ +
Astrocytoma malignant	
Peripheral nerve	+
Spinal cord	+
Respiratory System	
Lung	+ +
Carcinoma, metastatic, kidney	X
Leiomyosarcoma, metastatic, intestine small, jejunum	X
Mediastinum, osteosarcoma, metastatic, bone	
Nose	+ + + + + + + + + + + + + + + + M + + + + + + + + +
Trachea	+ +
Special Senses System	
Eye	+ +
Harderian gland	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg
(continued)

Number of Days on Study	658	674	702	700	702	710	726	732	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	08 1	09 7	05 8	09 0	10 0	08 0	06 0	07 1	05 2	05 9	06 2	06 3	06 4	06 7	06 8	07 3	07 4	07 6	07 7	07 9	08 2	08 9	09 2	09 4	09 5	Total Tissues/ Tumors	
Hematopoietic System (continued)																											
Lymph node, mesenteric	+	+	+	+	+	+	+	+																		33	
Carcinoma, metastatic, kidney																										1	
Leiomyosarcoma, metastatic, intestine small, jejunum																										1	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+			+	+	+	+	+		46	
Fibroma																X										1	
Thymus	+	+	+	+	+	+	+	+																		31	
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+																		32	
Carcinoma								X																		1	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Keratoacanthoma	X																									1	
Skin, site of application, basal cell adenoma								X																		1	
Subcutaneous tissue, fibroma																										1	
Subcutaneous tissue, skin, site of application, fibrous histiocytoma	X																									1	
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+																		32	
Rib, osteosarcoma						X																				1	
Skeletal muscle						+																				3	
Carcinoma, metastatic, kidney																										1	
Leiomyosarcoma, metastatic, intestine small, jejunum																										1	
Osteosarcoma, metastatic, bone						X																				1	
Nervous System																											
Brain	+	+	+	+	+	+	+	+																		33	
Astrocytoma malignant						X																				1	
Peripheral nerve																										1	
Spinal cord																										1	
Respiratory System																											
Lung	+	+	+	+	+	+	+	+																		33	
Carcinoma, metastatic, kidney																										1	
Leiomyosarcoma, metastatic, intestine small, jejunum																										1	
Mediastinum, osteosarcoma, metastatic, bone						X																				1	
Nose	+	+	+	+	+	+	+	+																		32	
Trachea	+	+	+	+	+	+	+	+																		33	
Special Senses System																											
Eye																										2	
Harderian gland																										1	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg
(continued)

Number of Days on Study	1 9 6	3 4 9	3 6 2	3 9 3	4 4 1	4 9 1	5 1 6	5 2 7	5 4 0	5 4 1	5 4 7	5 6 5	6 0 1	6 0 3	6 0 3	6 0 9	6 0 9	6 1 9	6 2 3	6 3 1	6 3 1	6 4 3	6 4 5	6 4 5	6 5 6
Carcass ID Number	0 6 9	0 9 9	0 8 6	0 9 6	0 7 2	0 5 6	0 7 0	0 8 7	0 9 1	0 5 7	0 5 4	0 6 6	0 9 3	0 8 4	0 9 8	0 5 1	0 8 8	0 6 1	0 8 5	0 5 5	0 7 8	0 6 5	0 5 3	0 8 3	0 7 5
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney																									X
Sarcoma						X																			
Renal tubule, carcinoma																									X
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear						X		X					X	X				X	X		X		X		

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg
(continued)

Number of Days on Study	658	674	702	702	702	710	726	732	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	08 1	09 7	05 8	09 0	10 0	08 0	06 0	07 1	05 2	05 9	06 2	06 3	06 4	06 7	06 8	07 3	07 4	07 6	07 7	07 9	08 2	08 9	09 2	09 4	09 5	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+																		33
Carcinoma, metastatic, kidney																										1
Sarcoma																										1
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+																		33
Mesothelioma malignant, metastatic, uncertain primary site		X																								1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X		X					X	X	X	X	X	X	X		X	X			X	X	X	X	X		24

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 120 mg/kg

Number of Days on Study	2 5 7	4 3 9	4 7 7	4 8 7	4 8 9	5 2 7	5 3 5	5 3 8	5 6 2	5 6 8	5 7 1	5 7 3	5 7 9	5 9 4	5 9 6	6 0 6	6 0 9	6 1 2	6 2 1	6 2 2	6 2 2	6 2 2	6 3 7	6 4 6	6 4 6
Carcass ID Number	1 3 7	1 1 3	1 4 8	1 5 0	1 4 4	1 3 5	1 3 2	1 0 2	1 4 1	1 3 6	1 0 5	1 1 0	1 2 1	1 1 9	1 4 6	1 0 9	1 3 4	1 3 0	1 2 4	1 2 0	1 1 7	1 2 7	1 4 7	1 2 3	1 3 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney							X																		
Leiomyosarcoma, metastatic, stomach, forestomach					X																				
Sarcoma, metastatic, mesentery																					X				
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, stomach, forestomach					X																				
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leiomyosarcoma, metastatic, stomach, forestomach					X																				
Mesentery		+	+		+	+	+					+									+				
Carcinoma, metastatic, kidney							X																		
Leiomyosarcoma, metastatic, stomach, forestomach					X																				
Sarcoma																					X				
Oral mucosa																			+						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney							X																		
Histiocytic sarcoma																									
Leiomyosarcoma, metastatic, stomach, forestomach					X																				
Mixed tumor benign									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma					X																				
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma					X																				
Sarcoma, metastatic, mesentery																					X				
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma, metastatic, stomach, forestomach					X																				
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign														X									X		
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney							X																		
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 120 mg/kg
(continued)

Number of Days on Study	650	652	653	659	666	672	722	733	695	700	704	708	708	715	718	726	735	735	735	735	735	735	735	735	735	
Carcass ID Number	115	108	122	138	118	128	143	133	126	101	145	111	125	229	106	142	103	107	112	114	116	120	131	140	149	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Carcinoma, metastatic, kidney																										1
Leiomyosarcoma, metastatic, stomach, forestomach																										1
Sarcoma, metastatic, mesentery																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Leiomyosarcoma, metastatic, stomach, forestomach																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+		+	47
Histiocytic sarcoma			X																							1
Leiomyosarcoma, metastatic, stomach, forestomach																										1
Mesentery							+	+																		9
Carcinoma, metastatic, kidney																										1
Leiomyosarcoma, metastatic, stomach, forestomach																										1
Sarcoma																										1
Oral mucosa														+	+											3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Carcinoma, metastatic, kidney																										1
Histiocytic sarcoma			X																							1
Leiomyosarcoma, metastatic, stomach, forestomach																										1
Mixed tumor benign																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Leiomyosarcoma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Leiomyosarcoma																										1
Sarcoma, metastatic, mesentery																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Leiomyosarcoma, metastatic, stomach, forestomach																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Pheochromocytoma benign													X													3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Carcinoma, metastatic, kidney																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										39

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 120 mg/kg
(continued)

Number of Days on Study	2 5 7	4 3 9	4 7 7	4 8 7	4 8 9	5 2 7	5 3 5	5 3 8	5 6 2	5 6 8	5 7 1	5 7 3	5 7 9	5 9 4	5 9 6	6 0 6	6 0 9	6 1 2	6 2 1	6 2 2	6 2 2	6 2 2	6 3 7	6 4 6	6 4 6
Carcass ID Number	1 3 7	1 1 3	1 4 8	1 5 0	1 4 4	1 3 5	1 3 2	1 0 2	1 4 1	1 3 6	1 0 5	1 1 0	1 2 1	1 1 9	1 4 6	1 0 9	1 3 4	1 3 0	1 2 4	1 0 4	1 1 7	1 2 7	1 4 7	1 2 3	1 3 9
Endocrine System (continued)																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma		X	X		X				X			X	X	X	X	X	X	X	X	X	X	X	X	X	
Pars distalis, adenoma, multiple						X				X	X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																					X				
Follicular cell, carcinoma						X																			
General Body System																									
None																									
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Carcinoma																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney							X																		
Leiomyosarcoma, metastatic, stomach, forestomach					X																				
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma								X												X					
Interstitial cell, adenoma							X		X	X						X									X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node	+	+	+	+	+	+	+	+	+	+		+				+	+	+	+			+	+	+	
Mediastinal, carcinoma, metastatic, kidney							X																		
Mediastinal, histiocytic sarcoma																									
Renal, carcinoma, metastatic, kidney							X																		
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leiomyosarcoma, metastatic, stomach, forestomach					X																				
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 120 mg/kg
(continued)

Number of Days on Study	650	655	653	659	666	672	722	733	695	700	704	708	708	715	718	726	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	11015	10108	11022	11038	11018	12028	14043	13033	12026	10201	14045	11011	12025	12029	10206	14202	10303	10707	11212	11414	11516	12020	13131	14049	14409		Total Tissues/ Tumors
Endocrine System (continued)																											
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											41
Pars distalis, adenoma	X	X		X	X		X	X	X	X	X	X	X		X	X											30
Pars distalis, adenoma, multiple														X													4
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											41
C-cell, adenoma																											1
Follicular cell, carcinoma																											1
General Body System																											
None																											
Genital System																											
Coagulating gland																+											1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											41
Preputial gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+											40
Adenoma																											1
Carcinoma										X																	1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											41
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											41
Carcinoma, metastatic, kidney																											1
Leiomyosarcoma, metastatic, stomach, forestomach																											1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											41
Bilateral, interstitial cell, adenoma						X			X		X																5
Interstitial cell, adenoma	X														X	X											8
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											41
Histiocytic sarcoma			X																								1
Lymph node	+	+	+	+	+	+		+	+			+	+	+	+	+											31
Mediastinal, carcinoma, metastatic, kidney																											1
Mediastinal, histiocytic sarcoma			X																								1
Renal, carcinoma, metastatic, kidney																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											40
Histiocytic sarcoma			X																								1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											41
Carcinoma, metastatic, kidney																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			+	+		+		47
Histiocytic sarcoma			X																								1
Leiomyosarcoma, metastatic, stomach, forestomach																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+											41

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 120 mg/kg
(continued)

Number of Days on Study	2 5 7	4 3 9	4 7 7	4 8 7	4 8 9	5 2 7	5 3 5	5 3 8	5 6 2	5 6 8	5 7 1	5 7 3	5 7 9	5 9 4	5 9 6	6 0 6	6 0 9	6 1 2	6 2 1	6 2 2	6 2 2	6 2 2	6 3 7	6 4 6	6 4 6
Carcass ID Number	1 3 7	1 1 3	1 4 8	1 5 0	1 4 4	1 3 5	1 3 2	1 0 2	1 4 1	1 3 6	1 0 5	1 1 0	1 2 1	1 1 9	1 4 6	1 0 9	1 3 4	1 3 0	1 2 4	1 0 4	1 1 7	1 2 7	1 4 7	1 2 3	1 3 9
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell papilloma																									
Skin, site of application, basal cell adenoma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, schwannoma malignant															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma										X															
Skeletal muscle							+																		
Carcinoma, metastatic, kidney							X																		
Histiocytic sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Oligodendroglioma malignant											X														
Peripheral nerve																									
Spinal cord																									
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, kidney							X																		
Histiocytic sarcoma																									
Osteosarcoma, metastatic, bone										X															
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																				+					
Zymbal's gland								+																	
Adenoma																									
Carcinoma								X																	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma							X																		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, carcinoma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Leukemia mononuclear			X						X																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 120 mg/kg
(continued)

Number of Days on Study	650	652	653	659	666	672	722	733	695	700	704	708	708	715	718	726	735	735	735	735	735	735	735	735	735	
Carcass ID Number	115	108	122	138	118	128	143	133	126	101	145	111	125	129	106	142	103	107	112	114	116	120	131	140	149	Total Tissues/ Tumors
Integumentary System																										
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+										40
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma					X																					1
Squamous cell papilloma																								X		1
Skin, site of application, basal cell adenoma							X																			1
Subcutaneous tissue, fibroma					X																					1
Subcutaneous tissue, schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Osteosarcoma																										1
Skeletal muscle			+																							2
Carcinoma, metastatic, kidney																										1
Histiocytic sarcoma			X																							1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Oligodendroglioma malignant																										1
Peripheral nerve		+																								1
Spinal cord		+																								1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Carcinoma, metastatic, kidney																										1
Histiocytic sarcoma			X																							1
Osteosarcoma, metastatic, bone																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Special Senses System																										
Eye				+																						2
Zymbal's gland	+																									2
Adenoma	X																									1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Renal tubule, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+										41
Transitional epithelium, carcinoma								X																		1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma			X																							1
Leukemia mononuclear	X			X	X	X		X		X			X				X	X	X			X	X		X	15

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 240 mg/kg

Number of Days on Study	382	428	433	480	520	524	525	527	530	541	547	556	561	562	567	568	582	590	594	616	629	631	638	642	652
Carcass ID Number	17414	15428	17436	17703	19101	16616	17000	19606	18606	17808	16000	18505	17711	18010	19505	15503	19313	18707	18811	19010	16404	19808	16303	16525	18828
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma			X																						
Mesothelioma malignant, metastatic, uncertain primary site											X														
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site											X														
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mesentery											+							+			+				
Histiocytic sarcoma																									
Mesothelioma malignant, metastatic, uncertain primary site											X														
Oral mucosa																					+			+	
Gingival, squamous cell carcinoma																								X	
Pharyngeal, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mesothelioma malignant, metastatic, uncertain primary site											X														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant													X												
Pheochromocytoma benign																								X	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma															X										
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	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								X						X											
Pars distalis, craniopharyngioma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 240 mg/kg
(continued)

Number of Days on Study	658	667	669	679	687	702	702	714	719	719	726	726	728	730	731	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	159	153	179	184	187	189	192	199	162	197	168	200	182	172	156	151	152	154	157	161	167	169	175	183	194	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Mesothelioma malignant, metastatic, uncertain primary site																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	1
Mesentery	+					+	+		+								+									8
Histiocytic sarcoma									X																	1
Mesothelioma malignant, metastatic, uncertain primary site						X																				2
Oral mucosa							+	+															+	+		6
Gingival, squamous cell carcinoma																										1
Pharyngeal, squamous cell carcinoma																								X		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	1
Mesothelioma malignant, metastatic, uncertain primary site						X																				2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site						X																				1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign						X	X	X		X	X						X		X						X	9
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X													X								3
Carcinoma																										1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X			X	X	X	X				X	X	X	X	X	X	X				X		X	31
Pars distalis, adenoma, multiple				X							X	X														5
Pars distalis, craniopharyngioma																			X							1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 240 mg/kg
(continued)

Number of Days on Study	382	428	433	480	520	522	525	527	530	541	547	556	561	562	567	568	582	590	594	616	629	631	638	642	652
Carcass ID Number	17404	15808	17606	17703	19101	16606	17000	19606	18606	17808	16004	18505	17101	18010	19505	15503	19303	18807	18901	19004	16404	19808	16303	16505	18808
Endocrine System (continued)																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
Bilateral, C-cell, carcinoma																									
C-cell, adenoma																X									
Follicular cell, carcinoma																									
General Body System																									
Peritoneum											+														
Mesothelioma malignant, metastatic, uncertain primary site											X														
Genital System																									
Coagulating gland																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site											X														
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site											X														
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site											X														
Bilateral, interstitial cell, adenoma							X				X		X			X								X	
Interstitial cell, adenoma		X	X	X					X						X					X			X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node		+		+	+	+	+	+	+	+	+	+		+	+	+		+	+		+	+	+	+	+
Mediastinal, histiocytic sarcoma																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Mesothelioma malignant, metastatic, uncertain primary site																									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma benign							X																		
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma								X																	
Subcutaneous tissue, histiocytic sarcoma																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 240 mg/kg
(continued)

Number of Days on Study	658	667	669	679	687	702	702	714	719	719	726	726	728	730	731	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	159	153	179	184	147	189	192	199	162	197	168	200	182	172	156	151	152	154	157	161	167	169	175	183	194	Total Tissues/ Tumors
Endocrine System (continued)																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma							X																			1
Bilateral, C-cell, carcinoma																	X									1
C-cell, adenoma												X			X	X						X				5
Follicular cell, carcinoma																									X	1
General Body System																										
Peritoneum						+																				2
Mesothelioma malignant, metastatic, uncertain primary site						X																				2
Genital System																										
Coagulating gland				+										+												2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site						X																				2
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site						X																				2
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site						X																				1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site						X																				2
Bilateral, interstitial cell, adenoma	X	X		X			X	X		X	X						X			X	X	X		X		17
Interstitial cell, adenoma						X									X	X		X					X		X	13
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	1
Lymph node	+	+		+		+	+		+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	41
Mediastinal, histiocytic sarcoma									X																	1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	1
Mesothelioma malignant, metastatic, uncertain primary site						X																				1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymoma benign																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma											X															1
Squamous cell papilloma																X										1
Subcutaneous tissue, fibroma													X						X							3
Subcutaneous tissue, histiocytic sarcoma									X																	1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 240 mg/kg
(continued)

Number of Days on Study	382	428	433	480	520	522	525	527	530	541	547	556	561	562	566	567	568	582	590	594	616	629	631	638	642	652
Carcass ID Number	17474	15848	17646	17733	19191	16166	17700	19696	18686	17878	16760	18845	17711	18010	19555	15553	19393	18787	18891	19090	16464	19898	16383	16525	18838
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye																	+									
Harderian gland																									+	
Squamous cell carcinoma, metastatic, oral mucosa																									X	
Zymbal's gland							+																			
Carcinoma							X																			
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site											X															
Renal tubule, adenoma																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant, metastatic, uncertain primary site											X															
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																										
Leukemia mononuclear										X		X		X	X	X			X		X	X				

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 240 mg/kg
(continued)

Number of Days on Study	658	667	669	699	687	702	702	714	719	719	726	726	728	730	731	735	735	735	735	735	735	735	735	735	735	
Carcass ID Number	159	153	179	184	187	189	192	199	196	197	168	200	182	272	256	251	252	254	257	161	167	169	175	183	194	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland																										1
Squamous cell carcinoma, metastatic, oral mucosa																										1
Zymbal's gland												+														2
Carcinoma												X														2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site						X																				2
Renal tubule, adenoma																			X							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant, metastatic, uncertain primary site						X																				2
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma									X																	1
Leukemia mononuclear	X						X	X		X		X	X		X	X	X	X	X	X	X	X	X	X	X	25

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	8/50 (16%)	5/33 (15%)[e]	3/41 (7%)[e]	9/50 (18%)
Adjusted rate[b]	44.8%			49.7%
Terminal rate[c]	1/7 (14%)			3/10 (30%)
First incidence (days)	554			642
Life table test[d]				P=0.482N
Logistic regression test[d]				P=0.557
Fisher exact test[d]				P=0.500
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	8/50 (16%)	5/33 (15%)[e]	3/41 (7%)[e]	10/50 (20%)
Adjusted rate	44.8%			51.0%
Terminal rate	1/7 (14%)			3/10 (30%)
First incidence (days)	554			561
Life table test				P=0.580N
Logistic regression test				P=0.429
Fisher exact test				P=0.398
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	3/50 (6%)	0/33 (0%)[e]	0/41 (0%)[e]	0/50 (0%)
Adjusted rate	13.8%			0.0%
Terminal rate	0/7 (0%)			0/10 (0%)
First incidence (days)	617			—[f]
Life table test				P=0.109N
Logistic regression test				P=0.120N
Fisher exact test				P=0.121N
Pancreatic Islets: Adenoma				
Overall rate	5/50 (10%)	0/33 (0%)[e]	0/41 (0%)[e]	3/50 (6%)
Adjusted rate	20.6%			16.5%
Terminal rate	0/7 (0%)			1/10 (10%)
First incidence (days)	492			556
Life table test				P=0.305N
Logistic regression test				P=0.354N
Fisher exact test				P=0.357N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	1/33 (3%)[e]	0/41 (0%)[e]	4/50 (8%)
Adjusted rate	20.6%			18.8%
Terminal rate	0/7 (0%)			1/10 (10%)
First incidence (days)	492			556
Life table test				P=0.446N
Logistic regression test				P=0.494N
Fisher exact test				P=0.500N

TABLE A3 #
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Pituitary Gland (Pars Distalis or Unspecified Site): Adenoma				
Overall rate	44/50 (88%)	27/33 (82%)[e]	34/41 (83%)[e]	36/50 (72%)
Adjusted rate	97.5%			89.0%
Terminal rate	6/7 (86%)			6/10 (60%)
First incidence (days)	441			428
Life table test				P=0.080N
Logistic regression test				P=0.041N
Fisher exact test				P=0.039N
Pituitary Gland (Pars Distalis or Unspecified Site): Adenoma or Carcinoma				
Overall rate	45/50 (90%)	27/33 (82%)[e]	34/41 (83%)[e]	36/50 (72%)
Adjusted rate	97.5%			89.0%
Terminal rate	6/7 (86%)			6/10 (60%)
First incidence (days)	441			428
Life table test				P=0.066N
Logistic regression test				P=0.021N
Fisher exact test				P=0.020N
Preputial Gland: Adenoma or Carcinoma				
Overall rate	1/50 (2%)	0/33 (0%)[e]	2/40 (5%)[e]	0/50 (0%)
Adjusted rate	6.7%			0.0%
Terminal rate	0/7 (0%)			0/10 (0%)
First incidence (days)	707			—
Life table test				P=0.464N
Logistic regression test				P=0.478N
Fisher exact test				P=0.500N
Skin: Squamous Cell Papilloma, Keratoacanthoma, or Basal Cell Adenoma				
Overall rate	0/50 (0%)	2/50 (4%)	3/50 (6%)	2/50 (4%)
Adjusted rate	0.0%	9.3%	19.6%	16.0%
Terminal rate	0/7 (0%)	0/17 (0%)	1/9 (11%)	1/10 (10%)
First incidence (days)	—	658	666	726
Life table test	P=0.244	P=0.350	P=0.130	P=0.339
Logistic regression test	P=0.241	P=0.262	P=0.116	P=0.313
Cochran-Armitage test[d]	P=0.237			
Fisher exact test		P=0.247	P=0.121	P=0.247
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	1/50 (2%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	4.5%	3.2%	4.8%	18.9%
Terminal rate	0/7 (0%)	0/17 (0%)	0/9 (0%)	1/10 (10%)
First incidence (days)	672	631	666	527
Life table test	P=0.165	P=0.743N	P=0.745	P=0.367
Logistic regression test	P=0.162	P=0.762N	P=0.761	P=0.307
Cochran-Armitage test	P=0.163			
Fisher exact test		P=0.753N	P=0.753N	P=0.309

TABLE A3 #
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Skin (Subcutaneous Tissue): Fibroma or Fibrous Histiocytoma				
Overall rate	1/50 (2%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	4.5%	7.1%	4.8%	18.9%
Terminal rate	0/7 (0%)	0/17 (0%)	0/9 (0%)	1/10 (10%)
First incidence (days)	672	631	666	527
Life table test	P=0.242	P=0.527	P=0.745	P=0.367
Logistic regression test	P=0.235	P=0.502	P=0.761	P=0.307
Cochran-Armitage test	P=0.237			
Fisher exact test		P=0.500	P=0.753N	P=0.309
Testes: Adenoma				
Overall rate	24/50 (48%)	8/33 (24%)[e]	13/41 (32%)[e]	30/50 (60%)
Adjusted rate	94.8%			95.7%
Terminal rate	6/7 (86%)			9/10 (90%)
First incidence (days)	534			428
Life table test				P=0.484
Logistic regression test				P=0.137
Fisher exact test				P=0.158
Thyroid Gland (C-cell): Adenoma				
Overall rate	9/50 (18%)	3/33 (9%)[e]	1/41 (2%)[e]	6/50 (12%)
Adjusted rate	54.2%			37.4%
Terminal rate	2/7 (29%)			2/10 (20%)
First incidence (days)	547			568
Life table test				P=0.157N
Logistic regression test				P=0.255N
Fisher exact test				P=0.288N
Thyroid Gland (C-cell): Adenoma or Carcinoma				
Overall rate	9/50 (18%)	3/33 (9%)[e]	1/41 (2%)[e]	7/50 (14%)
Adjusted rate	54.2%			45.2%
Terminal rate	2/7 (29%)			3/10 (30%)
First incidence (days)	547			568
Life table test				P=0.220N
Logistic regression test				P=0.351N
Fisher exact test				P=0.393N
All Organs: Mononuclear Cell Leukemia				
Overall rate	12/50 (24%)	24/50 (48%)	15/50 (30%)	25/50 (50%)
Adjusted rate	50.5%	83.8%	78.3%	100.0%
Terminal rate	1/7 (14%)	13/17 (76%)	6/9 (67%)	10/10 (100%)
First incidence (days)	547	491	477	541
Life table test	P=0.035	P=0.252	P=0.376	P=0.060
Logistic regression test	P=0.016	P=0.011	P=0.310	P=0.005
Cochran-Armitage test	P=0.024			
Fisher exact test		P=0.011	P=0.326	P=0.006

TABLE A3 #
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
All Organs: Benign Neoplasms				
Overall rate	49/50 (98%)	29/50 (58%)[e]	39/50 (78%)[e]	49/50 (98%)
Adjusted rate	100.0%			100.0%
Terminal rate	7/7 (100%)			10/10 (100%)
First incidence (days)	441			428
Life table test				P=0.286N
Logistic regression test				P=0.633
Fisher exact test				P=0.753N
All Organs: Malignant Neoplasms				
Overall rate	20/50 (40%)	29/50 (58%)[e]	25/50 (50%)[e]	32/50 (64%)
Adjusted rate	63.8%			100.0%
Terminal rate	1/7 (14%)			10/10 (100%)
First incidence (days)	527			433
Life table test				P=0.139
Logistic regression test				P=0.012
Fisher exact test				P=0.014
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	45/50 (90%)[e]	46/50 (92%)[e]	49/50 (98%)
Adjusted rate	100.0%			100.0%
Terminal rate	7/7 (100%)			10/10 (100%)
First incidence (days)	441			428
Life table test				P=0.252N
Logistic regression test				P=0.571N
Fisher exact test				P=0.500N

[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, lung, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a lower incidence in a dose group is indicated by **N**.
[e] Tissues (except skin) were examined microscopically only in those animals dying prior to terminal sacrifice or when it was observed to be abnormal at necropsy; thus statistical comparisons with the controls are not applicable. #
[f] Not applicable; no neoplasms in animal group

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	28	25	22	30
Natural deaths	15	8	19	10
Survivors				
Terminal sacrifice	7	17	9	10
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(33)	(41)	(50)
Parasite metazoan	4 (8%)	1 (3%)	2 (5%)	3 (6%)
Intestine large, rectum	(50)	(33)	(41)	(49)
Parasite metazoan		2 (6%)	1 (2%)	2 (4%)
Intestine large, cecum	(50)	(33)	(41)	(50)
Inflammation, chronic active		1 (3%)	2 (5%)	1 (2%)
Ulcer		1 (3%)	1 (2%)	1 (2%)
Intestine small, duodenum	(50)	(33)	(41)	(50)
Inflammation, chronic active	1 (2%)	1 (3%)		
Ulcer	1 (2%)	1 (3%)		
Intestine small, jejunum	(50)	(33)	(41)	(50)
Diverticulum			1 (2%)	
Inflammation, chronic active	1 (2%)	1 (3%)		
Necrosis	1 (2%)			
Ulcer		1 (3%)		
Intestine small, ileum	(50)	(33)	(41)	(50)
Inflammation, chronic active		2 (6%)		1 (2%)
Parasite metazoan				1 (2%)
Ulcer				1 (2%)
Liver	(50)	(45)	(47)	(50)
Angiectasis				1 (2%)
Basophilic focus	3 (6%)		3 (6%)	6 (12%)
Clear cell focus	3 (6%)			1 (2%)
Degeneration, cystic	12 (24%)	4 (9%)	8 (17%)	9 (18%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)		2 (4%)
Hepatodiaphragmatic nodule	6 (12%)	2 (4%)	3 (6%)	9 (18%)
Inflammation, chronic	20 (40%)	9 (20%)	10 (21%)	16 (32%)
Necrosis	8 (16%)	4 (9%)	4 (9%)	2 (4%)
Pigmentation, hemosiderin		1 (2%)		
Bile duct, hyperplasia	43 (86%)	29 (64%)	32 (68%)	43 (86%)
Central vein, thrombosis		1 (2%)		
Hepatocyte, hyperplasia	1 (2%)	1 (2%)		2 (4%)
Hepatocyte, vacuolization cytoplasmic	21 (42%)	11 (24%)	16 (34%)	20 (40%)
Hepatocyte, centrilobular, degeneration, fatty	2 (4%)	4 (9%)		
Hepatocyte, centrilobular, necrosis	1 (2%)	3 (7%)		
Mesentery	(8)	(7)	(9)	(8)
Mineralization	3 (38%)	1 (14%)	2 (22%)	2 (25%)
Artery, inflammation, chronic active		1 (14%)		
Fat, inflammation, chronic active	4 (50%)	3 (43%)	4 (44%)	2 (25%)
Fat, necrosis			1 (11%)	

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Alimentary System (continued)				
Oral mucosa	(2)	(1)	(3)	(6)
Gingival, dysplasia			1 (33%)	
Gingival, inflammation, chronic active	1 (50%)	1 (100%)	2 (67%)	4 (67%)
Pancreas	(50)	(33)	(41)	(50)
Inflammation, chronic active			1 (2%)	
Acinus, atrophy	25 (50%)	13 (39%)	16 (39%)	13 (26%)
Acinus, hyperplasia	3 (6%)		2 (5%)	1 (2%)
Artery, inflammation, chronic active			2 (5%)	
Stomach, forestomach	(50)	(33)	(41)	(50)
Cyst	1 (2%)			1 (2%)
Inflammation, chronic active	12 (24%)	11 (33%)	11 (27%)	13 (26%)
Mineralization	1 (2%)		2 (5%)	
Perforation				1 (2%)
Ulcer	8 (16%)	10 (30%)	10 (24%)	11 (22%)
Epithelium, hyperplasia	17 (34%)	11 (33%)	10 (24%)	17 (34%)
Stomach, glandular	(50)	(33)	(41)	(50)
Inflammation, chronic active	3 (6%)	4 (12%)		1 (2%)
Mineralization	9 (18%)	1 (3%)	5 (12%)	4 (8%)
Necrosis		1 (3%)	1 (2%)	2 (4%)
Ulcer	2 (4%)	3 (9%)		1 (2%)
Epithelium, erosion	1 (2%)	4 (12%)	3 (7%)	2 (4%)
Epithelium, hyperplasia		1 (3%)		
Tongue		(1)		
Cyst		1 (100%)		
Tooth	(1)			
Inflammation, chronic active	1 (100%)			
Cardiovascular System				
Blood vessel	(50)	(33)	(41)	(50)
Mineralization	8 (16%)		5 (12%)	2 (4%)
Thrombosis			1 (2%)	
Heart	(50)	(33)	(41)	(50)
Cardiomyopathy, chronic	29 (58%)	21 (64%)	27 (66%)	28 (56%)
Inflammation, chronic active	1 (2%)	1 (3%)		1 (2%)
Mineralization	7 (14%)	1 (3%)	4 (10%)	1 (2%)
Atrium, thrombosis	4 (8%)	6 (18%)	6 (15%)	8 (16%)
Endocrine System				
Adrenal cortex	(50)	(33)	(41)	(50)
Accessory adrenal cortical nodule	1 (2%)			1 (2%)
Atrophy			1 (2%)	
Degeneration, fatty	34 (68%)	23 (70%)	29 (71%)	33 (66%)
Hyperplasia	25 (50%)	6 (18%)	17 (41%)	17 (34%)
Hypertrophy		2 (6%)	1 (2%)	
Necrosis				1 (2%)
Adrenal medulla	(50)	(33)	(41)	(50)
Hyperplasia	30 (60%)	10 (30%)	17 (41%)	25 (50%)
Islets, pancreatic	(50)	(33)	(41)	(50)
Hyperplasia		2 (6%)	5 (12%)	1 (2%)
Parathyroid gland	(46)	(29)	(39)	(45)
Hyperplasia	13 (28%)	3 (10%)	8 (21%)	5 (11%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Endocrine System (continued)				
Pituitary gland	(50)	(33)	(41)	(50)
Angiectasis	38 (76%)	26 (79%)	30 (73%)	35 (70%)
Hemorrhage		1 (3%)		
Mineralization	5 (10%)		1 (2%)	
Necrosis		1 (3%)	1 (2%)	
Pigmentation, hematoidin	2 (4%)	1 (3%)	1 (2%)	
Pars distalis, atrophy			1 (2%)	
Pars distalis, cyst	8 (16%)	5 (15%)	10 (24%)	14 (28%)
Pars distalis, hyperplasia	12 (24%)	5 (15%)	7 (17%)	17 (34%)
Pars distalis, pigmentation, hemosiderin	33 (66%)	20 (61%)	26 (63%)	35 (70%)
Pars distalis, thrombosis		1 (3%)	1 (2%)	
Pars intermedia, cyst	2 (4%)	2 (6%)		3 (6%)
Pars nervosa, cyst	1 (2%)			
Thyroid gland	(50)	(33)	(41)	(50)
C-cell, hyperplasia	7 (14%)	8 (24%)	7 (17%)	12 (24%)
Follicle, cyst	2 (4%)		1 (2%)	4 (8%)
General Body System				
None				
Genital System				
Coagulating gland			(1)	(2)
Inflammation, chronic active			1 (100%)	2 (100%)
Epididymis	(50)	(33)	(41)	(50)
Atrophy	25 (50%)	10 (30%)	16 (39%)	25 (50%)
Inflammation, chronic active		1 (3%)		
Mineralization	1 (2%)		2 (5%)	
Preputial gland	(50)	(33)	(40)	(50)
Cyst				2 (4%)
Hyperplasia	1 (2%)	1 (3%)	1 (3%)	2 (4%)
Inflammation, chronic active	47 (94%)	27 (82%)	38 (95%)	46 (92%)
Duct, cyst	1 (2%)	1 (3%)	3 (8%)	
Prostate	(50)	(33)	(41)	(50)
Atrophy				1 (2%)
Cyst				3 (6%)
Inflammation, chronic active	49 (98%)	32 (97%)	38 (93%)	47 (94%)
Mineralization	1 (2%)			
Seminal vesicle	(50)	(33)	(41)	(50)
Atrophy	3 (6%)	7 (21%)	11 (27%)	13 (26%)
Inflammation, chronic active	2 (4%)	1 (3%)		
Mineralization	1 (2%)			
Testes	(50)	(33)	(41)	(50)
Artery, inflammation, chronic	10 (20%)	2 (6%)	8 (20%)	9 (18%)
Germinal epithelium, atrophy	20 (40%)	6 (18%)	19 (46%)	13 (26%)
Interstitial cell, hyperplasia	20 (40%)	13 (39%)	11 (27%)	14 (28%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Hematopoietic System				
Bone marrow	(50)	(32)	(41)	(50)
Hyperplasia	25 (50%)	13 (41%)	16 (39%)	38 (76%)
Lymph node	(41)	(25)	(31)	(41)
Lumbar, hyperplasia, lymphoid		1 (4%)		
Mediastinal, atrophy				1 (2%)
Mediastinal, ectasia	1 (2%)			
Mediastinal, infiltration cellular, histiocyte		1 (4%)		
Mediastinal, pigmentation, hemosiderin	37 (90%)	23 (92%)	27 (87%)	36 (88%)
Renal, ectasia			2 (6%)	1 (2%)
Renal, erythrophagocytosis				1 (2%)
Renal, pigmentation, hemosiderin			1 (3%)	1 (2%)
Lymph node, mesenteric	(50)	(33)	(41)	(50)
Atrophy				1 (2%)
Ectasia	1 (2%)	3 (9%)	2 (5%)	6 (12%)
Inflammation, granulomatous				1 (2%)
Spleen	(50)	(46)	(47)	(50)
Fibrosis	6 (12%)		4 (9%)	8 (16%)
Hematopoietic cell proliferation	12 (24%)	6 (13%)	7 (15%)	10 (20%)
Pigmentation, hemosiderin	4 (8%)		1 (2%)	4 (8%)
Lymphoid follicle, depletion cellular	1 (2%)			
Red pulp, depletion cellular				2 (4%)
Integumentary System				
Mammary gland	(50)	(32)	(40)	(50)
Hyperplasia, cystic	42 (84%)	26 (81%)	35 (88%)	41 (82%)
Inflammation, chronic active				1 (2%)
Duct, cyst		1 (3%)	3 (8%)	2 (4%)
Skin	(50)	(50)	(50)	(50)
Hyperkeratosis		1 (2%)		
Epidermis, skin, site of application, hyperplasia		1 (2%)	1 (2%)	2 (4%)
Sebaceous gland, skin, site of application, hyperplasia	1 (2%)	1 (2%)		
Skin, site of application, inflammation, chronic active		1 (2%)		
Subcutaneous tissue, inflammation, chronic active				1 (2%)
Musculoskeletal System				
Bone	(50)	(32)	(41)	(50)
Fibrous osteodystrophy	10 (20%)	1 (3%)	9 (22%)	8 (16%)
Femur, osteosclerosis				1 (2%)

TABLE A4
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Nervous System				
Brain	(50)	(33)	(41)	(50)
Hemorrhage, acute		1 (3%)		4 (8%)
Hydrocephalus	11 (22%)	12 (36%)	9 (22%)	5 (10%)
Mineralization	1 (2%)			
Necrosis	1 (2%)			
Spinal cord	(1)	(1)	(1)	
Axon, degeneration	1 (100%)		1 (100%)	
Respiratory System				
Lung	(50)	(33)	(41)	(50)
Congestion, acute	10 (20%)	9 (27%)	17 (41%)	6 (12%)
Inflammation, chronic active	3 (6%)	1 (3%)	2 (5%)	3 (6%)
Inflammation, granulomatous	2 (4%)		1 (2%)	
Inflammation, suppurative			1 (2%)	1 (2%)
Mineralization	7 (14%)		5 (12%)	
Necrosis			1 (2%)	
Thrombosis				1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	2 (6%)	1 (2%)	3 (6%)
Alveolus, hemorrhage, acute	3 (6%)	1 (3%)	1 (2%)	
Alveolus, infiltration cellular, histiocyte	24 (48%)	10 (30%)	16 (39%)	16 (32%)
Interstitium, inflammation, chronic active	7 (14%)		4 (10%)	3 (6%)
Nose	(50)	(32)	(41)	(50)
Inflammation, chronic active	5 (10%)	8 (25%)	4 (10%)	5 (10%)
Polyp inflammatory	1 (2%)			
Thrombosis		1 (3%)	1 (2%)	
Nasolacrimal duct, inflammation, suppurative	5 (10%)	3 (9%)	3 (7%)	3 (6%)
Special Senses System				
Eye	(3)	(2)	(2)	(1)
Anterior chamber, hemorrhage, acute	1 (33%)			
Cornea, inflammation, suppurative	1 (33%)			
Lens, cataract	2 (67%)	1 (50%)	1 (50%)	1 (100%)
Retina, degeneration	2 (67%)	2 (100%)	1 (50%)	1 (100%)
Harderian gland	(1)	(1)		(1)
Inflammation, chronic	1 (100%)	1 (100%)		
Urinary System				
Kidney	(50)	(33)	(41)	(50)
Accumulation, hyaline droplet			1 (2%)	
Infarct				2 (4%)
Mineralization	4 (8%)	3 (9%)	2 (5%)	1 (2%)
Nephropathy, chronic	50 (100%)	32 (97%)	41 (100%)	50 (100%)
Cortex, cyst	8 (16%)	1 (3%)	1 (2%)	10 (20%)
Urinary bladder	(50)	(33)	(41)	(50)
Inflammation, chronic active	1 (2%)			
Mineralization	1 (2%)			

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR DERMAL STUDY OF SODIUM XYLENESULFONATE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death	1			
Moribund	14	10	15	12
Natural deaths	13	24	18	22
Survivors				
Died last week of the study		1		
Terminal sacrifice	22	15	17	16
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(50)	(35)	(33)	(50)
Periesophageal tissue, lipoma		1 (3%)	1 (3%)	
Intestine small, duodenum	(50)	(35)	(33)	(50)
Liver	(50)	(35)	(33)	(50)
Mesentery	(2)	(4)	(4)	(4)
Oral mucosa	(1)			(2)
Gingival, squamous cell carcinoma	1 (100%)			
Pancreas	(50)	(35)	(33)	(50)
Stomach, glandular	(50)	(35)	(33)	(50)
Cardiovascular System				
Heart	(50)	(35)	(33)	(50)
Endocrine System				
Adrenal cortex	(50)	(35)	(33)	(50)
Adenoma	1 (2%)	1 (3%)		1 (2%)
Adrenal medulla	(50)	(35)	(33)	(50)
Pheochromocytoma benign	1 (2%)		1 (3%)	2 (4%)
Islets, pancreatic	(50)	(35)	(33)	(50)
Adenoma			1 (3%)	
Carcinoma	1 (2%)			
Pituitary gland	(50)	(35)	(33)	(50)
Pars distalis, adenoma	29 (58%)	16 (46%)	19 (58%)	27 (54%)
Pars distalis, adenoma, multiple	5 (10%)	1 (3%)		2 (4%)
Pars distalis, carcinoma	1 (2%)			
Pars intermedia, adenoma				1 (2%)
Thyroid gland	(50)	(35)	(33)	(50)
C-cell, adenoma	10 (20%)	1 (3%)	2 (6%)	7 (14%)
C-cell, adenoma, multiple				1 (2%)
Follicular cell, adenoma	1 (2%)	2 (6%)		1 (2%)
Follicular cell, carcinoma				1 (2%)
General Body System				
None				

TABLE B1 #
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Genital System				
Clitoral gland	(49)	(50)	(50)	(50)
Adenoma	1 (2%)	3 (6%)	3 (6%)	
Carcinoma			1 (2%)	2 (4%)
Bilateral, adenoma			1 (2%)	
Ovary	(50)	(35)	(33)	(50)
Uterus	(50)	(35)	(33)	(50)
Fibroma	1 (2%)			
Polyp stromal	2 (4%)	1 (3%)	1 (3%)	3 (6%)
Sarcoma stromal		1 (3%)	1 (3%)	
Vagina	(1)	(1)	(1)	
Squamous cell carcinoma			1 (100%)	
Hematopoietic System				
Bone marrow	(50)	(35)	(33)	(48)
Lymph node	(45)	(32)	(27)	(43)
Lymph node, mandibular	(50)	(35)	(33)	(50)
Lymph node, mesenteric	(49)	(35)	(33)	(48)
Spleen	(50)	(35)	(33)	(50)
Thymus	(49)	(35)	(31)	(49)
Integumentary System				
Mammary gland	(50)	(35)	(33)	(50)
Carcinoma	1 (2%)	1 (3%)		1 (2%)
Fibroadenoma	12 (24%)	4 (11%)	8 (24%)	6 (12%)
Fibroadenoma, multiple	4 (8%)			3 (6%)
Skin	(50)	(50)	(50)	(50)
Pinna, squamous cell papilloma	1 (2%)			
Subcutaneous tissue, lipoma		1 (2%)		
Subcutaneous tissue, sarcoma			1 (2%)	
Subcutaneous tissue, schwannoma malignant	1 (2%)			
Musculoskeletal System				
Bone	(50)	(35)	(33)	(48)
Humerus, osteosarcoma	1 (2%)			
Nervous System				
Brain	(50)	(35)	(33)	(50)
Astrocytoma malignant	1 (2%)	1 (3%)		
Carcinoma, metastatic, pituitary gland	1 (2%)			
Respiratory System				
Lung	(50)	(35)	(33)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			
Osteosarcoma, metastatic, bone	1 (2%)			

TABLE B1 #
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Special Senses System				
Zymbal's gland				(1)
Carcinoma				1 (100%)
Urinary System				
Kidney	(50)	(35)	(33)	(50)
Lipoma		1 (3%)		
Urinary bladder	(50)	(35)	(33)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	17 (34%)	5 (10%)	9 (18%)	10 (20%)
Mesothelioma benign				1 (2%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	45	25	27	41
Total primary neoplasms	93	40	50	70
Total animals with benign neoplasms	40	23	26	33
Total benign neoplasms	69	32	37	55
Total animals with malignant neoplasms	23	8	11	15
Total malignant neoplasms	24	8	13	15
Total animals with metastatic neoplasms	2			
Total metastatic neoplasms	2			

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: Vehicle Control

Number of Days on Study	3 0 3	3 9 3	4 0 8	4 2 0	4 2 0	4 8 0	4 8 5	4 8 8	4 9 0	4 9 0	5 4 5	5 4 8	5 7 5	5 9 1	6 0 5	6 2 9	6 4 6	6 5 6	6 5 7	6 7 4	6 8 2	6 9 2	6 9 3	6 9 8	7 0 8
Carcass ID Number	2 3 5	2 2 7	2 3 8	2 2 1	2 2 8	2 4 1	2 1 7	2 2 3	2 1 4	2 4 7	2 2 6	2 4 2	2 1 0	2 0 7	2 2 2	2 1 6	2 2 0	2 1 2	2 1 3	2 0 2	2 4 6	2 0 8	2 3 6	2 3 0	2 3 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery																				+					
Oral mucosa																									
Gingival, squamous cell carcinoma																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma															X										
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																								X	
Pars distalis, carcinoma					X																				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																							X	X	
Follicular cell, adenoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Polyp stromal			X																						
Vagina																				+					

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE B2 #
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	7 1 8	7 1 9	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 1 1	2 4 9	2 4 0	2 0 1	2 0 3	2 0 4	2 0 5	2 0 6	2 0 9	2 1 5	2 1 8	2 1 9	2 2 4	2 2 5	2 2 9	2 3 1	2 3 3	2 3 4	2 3 7	2 3 9	2 4 3	2 4 4	2 4 5	2 4 8	2 5 0	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery																							+					2
Oral mucosa																					+							1
Gingival, squamous cell carcinoma																					X							1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth												+																1
Cardiovascular System																												
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X				1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																								X				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																												1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X	X	X	X	X	X	X	X	X			X	X						X					X		29
Pars distalis, adenoma, multiple												X	X					X						X				5
Pars distalis, carcinoma																												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X					X		X							X			X		X				X	X	10
Follicular cell, adenoma					X																							1
General Body System																												
None																												
Genital System																												
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X								1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma						X																						1
Polyp stromal							X																					2
Vagina																												1

TABLE B2 #
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	3 0 3	3 9 3	4 0 8	4 2 0	4 2 0	4 8 0	4 8 5	4 8 8	4 9 0	4 9 0	5 4 5	5 4 8	5 7 5	5 9 1	6 0 5	6 2 9	6 4 6	6 5 6	6 5 7	6 7 4	6 8 2	6 8 9 2	6 9 3	6 9 8	7 0 8
Carcass ID Number	2 3 5	2 2 7	2 3 8	2 2 1	2 2 8	2 4 1	2 1 7	2 2 3	2 1 4	2 4 7	2 2 6	2 4 2	2 1 0	2 0 7	2 2 2	2 1 6	2 2 0	2 1 2	2 1 3	2 0 2	2 4 6	2 0 8	2 3 6	2 3 0	2 3 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+		+		+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma										X											X			X	X
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pinna, squamous cell papilloma																									
Subcutaneous tissue, schwannoma malignant		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Humerus, osteosarcoma			X																						
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant	X																								
Carcinoma, metastatic, pituitary gland					X																				
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Osteosarcoma, metastatic, bone			X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye															+						+		+		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X						X			X			X	X				X	

TABLE B2 #
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	7 1 8	7 1 9	7 3 2	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 1 1	2 4 9	2 4 0	2 0 1	2 0 3	2 0 4	2 0 5	2 0 6	2 0 9	2 1 5	2 1 8	2 1 9	2 2 4	2 2 5	2 2 9	2 3 1	2 3 3	2 3 4	2 3 7	2 3 9	2 4 3	2 4 4	2 4 5	2 4 8	2 5 0	Total Tissues/ Tumors
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		45
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma			X																									1
Fibroadenoma		X	X				X	X			X								X					X	X			12
Fibroadenoma, multiple						X							X	X							X							4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pinna, squamous cell papilloma					X																							1
Subcutaneous tissue, schwannoma malignant																												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Humerus, osteosarcoma																												1
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																												1
Carcinoma, metastatic, pituitary gland																												1
Respiratory System																												
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																						1
Osteosarcoma, metastatic, bone																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																												
Eye																												3
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X				X	X			X			X				X	X				X		X			17

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg

Number of Days on Study	201	277	301	367	386	446	447	486	697	255	288	288	373	411	447	470	509	593	632	825	855	900	922	926	1030	1043
Carcass ID Number	285	252	283	276	288	273	260	297	267	277	255	292	281	284	279	296	295	291	286	251	261	270	257	298	262	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Periesophageal tissue, lipoma																X										
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Mesentery							+	+																		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																			X							
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Pars distalis, adenoma								X		X	X		X	X	X	X	X				X	X			X	
Pars distalis, adenoma, multiple																										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
C-cell, adenoma																										
Follicular cell, adenoma																										
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adenoma																						X	X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Polyp stromal																X										
Sarcoma stromal						X																				
Vagina																										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg
(continued)

Number of Days on Study	6 4 4	6 4 5	6 4 5	6 6 6	6 9 4	7 0 1	7 0 8	7 2 2	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 5 6	2 7 4	2 7 5	2 5 8	3 0 0	2 0 8 2	2 6 6 3	2 8 8 7	2 5 9	2 5 3	2 5 5 4	2 6 6 4	2 6 6 5	2 6 6 6	2 6 6 8	2 6 6 9	2 7 7 1	2 7 7 2	2 7 7 8	2 8 8 0	2 8 8 9	2 9 9 0	2 9 9 3	2 9 9 4	2 9 9 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+																35
Periesophageal tissue, lipoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+																35
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+																35
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+																35
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+																35
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+																35
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+																35
Liver	+	+	+	+	+	+	+	+	+	+																35
Mesentery				+			+																			4
Pancreas	+	+	+	+	+	+	+	+	+	+																35
Salivary glands	+	+	+	+	+	+	+	+	+	+																35
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+																35
Stomach, glandular	+	+	+	+	+	+	+	+	+	+																35
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+																35
Heart	+	+	+	+	+	+	+	+	+	+																35
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+																35
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+																35
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+																35
Parathyroid gland	+	+	+	+	+	+	M	+	M	+																32
Pituitary gland	+	+	+	+	+	+	+	+	+	+																35
Pars distalis, adenoma		X	X		X		X			X																16
Pars distalis, adenoma, multiple								X																		1
Thyroid gland	+	+	+	+	+	+	+	+	+	+																35
C-cell, adenoma			X																							1
Follicular cell, adenoma							X		X																	2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X								3
Ovary	+	+	+	+	+	+	+	+	+	+																35
Uterus	+	+	+	+	+	+	+	+	+	+																35
Polyp stromal																										1
Sarcoma stromal																										1
Vagina				+																						1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg
(continued)

Number of Days on Study	201	207	301	367	386	446	447	486	497	525	528	538	537	541	547	550	559	563	582	585	590	622	626	630	643
Carcass ID Number	285	252	883	766	888	733	600	907	677	737	755	592	811	844	799	696	955	991	866	851	961	707	578	982	662
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+		+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																					X				
Fibroadenoma						X																			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, lipoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																						X			
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																	+					+			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma											X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear									X																

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 60 mg/kg
(continued)

Number of Days on Study	6 4 4	6 4 5	6 4 5	6 6 6	6 9 4	7 0 1	7 0 8	7 2 2	7 3 5	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	2 5 6	2 7 4	2 7 5	2 5 8	3 0 0	2 8 2	2 6 3	2 8 7	2 5 9	2 5 3	2 5 4	2 6 4	2 6 5	2 6 6	2 6 8	2 6 9	2 7 1	2 7 2	2 7 8	2 8 0	2 8 9	2 9 0	2 9 3	2 9 4	2 9 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+																35
Lymph node	+	+	+	+	+	+	+	+	+	+																32
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+																35
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+																35
Spleen	+	+	+	+	+	+	+	+	+	+																35
Thymus	+	+	+	+	+	+	+	+	+	+																35
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+																35
Carcinoma																										1
Fibroadenoma			X		X					X																4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, lipoma				X																						1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+																35
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+																35
Astrocytoma malignant																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+																35
Nose	+	+	+	+	+	+	+	+	+	+																35
Trachea	+	+	+	+	+	+	+	+	+	+																35
Special Senses System																										
Eye																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+																35
Lipoma																										1
Urinary Bladder	+	+	+	+	+	+	+	+	+	+																35
Systemic Lesions																										
Multiple Organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia Mononuclear				X	X	X				X																5

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 120 mg/kg

Number of Days on Study	4 4 1	4 4 4	4 4 5	4 6 2	4 9 2	5 0 1	5 1 0	5 1 7	5 2 7	5 3 2	5 4 2	5 4 7	5 5 9	5 6 4	5 6 8	5 9 4	6 0 2	6 0 3	6 2 5	6 3 8	6 4 3	6 4 5	6 4 6	6 4 8	6 6 0
Carcass ID Number	3 3 4	3 2 6	3 0 1	3 4 4	3 5 0	3 4 5	3 3 9	3 1 1	3 0 6	3 2 0	3 4 2	3 0 7	3 4 9	3 1 2	3 2 3	3 1 7	3 3 2	3 3 1	3 0 9	3 3 3	3 1 6	3 1 0	3 4 1	3 3 0	3 0 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Periesophageal tissue, lipoma																X									
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery															+							+	+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X						X	X	X		X		X	X	X		X	X	X	X				X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma													X								X				
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																	X								
Carcinoma					X																				
Bilateral, adenoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X																				
Sarcoma stromal																									
Vagina																									+
Squamous cell carcinoma																									X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 120 mg/kg
(continued)

Number of Days on Study	6 6 6	6 7 3	6 9 7	7 0 6	7 0 8	7 1 2	7 1 2	7 1 7	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 2 9	3 2 1	3 3 6	3 0 3	3 1 8	3 0 4	3 4 6	3 3 5	3 0 5	3 0 8	3 1 3	3 1 4	3 1 5	3 1 9	3 2 2	3 2 4	3 2 5	3 2 7	3 2 8	3 3 7	3 3 8	3 4 0	3 4 3	3 4 7	3 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+																		33
Periesophageal tissue, lipoma																										1
Intestine large, colon	+	+	+	+	+	+	+	+																		33
Intestine large, rectum	+	+	+	+	+	+	+	+																		33
Intestine large, cecum	+	+	+	+	+	+	+	+																		33
Intestine small, duodenum	+	+	+	+	+	+	+	+																		33
Intestine small, jejunum	+	+	+	+	+	+	+	+																		33
Intestine small, ileum	M	+	+	+	+	+	+	+																		32
Liver	+	+	+	+	+	+	+	+																		33
Mesentery						+																				4
Pancreas	+	+	+	+	+	+	+	+																		33
Salivary glands	+	+	+	+	+	+	+	+																		33
Stomach, forestomach	+	+	+	+	+	+	+	+																		33
Stomach, glandular	+	+	+	+	+	+	+	+																		33
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+																		33
Heart	+	+	+	+	+	+	+	+																		33
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+																		33
Adrenal medulla	+	+	+	+	+	+	+	+																		33
Pheochromocytoma benign				X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+																		33
Adenoma								X																		1
Parathyroid gland	+	+	+	+	+	+	+	+																		31
Pituitary gland	+	+	+	+	+	+	+	+																		33
Pars distalis, adenoma	X	X	X		X		X	X																		19
Thyroid gland	+	+	+	+	+	+	+	+																		33
C-cell, adenoma																										2
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma											X											X				3
Carcinoma																										1
Bilateral, adenoma							X																			1
Ovary	+	+	+	+	+	+	+	+																		33
Uterus	+	+	+	+	+	+	+	+																		33
Polyp stromal																										1
Sarcoma stromal				X																						1
Vagina																										1
Squamous cell carcinoma																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 120 mg/kg
(continued)

Number of Days on Study	4 4 1	4 4 4	4 4 5	4 6 2	4 9 2	5 0 1	5 1 0	5 1 7	5 2 7	5 3 2	5 4 2	5 4 7	5 5 9	5 6 4	5 6 8	5 9 4	6 0 2	6 0 3	6 2 5	6 3 8	6 4 3	6 4 5	6 4 6	6 4 8	6 6 0
Carcass ID Number	3 3 4	3 2 6	3 0 1	3 4 4	3 5 0	3 4 5	3 3 9	3 1 1	3 0 6	3 2 0	3 4 2	3 0 7	3 4 9	3 1 2	3 2 3	3 1 7	3 3 2	3 3 1	3 0 9	3 3 3	3 1 6	3 1 0	3 4 1	3 3 0	3 0 2
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+					+	+		+	+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma	X								X											X					X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye								+					+												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear								X		X							X	X				X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 120 mg/kg
(continued)

Number of Days on Study	6 6 6	6 7 3	6 9 7	7 0 6	7 0 8	7 1 2	7 1 2	7 1 7	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	7 3 6	
Carcass ID Number	3 2 9	3 2 1	3 3 6	3 0 3	3 1 8	3 0 4	3 4 6	3 3 5	3 0 5	3 0 8	3 1 3	3 1 4	3 1 5	3 1 9	3 2 2	3 2 4	3 2 5	3 2 7	3 2 8	3 3 7	3 3 8	3 4 0	3 4 3	3 4 7	3 4 8	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+																		33
Lymph node	+	+	+	+	+	+	+	+																		27
Lymph node, mandibular	+	+	+	+	+	+	+	+																		33
Lymph node, mesenteric	+	+	+	+	+	+	+	+																		33
Spleen	+	+	+	+	+	+	+	+																		33
Thymus	+	+	+	+	+	M	+	+																		31
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+																		33
Fibroadenoma	X				X	X		X																		8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+																		33
Nervous System																										
Brain	+	+	+	+	+	+	+	+																		33
Respiratory System																										
Lung	+	+	+	+	+	+	+	+																		33
Nose	+	+	+	+	+	+	+	+																		33
Trachea	+	+	+	+	+	+	+	+																		33
Special Senses System																										
Eye																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+																		33
Urinary bladder	+	+	+	+	+	+	+	+																		33
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X		X		X		X																		9

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 240 mg/kg

Number of Days on Study	2 8 9	3 2 4	3 3 8	3 7 9	3 9 1	3 9 6	4 1 2	4 4 1	5 0 7	5 1 5	5 2 0	5 2 6	5 5 6	5 7 2	5 8 9	5 9 1	5 9 6	6 1 1	6 1 5	6 3 0	6 3 3	6 3 4	6 4 0	6 4 6	6 5 1
Carcass ID Number	3 6 2	3 6 9	3 5 7	3 6 6	3 9 3	3 8 2	3 7 9	3 7 2	3 9 6	3 8 8	3 5 5	3 5 2	3 7 4	3 7 6	3 8 6	3 8 3	3 5 1	3 8 5	3 9 4	3 9 7	3 9 2	3 9 9	3 7 1	3 6 4	3 8 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery											+								+						
Oral mucosa																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									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
Pars distalis, adenoma, multiple																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																									
C-cell, adenoma, multiple																									
Follicular cell, adenoma														X											
Follicular cell, carcinoma																									
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																		X							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X																				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 240 mg/kg
(continued)

Number of Days on Study	653	674	707	695	696	706	711	714	728	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	40 00	39 00	35 09	36 03	37 05	35 03	36 08	36 01	39 05	35 04	35 06	35 08	36 00	36 05	36 07	37 00	37 03	37 07	37 08	38 00	38 01	38 04	38 07	39 01	39 08	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+										+															4
Oral mucosa								+														+				2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tooth																						+				1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																		X								2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X	X		X	X	X				X	X		X	X	X		X		X	X			27
Pars distalis, adenoma, multiple															X										X	2
Pars intermedia, adenoma																							X			1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma		X			X		X				X									X		X	X			7
C-cell, adenoma, multiple														X												1
Follicular cell, adenoma																										1
Follicular cell, carcinoma			X																							1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																					X					2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal														X											X	3

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 240 mg/kg
(continued)

Number of Days on Study	2 8 9	3 2 4	3 3 8	3 7 9	3 9 1	3 9 6	4 1 2	4 4 1	5 0 7	5 1 5	5 2 0	5 2 6	5 5 6	5 7 2	5 8 9	5 9 1	5 9 6	6 1 1	6 1 5	6 3 0	6 3 3	6 3 4	6 4 0	6 4 6	6 5 1
Carcass ID Number	3 6 2	3 6 9	3 5 7	3 6 6	3 9 3	3 8 2	3 7 9	3 7 2	3 9 6	3 8 8	3 5 5	3 5 2	3 7 4	3 7 6	3 8 6	3 8 3	3 5 1	3 8 5	3 9 4	3 9 7	3 9 2	3 9 9	3 7 1	3 6 4	3 8 9
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node		+	+	+	+		+	+	+	+	+		+	+	+	+		+	+	+	+	+	+		+
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X																	
Fibroadenoma										X													X		
Fibroadenoma, multiple																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye																									
Zymbal's gland			+																						
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear											X									X				X	X
Mesothelioma benign																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate: 240 mg/kg
(continued)

Number of Days on Study	653	674	677	695	696	706	711	711	728	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	736	
Carcass ID Number	40 00	39 00	35 09	36 03	37 05	35 03	36 08	36 01	39 05	35 04	35 06	35 08	36 00	36 05	36 07	37 00	37 03	37 07	37 08	38 00	38 01	38 04	38 07	39 01	39 08	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node	+	+		+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	43
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Fibroadenoma						X	X						X		X											6
Fibroadenoma, multiple																X		X							X	3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+					+											+				+				+	5
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X									X	X					X						X		X		10
Mesothelioma benign													X													1

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Clitoral Gland: Adenoma				
Overall rate[a]	1/49 (2%)	3/50 (6%)	4/50 (8%)	0/50 (0%)
Adjusted rate[b]	4.5%	12.7%	18.6%	0.0%
Terminal rate[c]	1/22 (5%)	1/16 (6%)	2/17 (12%)	0/16 (0%)
First incidence (days)	736 (T)	622	602	—[e]
Life table test[d]	P=0.388N	P=0.220	P=0.124	P=0.564N
Logistic regression test[d]	P=0.340N	P=0.263	P=0.146	P=0.564N
Cochran-Armitage test[d]	P=0.307N			
Fisher exact test[d]		P=0.316	P=0.187	P=0.495N
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	1/49 (2%)	3/50 (6%)	5/50 (10%)	2/50 (4%)
Adjusted rate	4.5%	12.7%	20.4%	9.1%
Terminal rate	1/22 (5%)	1/16 (6%)	2/17 (12%)	1/16 (6%)
First incidence (days)	736 (T)	622	492	611
Life table test	P=0.364	P=0.220	P=0.075	P=0.420
Logistic regression test	P=0.420	P=0.263	P=0.100	P=0.460
Cochran-Armitage test	P=0.445			
Fisher exact test		P=0.316	P=0.107	P=0.508
Mammary Gland: Fibroadenoma				
Overall rate	16/50 (32%)	4/35 (11%)[f]	8/33 (24%)[f]	9/50 (18%)
Adjusted rate	56.3%			41.8%
Terminal rate	10/22 (45%)			5/16 (31%)
First incidence (days)	490			515
Life table test				P=0.285N
Logistic regression test				P=0.151N
Fisher exact test				P=0.083N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	16/50 (32%)	5/35 (14%)[f]	8/33 (24%)[f]	10/50 (20%)
Adjusted rate	56.3%			43.1%
Terminal rate	10/22 (45%)			5/16 (31%)
First incidence (days)	490			441
Life table test				P=0.373N
Logistic regression test				P=0.202N
Fisher exact test				P=0.127N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	34/50 (68%)	17/35 (49%)[f]	19/33 (58%)[f]	29/50 (58%)
Adjusted rate	84.5%			81.4%
Terminal rate	16/22 (73%)			10/16 (63%)
First incidence (days)	420			396
Life table test				P=0.429
Logistic regression test				P=0.243N
Fisher exact test				P=0.204N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate
(continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	35/50 (70%)	17/35 (49%)[f]	19/33 (58%)[f]	29/50 (58%)
Adjusted rate	84.8%			81.4%
Terminal rate	16/22 (73%)			10/16 (63%)
First incidence (days)	420			396
Life table test				P=0.486
Logistic regression test				P=0.182N
Fisher exact test				P=0.149N
Thyroid Gland (C-cell): Adenoma				
Overall rate	10/50 (20%)	1/35 (3%)[f]	2/33 (6%)[f]	8/50 (16%)
Adjusted rate	39.3%			40.6%
Terminal rate	7/22 (32%)			5/16 (31%)
First incidence (days)	693			674
Life table test				P=0.529
Logistic regression test				P=0.601
Fisher exact test				P=0.398N
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	1/50 (2%)	2/35 (6%)[f]	0/33 (0%)[f]	1/50 (2%)
Adjusted rate	4.5%			2.7%
Terminal rate	1/22 (5%)			0/16 (0%)
First incidence (days)	736 (T)			572
Life table test				P=0.722
Logistic regression test				P=0.756
Fisher exact test				P=0.753N
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	2/35 (6%)[f]	0/33 (0%)[f]	2/50 (4%)
Adjusted rate	4.5%			6.9%
Terminal rate	1/22 (5%)			0/16 (0%)
First incidence (days)	736 (T)			572
Life table test				P=0.430
Logistic regression test				P=0.483
Fisher exact test				P=0.500
Uterus: Stromal Polyp				
Overall rate	2/50 (4%)	1/35 (3%)[f]	1/33 (3%)[f]	3/50 (6%)
Adjusted rate	6.5%			14.4%
Terminal rate	1/22 (5%)			2/16 (13%)
First incidence (days)	408			391
Life table test				P=0.401
Logistic regression test				P=0.524
Fisher exact test				P=0.500

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate
(continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	2/50 (4%)	2/35 (6%)[f]	2/33 (6%)[f]	3/50 (6%)
Adjusted rate	6.5%			14.4%
Terminal rate	1/22 (5%)			2/16 (13%)
First incidence (days)	408			391
Life table test				P=0.401
Logistic regression test				P=0.524
Fisher exact test				P=0.500
All Organs: Mononuclear Cell Leukemia				
Overall rate	17/50 (34%)	5/35 (14%)[f]	9/33 (27%)[f]	10/50 (20%)
Adjusted rate	53.3%			42.3%
Terminal rate	8/22 (36%)			5/16 (31%)
First incidence (days)	485			520
Life table test				P=0.301N
Logistic regression test				P=0.136N
Fisher exact test				P=0.088N
All Organs: Benign Neoplasms				
Overall rate	40/50 (80%)	23/50 (46%)[f]	26/50 (52%)[f]	33/50 (66%)
Adjusted rate	95.1%			86.1%
Terminal rate	20/22 (91%)			11/16 (69%)
First incidence (days)	408			391
Life table test				P=0.484
Logistic regression test				P=0.141N
Fisher exact test				P=0.088N
All Organs: Malignant Neoplasms				
Overall rate	23/50 (46%)	8/50 (16%)[f]	11/50 (22%)[f]	15/50 (30%)
Adjusted rate	61.2%			53.5%
Terminal rate	9/22 (41%)			6/16 (38%)
First incidence (days)	303			338
Life table test				P=0.312N
Logistic regression test				P=0.077N
Fisher exact test				P=0.074N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate
(continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	25/50 (50%)[f]	27/50 (54%)[f]	41/50 (82%)
Adjusted rate	95.7%			95.3%
Terminal rate	20/22 (91%)			14/16 (88%)
First incidence (days)	303			338
Life table test				P=0.272
Logistic regression test				P=0.273N
Fisher exact test				P=0.194N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for clitoral gland, mammary gland, pituitary gland, thyroid gland, and uterus; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Tissues (except skin) were examined microscopically only in those animals dying prior to terminal sacrifice; thus statistical comparisons with the controls are not applicable.

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death	1			
Moribund	14	10	15	12
Natural deaths	13	24	18	22
Survivors				
Died last week of the study		1		
Terminal sacrifice	22	15	17	16
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(35)	(33)	(50)
Parasite metazoan	2 (4%)	1 (3%)		3 (6%)
Intestine large, rectum	(50)	(35)	(33)	(50)
Parasite metazoan	4 (8%)	3 (9%)	1 (3%)	3 (6%)
Intestine large, cecum	(50)	(35)	(33)	(50)
Inflammation, chronic active		1 (3%)	1 (3%)	1 (2%)
Ulcer		1 (3%)		
Intestine small, duodenum	(50)	(35)	(33)	(50)
Inflammation, chronic active			1 (3%)	
Ulcer	1 (2%)		1 (3%)	
Liver	(50)	(35)	(33)	(50)
Angiectasis				1 (2%)
Basophilic focus	30 (60%)	12 (34%)	11 (33%)	26 (52%)
Clear cell focus	1 (2%)			1 (2%)
Hematopoietic cell proliferation				1 (2%)
Hepatodiaphragmatic nodule	10 (20%)	6 (17%)	11 (33%)	3 (6%)
Inflammation, chronic	21 (42%)	17 (49%)	19 (58%)	24 (48%)
Mixed cell focus				1 (2%)
Necrosis	3 (6%)	1 (3%)	3 (9%)	3 (6%)
Pigmentation, hemosiderin	3 (6%)	1 (3%)		
Pigmentation, melanin	1 (2%)			
Bile duct, hyperplasia	28 (56%)	13 (37%)	17 (52%)	21 (42%)
Central vein, thrombosis	1 (2%)			
Hepatocyte, hyperplasia	2 (4%)		1 (3%)	1 (2%)
Hepatocyte, vacuolization cytoplasmic	15 (30%)		4 (12%)	4 (8%)
Hepatocyte, centrilobular, degeneration, fatty	4 (8%)	1 (3%)	3 (9%)	2 (4%)
Portal vein, thrombosis				1 (2%)
Mesentery	(2)	(4)	(4)	(4)
Mineralization	1 (50%)		2 (50%)	1 (25%)
Artery, inflammation, chronic active		1 (25%)		
Fat, inflammation, chronic active	1 (50%)	2 (50%)	1 (25%)	2 (50%)
Fat, necrosis	1 (50%)		2 (50%)	
Oral mucosa	(1)			(2)
Gingival, inflammation, chronic active				2 (100%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Alimentary System (continued)				
Pancreas	(50)	(35)	(33)	(50)
Cyst			1 (3%)	
Hypertrophy, focal				1 (2%)
Inflammation, chronic active		1 (3%)	1 (3%)	
Acinus, atrophy	12 (24%)	3 (9%)	5 (15%)	8 (16%)
Artery, inflammation, chronic active	1 (2%)			1 (2%)
Stomach, forestomach	(50)	(35)	(33)	(50)
Inflammation, chronic active	2 (4%)	4 (11%)	3 (9%)	4 (8%)
Ulcer	2 (4%)	2 (6%)	3 (9%)	3 (6%)
Epithelium, hyperplasia	2 (4%)	4 (11%)	3 (9%)	5 (10%)
Stomach, glandular	(50)	(35)	(33)	(50)
Inflammation, chronic active		1 (3%)	1 (3%)	
Mineralization	1 (2%)		1 (3%)	
Necrosis	1 (2%)	1 (3%)		
Ulcer			1 (3%)	
Epithelium, erosion	1 (2%)	1 (3%)		
Epithelium, hemorrhage	1 (2%)			
Epithelium, necrosis	1 (2%)			
Tooth	(1)			(1)
Inflammation				1 (100%)
Peridontal tissue, inflammation, chronic active	1 (100%)			
Cardiovascular System				
Blood vessel	(50)	(35)	(33)	(50)
Mineralization	1 (2%)		1 (3%)	
Heart	(50)	(35)	(33)	(50)
Cardiomyopathy, chronic	16 (32%)	10 (29%)	15 (45%)	23 (46%)
Inflammation, chronic active			1 (3%)	
Mineralization	1 (2%)		1 (3%)	
Atrium, thrombosis	4 (8%)	1 (3%)	2 (6%)	2 (4%)
Endocrine System				
Adrenal cortex	(50)	(35)	(33)	(50)
Accessory adrenal cortical nodule	2 (4%)		1 (3%)	1 (2%)
Atrophy	1 (2%)			
Degeneration, fatty	24 (48%)	12 (34%)	7 (21%)	14 (28%)
Hyperplasia	17 (34%)	10 (29%)	6 (18%)	17 (34%)
Hypertrophy	1 (2%)		1 (3%)	1 (2%)
Karyomegaly			1 (3%)	1 (2%)
Necrosis	1 (2%)			
Pigmentation, hemosiderin	1 (2%)			
Pigmentation, lipofuscin	3 (6%)	2 (6%)	4 (12%)	7 (14%)
Adrenal medulla	(50)	(35)	(33)	(50)
Hyperplasia	9 (18%)	3 (9%)	1 (3%)	5 (10%)
Islets, pancreatic	(50)	(35)	(33)	(50)
Hyperplasia	1 (2%)			1 (2%)
Parathyroid gland	(48)	(32)	(31)	(45)
Hyperplasia	1 (2%)		1 (3%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Endocrine System (continued)				
Pituitary gland	(50)	(35)	(33)	(50)
Angiectasis	36 (72%)	21 (60%)	19 (58%)	31 (62%)
Mineralization	1 (2%)		1 (3%)	
Pigmentation, hematoidin	1 (2%)	1 (3%)		1 (2%)
Pars distalis, atypia cellular	1 (2%)			
Pars distalis, cyst	21 (42%)	11 (31%)	15 (45%)	29 (58%)
Pars distalis, hyperplasia	9 (18%)	11 (31%)	7 (21%)	17 (34%)
Pars distalis, pigmentation, hemosiderin	32 (64%)	20 (57%)	20 (61%)	31 (62%)
Pars distalis, thrombosis		1 (3%)		
Pars intermedia, cyst		2 (6%)		2 (4%)
Thyroid gland	(50)	(35)	(33)	(50)
Ultimobranchial cyst	1 (2%)			
C-cell, hyperplasia	7 (14%)	5 (14%)	5 (15%)	8 (16%)
Follicle, cyst		1 (3%)		1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(49)	(50)	(50)	(50)
Hyperplasia	2 (4%)	2 (4%)	1 (2%)	10 (20%)
Inflammation, chronic active	6 (12%)	4 (8%)	4 (8%)	7 (14%)
Duct, cyst	1 (2%)		2 (4%)	2 (4%)
Duct, hyperplasia			2 (4%)	
Ovary	(50)	(35)	(33)	(50)
Cyst	3 (6%)	1 (3%)	2 (6%)	4 (8%)
Inflammation, chronic active			1 (3%)	
Interstitial cell, hyperplasia			2 (6%)	
Uterus	(50)	(35)	(33)	(50)
Cyst	2 (4%)		1 (3%)	
Vagina	(1)	(1)	(1)	
Inflammation, suppurative		1 (100%)		
Hematopoietic System				
Bone marrow	(50)	(35)	(33)	(48)
Hyperplasia	19 (38%)	4 (11%)	12 (36%)	10 (21%)
Inflammation, granulomatous				1 (2%)
Lymph node	(45)	(32)	(27)	(43)
Lumbar, hyperplasia, lymphoid				1 (2%)
Mediastinal, hyperplasia, plasma cell				1 (2%)
Mediastinal, pigmentation, hemosiderin	44 (98%)	31 (97%)	27 (100%)	40 (93%)
Pancreatic, pigmentation, hemosiderin	1 (2%)			
Renal, pigmentation, hemosiderin	1 (2%)			
Lymph node, mandibular	(50)	(35)	(33)	(50)
Pigmentation, hemosiderin	2 (4%)	5 (14%)	6 (18%)	4 (8%)
Lymph node, mesenteric	(49)	(35)	(33)	(48)
Ectasia	1 (2%)			
Inflammation, suppurative	1 (2%)			
Pigmentation, hemosiderin	1 (2%)			

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Hematopoietic System (continued)				
Spleen	(50)	(35)	(33)	(50)
Accessory spleen	2 (4%)			
Fibrosis	3 (6%)			
Hematopoietic cell proliferation	2 (4%)	4 (11%)	3 (9%)	1 (2%)
Necrosis		1 (3%)		
Pigmentation, hemosiderin	4 (8%)	5 (14%)	9 (27%)	11 (22%)
Capsule, fibrosis		1 (3%)		
Capsule, inflammation, chronic active		1 (3%)		
Lymphoid follicle, depletion cellular		1 (3%)		
Thymus	(49)	(35)	(31)	(49)
Cyst	1 (2%)	1 (3%)		
Integumentary System				
Mammary gland	(50)	(35)	(33)	(50)
Hyperplasia, cystic	42 (84%)	23 (66%)	27 (82%)	42 (84%)
Duct, cyst	1 (2%)			1 (2%)
Skin	(50)	(50)	(50)	(50)
Hyperkeratosis			1 (2%)	
Hyperplasia, basal cell			1 (2%)	
Inflammation, chronic active			1 (2%)	
Epidermis, hyperplasia			1 (2%)	
Epidermis, ulcer			1 (2%)	
Epidermis, skin, site of application, exudate				2 (4%)
Epidermis, skin, site of application, hyperplasia	1 (2%)		4 (8%)	5 (10%)
Epidermis, skin, site of application, inflammation, chronic active				1 (2%)
Epidermis, skin, site of application, ulcer	1 (2%)		2 (4%)	2 (4%)
Sebaceous gland, skin, site of application, hyperplasia	2 (4%)		2 (4%)	2 (4%)
Skin, site of application, inflammation, chronic active	1 (2%)		2 (4%)	2 (4%)
Musculoskeletal System				
Bone	(50)	(35)	(33)	(48)
Fibrous osteodystrophy	1 (2%)		1 (3%)	
Osteopetrosis	1 (2%)		1 (3%)	
Femur, osteosclerosis		1 (3%)		1 (2%)
Femur, tibia, osteosclerosis				1 (2%)
Joint, arthrosis			1 (3%)	
Joint, tarsal, arthrosis			1 (3%)	
Tibia, fracture		1 (3%)		
Skeletal muscle		(1)		
Inflammation, chronic active		1 (100%)		
Nervous System				
Brain	(50)	(35)	(33)	(50)
Hemorrhage, acute	1 (2%)			1 (2%)
Hydrocephalus	8 (16%)	5 (14%)	3 (9%)	7 (14%)

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	60 mg/kg	120 mg/kg	240 mg/kg
Respiratory System				
Lung	(50)	(35)	(33)	(50)
Congestion, acute	13 (26%)	14 (40%)	8 (24%)	16 (32%)
Foreign body			1 (3%)	
Inflammation, chronic active	3 (6%)	2 (6%)	2 (6%)	4 (8%)
Inflammation, granulomatous				2 (4%)
Inflammation, suppurative	1 (2%)			
Mineralization	1 (2%)		1 (3%)	
Pigmentation, hemosiderin			1 (3%)	
Alveolar epithelium, hyperplasia		1 (3%)		4 (8%)
Alveolus, hemorrhage, acute			1 (3%)	
Alveolus, infiltration cellular, histiocyte	32 (64%)	23 (66%)	20 (61%)	39 (78%)
Interstitium, inflammation, chronic active	9 (18%)	4 (11%)	2 (6%)	5 (10%)
Nose	(50)	(35)	(33)	(50)
Inflammation, chronic active	4 (8%)		2 (6%)	6 (12%)
Nasolacrimal duct, inflammation, chronic active	1 (2%)			
Nasolacrimal duct, inflammation, suppurative	10 (20%)	3 (9%)	1 (3%)	6 (12%)
Special Senses System				
Eye	(3)	(2)	(2)	(5)
Cornea, inflammation, suppurative	1 (33%)			
Lens, cataract	1 (33%)	2 (100%)	2 (100%)	3 (60%)
Retina, degeneration	1 (33%)	1 (50%)	2 (100%)	4 (80%)
Retina, hemorrhage				1 (20%)
Urinary System				
Kidney	(50)	(35)	(33)	(50)
Infarct		1 (3%)		
Mineralization	10 (20%)	22 (63%)	7 (21%)	11 (22%)
Nephropathy, chronic	44 (88%)	25 (71%)	27 (82%)	37 (74%)
Pelvis, transitional epithelium, hyperplasia		1 (3%)		
Renal tubule, pigmentation, hemosiderin			1 (3%)	

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR DERMAL STUDY OF SODIUM XYLENESULFONATE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	3	8	6
Natural deaths	11	10	3	9
Survivors				
Terminal sacrifice	32	37	39	35
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, jejunum	(50)	(12)	(11)	(50)
Liver	(50)	(50)	(50)	(50)
Hemangioma	2 (4%)			1 (2%)
Hemangiosarcoma	2 (4%)		2 (4%)	1 (2%)
Hemangiosarcoma, multiple	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Hemangiosarcoma, metastatic, spleen	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Hepatoblastoma		4 (8%)		2 (4%)
Hepatocellular carcinoma	21 (42%)	17 (34%)	12 (24%)	15 (30%)
Hepatocellular carcinoma, multiple	14 (28%)	14 (28%)	10 (20%)	11 (22%)
Hepatocellular adenoma	15 (30%)	21 (42%)	14 (28%)	13 (26%)
Hepatocellular adenoma, multiple	22 (44%)	11 (22%)	7 (14%)	16 (32%)
Hepatocholangiocarcinoma	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Osteosarcoma, metastatic, uncertain primary site			1 (2%)	
Mesentery	(5)			(4)
Hemangiosarcoma, metastatic, spleen	1 (20%)			
Hepatocholangiocarcinoma, metastatic, liver	1 (20%)			
Liposarcoma, multiple				1 (25%)
Pancreas	(50)	(13)	(11)	(50)
Liposarcoma, metastatic, mesentery				1 (2%)
Salivary glands	(50)	(13)	(11)	(50)
Stomach, forestomach	(50)	(13)	(11)	(50)
Squamous cell papilloma	1 (2%)			1 (2%)
Stomach, glandular	(50)	(13)	(11)	(50)
Cardiovascular System				
Heart	(50)	(13)	(11)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (8%)		
Hemangiosarcoma, metastatic, spleen				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(12)	(11)	(50)
Adrenal medulla	(50)	(12)	(11)	(50)
Pheochromocytoma benign				2 (4%)
Pituitary gland	(49)	(12)	(10)	(50)
Pars distalis, adenoma	1 (2%)			
Thyroid gland	(50)	(13)	(11)	(50)
Follicular cell, adenoma	2 (4%)		1 (9%)	1 (2%)

TABLE C1 #
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
General Body System				
None				
Genital System				
Epididymis	(50)	(13)	(11)	(50)
Liposarcoma, metastatic, mesentery				1 (2%)
Prostate	(50)	(13)	(11)	(50)
Liposarcoma, metastatic, mesentery				1 (2%)
Seminal vesicle	(50)	(13)	(11)	(50)
Hematopoietic System				
Bone marrow	(50)	(13)	(11)	(50)
Hemangiosarcoma			1 (9%)	
Hemangiosarcoma, metastatic, spleen	1 (2%)		1 (9%)	
Lymph node	(3)	(2)	(2)	(3)
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung		1 (50%)		
Mediastinal, hemangiosarcoma, metastatic, liver	1 (33%)			
Mediastinal, hepatocholangiocarcinoma, metastatic, liver	1 (33%)			
Mediastinal, histiocytic sarcoma		1 (50%)		
Lymph node, mandibular	(43)	(7)	(8)	(42)
Lymph node, mesenteric	(50)	(9)	(10)	(47)
Hemangioma	1 (2%)			1 (2%)
Hemangiosarcoma, metastatic, spleen				1 (2%)
Spleen	(50)	(13)	(12)	(49)
Hemangiosarcoma	2 (4%)	1 (8%)	1 (8%)	3 (6%)
Hemangiosarcoma, metastatic, bone marrow			1 (8%)	
Liposarcoma, metastatic, mesentery				1 (2%)
Thymus	(37)	(11)	(6)	(34)
Alveolar/bronchiolar carcinoma, metastatic, lung		1 (9%)		
Hepatocholangiocarcinoma, metastatic, liver	1 (3%)			
Histiocytic sarcoma		1 (9%)		
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Subcutaneous tissue, fibrosarcoma				1 (2%)
Subcutaneous tissue, skin, site of application, hemangioma			1 (2%)	
Subcutaneous tissue, skin, site of application, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, skin, site of application, histiocytic sarcoma		2 (4%)		
Subcutaneous tissue, skin, site of application, lymphoma malignant			1 (2%)	
Musculoskeletal System				
Skeletal muscle				(3)
Hepatocellular carcinoma, metastatic, liver				1 (33%)
Liposarcoma, metastatic, mesentery				1 (33%)

TABLE C1 #
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Nervous System				
Brain	(50)	(13)	(11)	(50)
Respiratory System				
Lung	(50)	(16)	(15)	(50)
Alveolar/bronchiolar adenoma	12 (24%)	4 (25%)	2 (13%)	7 (14%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			2 (4%)
Alveolar/bronchiolar carcinoma	2 (4%)	1 (6%)	1 (7%)	1 (2%)
Hemangiosarcoma, metastatic, spleen				1 (2%)
Hepatoblastoma, metastatic, liver				2 (4%)
Hepatocellular carcinoma, metastatic, liver	12 (24%)	5 (31%)	7 (47%)	11 (22%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma		1 (6%)		
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung		1 (6%)		
Special Senses System				
Harderian gland	(2)		(1)	(3)
Adenoma	1 (50%)		1 (100%)	1 (33%)
Carcinoma				1 (33%)
Urinary System				
Kidney	(50)	(13)	(11)	(50)
Hepatocellular carcinoma, metastatic, liver		1 (8%)		1 (2%)
Renal tubule, adenoma				1 (2%)
Renal tubule, carcinoma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		2 (4%)		
Lymphoma malignant	5 (10%)		4 (8%)	6 (12%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	49	41	36	47
Total primary neoplasms	108	78	60	90
Total animals with benign neoplasms	43	33	24	37
Total benign neoplasms	58	36	26	46
Total animals with malignant neoplasms	39	33	28	33
Total malignant neoplasms	50	42	34	44
Total animals with metastatic neoplasms	15	6	10	16
Total metastatic neoplasms	21	11	11	26
Total animals with malignant neoplasms of uncertain primary site			1	

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: Vehicle Control

Number of Days on Study	4 9 4	5 6 4	5 7 5	5 7 5	6 4 6	6 4 7	6 5 1	6 7 4	6 8 0	6 8 6	6 8 7	6 9 0	6 9 1	6 9 1	6 9 7	7 0 2	7 0 5	7 0 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	0 4 1	0 2 7	0 1 0	0 4 0	0 1 6	0 0 5	0 0 4	0 5 0	0 1 3	0 3 6	0 1 1	0 0 9	0 0 2	0 4 2	0 2 1	0 3 7	0 2 5	0 0 7	0 1 4	0 2 0	0 2 2	0 2 8	0 3 0	0 3 3	0 3 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																		X							
Hemangiosarcoma											X														
Hemangiosarcoma, multiple						X																			X
Hemangiosarcoma, metastatic, spleen										X															
Hepatocellular carcinoma				X	X			X	X	X	X		X	X					X	X			X		X
Hepatocellular carcinoma, multiple	X		X				X									X	X								
Hepatocellular adenoma			X	X	X	X	X				X		X								X		X		X
Hepatocellular adenoma, multiple		X							X			X						X	X			X		X	
Hepatocholangiocarcinoma													X												
Mesentery					+					+			+					+							
Hemangiosarcoma, metastatic, spleen										X															
Hepatocholangiocarcinoma, metastatic, liver													X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma		X																							
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X												
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																X									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																X									
General Body System																									
None																									

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE C2 #
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 3 5	0 3 9	0 4 3	0 0 1	0 0 8	0 1 5	0 2 3	0 2 9	0 3 1	0 3 2	0 4 5	0 0 3	0 0 6	0 1 2	0 1 7	0 1 8	0 1 9	0 2 4	0 2 6	0 3 8	0 4 4	0 4 6	0 4 7	0 4 8	0 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma									X																	2
Hemangiosarcoma																								X		2
Hemangiosarcoma, multiple																		X								3
Hemangiosarcoma, metastatic, spleen																										1
Hepatocellular carcinoma					X	X				X				X	X		X				X		X	X		21
Hepatocellular carcinoma, multiple	X	X	X	X			X				X		X			X									X	14
Hepatocellular adenoma				X						X						X							X	X		15
Hepatocellular adenoma, multiple	X	X	X			X	X	X	X		X			X	X		X	X		X	X				X	22
Hepatocholangiocarcinoma																										1
Mesentery																							+			5
Hemangiosarcoma, metastatic, spleen																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma	X																									2
General Body System																										
None																										

TABLE C2 #
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	4 9 4	5 6 4	5 7 5	5 7 5	6 4 6	6 4 7	6 5 1	6 7 4	6 8 0	6 8 6	6 8 7	6 9 0	6 9 1	6 9 1	6 9 7	7 0 2	7 0 5	7 0 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	0 4 1	0 2 7	0 1 0	0 4 0	0 1 6	0 0 5	0 0 4	0 5 0	0 1 3	0 3 6	0 1 1	0 0 9	0 0 2	0 4 2	0 2 1	0 3 7	0 2 5	0 0 7	0 1 4	0 2 0	0 2 2	0 2 8	0 3 0	0 3 3	0 3 4
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen										X															
Lymph node							+						+												
Mediastinal, hemangiosarcoma, metastatic, liver																									
Mediastinal, hepatocholangiocarcinoma, metastatic, liver													X												
Lymph node, mandibular	+	+	+	M	M	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma			X																						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Thymus	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	M	M	M	+	+	+	+	M	+	+
Hepatocholangiocarcinoma, metastatic, liver													X												
Integumentary System																									
Mammary gland	+	M	M	M	M	+	M	M	+	M	M	+	M	M	M	+	M	M	M	+	M	M	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																			X	X		X			
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma				X					X																
Hepatocellular carcinoma, metastatic, liver			X						X		X						X			X					
Hepatocholangiocarcinoma, metastatic, liver													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2 #
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 3 5	0 3 9	0 4 3	0 0 1	0 0 8	0 1 5	0 2 3	0 2 9	0 3 1	0 3 2	0 4 5	0 0 3	0 0 6	0 1 2	0 1 7	0 1 8	0 1 9	0 2 4	0 2 6	0 3 8	0 4 4	0 4 6	0 4 7	0 4 8	0 4 9	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																										1
Lymph node																		+								3
Mediastinal, hemangiosarcoma, metastatic, liver																		X								1
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																		X								2
Thymus	+	+	+	M	M	+	+	+	+	M	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	37
Hepatocholangiocarcinoma, metastatic, liver																										1
Integumentary System																										
Mammary gland	+	+	M	+	M	+	+	M	M	M	+	+	M	M	M	+	+	M	+	M	M	+	M	M	M	18
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X	X		X	X				X				X		X				X			X	12
Alveolar/bronchiolar adenoma, multiple																					X					1
Alveolar/bronchiolar carcinoma																										2
Hepatocellular carcinoma, metastatic, liver						X				X	X			X			X						X	X		12
Hepatocholangiocarcinoma, metastatic, liver																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2 #
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	4 9 4	5 6 4	5 7 5	5 7 5	6 4 6	6 4 7	6 5 1	6 7 4	6 8 0	6 8 6	6 8 7	6 9 0	6 9 1	6 9 1	6 9 7	7 0 2	7 0 5	7 0 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	0 4 1	0 2 7	0 1 0	0 4 0	0 1 6	0 0 5	0 0 4	0 5 0	0 1 3	0 3 6	0 1 1	0 0 9	0 0 2	0 4 2	0 2 1	0 3 7	0 2 5	0 0 7	0 1 4	0 2 0	0 2 2	0 2 8	0 3 0	0 3 3	0 3 4
Special Senses System																										
Harderian gland										+																
Adenoma										X																
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant							X		X			X			X		X									

TABLE C2 #
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 3 5	0 3 9	0 4 3	0 0 1	0 0 8	0 1 5	0 2 3	0 2 9	0 3 1	0 3 2	0 4 5	0 0 3	0 0 6	0 1 2	0 1 7	0 1 8	0 1 9	0 2 4	0 2 6	0 3 8	0 4 4	0 4 6	0 4 7	0 4 8	0 4 9	Total Tissues/ Tumors
Special Senses System																										
Harderian gland																			+							2
Adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant																										5

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 182 mg/kg

Number of Days on Study	3 2 2	5 4 0	5 8 8	6 1 0	6 2 0	6 3 9	6 5 8	6 5 9	6 7 4	6 8 0	6 8 7	7 0 2	7 0 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 3 4
Carcass ID Number	0 0 6 0	0 6 7	1 0 0	0 7 8	0 8 8	0 8 0	0 7 1	0 9 8	0 5 1	0 7 3	0 6 6	0 5 9	0 9 1	0 5 6	0 5 8 1	0 8 2	0 8 5	0 8 7	0 9 0	0 9 3	0 9 5	0 5 3	0 5 4	0 6 1	0 6 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+												
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+												
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+												
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	M												
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	M												
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+												
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, multiple							X						X	X											
Hemangiosarcoma, metastatic, spleen		X																							
Hepatoblastoma																				X		X			
Hepatocellular carcinoma					X	X				X	X		X							X					
Hepatocellular carcinoma, multiple				X					X			X		X							X	X	X		X
Hepatocellular adenoma	X	X			X						X		X	X			X					X			X
Hepatocellular adenoma, multiple							X					X			X			X		X	X				
Histiocytic sarcoma				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+												
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+												
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+												
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+												
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+												
Alveolar/bronchiolar carcinoma, metastatic, lung												X													
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	M												
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	M												
Islets, pancreatic	+	+	A	+	+	+	+	+	+	+	+	+	+												
Parathyroid gland	+	+	+	M	M	+	M	+	+	+	+	M	+												
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+												
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+												
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+												
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+												
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+												
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+												
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+												
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+												
Lymph node				+								+													
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung												X													
Mediastinal, histiocytic sarcoma				X																					

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 182 mg/kg
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 0 6 4	0 0 6 5	0 0 6 8	0 0 7 2	0 0 7 5	0 0 7 9	0 0 8 3	0 0 8 6	0 0 8 9	0 0 9 2	0 0 9 4	0 0 9 6	0 0 5 2	0 0 5 5	0 0 5 7	0 0 5 8	0 0 6 2	0 0 6 9	0 0 7 0	0 0 7 4	0 0 7 6	0 0 7 7	0 0 8 4	0 0 9 7	0 0 9 9	Total Tissues/ Tumors
Alimentary System																											
Esophagus																											13
Gallbladder																											12
Intestine large, colon																											13
Intestine large, rectum																											13
Intestine large, cecum																											13
Intestine small, duodenum																											12
Intestine small, jejunum																											12
Intestine small, ileum																											13
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, multiple																											3
Hemangiosarcoma, metastatic, spleen																											1
Hepatoblastoma			X																				X				4
Hepatocellular carcinoma		X	X			X	X	X						X	X				X	X		X			X		17
Hepatocellular carcinoma, multiple	X								X		X	X						X					X				14
Hepatocellular adenoma	X	X				X	X		X	X				X	X	X		X		X	X						21
Hepatocellular adenoma, multiple			X		X						X								X				X				11
Histiocytic sarcoma																											1
Pancreas																											13
Salivary glands																											13
Stomach, forestomach																											13
Stomach, glandular																											13
Cardiovascular System																											
Blood vessel																											13
Heart																											13
Alveolar/bronchiolar carcinoma, metastatic, lung																											1
Endocrine System																											
Adrenal cortex																											12
Adrenal medulla																											12
Islets, pancreatic																											12
Parathyroid gland																											9
Pituitary gland																											12
Thyroid gland																											13
General Body System																											
None																											
Genital System																											
Epididymis																											13
Preputial gland																											13
Prostate																											13
Seminal vesicle																											13
Testes																											13
Hematopoietic System																											
Bone marrow																											13
Lymph node																											2
Mediastinal, alveolar/bronchiolar carcinoma, metastatic, lung																											1
Mediastinal, histiocytic sarcoma																											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 182 mg/kg
(continued)

Number of Days on Study	3 2 2	5 4 0	5 8 8	6 1 0	6 2 0	6 3 9	6 5 8	6 5 9	6 7 4	6 8 0	6 8 7	7 0 2	7 0 6	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 4 4	7 4 4	7 3 4
Carcass ID Number	0 6 0	0 6 7	1 0 0	0 7 8	0 8 8	0 8 0	0 8 1	0 9 8	0 5 1	0 7 3	0 6 6	0 5 9	0 9 1	0 5 6	0 8 1	0 8 2	0 8 5	0 8 7	0 9 0	0 9 3	0 9 5	0 5 3	0 5 4	0 6 1	0 6 3
Hematopoietic System (continued)																									
Lymph node, mandibular	+	+	M	M	+	+	+	+	M	M	M	M	+												
Lymph node, mesenteric	+	+	M	+	M	+	+	+	M	+	+	M	+												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+												
Hemangiosarcoma		X																							
Thymus	+	+	+	+	+	+	M	M	+	+	+	+	+												
Alveolar/bronchiolar carcinoma, metastatic, lung												X													
Histiocytic sarcoma				X																					
Integumentary System																									
Mammary gland	M	M	+	M	+	M	M	M	M	M	M	M	M												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, skin, site of application, histiocytic sarcoma				X																X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+												
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+												
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+												
Alveolar/bronchiolar adenoma		X			X		X			X															
Alveolar/bronchiolar carcinoma												X													
Hepatocellular carcinoma, metastatic, liver												X	X												
Histiocytic sarcoma				X																					
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	#											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	#											
Special Senses System																									
None																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+												
Hepatocellular carcinoma, metastatic, liver												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+												
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X																X					

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 182 mg/kg
(continued)

Number of Days on Study	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	0 6 4	0 6 5	0 6 8	0 7 2	0 7 5	0 7 9	0 8 3	0 8 6	0 8 9	0 9 2	0 9 4	0 9 6	0 5 2	0 5 5	0 5 7	0 5 8	0 6 2	0 6 9	0 7 0	0 7 4	0 7 6	0 7 7	0 8 4	0 9 7	0 9 9	Total Tissues/ Tumors
Hematopoietic System (continued)																										
Lymph node, mandibular																										7
Lymph node, mesenteric																										9
Spleen																										13
Hemangiosarcoma																										1
Thymus																										11
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland																										2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, skin, site of application, histiocytic sarcoma																										2
Musculoskeletal System																										
Bone																										13
Nervous System																										
Brain																										13
Respiratory System																										
Lung									+					+					+							16
Alveolar/bronchiolar adenoma																										4
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver									X					X					X							5
Histiocytic sarcoma																										1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nose																										13
Trachea																										13
Special Senses System																										
None																										
Urinary System																										
Kidney																										13
Hepatocellular carcinoma, metastatic, liver																										1
Urinary bladder																										13
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 364 mg/kg

Number of Days on Study	5 0 6	5 4 8	5 6 1	5 7 2	6 1 2	6 3 6	6 4 4	6 8 6	6 8 7	7 1 8	7 2 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 4 0	1 0 3	1 0 6	1 0 9	1 3 0	1 2 2	1 1 0	1 0 2	1 1 8	1 1 4	1 3 9	1 0 5	1 1 5	1 1 6	1 2 0	1 2 4	1 2 6	1 2 9	1 3 2	1 3 6	1 3 7	1 3 8	1 4 2	1 4 4	1 4 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+														
Gallbladder	+	+	+	+	+	+	+	+	+	+	+														
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+														
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+														
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+														
Intestine small, duodenum	+	+	+	+	+	+	M	+	+	+	+														
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+														
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+														
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																						X			
Hemangiosarcoma, multiple																									
Hemangiosarcoma, metastatic, spleen					X																				
Hepatocellular carcinoma		X		X					X	X				X											
Hepatocellular carcinoma, multiple	X		X				X					X			X	X									
Hepatocellular adenoma					X			X						X	X				X						
Hepatocellular adenoma, multiple												X					X					X			
Osteosarcoma, metastatic, uncertain primary site																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+														
Salivary glands	+	+	+	+	+	+	+	+	+	+	+														
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+														
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+														
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+														
Heart	+	+	+	+	+	+	+	+	+	+	+														
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+														
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+														
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+														
Parathyroid gland	+	+	M	M	+	+	M	+	+	M	+														
Pituitary gland	+	+	+	+	+	+	+	+	M	+	+														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+														
Follicular cell, adenoma										X															
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+														
Preputial gland	+	+	+	+	+	+	M	+	+	+	+														
Prostate	+	+	+	+	+	+	+	+	+	+	+														
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+														
Testes	+	+	+	+	+	+	+	+	+	+	+														

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 364 mg/kg
(continued)

Number of Days on Study	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 5 0	1 0 7	1 0 8	1 1 1	1 2 3	1 2 5	1 2 7	1 2 8	1 3 1	1 3 4	1 3 5	1 4 1	1 4 5	1 4 7	1 4 9	1 0 1	1 0 4	1 1 2	1 1 3	1 1 7	1 1 9	1 2 1	1 3 3	1 4 3	1 4 8	Total Tissues/ Tumors
Alimentary System																											
Esophagus																											11
Gallbladder																											11
Intestine large, colon																											11
Intestine large, rectum																											11
Intestine large, cecum																											11
Intestine small, duodenum																											10
Intestine small, jejunum																											11
Intestine small, ileum																											11
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																										2
Hemangiosarcoma, multiple								X														X					2
Hemangiosarcoma, metastatic, spleen																											1
Hepatocellular carcinoma			X					X	X	X												X	X	X			12
Hepatocellular carcinoma, multiple							X								X				X							X	10
Hepatocellular adenoma					X		X	X										X	X		X	X	X			X	14
Hepatocellular adenoma, multiple				X					X	X					X												7
Osteosarcoma, metastatic, uncertain primary site											X																1
Pancreas																											11
Salivary glands																											11
Stomach, forestomach																											11
Stomach, glandular																											11
Cardiovascular System																											
Blood vessel																											11
Heart																											11
Endocrine System																											
Adrenal cortex																											11
Adrenal medulla																											11
Islets, pancreatic																											11
Parathyroid gland																											7
Pituitary gland																											10
Thyroid gland																											11
Follicular cell, adenoma																											1
General Body System																											
None																											
Genital System																											
Epididymis																											11
Preputial gland																											10
Prostate																											11
Seminal vesicle																											11
Testes																											11

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 364 mg/kg
(continued)

Number of Days on Study	5 0 6	5 4 8	5 6 1	5 7 2	6 1 2	6 3 6	6 4 4	6 8 6	6 8 7	7 1 8	7 2 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 4 0	1 0 3	1 0 6	1 0 9	1 3 0	1 2 2	1 1 0	1 0 2	1 1 8	1 1 4	1 3 9	1 0 5	1 1 5	1 1 6	1 2 0	1 2 4	1 2 6	1 2 9	1 3 2	1 3 6	1 3 7	1 3 8	1 4 2	1 4 4	1 4 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+														
Hemangiosarcoma								X																	
Hemangiosarcoma, metastatic, spleen					X																				
Lymph node		+				+																			
Lymph node, mandibular	+	M	+	+	+	+	+	M	+	M	+														
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+														
Spleen	+	+	+	+	+	+	+	+	+	+	+														
Hemangiosarcoma					X																				
Hemangiosarcoma, metastatic, bone marrow								X																	
Thymus	+	M	M	+	+	+	M	+	M	+	M														
Integumentary System																									
Mammary gland	M	+	+	M	M	M	M	M	M	M	M														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, skin, site of application, hemangioma																									
Subcutaneous tissue, skin, site of application, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+														
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+														
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+			+										
Alveolar/bronchiolar adenoma								X		X															
Alveolar/bronchiolar carcinoma						X																			
Hepatocellular carcinoma, metastatic, liver							X		X	X		X				X									
Nose	+	+	+	+	+	+	+	+	+	+	+														
Trachea	+	+	+	+	+	+	+	+	+	+	+														
Special Senses System																									
Harderian gland											+														
Adenoma											X														
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+														
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant		X				X																			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 364 mg/kg
(continued)

Number of Days on Study	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 5 0	1 0 7	1 0 8	1 1 1	1 2 3	1 2 5	1 2 7	1 2 8	1 3 1	1 3 4	1 3 5	1 4 1	1 4 5	1 4 7	1 4 9	1 0 1	1 0 4	1 1 2	1 1 3	1 1 7	1 1 9	1 2 1	1 3 3	1 4 3	1 4 8	Total Tissues/ Tumors
Hematopoietic System																											
Bone marrow																											11
Hemangiosarcoma																											1
Hemangiosarcoma, metastatic, spleen																											1
Lymph node																											2
Lymph node, mandibular																											8
Lymph node, mesenteric																											10
Spleen													+														12
Hemangiosarcoma																											1
Hemangiosarcoma, metastatic, bone marrow																											1
Thymus																											6
Integumentary System																											
Mammary gland																											2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, skin, site of application, hemangioma						X																					1
Subcutaneous tissue, skin, site of application, hemangiosarcoma	X																										1
Musculoskeletal System																											
Bone																											11
Nervous System																											
Brain																											11
Respiratory System																											
Lung								+																+			15
Alveolar/bronchiolar adenoma																											2
Alveolar/bronchiolar carcinoma																											1
Hepatocellular carcinoma, metastatic, liver								X																X			7
Nose																											11
Trachea																											11
Special Senses System																											
Harderian gland																											1
Adenoma																											1
Urinary System																											
Kidney																											11
Urinary bladder																											11
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant	X												X														4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg

Number of Days on Study	4 5 7	5 4 3	5 6 9	5 8 5	6 2 1	6 3 1	6 3 4	6 5 8	6 6 4	6 9 1	7 0 7	7 0 7	7 1 2	7 1 2	7 2 1	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 9 3	1 6 0	1 5 7	2 0 0	1 9 0	1 8 6	1 5 2	1 9 5	1 8 5	1 7 1	1 5 9	1 8 0	1 7 8	1 9 8	1 6 4	1 5 3	1 5 4	1 6 3	1 6 6	1 6 8	1 6 9	1 7 0	1 7 2	1 7 3	1 7 4
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma						X																			
Hemangiosarcoma																									
Hemangiosarcoma, multiple																									
Hemangiosarcoma, metastatic, spleen										X													X		
Hepatoblastoma																		X				X			
Hepatocellular carcinoma	X	X					X			X				X			X					X	X		
Hepatocellular carcinoma, multiple					X			X	X		X		X		X			X							X
Hepatocellular adenoma				X		X				X						X					X	X			X
Hepatocellular adenoma, multiple									X										X	X			X	X	
Mesentery			+		+	+																		+	
Liposarcoma, multiple					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma, metastatic, mesentery					X																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign											X				X										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 8 2	1 8 3	1 8 7	1 9 4	1 9 9	1 5 1	1 5 5	1 6 1	1 6 7	1 7 5	1 7 7	1 8 4	1 8 9	1 9 1	1 9 6	1 5 6	1 5 8	1 6 2	1 6 5	1 7 6	1 7 9	1 8 1	1 8 8	1 9 2	1 9 7	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma	X																									1
Hemangiosarcoma, multiple																				X						1
Hemangiosarcoma, metastatic, spleen								X																		3
Hepatoblastoma																										2
Hepatocellular carcinoma				X	X			X					X						X		X		X			15
Hepatocellular carcinoma, multiple									X											X		X				11
Hepatocellular adenoma			X	X										X			X			X					X	13
Hepatocellular adenoma, multiple	X					X	X		X	X	X	X				X			X			X		X		16
Mesentery																										4
Liposarcoma, multiple																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma, metastatic, mesentery																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma					X																					1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen								X																		1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																						X				1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg
(continued)

Number of Days on Study	4 5 7	5 4 3	5 6 9	5 8 5	6 2 1	6 3 1	6 3 4	6 5 8	6 6 4	6 9 1	7 0 7	7 0 7	7 1 2	7 1 2	7 2 1	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 9 3	1 6 0	1 5 7	2 0 0	1 9 0	1 8 6	1 5 2	1 9 5	1 8 5	1 7 1	1 5 9	1 8 0	1 7 8	1 9 8	1 6 4	1 5 3	1 5 4	1 6 3	1 6 6	1 6 8	1 6 9	1 7 0	1 7 2	1 7 3	1 7 4
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma, metastatic, mesentery					X																			
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma, metastatic, mesentery					X																			
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node												+												
Lymph node, mandibular	+	+	+	M	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma							X																	
Hemangiosarcoma, metastatic, spleen										X														
Spleen	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X													X	
Liposarcoma, metastatic, mesentery					X																			
Thymus	+	M	+	+	M	+	+	M	+	+	M	+	M	+	+	+	M	+	M	+	+	M	M	M	+
Integumentary System																								
Mammary gland	+	M	+	+	M	M	M	+	M	M	M	M	M	M	M	+	M	M	+	M	M	M	+	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																	X							
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+	+								+										
Hepatocellular carcinoma, metastatic, liver														X										
Liposarcoma, metastatic, mesentery					X																			
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X									X	X				X								
Alveolar/bronchiolar adenoma, multiple																								
Alveolar/bronchiolar carcinoma						X																		
Hemangiosarcoma, metastatic, spleen																								
Hepatoblastoma, metastatic, liver																		X				X		
Hepatocellular carcinoma, metastatic, liver	X				X		X	X	X		X			X	X								X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 8 2	1 8 3	1 8 7	1 9 4	1 9 9	1 5 1	1 5 5	1 6 1	1 6 7	1 7 5	1 7 7	1 8 4	1 8 9	1 9 1	1 9 6	1 5 6	1 5 8	1 6 2	1 6 5	1 6 6	1 7 9	1 8 1	1 8 8	1 9 2	1 9 7	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma, metastatic, mesentery																										1
Preputial gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma, metastatic, mesentery																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																					+	+				3
Lymph node, mandibular	+	+	+	M	+	+	M	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	42
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	47
Hemangioma																										1
Hemangiosarcoma, metastatic, spleen																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma								X																		3
Liposarcoma, metastatic, mesentery																										1
Thymus	+	M	M	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	34
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	+	M	+	M	+	M	M	M	M	+	+	+	+	M	+	M	M	15
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										3
Hepatocellular carcinoma, metastatic, liver																										1
Liposarcoma, metastatic, mesentery																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X				X					X											7
Alveolar/bronchiolar adenoma, multiple					X												X									2
Alveolar/bronchiolar carcinoma																										1
Hemangiosarcoma, metastatic, spleen								X																		1
Hepatoblastoma, metastatic, liver																										2
Hepatocellular carcinoma, metastatic, liver				X																X						11
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg
(continued)

Number of Days on Study	4 5 7	5 4 3	5 6 9	5 8 5	6 2 1	6 3 1	6 3 4	6 5 8	6 6 4	6 9 1	7 0 7	7 0 7	7 1 2	7 1 2	7 2 1	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3
Carcass ID Number	1 9 3	1 6 0	1 5 7	2 0 0	1 9 0	1 8 6	1 5 2	1 9 5	1 8 5	1 7 1	1 5 9	1 8 0	1 7 8	1 9 8	1 6 4	1 5 3	1 5 4	1 6 3	1 6 6	1 6 8	1 6 9	1 7 0	1 7 2	1 7 3	1 7 4
Special Senses System																									
Ear												+					+								
Harderian gland																							+		
Adenoma																							X		
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver											X														
Renal tubule, adenoma																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant						X						X													

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg
(continued)

Number of Days on Study	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 4	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	7 3 5	
Carcass ID Number	1 8 2	1 8 3	1 8 7	1 9 4	1 9 9	1 5 1	1 5 5	1 6 1	1 6 7	1 7 5	1 7 7	1 8 4	1 8 9	1 9 1	1 9 6	1 5 6	1 5 8	1 6 2	1 6 5	1 7 6	1 7 9	1 8 1	1 8 8	1 9 2	1 9 7	Total Tissues/ Tumors
Special Senses System																										
Ear																										2
Harderian gland						+																	+			3
Adenoma																										1
Carcinoma						X																				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Renal tubule, adenoma																							X			1
Renal tubule, carcinoma										X																1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant			X	X																		X	X			6

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Liver: Hemangiosarcoma				
Overall rate[a]	5/50 (10%)	3/50 (6%)	4/50 (8%)	2/50 (4%)
Adjusted rate[b]	13.6%	7.4%	10.3%	5.7%
Terminal rate[c]	3/32 (9%)	1/37 (3%)	4/39 (10%)	2/35 (6%)
First incidence (days)	647	658	733 (T)	733 (T)
Life table test[d]	P=0.178N	P=0.313N	P=0.405N	P=0.196N
Logistic regression test[d]	P=0.196N	P=0.356N	P=0.481N	P=0.213N
Cochran-Armitage test[d]	P=0.200N			
Fisher exact test[d]		P=0.357N	P=0.500N	P=0.218N
Liver: Hepatocellular Adenoma				
Overall rate	37/50 (74%)	32/50 (64%)	21/50 (42%)	29/50 (58%)
Adjusted rate	85.6%	72.5%	51.0%	74.0%
Terminal rate	26/32 (81%)	25/37 (68%)	19/39 (49%)	25/35 (71%)
First incidence (days)	564	322	612	585
Life table test	P=0.029N	P=0.080N	P<0.001N	P=0.036N
Logistic regression test	P=0.043N	P=0.194N	P<0.001N	P=0.063N
Cochran-Armitage test	P=0.046N			
Fisher exact test		P=0.194N	P=0.001N	P=0.069N
Liver: Hepatocellular Carcinoma				
Overall rate	35/50 (70%)	31/50 (62%)	22/50 (44%)	26/50 (52%)
Adjusted rate	77.3%	68.8%	47.3%	56.2%
Terminal rate	22/32 (69%)	23/37 (62%)	15/39 (38%)	15/35 (43%)
First incidence (days)	494	610	506	457
Life table test	P=0.037N	P=0.144N	P=0.005N	P=0.056N
Logistic regression test	P=0.030N	P=0.264N	P=0.009N	P=0.051N
Cochran-Armitage test	P=0.030N			
Fisher exact test		P=0.263N	P=0.007N	P=0.050N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	46/50 (92%)	41/50 (82%)	31/50 (62%)	45/50 (90%)
Adjusted rate	93.8%	85.4%	64.3%	93.7%
Terminal rate	29/32 (91%)	30/37 (81%)	22/39 (56%)	32/35 (91%)
First incidence (days)	494	322	506	457
Life table test	P=0.326N	P=0.079N	P=0.001N	P=0.290N
Logistic regression test	P=0.448N	P=0.119N	P<0.001N	P=0.501N
Cochran-Armitage test	P=0.439N			
Fisher exact test		P=0.117N	P<0.001N	P=0.500N
Liver: Hepatoblastoma				
Overall rate	0/50 (0%)	4/50 (8%)	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	10.8%	0.0%	5.7%
Terminal rate	0/32 (0%)	4/37 (11%)	0/39 (0%)	2/35 (6%)
First incidence (days)	—[e]	733 (T)	—	733 (T)
Life table test	P=0.466	P=0.082	—	P=0.258
Logistic regression test	P=0.466	P=0.082	—	P=0.258
Cochran-Armitage test	P=0.444			
Fisher exact test		P=0.059	—	P=0.247

TABLE C3 #
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	35/50 (70%)	31/50 (62%)	22/50 (44%)	26/50 (52%)
Adjusted rate	77.3%	68.8%	47.3%	56.2%
Terminal rate	22/32 (69%)	23/37 (62%)	15/39 (38%)	15/35 (43%)
First incidence (days)	494	610	506	457
Life table test	P=0.037N	P=0.144N	P=0.005N	P=0.056N
Logistic regression test	P=0.030N	P=0.264N	P=0.009N	P=0.051N
Cochran-Armitage test	P=0.030N			
Fisher exact test		P=0.263N	P=0.007N	P=0.050N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	46/50 (92%)	41/50 (82%)	31/50 (62%)	45/50 (90%)
Adjusted rate	93.8%	85.4%	64.3%	93.7%
Terminal rate	29/32 (91%)	30/37 (81%)	22/39 (56%)	32/35 (91%)
First incidence (days)	494	322	506	457
Life table test	P=0.326N	P=0.079N	P=0.001N	P=0.290N
Logistic regression test	P=0.448N	P=0.119N	P<0.001N	P=0.501N
Cochran-Armitage test	P=0.439N			
Fisher exact test		P=0.117N	P<0.001N	P=0.500N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	13/50 (26%)	4/16 (25%)[f]	2/15 (13%)[f]	9/50 (18%)
Adjusted rate	40.6%			22.9%
Terminal rate	13/32 (41%)			6/35 (17%)
First incidence (days)	733 (T)			543
Life table test				P=0.160N
Logistic regression test				P=0.212N
Fisher exact test				P=0.235N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	1/16 (6%)[f]	1/15 (7%)[f]	1/50 (2%)
Adjusted rate	4.4%			2.2%
Terminal rate	0/32 (0%)			0/35 (0%)
First incidence (days)	575			631
Life table test				P=0.508N
Logistic regression test				P=0.470N
Fisher exact test				P=0.500N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	15/50 (30%)	5/16 (31%)[f]	3/15 (20%)[f]	10/50 (20%)
Adjusted rate	43.2%			24.6%
Terminal rate	13/32 (41%)			6/35 (17%)
First incidence (days)	575			543
Life table test				P=0.128N
Logistic regression test				P=0.175N
Fisher exact test				P=0.178N

TABLE C3 #
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Spleen: Hemangiosarcoma				
Overall rate	2/50 (4%)	1/13 (8%)[f]	1/12 (8%)[f]	3/49 (6%)
Adjusted rate	5.5%			8.0%
Terminal rate	1/32 (3%)			2/35 (6%)
First incidence (days)	686			691
Life table test				P=0.531
Logistic regression test				P=0.498
Fisher exact test				P=0.490
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	2/50 (4%)	0/13 (0%)[f]	1/11 (9%)[f]	1/50 (2%)
Adjusted rate	5.9%			2.9%
Terminal rate	1/32 (3%)			1/35 (3%)
First incidence (days)	702			733 (T)
Life table test				P=0.464N
Logistic regression test				P=0.490N
Fisher exact test				P=0.500N
All Organs: Hemangioma				
Overall rate	3/50 (6%)	0/50 (0%)[f]	1/50 (2%)[f]	2/50 (4%)
Adjusted rate	8.0%			4.4%
Terminal rate	1/32 (3%)			0/35 (0%)
First incidence (days)	575			631
Life table test				P=0.483N
Logistic regression test				P=0.484N
Fisher exact test				P=0.500N
All Organs: Hemangiosarcoma				
Overall rate	6/50 (12%)	4/50 (8%)[f]	6/50 (12%)[f]	5/50 (10%)
Adjusted rate	15.7%			13.6%
Terminal rate	3/32 (9%)			4/35 (11%)
First incidence (days)	647			691
Life table test				P=0.458N
Logistic regression test				P=0.496N
Fisher exact test				P=0.500N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	9/50 (18%)	4/50 (8%)[f]	7/50 (14%)[f]	7/50 (14%)
Adjusted rate	22.7%			17.4%
Terminal rate	4/32 (13%)			4/35 (11%)
First incidence (days)	575			631
Life table test				P=0.356N
Logistic regression test				P=0.393N
Fisher exact test				P=0.393N

TABLE C3 #
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
All Organs: Malignant Lymphoma				
Overall rate	5/50 (10%)	0/50 (0%)[f]	4/50 (27%)[f]	6/50 (12%)
Adjusted rate	12.3%			15.6%
Terminal rate	0/32 (0%)			4/35 (11%)
First incidence (days)	651			631
Life table test				P=0.550
Logistic regression test				P=0.500
Fisher exact test				P=0.500
All Organs: Benign Neoplasms				
Overall rate	43/50 (86%)	33/50 (66%)[f]	24/50 (48%)[f]	37/50 (74%)
Adjusted rate	95.4%			83.9%
Terminal rate	30/32 (94%)			28/35 (80%)
First incidence (days)	564			543
Life table test				P=0.071N
Logistic regression test				P=0.100N
Fisher exact test				P=0.105N
All Organs: Malignant Neoplasms				
Overall rate	39/50 (78%)	33/50 (66%)[f]	29/50 (58%)[f]	33/50 (66%)
Adjusted rate	81.1%			68.7%
Terminal rate	23/32 (72%)			20/35 (57%)
First incidence (days)	494			457
Life table test				P=0.129N
Logistic regression test				P=0.136N
Fisher exact test				P=0.133N
All Organs: Benign or Malignant Neoplasms				
Overall rate	49/50 (98%)	41/50 (82%)[f]	37/50 (74%)[f]	47/50 (94%)
Adjusted rate	98.0%			95.9%
Terminal rate	31/32 (97%)			33/35 (94%)
First incidence (days)	494			457
Life table test				P=0.218N
Logistic regression test				P=0.305N
Fisher exact test				P=0.309N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, spleen, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Tissues (except skin) were examined microscopically only in those animals dying prior to terminal sacrifice or when it was observed to be abnormal at necropsy; thus statistical comparisons with the controls are not applicable.

TABLE C4
Historical Incidence of Hepatocellular Neoplasms in Control Male B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus: Dermal (Acetone) Studies			
4-Vinyl-1-cyclohexene Diepoxide	18/50	6/50	23/50
Triethanolamine	27/50	15/50	31/50
Overall Historical Incidence: Dermal (Acetone) Studies			
Total	51/150 (34.0%)	25/150 (16.7%)	63/150 (42.0%)
Standard deviation	21.1%	11.7%	22.3%
Range	12%-54%	8%-30%	18%-62%
Historical Incidence at Battelle Columbus: Dermal (Ethanol) Study			
Benzethonium Chloride	24/50 (48.0%)	10/50 (20.0%)	29/50 (58.0%)
Historical Incidence at Battelle Columbus: Feed Studies			
4,4-Thiobis(6-*t*-butyl-*m*-cresol)	17/50	11/50	25/50
5,5-Diphenylhydantoin	19/50	13/50	29/50
Pentachlorophenol (Dowicide EC-7)	5/35	1/35	6/35
Ethylene Thiourea	11/49	13/49	20/49
Polybrominated Biphenyls (Firemaster FF-1®)	9/50	8/50	16/50
Manganese (II) Sulfate Monohydrate	30/50	9/50	34/50
Oxazepam	17/49	9/49	23/49
Technical Grade Pentachlorophenol	5/32	2/32	7/32
Triamterene	17/50	5/50	20/50
Triamterene	21/50	9/50	25/50
Tricresyl Phosphate	18/52	15/52	28/52
Overall Historical Incidence: Feed Studies			
Total	413/1,465 (29.2%)	252/1,465 (17.2%)	596/1,465 (40.7%)
Standard deviation	14.2%	7.1%	14.5%
Range	4%-60%	3%-29%	10%-68%

[a] Data as of 12 May 1995

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	7	3	8	6
Natural deaths	11	10	3	9
Survivors				
Terminal sacrifice	32	37	39	35
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, duodenum	(50)	(12)	(10)	(50)
Necrosis	1 (2%)			
Ulcer	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis	2 (4%)	2 (4%)		1 (2%)
Basophilic focus	2 (4%)	6 (12%)	3 (6%)	4 (8%)
Clear cell focus	4 (8%)	3 (6%)	3 (6%)	8 (16%)
Eosinophilic focus	13 (26%)	11 (22%)	12 (24%)	9 (18%)
Hematopoietic cell proliferation	3 (6%)		1 (2%)	
Hemorrhage	1 (2%)			
Infarct			1 (2%)	
Inflammation, chronic active	46 (92%)	44 (88%)	41 (82%)	43 (86%)
Mixed cell focus	3 (6%)	4 (8%)	5 (10%)	7 (14%)
Necrosis	8 (16%)	5 (10%)	2 (4%)	8 (16%)
Thrombosis	1 (2%)		1 (2%)	
Vacuolization cytoplasmic		2 (4%)	1 (2%)	1 (2%)
Bile duct, hyperplasia	43 (86%)	41 (82%)	36 (72%)	37 (74%)
Kupffer cell, pigmentation	1 (2%)			
Mesentery	(5)			(4)
Hemorrhage				1 (25%)
Artery, inflammation, chronic active	1 (20%)			1 (25%)
Fat, inflammation	1 (20%)			
Vein, thrombosis	1 (20%)			1 (25%)
Pancreas	(50)	(13)	(11)	(50)
Atrophy	3 (6%)		1 (9%)	4 (8%)
Cytoplasmic alteration	4 (8%)			
Necrosis	1 (2%)		1 (9%)	
Artery, inflammation, chronic active	2 (4%)			
Salivary glands	(50)	(13)	(11)	(50)
Atrophy				1 (2%)
Necrosis			1 (9%)	
Stomach, forestomach	(50)	(13)	(11)	(50)
Cyst	1 (2%)			
Hyperplasia, focal	1 (2%)		1 (9%)	2 (4%)
Ulcer	2 (4%)			
Stomach, glandular	(50)	(13)	(11)	(50)
Erosion				1 (2%)
Mineralization				1 (2%)
Artery, inflammation, chronic active				1 (2%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Cardiovascular System				
Blood vessel	(50)	(13)	(11)	(50)
Aorta, inflammation, chronic active	1 (2%)		1 (9%)	1 (2%)
Heart	(50)	(13)	(11)	(50)
Degeneration	2 (4%)	1 (8%)	1 (9%)	1 (2%)
Mineralization	1 (2%)			2 (4%)
Artery, inflammation, chronic active	1 (2%)			1 (2%)
Atrium, thrombosis	1 (2%)	1 (8%)	1 (9%)	1 (2%)
Ventricle, thrombosis		1 (8%)		
Endocrine System				
Adrenal cortex	(50)	(12)	(11)	(50)
Accessory adrenal cortical nodule	2 (4%)		1 (9%)	1 (2%)
Degeneration, cystic				1 (2%)
Hemorrhage				1 (2%)
Hyperplasia	11 (22%)	1 (8%)	1 (9%)	19 (38%)
Inflammation, chronic active				1 (2%)
Capsule, hyperplasia, adenomatous				4 (8%)
Adrenal medulla	(50)	(12)	(11)	(50)
Hyperplasia	2 (4%)	2 (17%)	1 (9%)	1 (2%)
Islets, pancreatic	(50)	(12)	(11)	(50)
Hyperplasia	9 (18%)		2 (18%)	9 (18%)
Parathyroid gland	(46)	(9)	(7)	(42)
Cyst				1 (2%)
Pituitary gland	(49)	(12)	(10)	(50)
Cyst	2 (4%)			2 (4%)
Pars distalis, hyperplasia	2 (4%)			2 (4%)
Pars intermedia, hyperplasia				2 (4%)
Thyroid gland	(50)	(13)	(11)	(50)
Follicular cell, hyperplasia	6 (12%)	2 (15%)		10 (20%)
General Body System				
None				
Genital System				
Epididymis	(50)	(13)	(11)	(50)
Granuloma sperm	2 (4%)			2 (4%)
Artery, inflammation, chronic active			1 (9%)	1 (2%)
Preputial gland	(50)	(13)	(10)	(49)
Inflammation, chronic active	1 (2%)			
Duct, cyst	7 (14%)	1 (8%)	4 (40%)	6 (12%)
Prostate	(50)	(13)	(11)	(50)
Degeneration			1 (9%)	
Artery, inflammation, chronic active			1 (9%)	1 (2%)
Seminal vesicle	(50)	(13)	(11)	(50)
Degeneration			1 (9%)	
Testes	(50)	(13)	(11)	(50)
Atrophy				2 (4%)
Artery, inflammation, chronic active				1 (2%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Hematopoietic System				
Bone marrow	(50)	(13)	(11)	(50)
Angiectasis	1 (2%)			
Hyperplasia	17 (34%)	3 (23%)	4 (36%)	23 (46%)
Infiltration cellular, mast cell	1 (2%)			
Infiltration cellular, plasma cell	1 (2%)			
Myelofibrosis	1 (2%)			
Thrombosis				1 (2%)
Lymph node	(3)	(2)	(2)	(3)
Mediastinal, angiectasis				1 (33%)
Mediastinal, hematopoietic cell proliferation	1 (33%)			
Lymph node, mesenteric	(50)	(9)	(10)	(47)
Angiectasis	1 (2%)			
Hematopoietic cell proliferation	1 (2%)		1 (10%)	
Hyperplasia, histiocytic				1 (2%)
Hyperplasia, lymphoid	1 (2%)		1 (10%)	
Hyperplasia, plasma cell				1 (2%)
Spleen	(50)	(13)	(12)	(49)
Hematopoietic cell proliferation	27 (54%)	8 (62%)	8 (67%)	25 (51%)
Lymphoid follicle, depletion cellular				1 (2%)
Lymphoid follicle, hyperplasia	1 (2%)			
Thymus	(37)	(11)	(6)	(34)
Atrophy	9 (24%)	5 (45%)	2 (33%)	6 (18%)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Epidermis, skin, site of application, exudate		1 (2%)	1 (2%)	1 (2%)
Epidermis, skin, site of application, hyperkeratosis			1 (2%)	
Epidermis, skin, site of application, hyperplasia	1 (2%)		4 (8%)	5 (10%)
Epidermis, skin, site of application, ulcer				1 (2%)
Subcutaneous tissue, edema	1 (2%)		1 (2%)	1 (2%)
Subcutaneous tissue, inflammation, suppurative			1 (2%)	
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(13)	(11)	(50)
Inflammation			1 (9%)	
Artery, inflammation, chronic active			1 (9%)	
Corpus callosum, degeneration				1 (2%)
Neuron, necrosis		1 (8%)	1 (9%)	

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Respiratory System				
Lung	(50)	(16)	(15)	(50)
Inflammation			1 (7%)	
Pigmentation, hemosiderin			1 (7%)	
Thrombosis			1 (7%)	
Alveolar epithelium, hyperplasia		2 (13%)	1 (7%)	2 (4%)
Mediastinum, angiectasis	1 (2%)			
Nose	(50)	(13)	(11)	(50)
Inflammation, suppurative				1 (2%)
Special Senses System				
Ear				(2)
Inflammation				1 (50%)
Harderian gland	(2)		(1)	(3)
Hyperplasia	1 (50%)			1 (33%)
Urinary System				
Kidney	(50)	(13)	(11)	(50)
Cyst	5 (10%)			8 (16%)
Glomerulosclerosis	2 (4%)	1 (8%)		4 (8%)
Hydronephrosis				1 (2%)
Infarct	1 (2%)			1 (2%)
Mineralization				4 (8%)
Nephropathy	43 (86%)	10 (77%)	8 (73%)	43 (86%)
Pigmentation, hemosiderin	1 (2%)		1 (9%)	1 (2%)
Artery, inflammation, chronic active			1 (9%)	1 (2%)
Glomerulus, infarct	1 (2%)			
Glomerulus, thrombosis			1 (9%)	
Renal tubule, hyperplasia				1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR DERMAL STUDY OF SODIUM XYLENESULFONATE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	12	7	9	6
Natural deaths	7	10	9	8
Survivors				
Terminal sacrifice	31	32	32	36
Missing		1		
Animals examined microscopically	50	49	50	50
Alimentary System				
Gallbladder	(49)	(17)	(18)	(50)
Leiomyosarcoma, metastatic, intestine small, jejunum			1 (6%)	
Intestine large, cecum	(50)	(16)	(18)	(50)
Leiomyosarcoma			1 (6%)	
Intestine small, jejunum	(49)	(16)	(18)	(50)
Fibrosarcoma, metastatic, skin				1 (2%)
Leiomyosarcoma			1 (6%)	
Liver	(50)	(49)	(50)	(50)
Hemangioma	2 (4%)			
Hemangiosarcoma		1 (2%)	1 (2%)	
Hepatocellular carcinoma	9 (18%)	10 (20%)	7 (14%)	8 (16%)
Hepatocellular carcinoma, multiple	1 (2%)	3 (6%)		2 (4%)
Hepatocellular adenoma	10 (20%)	8 (16%)	14 (28%)	19 (38%)
Hepatocellular adenoma, multiple	8 (16%)	9 (18%)	4 (8%)	9 (18%)
Hepatocholangiocarcinoma	1 (2%)		1 (2%)	2 (4%)
Histiocytic sarcoma	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Leiomyosarcoma, metastatic, intestine small, jejunum			1 (2%)	
Mesentery	(7)	(6)	(5)	(12)
Fibrosarcoma, metastatic, skin				1 (8%)
Hemangioma				1 (8%)
Hepatocholangiocarcinoma, metastatic, liver	1 (14%)		1 (20%)	2 (17%)
Histiocytic sarcoma	1 (14%)	1 (17%)	1 (20%)	
Leiomyosarcoma, metastatic, intestine small, jejunum			1 (20%)	
Pancreas	(50)	(17)	(18)	(50)
Fibrosarcoma, metastatic, skin				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)		1 (6%)	
Histiocytic sarcoma	1 (2%)	1 (6%)	1 (6%)	
Leiomyosarcoma, metastatic, intestine small, jejunum			1 (6%)	
Salivary glands	(50)	(17)	(18)	(50)
Stomach, forestomach	(50)	(17)	(18)	(50)
Squamous cell papilloma		2 (12%)		
Stomach, glandular	(50)	(17)	(18)	(50)
Carcinoma			1 (6%)	
Hepatocholangiocarcinoma, metastatic, liver			1 (6%)	
Histiocytic sarcoma	1 (2%)			

TABLE D1 #
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Cardiovascular System				
Blood vessel	(50)	(17)	(18)	(50)
Aorta, hepatocholangiocarcinoma, metastatic, liver			1 (6%)	
Heart	(50)	(17)	(18)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (6%)	
Histiocytic sarcoma	2 (4%)	1 (6%)		
Endocrine System				
Adrenal cortex	(50)	(17)	(18)	(50)
Hepatocholangiocarcinoma, metastatic, liver			1 (6%)	
Capsule, adenoma	1 (2%)			1 (2%)
Adrenal medulla	(50)	(17)	(18)	(48)
Pheochromocytoma benign				1 (2%)
Islets, pancreatic	(50)	(17)	(18)	(50)
Adenoma	1 (2%)		1 (6%)	
Carcinoma	1 (2%)			
Pituitary gland	(50)	(17)	(18)	(49)
Meningioma malignant, metastatic, brain		1 (6%)		
Pars distalis, adenoma	7 (14%)	3 (18%)	1 (6%)	5 (10%)
Pars intermedia, adenoma	1 (2%)			2 (4%)
Pars intermedia, carcinoma				1 (2%)
Thyroid gland	(50)	(48)	(50)	(50)
Follicular cell, adenoma	1 (2%)	5 (10%)	1 (2%)	6 (12%)
Follicular cell, adenoma, multiple	1 (2%)			
Follicular cell, carcinoma				1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(49)	(15)	(15)	(46)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Ovary	(50)	(17)	(18)	(49)
Cystadenoma		1 (6%)		1 (2%)
Fibrosarcoma, metastatic, skin				1 (2%)
Hemangioma			1 (6%)	
Hepatocholangiocarcinoma, metastatic, liver			1 (6%)	
Histiocytic sarcoma	1 (2%)	1 (6%)	1 (6%)	1 (2%)
Teratoma benign	1 (2%)			
Uterus	(50)	(17)	(18)	(50)
Hemangiosarcoma				1 (2%)
Histiocytic sarcoma		2 (12%)		1 (2%)
Leiomyosarcoma, metastatic, intestine small, jejunum			1 (6%)	
Polyp stromal	3 (6%)	1 (6%)		

TABLE D1 #
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Hematopoietic System				
Bone marrow	(50)	(17)	(18)	(50)
Histiocytic sarcoma	1 (2%)	2 (12%)		
Lymph node	(7)	(3)	(6)	(6)
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung			1 (17%)	
Inguinal, histiocytic sarcoma			1 (17%)	
Lumbar, histiocytic sarcoma		2 (67%)		2 (33%)
Mediastinal, hepatocholangiocarcinoma, metastatic, liver	1 (14%)		1 (17%)	1 (17%)
Mediastinal, histiocytic sarcoma	1 (14%)	1 (33%)		1 (17%)
Pancreatic, histiocytic sarcoma			1 (17%)	
Renal, hepatocholangiocarcinoma, metastatic, liver				1 (17%)
Renal, histiocytic sarcoma			1 (17%)	1 (17%)
Thoracic, fibrosarcoma, metastatic, skin	1 (14%)			
Lymph node, mandibular	(49)	(15)	(15)	(48)
Carcinoma, metastatic, harderian gland		1 (7%)		
Histiocytic sarcoma	2 (4%)			1 (2%)
Lymph node, mesenteric	(48)	(17)	(17)	(50)
Fibrosarcoma, metastatic, skin				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver			1 (6%)	2 (4%)
Histiocytic sarcoma	2 (4%)	2 (12%)	1 (6%)	2 (4%)
Leiomyosarcoma, metastatic, intestine small, jejunum			1 (6%)	
Spleen	(50)	(17)	(18)	(50)
Hemangiosarcoma		1 (6%)		2 (4%)
Histiocytic sarcoma	3 (6%)		1 (6%)	1 (2%)
Thymus	(38)	(16)	(16)	(44)
Alveolar/bronchiolar carcinoma, metastatic, lung			1 (6%)	
Hepatocholangiocarcinoma, metastatic, liver			1 (6%)	2 (5%)
Histiocytic sarcoma	1 (3%)			1 (2%)
Integumentary System				
Mammary gland	(50)	(17)	(16)	(50)
Carcinoma				1 (2%)
Skin	(50)	(49)	(50)	(50)
Subcutaneous tissue, fibrosarcoma	1 (2%)			1 (2%)
Subcutaneous tissue, hemangiosarcoma				1 (2%)
Subcutaneous tissue, skin, site of application, fibrosarcoma		1 (2%)	1 (2%)	
Musculoskeletal System				
Bone	(50)	(17)	(18)	(50)
Osteosarcoma	1 (2%)			
Skeletal muscle			(1)	(3)
Fibrosarcoma, metastatic, skin				1 (33%)
Hepatocholangiocarcinoma, metastatic, liver			1 (100%)	2 (67%)

TABLE D1 #
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Nervous System				
Brain	(50)	(17)	(18)	(50)
Carcinoma, metastatic, harderian gland		1 (6%)		
Histiocytic sarcoma	1 (2%)			
Meningioma malignant		1 (6%)		
Respiratory System				
Lung	(50)	(18)	(18)	(50)
Alveolar/bronchiolar adenoma	4 (8%)	1 (6%)	2 (11%)	6 (12%)
Alveolar/bronchiolar carcinoma	2 (4%)		1 (6%)	
Carcinoma, metastatic, harderian gland	1 (2%)	2 (11%)		1 (2%)
Fibrosarcoma, metastatic, skin	1 (2%)			
Hepatocellular carcinoma, metastatic, liver	2 (4%)	2 (11%)	1 (6%)	3 (6%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)		1 (6%)	2 (4%)
Histiocytic sarcoma	3 (6%)	1 (6%)		2 (4%)
Leiomyosarcoma, metastatic, intestine small, jejunum			1 (6%)	
Leiomyosarcoma, metastatic, intestine large, cecum			1 (6%)	
Squamous cell carcinoma, metastatic, urinary bladder				1 (2%)
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung			1 (6%)	
Nose	(50)	(17)	(18)	(50)
Histiocytic sarcoma				1 (2%)
Special Senses System				
Eye	(1)	(2)		
Carcinoma, metastatic, harderian gland		1 (50%)		
Harderian gland	(5)	(2)	(1)	(3)
Adenoma	2 (40%)			1 (33%)
Carcinoma	1 (20%)	2 (100%)	1 (100%)	2 (67%)
Bilateral, adenoma	1 (20%)			
Urinary System				
Kidney	(50)	(17)	(18)	(50)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	3 (6%)	2 (12%)		
Urinary bladder	(50)	(17)	(18)	(50)
Squamous cell carcinoma				1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(49)	(50)	(50)
Histiocytic sarcoma	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Lymphoma malignant	8 (16%)	3 (6%)	3 (6%)	5 (10%)

TABLE D1 #
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued) #

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Neoplasm Summary				
Total animals with primary neoplasms[c]	45	34	31	44
Total primary neoplasms	71	54	44	82
Total animals with benign neoplasms	29	22	20	35
Total benign neoplasms	43	30	24	52
Total animals with malignant neoplasms	25	22	18	26
Total malignant neoplasms	28	24	20	30
Total animals with metastatic neoplasms	5	5	5	8
Total metastatic neoplasms	9	8	24	25

[a] Number of animals examined microscopically at the site and the number of animals with neoplasm
[b] Number of animals with any tissue examined microscopically
[c] Primary neoplasms: all neoplasms except metastatic neoplasms

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: Vehicle Control

Number of Days on Study	2 9 2	4 5 3	4 6 1	4 9 5	4 9 9	5 8 9	6 2 0	6 2 1	6 2 1	6 5 9	6 5 9	6 7 0	6 7 9	6 8 0	6 9 2	7 0 1	7 2 2	7 2 6	7 3 4	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0
Carcass ID Number	2 0 3	2 3 2	2 4 8	2 0 5	2 4 0	2 4 6	2 2 6	2 2 1	2 3 0	2 1 1	2 3 7	2 1 5	2 1 6	2 1 0	2 4 1	2 4 7	2 4 9	2 0 9	2 3 5	2 0 6	2 0 8	2 1 4	2 2 2	2 2 3	2 2 5
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma												X													
Hepatocellular carcinoma				X	X					X				X		X								X	
Hepatocellular carcinoma, multiple																			X						
Hepatocellular adenoma								X									X								X
Hepatocellular adenoma, multiple																							X		
Hepatocholangiocarcinoma							X																		
Histiocytic sarcoma					X				X				X												
Mesentery							+			+			+		+							+			
Hepatocholangiocarcinoma, metastatic, liver							X																		
Histiocytic sarcoma													X												
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver							X																		
Histiocytic sarcoma									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X								X												
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Carcinoma				X																					
Parathyroid gland	+	+	+	+	+	+	+	M	+	M	M	+	M	M	+	+	+	+	M	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X								X									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																							X		
Follicular cell, adenoma, multiple								X																	

+: Tissue examined microscopically
A: Autolysis precludes examination
M: Missing tissue
I: Insufficient tissue
X: Lesion present
Blank: Not examined

TABLE D2 #
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	2 3 1	2 3 8	2 4 3	2 4 5	2 0 1	2 0 4	2 2 4	2 2 8	2 3 4	2 3 6	2 4 2	2 5 0	2 0 2	2 0 7	2 1 2	2 1 3	2 1 7	2 1 8	2 1 9	2 2 0	2 2 7	2 2 9	2 3 3	2 3 9	2 4 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																			X							2
Hepatocellular carcinoma		X					X																		X	9
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma						X						X			X		X			X				X	X	10
Hepatocellular adenoma, multiple	X		X					X	X				X									X	X			8
Hepatocholangiocarcinoma																										1
Histiocytic sarcoma																										3
Mesentery																					+				+	7
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma				X																						1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Parathyroid gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	M	+	+	+	+	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X			X		X							X				X							7
Pars intermedia, adenoma																			X							1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
Follicular cell, adenoma, multiple																										1

TABLE D2 #
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	2 9 2	4 5 3	4 6 1	4 9 5	4 9 9	5 8 9	6 2 0	6 2 1	6 2 1	6 5 9	6 5 9	6 7 0	6 7 9	6 8 0	6 9 2	7 0 1	7 2 2	7 2 6	7 3 4	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0
Carcass ID Number	2 0 3	2 3 2	2 4 8	2 0 5	2 4 0	2 4 6	2 2 6	2 2 1	2 3 0	2 1 1	2 3 7	2 1 5	2 1 6	2 1 0	2 4 1	2 4 7	2 4 9	2 0 9	2 3 5	2 0 6	2 0 8	2 1 4	2 2 2	2 2 3	2 2 5
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Teratoma benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																			X						
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Lymph node							+		+						+		+	+						+	
Mediastinal, hepatocholangiocarcinoma, metastatic, liver							X																		
Mediastinal, histiocytic sarcoma									X																
Thoracic, fibrosarcoma, metastatic, skin																	X								
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X				X																
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X				X																
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X				X				X												
Thymus	+	+	+	M	+	+	M	+	+	M	M	+	+	M	+	+	M	+	M	+	+	M	M	+	+
Histiocytic sarcoma					X																				
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma																	X								
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Peripheral nerve				+																					
Spinal cord				+																					

TABLE D2 #
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	2 3 1	2 3 8	2 4 3	2 4 5	2 0 1	2 0 4	2 2 4	2 2 8	2 3 4	2 3 6	2 4 2	2 5 0	2 0 2	2 0 7	2 1 2	2 1 3	2 1 7	2 1 8	2 1 9	2 2 0	2 2 7	2 2 9	2 3 3	2 3 9	2 4 4	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Teratoma benign										X																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal				X							X															3
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node																			+							7
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																										1
Mediastinal, histiocytic sarcoma																										1
Thoracic, fibrosarcoma, metastatic, skin																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	48
Histiocytic sarcoma																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Thymus	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	38
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma					X																					1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Peripheral nerve																										1
Spinal cord																										1

TABLE D2 #
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	2 9 2	4 5 3	4 6 1	4 9 5	4 9 9	5 8 9	6 2 0	6 2 1	6 2 1	6 5 9	6 5 9	6 7 0	6 7 9	6 8 0	6 9 2	7 0 1	7 2 2	7 2 6	7 3 4	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0
Carcass ID Number	2 0 3	2 3 2	2 4 8	2 0 5	2 4 0	2 4 6	2 2 6	2 2 1	2 3 0	2 1 1	2 3 7	2 1 5	2 1 6	2 1 0	2 4 1	2 4 7	2 4 9	2 0 9	2 3 5	2 0 6	2 0 8	2 1 4	2 2 2	2 2 3	2 2 5
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X							X				X			
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, harderian gland		X																							
Fibrosarcoma, metastatic, skin																	X								
Hepatocellular carcinoma, metastatic, liver										X				X											
Hepatocholangiocarcinoma, metastatic, liver							X																		
Histiocytic sarcoma					X				X				X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye												+													
Harderian gland		+										+										+	+		
Adenoma												X													
Carcinoma		X																							
Bilateral, adenoma																						X			
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X				X				X												
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X				X				X												
Lymphoma malignant															X						X			X	

TABLE D2 #
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: # Vehicle Control (continued) #

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	2 3 1	2 3 8	2 4 3	2 4 5	2 0 1	2 0 4	2 2 4	2 2 8	2 3 4	2 3 6	2 4 2	2 5 0	2 0 2	2 0 7	2 1 2	2 1 3	2 1 7	2 1 8	2 1 9	2 2 0	2 2 7	2 2 9	2 3 3	2 3 9	2 4 4	Total Tissues/ Tumors
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																4
Alveolar/bronchiolar carcinoma										X											X					2
Carcinoma, metastatic, harderian gland																										1
Fibrosarcoma, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																										2
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye																										1
Harderian gland																			+							5
Adenoma																			X							2
Carcinoma																										1
Bilateral, adenoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										3
Lymphoma malignant	X					X			X									X	X							8

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 182 mg/kg

Number of Days on Study	0 2 4	3 3 7	4 1 1	4 4 6	4 6 7	5 3 8	6 0 4	6 2 5	6 3 6	6 4 2	6 5 9	6 6 6	6 7 4	7 1 2	7 1 8	7 3 1	7 3 5	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0
Carcass ID Number	2 7 1	2 8 6	2 8 9	2 5 5	2 9 5	2 7 0	2 7 7	2 8 7	2 5 7	2 9 0	2 8 3	2 7 8	2 5 2	2 9 4	2 8 2	2 9 6	2 6 5	2 5 1	2 5 3	2 5 9	2 6 1	2 6 2	2 6 3	2 6 4
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+							
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+							
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+							
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Hepatocellular carcinoma			X					X									X	X	X			X	X	
Hepatocellular carcinoma, multiple																								
Hepatocellular adenoma				X																				
Hepatocellular adenoma, multiple								X						X				X			X			X
Histiocytic sarcoma					X										X									
Mesentery					+			+					+	+		+	+							
Histiocytic sarcoma					X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Histiocytic sarcoma					X																			
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Squamous cell papilloma												X				X								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Histiocytic sarcoma															X									
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Parathyroid gland	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	M	M							
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Meningioma malignant, metastatic, brain		X																						
Pars distalis, adenoma												X	X	X										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Follicular cell, adenoma																								
General Body System																								
None																								
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Cystadenoma																X								
Histiocytic sarcoma					X																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Histiocytic sarcoma					X										X									
Polyp stromal																	X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 182 mg/kg
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	2 6 9	2 7 4	2 7 6	2 8 0	2 8 5	2 9 1	2 9 2	2 9 3	2 5 4	2 5 6	2 5 8	2 6 0	2 6 6	2 6 8	2 7 2	2 8 4	2 8 8	3 0 0	2 7 3	2 7 5	2 7 9	2 8 1	2 9 7	2 9 8	2 9 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus																										16
Gallbladder																										17
Intestine large, colon																										17
Intestine large, rectum																										17
Intestine large, cecum																										16
Intestine small, duodenum																										17
Intestine small, jejunum																										16
Intestine small, ileum																										17
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																				X						1
Hepatocellular carcinoma		X		X																					X	10
Hepatocellular carcinoma, multiple						X		X									X									3
Hepatocellular adenoma	X	X								X				X				X	X						X	8
Hepatocellular adenoma, multiple				X	X			X					X													9
Histiocytic sarcoma																										2
Mesentery																										6
Histiocytic sarcoma																										1
Pancreas																										17
Histiocytic sarcoma																										1
Salivary glands																										17
Stomach, forestomach																										17
Squamous cell papilloma																										2
Stomach, glandular																										17
Cardiovascular System																										
Blood vessel																										17
Heart																										17
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex																										17
Adrenal medulla																										17
Islets, pancreatic																										17
Parathyroid gland																										12
Pituitary gland																										17
Meningioma malignant, metastatic, brain																										1
Pars distalis, adenoma																										3
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell, adenoma	X		X					X											X						X	5
General Body System																										
None																										
Genital System																										
Clitoral gland																										15
Ovary																										17
Cystadenoma																										1
Histiocytic sarcoma																										1
Uterus																										17
Histiocytic sarcoma																										2
Polyp stromal																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 182 mg/kg
(continued)

Number of Days on Study	0 2 4	3 3 7	4 1 1	4 4 6	4 6 7	5 3 8	6 0 4	6 2 5	6 3 6	6 4 2	6 5 9	6 6 6	6 7 4	7 1 2	7 1 8	7 3 1	7 3 5	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0
Carcass ID Number	2 7 1	2 8 6	2 8 9	2 5 5	2 9 5	2 7 0	2 7 7	2 8 7	2 5 7	2 9 0	2 8 3	2 7 8	2 5 2	2 9 4	2 8 2	2 9 6	2 6 5	2 5 1	2 5 3	2 5 9	2 6 1	2 6 2	2 6 3	2 6 4
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Histiocytic sarcoma					X										X									
Lymph node					+										+	+								
Lumbar, histiocytic sarcoma					X										X									
Mediastinal, histiocytic sarcoma					X																			
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+							
Carcinoma, metastatic, harderian gland									X															
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Histiocytic sarcoma					X										X									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Hemangiosarcoma										X														
Thymus	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+							
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, skin, site of application, fibrosarcoma				X																				
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Carcinoma, metastatic, harderian gland									X															
Meningioma malignant		X																						
Peripheral nerve		+																						
Spinal cord		+																						
Respiratory System																								
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Alveolar/bronchiolar adenoma												X												
Carcinoma, metastatic, harderian gland									X		X													
Hepatocellular carcinoma, metastatic, liver																	X							
Histiocytic sarcoma					X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Special Senses System																								
Eye	+								+															
Carcinoma, metastatic, harderian gland									X															
Harderian gland									+		+													
Carcinoma									X		X													
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Histiocytic sarcoma					X										X									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X										X									
Lymphoma malignant								X								X	X							

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 182 mg/kg
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	2 6 9	2 7 4	2 7 6	2 8 0	2 8 5	2 9 1	2 9 2	2 9 3	2 5 4	2 5 6	2 5 8	2 6 0	2 6 6	2 6 8	2 7 2	2 8 4	2 8 8	3 0 0	2 7 3	2 7 5	2 7 9	2 8 1	2 9 7	2 9 8	2 9 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow																										17
Histiocytic sarcoma																										2
Lymph node																										3
Lumbar, histiocytic sarcoma																										2
Mediastinal, histiocytic sarcoma																										1
Lymph node, mandibular																										15
Carcinoma, metastatic, harderian gland																										1
Lymph node, mesenteric																										17
Histiocytic sarcoma																										2
Spleen																										17
Hemangiosarcoma																										1
Thymus																										16
Integumentary System																										
Mammary gland																										17
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Subcutaneous tissue, skin, site of application, fibrosarcoma																										1
Musculoskeletal System																										
Bone																										17
Nervous System																										
Brain																										17
Carcinoma, metastatic, harderian gland																										1
Meningioma malignant																										1
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung																	+									18
Alveolar/bronchiolar adenoma																										1
Carcinoma, metastatic, harderian gland																										2
Hepatocellular carcinoma, metastatic, liver																	X									2
Histiocytic sarcoma																										1
Nose																										17
Trachea																										17
Special Senses System																										
Eye																										2
Carcinoma, metastatic, harderian gland																										1
Harderian gland																										2
Carcinoma																										2
Urinary System																										
Kidney																										17
Histiocytic sarcoma																										2
Urinary bladder																										17
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Lymphoma malignant																										3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 364 mg/kg

Number of Days on Study	561	562	575	588	601	602	622	636	642	645	659	661	672	674	679	685	728	732	740	740	740	740	740	740	740	740
Carcass ID Number	341	316	325	312	337	324	336	303	346	343	402	301	306	307	311	314	313	310	309	315	317	318	323	399	342	
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Leiomyosarcoma, metastatic, intestine small, jejunum																		X								
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Leiomyosarcoma															X											
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Leiomyosarcoma																		X								
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma																										
Hepatocellular carcinoma			X		X				X			X				X							X			
Hepatocellular adenoma					X		X								X							X	X			
Hepatocellular adenoma, multiple											X														X	
Hepatocholangiocarcinoma							X																			
Histiocytic sarcoma																	X									
Leiomyosarcoma, metastatic, intestine small, jejunum																		X								
Mesentery				+		+					+						+	+								
Hepatocholangiocarcinoma, metastatic, liver						X																				
Histiocytic sarcoma																	X									
Leiomyosarcoma, metastatic, intestine small, jejunum																		X								
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Hepatocholangiocarcinoma, metastatic, liver						X																				
Histiocytic sarcoma																	X									
Leiomyosarcoma, metastatic, intestine small, jejunum																		X								
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Carcinoma											X															
Hepatocholangiocarcinoma, metastatic, liver						X																				
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Aorta, hepatocholangiocarcinoma, metastatic, liver						X																				
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Alveolar/bronchiolar carcinoma, metastatic, lung							X																			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 364 mg/kg
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	3 4 4	3 4 8	3 4 4	3 5 5	3 5 9	3 6 0	3 6 8	3 6 9	3 7 2	3 7 3	3 7 4	3 7 5	3 7 7	3 7 9	3 8 0	3 8 5	3 9 0	3 9 1	3 9 8	3 9 1	3 9 2	3 9 6	3 9 7	3 9 0	3 9 8	3 9 0	3 9 5	Total Tissues/ Tumors
Alimentary System																											
Esophagus																											18
Gallbladder																											18
Leiomyosarcoma, metastatic, intestine small, jejunum																											1
Intestine large, colon																											18
Intestine large, rectum																											18
Intestine large, cecum																											18
Leiomyosarcoma																											1
Intestine small, duodenum																											18
Intestine small, jejunum																											18
Leiomyosarcoma																											1
Intestine small, ileum																											18
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																	X										1
Hepatocellular carcinoma						X																					7
Hepatocellular adenoma			X	X						X	X					X			X	X	X			X			14
Hepatocellular adenoma, multiple							X															X					4
Hepatocholangiocarcinoma																											1
Histiocytic sarcoma																						X					2
Leiomyosarcoma, metastatic, intestine small, jejunum																											1
Mesentery																											5
Hepatocholangiocarcinoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Leiomyosarcoma, metastatic, intestine small, jejunum																											1
Pancreas																											18
Hepatocholangiocarcinoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Leiomyosarcoma, metastatic, intestine small, jejunum																											1
Salivary glands																											18
Stomach, forestomach																											18
Stomach, glandular																											18
Carcinoma																											1
Hepatocholangiocarcinoma, metastatic, liver																											1
Cardiovascular System																											
Blood vessel																											18
Aorta, hepatocholangiocarcinoma, metastatic, liver																											1
Heart																											18
Alveolar/bronchiolar carcinoma, metastatic, lung																											1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 364 mg/kg
(continued)

Number of Days on Study	561	562	575	588	601	602	622	636	642	645	659	661	672	674	679	685	728	732	740	744	800	804	800	804	800	804
Carcass ID Number	34101	31606	32505	31302	33707	32404	33606	30303	34406	34403	30302	33101	30306	30607	31101	31404	31103	31003	30109	31015	31157	31183	32339	33902	34042
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Hepatocholangiocarcinoma, metastatic, liver						X																				
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Adenoma										X																
Parathyroid gland	M	M	+	+	+	M	M	+	+	M	M	+	+	+	+	M	+	+								
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Pars distalis, adenoma								X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																										X
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Hemangioma										X																
Hepatocholangiocarcinoma, metastatic, liver						X																				
Histiocytic sarcoma																	X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Leiomyosarcoma, metastatic, intestine small, jejunum																		X								
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Lymph node				+		+	+					+				+	+									
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung							X																			
Inguinal, histiocytic sarcoma																	X									
Mediastinal, hepatocholangiocarcinoma, metastatic, liver						X																				
Pancreatic, histiocytic sarcoma																	X									
Renal, histiocytic sarcoma																	X									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M								
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Hepatocholangiocarcinoma, metastatic, liver						X																				
Histiocytic sarcoma																	X									
Leiomyosarcoma, metastatic, intestine small, jejunum																		X								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+								
Histiocytic sarcoma																	X									
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M								
Alveolar/bronchiolar carcinoma, metastatic, lung							X																			
Hepatocholangiocarcinoma, metastatic, liver						X																				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 364 mg/kg
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	3 4 4	3 4 8	3 4 4	3 0 5	3 0 9	3 1 0	3 2 8	3 2 9	3 3 2	3 3 3	3 3 4	3 3 5	3 4 7	3 4 9	3 5 0	3 0 1	3 0 8	3 2 1	3 2 2	3 2 6	3 2 7	3 3 0	3 3 8	3 4 0	3 4 5	Total Tissues/ Tumors
Endocrine System																										
Adrenal cortex																										18
Hepatocholangiocarcinoma, metastatic, liver																										1
Adrenal medulla																										18
Islets, pancreatic																										18
Adenoma																										1
Parathyroid gland																										11
Pituitary gland																										18
Pars distalis, adenoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland																										15
Ovary																										18
Hemangioma																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Uterus																										18
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Hematopoietic System																										
Bone marrow																										18
Lymph node																										6
Bronchial, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Inguinal, histiocytic sarcoma																										1
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																										1
Pancreatic, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular																										15
Lymph node, mesenteric																										17
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Spleen																										18
Histiocytic sarcoma																										1
Thymus																										16
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hepatocholangiocarcinoma, metastatic, liver																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 364 mg/kg
(continued)

Number of Days on Study	561	562	575	588	601	602	622	636	642	645	655	661	672	674	679	685	728	732	740	740	740	740	740	740	740
Carcass ID Number	341	316	325	312	337	324	346	303	346	343	302	301	306	307	311	343	310	309	315	317	318	339	342		
Integumentary System																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, skin, site of application, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Skeletal muscle						+																			
Hepatocholangiocarcinoma, metastatic, liver						X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Alveolar/bronchiolar adenoma										X								X							
Alveolar/bronchiolar carcinoma							X																		
Hepatocellular carcinoma, metastatic, liver																X									
Hepatocholangiocarcinoma, metastatic, liver						X																			
Leiomyosarcoma, metastatic, intestine small, jejunum																		X							
Leiomyosarcoma, metastatic, intestine large, cecum															X										
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Special Senses System																									
Harderian gland														+											
Carcinoma														X											
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+							
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																		X							
Lymphoma malignant				X								X				X									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 364 mg/kg
(continued)

Number of Days on Study	7 4 0	7 4 0	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	3 4 4	3 4 8	3 4 4	3 0 5	3 1 9	3 2 0	3 2 8	3 2 9	3 3 2	3 3 3	3 3 4	3 3 5	3 4 7	3 4 9	3 5 0	3 0 1	3 0 8	3 2 1	3 2 2	3 2 6	3 2 7	3 3 0	3 3 8	3 4 0	3 4 5	Total Tissues/ Tumors
Integumentary System																										
Mammary gland																										16
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, skin, site of application, fibrosarcoma										X																1
Musculoskeletal System																										
Bone																										18
Skeletal muscle																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Nervous System																										
Brain																										18
Respiratory System																										
Lung																										18
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Leiomyosarcoma, metastatic, intestine small, jejunum																										1
Leiomyosarcoma, metastatic, intestine large, cecum																										1
Mediastinum, alveolar/bronchiolar carcinoma, metastatic, lung																										1
Nose																										18
Trachea																										18
Special Senses System																										
Harderian gland																										1
Carcinoma																										1
Urinary System																										
Kidney																										18
Urinary bladder																										18
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																				X						2
Lymphoma malignant																										3

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg

Number of Days on Study	0 7 2	4 0 3	5 3 4	6 1 2	6 2 7	6 2 9	6 7 5	6 8 6	6 9 1	6 9 4	7 0 7	7 1 7	7 3 0	7 3 8	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 1
Carcass ID Number	3 9 5	3 5 4	3 6 6	3 6 0	3 8 0	3 6 4	3 8 1	3 6 5	3 9 0	3 7 2	3 9 6	3 5 6	3 7 1	3 9 1	3 5 1	3 5 2	3 5 7	3 6 8	3 7 6	3 7 8	3 8 2	3 8 6	3 8 8	3 9 3	3 5 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin								X																	
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma							X					X		X										X	
Hepatocellular carcinoma, multiple										X						X									
Hepatocellular adenoma								X		X	X				X			X	X				X	X	
Hepatocellular adenoma, multiple									X							X									
Hepatocholangiocarcinoma			X		X																				
Histiocytic sarcoma														X									X		
Mesentery			+	+	+			+	+			+			+										
Fibrosarcoma, metastatic, skin								X																	
Hemangioma												X													
Hepatocholangiocarcinoma, metastatic, liver			X		X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin								X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma													X												
Adrenal medulla	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pheochromocytoma benign								X																	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma								X			X														
Pars intermedia, adenoma																									X
Pars intermedia, carcinoma						X																			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma											X											X			
Follicular cell, carcinoma																									
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg
(continued)

Number of Days on Study	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	3 5 9	3 6 1	3 6 3	3 6 7	3 6 9	3 7 5	3 8 4	3 8 5	3 8 7	3 9 2	3 9 7	4 0 0	3 5 5	3 5 8	3 6 2	3 7 0	3 7 3	3 7 4	3 7 7	3 7 9	3 8 3	3 8 9	3 9 4	3 9 8	3 9 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X							X		X			X											8
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma	X					X		X				X	X		X		X	X	X		X	X				19
Hepatocellular adenoma, multiple		X		X	X		X				X			X		X										9
Hepatocholangiocarcinoma																										2
Histiocytic sarcoma																										2
Mesentery					+	+	+		+											+						12
Fibrosarcoma, metastatic, skin																										1
Hemangioma																										1
Hepatocholangiocarcinoma, metastatic, liver																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	M	+	M	+	M	+	+	+	+	M	+	M	M	+	+	+	+	+	+	M	+	+	36
Pituitary gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X			X		X																				5
Pars intermedia, adenoma																							X			2
Pars intermedia, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma	X											X		X										X		6
Follicular cell, carcinoma													X													1
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg
(continued)

Number of Days on Study	0 7 2	4 0 3	5 3 4	6 1 2	6 2 7	6 2 9	6 7 5	6 8 6	6 9 1	6 9 4	7 0 7	7 1 7	7 3 0	7 3 8	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 1
Carcass ID Number	3 9 5	3 5 4	3 6 6	3 6 0	3 8 0	3 6 4	3 8 1	3 6 5	3 9 0	3 7 2	3 9 6	3 5 6	3 7 1	3 9 1	3 5 1	3 5 2	3 5 7	3 6 8	3 7 6	3 7 8	3 8 2	3 8 6	3 8 8	3 9 3	3 5 3
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver					X																				
Ovary	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Fibrosarcoma, metastatic, skin								X																	
Histiocytic sarcoma																							X		
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma																							X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+			+			+			+			+									+		
Lumbar, histiocytic sarcoma														X									X		
Mediastinal, hepatocholangiocarcinoma, metastatic, liver					X																				
Mediastinal, histiocytic sarcoma														X											
Renal, hepatocholangiocarcinoma, metastatic, liver					X																				
Renal, histiocytic sarcoma														X											
Lymph node, mandibular	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin								X																	
Hepatocholangiocarcinoma, metastatic, liver			X		X																				
Histiocytic sarcoma														X									X		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X							
Histiocytic sarcoma														X											
Thymus	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver			X		X																				
Histiocytic sarcoma														X											
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrosarcoma								X																	
Subcutaneous tissue, hemangiosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle			+		+			+																	
Fibrosarcoma, metastatic, skin								X																	
Hepatocholangiocarcinoma, metastatic, liver			X		X																				

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg
(continued)

Number of Days on Study	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 1	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	7 4 2	
Carcass ID Number	3 5 9	3 6 1	3 6 3	3 6 7	3 6 9	3 7 5	3 8 4	3 8 5	3 8 7	3 9 2	3 9 7	4 0 0	3 5 5	3 5 8	3 6 2	3 7 0	3 7 3	3 7 4	3 7 7	3 7 9	3 8 3	3 8 9	3 9 4	3 9 8	3 9 9	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	46
Hepatocholangiocarcinoma, metastatic, liver																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																								X		1
Fibrosarcoma, metastatic, skin																										1
Histiocytic sarcoma																										1
Oviduct																					+					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X														1
Histiocytic sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										6
Lumbar, histiocytic sarcoma																										2
Mediastinal, hepatocholangiocarcinoma, metastatic, liver																										1
Mediastinal, histiocytic sarcoma																										1
Renal, hepatocholangiocarcinoma, metastatic, liver																										1
Renal, histiocytic sarcoma																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Hepatocholangiocarcinoma, metastatic, liver																										2
Histiocytic sarcoma																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		2
Histiocytic sarcoma																										1
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	44
Hepatocholangiocarcinoma, metastatic, liver																										2
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																					X					1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma			X																							1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										3
Fibrosarcoma, metastatic, skin																										1
Hepatocholangiocarcinoma, metastatic, liver																										2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg
(continued)

Number of Days on Study	0 7 2	4 0 3	5 3 4	6 1 2	6 2 7	6 2 9	6 7 5	6 8 6	6 9 1	6 9 4	7 0 7	7 1 7	7 3 0	7 3 8	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 0	7 4 1
Carcass ID Number	3 9 5	3 5 4	3 6 6	3 6 0	3 8 0	3 6 4	3 8 1	3 6 5	3 9 0	3 7 2	3 9 6	3 5 6	3 7 1	3 9 1	3 5 1	3 5 2	3 5 7	3 6 8	3 7 6	3 7 8	3 8 2	3 8 6	3 8 8	3 9 3	3 5 3
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve	+																								
Spinal cord	+																								
Respiratory System																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma															X			X							
Carcinoma, metastatic, harderian gland																	X								
Hepatocellular carcinoma, metastatic, liver										X															
Hepatocholangiocarcinoma, metastatic, liver			X		X																				
Histiocytic sarcoma														X									X		
Squamous cell carcinoma, metastatic, urinary bladder													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Harderian gland											+						+							+	
Adenoma											X														
Carcinoma																	X							X	
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver			X																						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma													X												
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X									X		
Lymphoma malignant		X		X							X														

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate: 727 mg/kg
(continued)

Number of Days on Study	741	741	741	741	741	741	741	741	741	741	741	741	742	742	742	742	742	742	742	742	742	742	742	742	742	
Carcass ID Number	35 9	36 1	36 3	36 7	36 9	37 5	38 4	38 5	38 7	39 2	39 7	40 0	35 5	35 8	36 2	37 0	37 3	37 4	37 7	37 9	38 3	38 9	39 4	39 8	39 9	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve																										1
Spinal cord																										1
Respiratory System																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X															X	X					X		6
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver										X					X											3
Hepatocholangiocarcinoma, metastatic, liver																										2
Histiocytic sarcoma																										2
Squamous cell carcinoma, metastatic, urinary bladder																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Harderian gland																										3
Adenoma																										1
Carcinoma																										2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant											X					X										5

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Harderian Gland: Adenoma				
Overall rate[a]	3/50 (6%)	0/49 (0%)[e]	0/50 (0%)[e]	1/50 (2%)
Adjusted rate[b]	8.9%			2.5%
Terminal rate[c]	2/31 (6%)			0/36 (0%)
First incidence (days)	670			707
Life table test[d]				P=0.258N
Logistic regression test[d]				P=0.292N
Fisher exact test[d]				P=0.309N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	2/49 (4%)[e]	1/50 (2%)[e]	3/50 (6%)
Adjusted rate	10.7%			7.9%
Terminal rate	2/31 (6%)			2/36 (6%)
First incidence (days)	453			707
Life table test				P=0.435N
Logistic regression test				P=0.506N
Fisher exact test				P=0.500N
Liver: Hepatocellular Adenoma				
Overall rate	18/50 (36%)	17/49 (35%)	18/50 (36%)	28/50 (56%)
Adjusted rate	54.1%	47.8%	49.0%	69.8%
Terminal rate	16/31 (52%)	14/32 (44%)	14/32 (44%)	24/36 (67%)
First incidence (days)	621	446	601	686
Life table test	P=0.060	P=0.459N	P=0.540N	P=0.118
Logistic regression test	P=0.034	P=0.533N	P=0.553N	P=0.080
Cochran-Armitage test[d]	P=0.016			
Fisher exact test		P=0.530N	P=0.582N	P=0.035
Liver: Hepatocellular Carcinoma				
Overall rate	10/50 (20%)	13/49 (27%)	7/50 (14%)	10/50 (20%)
Adjusted rate	25.5%	36.3%	17.0%	24.7%
Terminal rate	4/31 (13%)	10/32 (31%)	2/32 (6%)	6/36 (17%)
First incidence (days)	495	411	575	675
Life table test	P=0.292N	P=0.342	P=0.297N	P=0.469N
Logistic regression test	P=0.397N	P=0.293	P=0.360N	P=0.595N
Cochran-Armitage test	P=0.399N			
Fisher exact test		P=0.298	P=0.298N	P=0.598N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	27/50 (54%)	23/49 (47%)	23/50 (46%)	33/50 (66%)
Adjusted rate	68.6%	61.4%	56.4%	76.7%
Terminal rate	19/31 (61%)	18/32 (56%)	15/32 (47%)	26/36 (72%)
First incidence (days)	495	411	575	675
Life table test	P=0.295	P=0.254N	P=0.259N	P=0.448
Logistic regression test	P=0.131	P=0.326N	P=0.237N	P=0.237
Cochran-Armitage test	P=0.088			
Fisher exact test		P=0.308N	P=0.274N	P=0.154

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate
(continued)

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/50 (8%)	1/18 (6%)[e]	2/18 (11%)[e]	6/50 (12%)
Adjusted rate	11.5%			16.7%
Terminal rate	2/31 (6%)			6/36 (17%)
First incidence (days)	659			740 (T)
Life table test				P=0.461
Logistic regression test				P=0.433
Fisher exact test				P=0.370
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	2/50 (4%)	0/18 (0%)[e]	1/18 (6%)[e]	0/50 (0%)
Adjusted rate	6.5%			0.0%
Terminal rate	2/31 (6%)			0/36 (0%)
First incidence (days)	740 (T)			—[f]
Life table test				P=0.206N
Logistic regression test				P=0.206N
Fisher exact test				P=0.247N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	5/50 (10%)	1/18 (6%)[e]	3/18 (17%)[e]	6/50 (12%)
Adjusted rate	14.6%			16.7%
Terminal rate	3/31 (10%)			6/36 (17%)
First incidence (days)	659			740 (T)
Life table test				P=0.598
Logistic regression test				P=0.574
Fisher exact test				P=0.500
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	2/50 (4%)	0/17 (0%)[e]	1/18 (6%)[e]	0/50 (0%)
Adjusted rate	4.3%			0.0%
Terminal rate	0/31 (0%)			0/36 (0%)
First incidence (days)	495			—
Life table test				P=0.233N
Logistic regression test				P=0.204N
Fisher exact test				P=0.247N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	7/50 (14%)	3/17 (18%)[e]	1/18 (6%)[e]	5/49 (10%)
Adjusted rate	20.4%			12.9%
Terminal rate	5/31 (16%)			3/35 (9%)
First incidence (days)	621			686
Life table test				P=0.299N
Logistic regression test				P=0.357N
Fisher exact test				P=0.394N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate
(continued)

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Pituitary Gland (Pars Intermedia): Adenoma or Carcinoma				
Overall rate	1/50 (2%)	0/17 (0%)[e]	0/18 (0%)[e]	3/49 (6%)
Adjusted rate	3.2%			7.8%
Terminal rate	1/31 (3%)			2/35 (6%)
First incidence (days)	740 (T)			629
Life table test				P=0.348
Logistic regression test				P=0.307
Fisher exact test				P=0.301
Spleen: Hemangiosarcoma				
Overall rate	0/50 (0%)	1/17 (6%)[e]	0/18 (0%)[e]	2/50 (4%)
Adjusted rate	0.0%			5.6%
Terminal rate	0/31 (0%)			2/36 (6%)
First incidence (days)	—			740 (T)
Life table test				P=0.272
Logistic regression test				P=0.272
Fisher exact test				P=0.247
Thyroid Gland (Follicular Cell): Adenoma				
Overall rate	2/50 (4%)	5/48 (10%)	1/50 (2%)	6/50 (12%)
Adjusted rate	5.5%	16.1%	3.1%	16.0%
Terminal rate	1/31 (3%)	5/31 (16%)	1/32 (3%)	5/36 (14%)
First incidence (days)	621	740 (T)	740 (T)	707
Life table test	P=0.214	P=0.215	P=0.490N	P=0.187
Logistic regression test	P=0.197	P=0.197	P=0.498N	P=0.151
Cochran-Armitage test	P=0.157			
Fisher exact test		P=0.201	P=0.500N	P=0.134
Thyroid Gland (Follicular Cell): Adenoma or Carcinoma				
Overall rate	2/50 (4%)	5/48 (10%)	1/50 (2%)	7/50 (14%)
Adjusted rate	5.5%	16.1%	3.1%	18.8%
Terminal rate	1/31 (3%)	5/31 (16%)	1/32 (3%)	6/36 (17%)
First incidence (days)	621	740 (T)	740 (T)	707
Life table test	P=0.124	P=0.215	P=0.490N	P=0.122
Logistic regression test	P=0.112	P=0.197	P=0.498N	P=0.096
Cochran-Armitage test	P=0.084			
Fisher exact test		P=0.201	P=0.500N	P=0.080
Uterus: Stromal Polyp				
Overall rate	3/50 (6%)	1/17 (6%)[e]	0/18 (0%)[e]	0/50 (0%) #
Adjusted rate	9.4%			0.0% #
Terminal rate	2/31 (6%)			0/36 (0%) #
First incidence (days)	734			—
Life table test				P=0.098N
Logistic regression test				P=0.096N
Fisher exact test				P=0.121N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate
(continued)

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
All Organs: Hemangiosarcoma				
Overall rate	0/50 (0%)	2/49 (4%)[e]	1/50 (2%)[e]	4/50 (8%)
Adjusted rate	0.0%			11.1%
Terminal rate	0/31 (0%)			4/36 (11%)
First incidence (days)	—			740 (T)
Life table test				P=0.083
Logistic regression test				P=0.083
Fisher exact test				P=0.059
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	2/49 (4%)[e]	2/50 (4%)[e]	5/50 (10%)
Adjusted rate	5.7%			13.4%
Terminal rate	1/31 (3%)			4/36 (11%)
First incidence (days)	670			717
Life table test				P=0.281
Logistic regression test				P=0.249
Fisher exact test				P=0.218
All Organs: Histiocytic Sarcoma				
Overall rate	3/50 (6%)	2/49 (4%)[e]	2/50 (4%)[e]	2/50 (4%)
Adjusted rate	7.0%			5.4%
Terminal rate	0/31 (0%)			1/36 (3%)
First incidence (days)	499			738
Life table test				P=0.450N
Logistic regression test				P=0.507N
Fisher exact test				P=0.500N
All Organs: Malignant Lymphoma				
Overall rate	8/50 (16%)	3/17 (18%)[e]	3/18 (17%)[e]	5/50 (10%)
Adjusted rate	24.7%			11.7%
Terminal rate	7/31 (23%)			2/36 (6%)
First incidence (days)	692			403
Life table test				P=0.204N
Logistic regression test				P=0.275N
Fisher exact test				P=0.277N
All Organs: Benign Neoplasms				
Overall rate	29/50 (58%)	22/49 (45%)[e]	20/50 (40%)[e]	35/50 (70%)
Adjusted rate	74.1%			83.3%
Terminal rate	21/31 (68%)			29/36 (81%)
First incidence (days)	589			686
Life table test				P=0.471
Logistic regression test				P=0.303
Fisher exact test				P=0.149

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate
(continued)

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
All Organs: Malignant Neoplasms				
Overall rate	25/50 (50%)	22/49 (45%)[e]	18/50 (36%)[e]	26/50 (52%)
Adjusted rate	57.3%			54.0%
Terminal rate	13/31 (42%)			14/36 (39%)
First incidence (days)	453			403
Life table test				P=0.421N
Logistic regression test				P=0.331
Fisher exact test				P=0.500
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	34/49 (69%)[e]	31/50 (62%)[e]	44/50 (88%)
Adjusted rate	93.7%			89.8%
Terminal rate	28/31 (90%)			31/36 (86%)
First incidence (days)	453			403
Life table test				P=0.164N
Logistic regression test				P=0.465N
Fisher exact test				P=0.500N

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, pancreatic islets, pituitary gland, spleen, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Kaplan-Meier estimated neoplasm incidence at the end of the study after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the controls and that dosed group. The life table test regards neoplasms in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The logistic regression test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. For all tests, a negative trend or a lower incidence in a dose group is indicated by **N**.
[e] Tissues (except skin) were examined microscopically only in those animals dying prior to terminal sacrifice or when it was observed to be abnormal at necropsy; thus statistical comparison with the controls are not applicable. #
[f] Not applicable; no neoplasms in animal group

TABLE D4
Historical Incidence of Hepatocellular Neoplasms in Control Female B6C3F$_1$ Mice[a]

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Columbus: Dermal (Acetone) Studies			
4-Vinyl-1-cyclohexene Diepoxide	8/50	2/50	10/50
Triethanolamine	22/50	1/50	23/50
Overall Historical Incidence: Dermal (Acetone) Studies			
Total	34/150 (22.7%)	7/150 (4.7%)	40/150 (26.7%)
Standard deviation	18.9%	3.1%	17.0%
Range	8%-44%	2%-8%	14%-46%
Historical Incidence at Battelle Columbus: Dermal (Ethanol) Study			
Benzethonium Chloride	20/52 (38.5%)	12/52 (23.1%)	27/52 (51.9%)
Historical Incidence at Battelle Columbus: Feed Studies			
4,4-Thiobis(6-*t*-butyl-*m*-cresol)	17/51	4/51	20/51
5,5-Diphenylhydantoin	5/48	0/48	5/48
Pentachlorophenol (Dowicide EC-7)	1/34	0/34	1/34
Ethylene Thiourea	2/50	2/50	4/50
Polybrominated Biphenyls (Firemaster FF-1®)	4/50	1/50	5/50
Manganese (II) Sulfate Monohydrate	12/51	3/51	13/51
Oxazepam	25/50	9/50	28/50
Technical Grade Pentachlorophenol	3/33	0/33	3/33
Triamterene	10/50	4/50	13/50
Triamterene	7/50	5/50	10/50
Tricresyl Phosphate	12/50	10/50	21/50
Overall Historical Incidence: Feed Studies			
Total	231/1,464 (15.8%)	108/1,464 (7.4%)	313/1,464 (21.4%)
Standard deviation	10.6%	6.1%	13.0%
Range	2%-50%	0%-20%	3%-56%

[a] Data as of 12 May 1995

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	12	7	9	6
Natural deaths	7	10	9	8
Survivors				
Terminal sacrifice	31	32	32	36
Missing		1		
Animals examined microscopically	50	49	50	50
Alimentary System				
Esophagus	(50)	(16)	(18)	(50)
Inflammation		1 (6%)		
Intestine small, duodenum	(50)	(17)	(18)	(50)
Inflammation	1 (2%)			
Intestine small, ileum	(50)	(17)	(18)	(50)
Hyperplasia, lymphoid	1 (2%)			
Liver	(50)	(49)	(50)	(50)
Angiectasis	1 (2%)			
Basophilic focus		3 (6%)	2 (4%)	1 (2%)
Clear cell focus		1 (2%)		
Eosinophilic focus	14 (28%)	11 (22%)	11 (22%)	10 (20%)
Hematopoietic cell proliferation	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Infarct				1 (2%)
Inflammation, chronic active	22 (44%)	28 (57%)	24 (48%)	21 (42%)
Mixed cell focus	10 (20%)	3 (6%)	1 (2%)	7 (14%)
Necrosis	3 (6%)	4 (8%)	9 (18%)	3 (6%)
Pigmentation, hemosiderin	1 (2%)			1 (2%)
Bile duct, cyst	2 (4%)			
Bile duct, hyperplasia	4 (8%)	2 (4%)	4 (8%)	2 (4%)
Serosa, necrosis			1 (2%)	
Mesentery	(7)	(6)	(5)	(12)
Inflammation	1 (14%)		1 (20%)	
Fat, necrosis	3 (43%)	2 (33%)		7 (58%)
Pancreas	(50)	(17)	(18)	(50)
Atrophy	3 (6%)		1 (6%)	6 (12%)
Cytoplasmic alteration	1 (2%)			1 (2%)
Inflammation	1 (2%)			
Necrosis				1 (2%)
Duct, cyst	2 (4%)	2 (12%)	1 (6%)	5 (10%)
Salivary glands	(50)	(17)	(18)	(50)
Atrophy	1 (2%)			1 (2%)
Fibrosis				1 (2%)
Stomach, forestomach	(50)	(17)	(18)	(50)
Erosion			1 (6%)	
Hyperplasia, focal	1 (2%)	1 (6%)		3 (6%)

[a] Number of animals examined microscopically at the site and the number of animals with lesion

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Cardiovascular System				
Blood vessel	(50)	(17)	(18)	(50)
Aorta, inflammation, chronic active				1 (2%)
Heart	(50)	(17)	(18)	(50)
Degeneration		2 (12%)		
Mineralization	5 (10%)			1 (2%)
Atrium, thrombosis				1 (2%)
Epicardium, inflammation, suppurative			1 (6%)	
Endocrine System				
Adrenal cortex	(50)	(17)	(18)	(50)
Accessory adrenal cortical nodule	1 (2%)			
Degeneration				1 (2%)
Hyperplasia			1 (6%)	2 (4%)
Capsule, hyperplasia, adenomatous	1 (2%)			
Adrenal medulla	(50)	(17)	(18)	(48)
Hyperplasia	3 (6%)		1 (6%)	3 (6%)
Islets, pancreatic	(50)	(17)	(18)	(50)
Hyperplasia	7 (14%)	1 (6%)	2 (11%)	4 (8%)
Pituitary gland	(50)	(17)	(18)	(49)
Cyst	1 (2%)			
Pars distalis, hyperplasia	25 (50%)	6 (35%)	11 (61%)	26 (53%)
Thyroid gland	(50)	(48)	(50)	(50)
Inflammation			1 (2%)	
Follicle, cyst	1 (2%)			
Follicular cell, hyperplasia	26 (52%)	19 (40%)	19 (38%)	25 (50%)
General Body System				
None				
Genital System				
Ovary	(50)	(17)	(18)	(49)
Cyst	10 (20%)		2 (11%)	13 (27%)
Hemorrhage	1 (2%)			
Inflammation, chronic active	1 (2%)			
Metaplasia	1 (2%)			
Thrombosis			1 (6%)	
Oviduct				(1)
Inflammation, chronic				1 (100%)
Uterus	(50)	(17)	(18)	(50)
Hemorrhage			1 (6%)	
Hyperplasia, cystic	21 (42%)	2 (12%)	4 (22%)	22 (44%)
Pigmentation, hemosiderin	1 (2%)			
Lymphatic, angiectasis	1 (2%)			
Lymphatic, cyst	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Hematopoietic System				
Bone marrow	(50)	(17)	(18)	(50)
Hyperplasia	12 (24%)	1 (6%)	4 (22%)	11 (22%)
Myelofibrosis	1 (2%)			4 (8%)
Lymph node	(7)	(3)	(6)	(6)
Mediastinal, hyperplasia, lymphoid	1 (14%)			
Mediastinal, infiltration cellular, histiocyte				1 (17%)
Lymph node, mesenteric	(48)	(17)	(17)	(50)
Angiectasis	1 (2%)			2 (4%)
Hematopoietic cell proliferation	2 (4%)			
Hemorrhage		1 (6%)		
Hyperplasia, lymphoid	1 (2%)			
Inflammation, suppurative	1 (2%)			
Spleen	(50)	(17)	(18)	(50)
Angiectasis				1 (2%)
Hematopoietic cell proliferation	19 (38%)	8 (47%)	12 (67%)	11 (22%)
Thymus	(38)	(16)	(16)	(44)
Atrophy	5 (13%)	7 (44%)	4 (25%)	4 (9%)
Cyst			1 (6%)	
Hyperplasia, lymphoid	2 (5%)	1 (6%)		
Integumentary System				
Mammary gland	(50)	(17)	(16)	(50)
Hyperplasia	5 (10%)	1 (6%)	3 (19%)	6 (12%)
Skin	(50)	(49)	(50)	(50)
Epidermis, skin, site of application, exudate	1 (2%)	4 (8%)	4 (8%)	1 (2%)
Epidermis, skin, site of application, hyperplasia	4 (8%)	1 (2%)	4 (8%)	4 (8%)
Epidermis, skin, site of application, ulcer		1 (2%)	1 (2%)	1 (2%)
Skin, site of application, inflammation, chronic	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Skin, site of application, parakeratosis			1 (2%)	
Subcutaneous tissue, edema		1 (2%)		
Subcutaneous tissue, skin, site of application, inflammation, chronic active		1 (2%)	2 (4%)	
Subcutaneous tissue, skin, site of application, inflammation, suppurative	1 (2%)			
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(17)	(18)	(50)
Inflammation			1 (6%)	
Neuron, necrosis	2 (4%)	1 (6%)	4 (22%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate (continued)

	Vehicle Control	182 mg/kg	364 mg/kg	727 mg/kg
Respiratory System				
Lung	(50)	(18)	(18)	(50)
Hemorrhage	1 (2%)			1 (2%)
Hyperplasia, lymphoid				1 (2%)
Inflammation	1 (2%)			
Pigmentation, hemosiderin	1 (2%)			
Thrombosis			1 (6%)	
Alveolar epithelium, hyperplasia	2 (4%)			2 (4%)
Bronchiole, hyperplasia	1 (2%)			1 (2%)
Nose	(50)	(17)	(18)	(50)
Inflammation, suppurative	1 (2%)			
Special Senses System				
Eye	(1)	(2)		
Degeneration		1 (50%)		
Cornea, inflammation	1 (100%)			
Harderian gland	(5)	(2)	(1)	(3)
Hyperplasia	1 (20%)			
Urinary System				
Kidney	(50)	(17)	(18)	(50)
Hydronephrosis				1 (2%)
Infarct			1 (6%)	
Inflammation, chronic active	1 (2%)			
Mineralization	1 (2%)			
Nephropathy	22 (44%)	1 (6%)	6 (33%)	17 (34%)
Pigmentation	2 (4%)			
Artery, inflammation, chronic active			1 (6%)	

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1987). Sodium xylenesulfonate was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, or 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. Top agar supplemented with *l*-histidine and *d*-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these plates were counted following incubation for 2 days at 37° C.

Each trial consisted of triplicate plates of concurrent positive and negative controls and five doses of sodium xylenesulfonate. The high dose was limited by experimental design to 10,000 μL/plate. All trials were repeated.

In this assay, a positive response is defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response is defined as an increase in revertants which is not dose-related, is not reproducible, or is of insufficient magnitude to support a determination of mutagenicity. A negative response is obtained when no increase in revertant colonies is observed following chemical treatment. There is no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

MOUSE LYMPHOMA MUTAGENICITY TEST PROTOCOL

The experimental protocol is presented in detail by Myhr *et al.* (1985). Sodium xylenesulfonate was supplied as a coded aliquot by Radian Corporation. The high dose of sodium xylenesulfonate was determined by toxicity. L5178Y mouse lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with *l*-glutamine, sodium pyruvate, pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring trifluorothymidine-resistant cells, subcultures were exposed to medium containing THMG (thymidine, hypoxanthine, methotrexate, and glycine) for 1 day, to medium containing THG (thymidine, hypoxanthine, and glycine) for 1 day, and to normal medium for 3 to 5 days. For cloning, the horse serum content was increased and Noble agar was added.

All treatment levels within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with sodium xylenesulfonate continued for 4 hours, at which time the medium plus sodium xylenesulfonate was removed and the cells were resuspended in fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, cells were plated in medium and soft agar supplemented with trifluorothymidine (TFT) for selection of TFT-resistant ($TK^{-/-}$) cells; cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C in 5% CO_2 for 10 to 12 days. The test was initially performed without S9. If a clearly positive response was not obtained, the test was repeated using freshly prepared S9 from the livers of Aroclor 1254-induced male Fischer 344/N rats.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Caspary *et al.* (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ($P \leq 0.05$) for sodium xylenesulfonate to be

considered positive, i.e., capable of inducing TFT resistance. A single significant response led to a "questionable" conclusion, and the absence of both a trend and peak response resulted in a "negative" call.

CHINESE HAMSTER OVARY CELL CYTOGENETICS PROTOCOLS

Testing was performed as reported by Galloway *et al.* (1987). Sodium xylenesulfonate was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations (Abs), 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-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of sodium xylenesulfonate; in the absence of toxicity, 5 mg/mL was selected as the high dose. A single flask per dose was used, and tests yielding equivocal or positive results were repeated.

Sister Chromatid Exchange Test: In the SCE test without S9, CHO cells were incubated for 25.5 hours with sodium xylenesulfonate in McCoy's supplemented 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 25.5 hours, the medium containing sodium xylenesulfonate was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 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 sodium xylenesulfonate, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no sodium xylenesulfonate and incubation proceeded for an additional 25.5 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Because significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable (second-division metaphase) cells.

Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway *et al.*, 1987). 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. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P < 0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal.

Chromosomal Aberrations Test: In the Abs test without S9, cells were incubated in McCoy's 5A medium with sodium xylenesulfonate for 18 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the Abs test with S9, cells were treated with sodium xylenesulfonate 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. The harvest time for the Abs test was based on the cell cycle information obtained in the SCE test; cell cycle delay was anticipated, and the incubation period was extended.

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. Two hundred first-division metaphase cells were scored at each dose level. 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).

Chromosomal aberration data are presented as percentage of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P \leq 0.05$) difference for one dose point and a significant trend ($P \leq 0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at any one dose resulted in an equivocal call (Galloway *et al.*, 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the reviewers.

RESULTS

Sodium xylenesulfonate (100 to 10,000 μg/plate) was not mutagenic in *S. typhimiurium* strain TA98, TA100, TA1535, or TA1537, with and without induced S9 (Zeiger *et al.*, 1987; Table E1). Results obtained with sodium xylenesulfonate in a mammalian gene mutation assay with cultured L5178Y mouse lymphoma cells in the presence of S9 (Table E2) were concluded to be equivocal because the significant increase in mutant colonies noted in the first trial with S9 was not convincingly repeated in the second trial. Without S9, no significant increase in mutations was noted. Sodium xylenesulfonate induced dose-related increases in SCEs in cultured CHO cells at concentrations that produced cell cycle delay (2,513 to 5,000 μg/mL) in the absence of S9; with S9, no increases in SCEs were noted (Table E3). Finally, no induction of Abs was observed in cultured CHO cells treated with sodium xylenesulfonate (2,513 to 5,000 μg/mL) with or without S9 (Table E4).

TABLE E1
Mutagenicity of Sodium Xylenesulfonate in *Salmonella typhimurium*[a]

Strain	Dose (μg/plate)	Revertants/plate[b] -S9 Trial 1	-S9 Trial 2	+10% hamster S9 Trial 1	+10% hamster S9 Trial 2	+10% rat S9 Trial 1	+10% rat S9 Trial 2
TA100	0	95 ± 3.9	78 ± 11.2	144 ± 6.2	88 ± 4.5	129 ± 7.5	135 ± 5.8
	100	92 ± 3.6	72 ± 2.7	101 ± 2.5	76 ± 6.7	147 ± 13.7	111 ± 8.1
	333	103 ± 1.5	73 ± 6.1	120 ± 6.0	85 ± 7.5	154 ± 3.5	114 ± 19.7
	1,000	93 ± 1.7	69 ± 3.7	117 ± 1.7	112 ± 14.7	152 ± 2.8	122 ± 5.2
	3,333	90 ± 5.0	69 ± 2.3	119 ± 3.2	100 ± 9.2	112 ± 2.0	103 ± 9.9
	10,000	98 ± 5.0	63 ± 8.5	125 ± 5.6	95 ± 3.2	110 ± 4.7	85 ± 4.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[c]		620 ± 83.1	330 ± 31.2	2,509 ± 107.6	1,708 ± 271.3	1,091 ± 111.2	717 ± 86.1
TA1535	0	5 ± 1.5	5 ± 0.6	4 ± 1.2	5 ± 0.3	4 ± 0.3	4 ± 2.0
	100	6 ± 0.3	4 ± 0.9	11 ± 0.3	2 ± 1.3	4 ± 2.0	2 ± 1.0
	333	2 ± 0.6	1 ± 0.7	3 ± 1.2	2 ± 1.0	3 ± 0.7	3 ± 0.6
	1,000	2 ± 0.3	3 ± 1.2	7 ± 1.5	5 ± 1.9	6 ± 0.9	4 ± 1.7
	3,333	3 ± 0.3	2 ± 0.9	4 ± 1.5	3 ± 1.5	4 ± 0.6	2 ± 1.0
	10,000	1 ± 0.3	1 ± 0.9	6 ± 0.9	4 ± 2.0	6 ± 0.9	3 ± 1.9
Trial summary		Negative	Negative	Equivocal	Negative	Negative	Negative
Positive control		108 ± 7.1	134 ± 7.5	93 ± 26.7	48 ± 4.9	115 ± 2.7	56 ± 2.9
TA1537	0	6 ± 2.4	4 ± 0.7	5 ± 0.6	10 ± 1.5	3 ± 0.5	12 ± 3.0
	100	3 ± 0.9	2 ± 0.3	10 ± 0.0	12 ± 3.2	5 ± 0.7	15 ± 2.7
	333	5 ± 0.6	3 ± 1.2	11 ± 1.8	11 ± 4.6	14 ± 3.0	17 ± 5.9
	1,000	4 ± 0.3	3 ± 0.9	5 ± 0.3	8 ± 0.7	10 ± 1.3	18 ± 1.9
	3,333	2 ± 0.3	2 ± 1.0	9 ± 0.3	13 ± 2.0	9 ± 1.5	18 ± 2.6
	10,000	4 ± 1.9	2 ± 0.9	7 ± 0.3	9 ± 2.0	7 ± 1.5	11 ± 1.3
Trial summary		Negative	Negative	Negative	Negative	Equivocal	Negative
Positive control		918 ± 78.8	757± 113.8	63 ± 1.3	675 ± 15.3	79 ± 7.9	121 ± 4.1
TA98	0	15 ± 0.9	12 ± 2.0	23 ± 1.7	19 ± 2.1	20 ± 3.1	26 ± 2.3
	100	15 ± 2.3	17 ± 6.6	24 ± 0.9	20 ± 1.7	24 ± 2.5	22 ± 5.2
	333	19 ± 0.3	16 ± 1.0	18 ± 4.1	19 ± 2.0	20 ± 2.8	23 ± 2.2
	1,000	14 ± 0.9	14 ± 1.7	16 ± 0.7	17 ± 3.8	23 ± 1.5	30 ± 9.5
	3,333	21 ± 3.2	14 ± 1.0	23 ± 0.7	18 ± 1.2	22 ± 3.2	21 ± 3.9
	10,000	23 ± 4.2	13 ± 2.4	26 ± 2.3	17 ± 2.9	26 ± 2.1	24 ± 5.2
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		301 ± 5.3	269 ± 21.5	2,369 ± 46.4	1,591 ± 75.9	617 ± 103.7	362 ± 25.0

[a] Study performed at Case Western Reserve University. The detailed protocol and these data are presented in Zeiger *et al.* (1987).
[b] Revertants are presented as mean ± standard error from three plates.
[c] The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA1537), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Sodium Xylenesulfonate[a]

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction[b]	Average Mutant Fraction[c]
-S9						
Trial 1						
Dimethylsulfoxide		103	102	79	26	
		96	98	51	18	22
Methyl methanesulfonate	5	79	47	381	160	
		98	60	403	137	
		60	36	446	246	181*
Sodium xylenesulfonate	125	93	91	64	23	
		86	67	65	25	
		66	63	60	30	26
	250	85	69	51	20	
		79	57	43	18	
		94	77	67	24	21
	500	87	74	71	27	
		105	76	51	16	
		99	71	62	21	21
	1,000	100	76	48	16	
		110	101	64	19	18
	2,000	83	75	63	25	
		116	94	75	22	
		109	88	56	17	21
	2,500	77	43	50	22	
		120	78	74	21	21

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Sodium Xylenesulfonate (continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9						
Trial 2						
Dimethylsulfoxide		70	83	47	23	
		79	105	62	26	
		67	91	47	23	
		80	121	58	24	24
Methyl methanesulfonate	5	46	55	354	257	
		57	35	397	234	
		53	32	444	280	257*
Sodium xylenesulfonate	250	89	90	50	19	
		76	82	61	27	
		62	78	45	24	23
	500	75	74	69	31	
		77	80	47	20	
		72	75	56	26	26
	750	80	73	66	28	
		91	75	46	17	
		77	73	65	28	24
	1,000	80	80	42	18	
		93	90	51	18	
		75	78	62	28	21
	2,000	86	81	59	23	
		80	82	62	26	
		74	68	71	32	27
	2,500	79	59	45	19	
		64	54	59	31	
		68	61	77	38	29

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Sodium Xylenesulfonate (continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
-S9						
Trial 3						
Supplemented Fischer's Medium		79	114	72	31	
		87	100	72	27	
		80	93	88	37	
		89	93	67	25	30
Methyl methanesulfonate	5	39	25	435	377	
		30	5	352	391	
		34	13	267	260	343*
Sodium xylenesulfonate	500	72	64	69	32	
		57	22	81	48	40
	1,000	77	63	84	36	
		108	62	105	32	
		81	16	91	38	35
	2,000	57	66	106	62	
		79	45	79	33	47
		Lethal				
	3,000	103	41	80	26	
		84	27	64	25	
		92	74	79	29	27
	4,000	82	65	89	36	
		78	61	106	45	41
	5,000	76	54	81	36	
		65	9	93	48	
		78	13	96	41	41

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Sodium Xylenesulfonate (continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9						
Trial 1						
Supplemented Fischer's Medium		85	104	76	30	
		80	86	80	33	
		98	101	94	32	
		79	109	94	40	34
Methylcholanthrene	2.5	46	16	595	436	
		46	8	747	545	
		41	15	614	499	493*
Sodium xylenesulfonate	250	99	97	93	31	
		78	92	52	22	
		110	97	115	35	29
	500	85	94	68	27	
		103	99	82	27	
		78	96	87	37	30
	1,000	69	110	72	35	
		61	87	55	30	
		60	81	73	41	35
	2,000	76	52	85	37	
		109	81	107	33	
		108	63	87	27	32
	3,000	83	18	107	43	
		90	24	121	45	
		78	26	91	39	42
	4,000	102	8	186	61	
		75	10	168	75	68*
		Lethal				
	5,000	Lethal				
		Lethal				
		Lethal				

TABLE E2
Induction of Trifluorothymidine Resistance in L5178Y Mouse Lymphoma Cells by Sodium Xylenesulfonate (continued)

Compound	Concentration (μg/mL)	Cloning Efficiency (%)	Relative Total Growth (%)	Mutant Count	Mutant Fraction	Average Mutant Fraction
+S9						
Trial 2						
Supplemented Fischer's Medium		102	104	77	25	
		102	69	89	29	
		98	90	61	21	
		101	138	70	23	25
Methylcholanthrene	2.5	79	15	458	194	
		92	37	387	141	
		103	58	435	141	158*
Sodium xylenesulfonate	250	95	130	40	14	
		102	133	88	29	
		82	60	53	22	21
	500	107	153	55	17	
		98	100	106	36	
		114	140	70	20	25
	1,000	114	95	96	28	
		104	120	82	26	
		106	111	78	25	26
	2,000	95	51	107	38	
		109	69	106	32	
		104	72	86	28	33
	3,000	101	40	134	44	
		95	53	104	37	40*
		Lethal				
	4,000	Lethal				
		Lethal				

* Significant positive response ($P \leq 0.05$)
[a] Study performed at Litton Bionetics, Inc. The detailed protocol is presented in Myhr *et al*. (1985).
[b] Mutant fraction (MF) (frequency) is a ratio of the mutant count to the cloning efficiency, divided by 3 (to arrive at $MF/10^6$ cells treated);
[c] Mean from three replicated plates of approximately 10^6 cells each

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Sodium Xylenesulfonate[a]

Compound	Dose (μg/mL)	Total Cells Scored	No. of Chromo-somes	No. of SCEs	SCEs/ Chromo-some	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome[b] (%)
-S9								
Trial 1								
Summary: Weakly Positive								
Negative		50	1,029	392	0.38	7.8	25.5	
Mitomycin-C								
	0.001	50	1,036	556	0.53	11.1	25.5	40.88
	0.010	5	105	192	1.82	38.4	25.5	380.00
Sodium xylenesulfonate								
	500	50	1,041	436	0.41	8.7	25.5	9.94
	1,667	50	1,012	432	0.42	8.6	25.5	12.05
	5,000	50	1,023	528	0.51	10.6	30.7[c]	35.48*
					P < 0.001[d]			
Trial 2								
Summary: Positive								
Negative		25	512	172	0.33	6.9	25.5	
Mitomycin-C								
	0.001	25	506	295	0.58	11.8	25.5	73.55
	0.010	5	103	195	1.89	39.0	25.5	463.57
Sodium xylenesulfonate								
	2,513	25	517	225	0.43	9.0	32.5[c]	29.55*
	3,750	25	513	241	0.46	9.6	32.5[c]	39.84*
	5,000	25	521	265	0.50	10.6	32.5[c]	51.41*
					P < 0.001			

TABLE E3
Induction of Sister Chromatid Exchanges in Chinese Hamster Ovary Cells by Sodium Xylenesulfonate
(continued)

Compound	Dose (μg/mL)	Total Cells Scored	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hrs in BrdU	Relative Change of SCEs/ Chromosome (%)
+S9								
Summary: Negative								
Negative		50	1,034	392	0.37	7.8	25.5	
Cyclophosphamide	0.4	50	1,039	631	0.60	12.6	25.5	60.19
	2.0	5	103	169	1.64	33.8	25.5	332.80
Sodium xylenesulfonate	500	50	1,039	413	0.39	8.3	25.5	4.85
	1,667	50	1,036	391	0.37	7.8	25.5	−0.45
	5,000	50	1,032	396	0.38	7.9	25.5	1.22
					P=0.532			

* #Positive response (≥20% increase over solvent control)
[a] Study performed at Litton Bionetics, Inc. A detailed description of the protocol is presented in Galloway *et al.* (1987).
SCE=sister chromatid exchange; BrdU=bromodeoxyuridine
[b] SCEs/chromosome in treated cells versus SCEs/chromosome in solvent control cells
[c] Because sodium xylenesulfonate induced a delay in the cell division cycle, harvest time was extended to maximize the proportion of second division cells available for analysis.
[d] Significance of SCEs/chromosome tested by the linear regression trend test versus log of the dose

TABLE E4
Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by Sodium Xylenesulfonate[a]

-S9					+S9				
Dose (μg/mL)	Total Cells Scored	No. of Abs	Abs/ Cell	Cells with Abs (%)	Dose (μg/mL)	Total Cells Scored	No. of Abs	Abs/ Cell	Cells with Abs (%)
Harvest time: 20.0 hours[b]					Harvest time: 12.0 hours				
Summary: Negative					Summary: Negative				
Negative					Negative				
	200	3	0.02	1.0		200	7	0.04	3.5
Mitomycin-C					Cyclophosphamide				
0.05	200	56	0.28	20.5	7.5	200	40	0.20	16.0
0.08	25	23	0.92	48.0	37.5	25	21	0.84	48.0
Sodium xylenesulfonate					Sodium xylenesulfonate				
2,513	200	7	0.04	3.0	2,513	200	9	0.05	4.5
3,750	200	8	0.04	3.5	3,750	200	8	0.04	3.0
5,000	200	6	0.03	3.0	5,000	200	8	0.04	3.5
				P=0.094[c]					P=0.612

[a] Study performed at Litton Bionetics, Inc. The detailed protocol and these data are presented in Galloway *et al*. (1987). Abs=aberrations.
[b] Because of significant chemical-induced cell cycle delay, incubation time prior to the addition of colcemid was lengthened to provide sufficient metaphase cells at harvest.
[c] Significance of percent cells with aberrations tested by the linear regression trend test versus log of the dose

APPENDIX F
ORGAN WEIGHTS AND ORGAN-WEIGHT-TO-BODY-WEIGHT RATIOS

TABLE F1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 17-Day Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	5 mg/mL	15 mg/mL	44 mg/mL	133 mg/mL	400 mg/mL
n	5	5	5	5	5	5
Male						
Necropsy body wt	181 ± 7	188 ± 6	188 ± 8	174 ± 7	188 ± 12	186 ± 8
Heart						
Absolute	0.690 ± 0.033	0.714 ± 0.036	0.696 ± 0.023	0.662 ± 0.027	0.716 ± 0.037	0.694 ± 0.018
Relative	3.81 ± 0.13	3.79 ± 0.12	3.74 ± 0.11	3.82 ± 0.10	3.82 ± 0.09	3.75 ± 0.10
R. Kidney						
Absolute	0.972 ± 0.043	1.008 ± 0.031	1.014 ± 0.028	0.962 ± 0.037	1.048 ± 0.062	1.040 ± 0.029
Relative	5.36 ± 0.08	5.36 ± 0.13	5.45 ± 0.12	5.56 ± 0.18	5.58 ± 0.07	5.63 ± 0.21
Liver						
Absolute	9.488 ± 0.455	9.616 ± 0.274	9.670 ± 0.504	9.274 ± 0.521	10.758 ± 0.700	11.102 ± 0.400
Relative	52.25 ± 0.87	51.08 ± 0.95	51.72 ± 0.97	53.33 ± 0.87	57.21 ± 0.66**	59.87 ± 1.36**
Lung						
Absolute	0.954 ± 0.015	0.988 ± 0.032	0.954 ± 0.045	1.034 ± 0.039	0.936 ± 0.059	1.120 ± 0.132
Relative	5.28 ± 0.18	5.25 ± 0.11	5.11 ± 0.16	6.00 ± 0.33	4.99 ± 0.13	6.07 ± 0.75
R. Testis						
Absolute	1.072 ± 0.046	1.004 ± 0.058	1.074 ± 0.066	1.077 ± 0.059	1.032 ± 0.081	1.009 ± 0.041
Relative	5.91 ± 0.13	5.33 ± 0.24	5.77 ± 0.34	6.20 ± 0.19	5.48 ± 0.19	5.47 ± 0.32
Thymus						
Absolute	0.465 ± 0.013	0.472 ± 0.007	0.439 ± 0.020	0.484 ± 0.018	0.473 ± 0.032	0.462 ± 0.016
Relative	2.59 ± 0.15	2.51 ± 0.09	2.35 ± 0.07	2.80 ± 0.13	2.52 ± 0.08	2.50 ± 0.08
Female						
Necropsy body wt	136 ± 5	137 ± 5	137 ± 5	133 ± 4	139 ± 5	134 ± 5
Heart						
Absolute	0.550 ± 0.028	0.540 ± 0.016	0.590 ± 0.041	0.550 ± 0.023	0.576 ± 0.011	0.580 ± 0.036
Relative	4.06 ± 0.17	3.94 ± 0.15	4.31 ± 0.23	4.15 ± 0.13	4.17 ± 0.21	4.34 ± 0.23
R. Kidney						
Absolute	0.748 ± 0.038	0.796 ± 0.035	0.764 ± 0.026	0.744 ± 0.021	0.800 ± 0.014	0.838 ± 0.045
Relative	5.51 ± 0.15	5.79 ± 0.15	5.58 ± 0.08	5.62 ± 0.09	5.77 ± 0.19	6.26 ± 0.22**
Liver						
Absolute	6.088 ± 0.380	6.290 ± 0.143	6.266 ± 0.154	6.162 ± 0.125	7.160 ± 0.430	6.954 ± 0.309
Relative	44.74 ± 1.22	45.86 ± 0.89	45.87 ± 0.96	46.58 ± 0.79	51.37 ± 1.90**	52.00 ± 1.40**
Lung						
Absolute	0.856 ± 0.045	0.868 ± 0.037	0.860 ± 0.027	0.806 ± 0.047	0.926 ± 0.045	0.852 ± 0.074
Relative	6.32 ± 0.28	6.34 ± 0.31	6.29 ± 0.10	6.07 ± 0.22	6.73 ± 0.57	6.42 ± 0.67
Thymus						
Absolute	0.408 ± 0.018	0.393 ± 0.018	0.395 ± 0.008	0.396 ± 0.025	0.353 ± 0.027	0.340 ± 0.025
Relative	3.02 ± 0.17	2.86 ± 0.07	2.89 ± 0.06	2.98 ± 0.11	2.54 ± 0.21	2.54 ± 0.14

** Significantly different ($P \leq 0.01$) from the control group by Williams' or Dunnett's test

[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE F2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 14-Week Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	5 mg/mL	15 mg/mL	44 mg/mL	133 mg/mL	400 mg/mL
n	10	10	10	10	10	10
Male						
Necropsy body wt	360 ± 8	355 ± 4	354 ± 5	334 ± 6*	342 ± 8	350 ± 6
Heart						
Absolute	1.111 ± 0.025	1.095 ± 0.016	1.042 ± 0.015	1.013 ± 0.024**	1.041 ± 0.025	1.070 ± 0.018
Relative	3.09 ± 0.05	3.09 ± 0.04	2.95 ± 0.04	3.04 ± 0.06	3.05 ± 0.06	3.06 ± 0.07
R. Kidney						
Absolute	1.429 ± 0.057	1.470 ± 0.020	1.435 ± 0.041	1.362 ± 0.042	1.386 ± 0.035	1.459 ± 0.031
Relative	3.96 ± 0.09	4.15 ± 0.05	4.06 ± 0.09	4.07 ± 0.07	4.06 ± 0.06	4.17 ± 0.08
Liver						
Absolute	18.010 ± 1.033	16.720 ± 0.303	16.530 ± 0.480	15.426 ± 0.596**	14.856 ± 0.546**	15.904 ± 0.353**
Relative	49.75 ± 1.94	47.22 ± 1.03	46.70 ± 0.84	46.06 ± 1.02*	43.39 ± 0.75**	45.47 ± 0.74**
Lung						
Absolute	1.466 ± 0.063	1.354 ± 0.017	1.390 ± 0.040	1.297 ± 0.021*	1.310 ± 0.031*	1.365 ± 0.041
Relative	4.06 ± 0.13	3.82 ± 0.07	3.94 ± 0.12	3.89 ± 0.08	3.84 ± 0.07	3.90 ± 0.10
R. Testis						
Absolute	1.483 ± 0.015	1.488 ± 0.021	1.512 ± 0.015	1.440 ± 0.020	1.486 ± 0.031	1.469 ± 0.021
Relative	4.13 ± 0.06	4.20 ± 0.07	4.28 ± 0.05	4.32 ± 0.07	4.36 ± 0.09	4.20 ± 0.06
Thymus						
Absolute	0.321 ± 0.027	0.287 ± 0.016	0.304 ± 0.012	0.322 ± 0.021	0.312 ± 0.019	0.317 ± 0.022
Relative	0.89 ± 0.07	0.81 ± 0.05	0.86 ± 0.04	0.96 ± 0.05	0.91 ± 0.04	0.90 ± 0.05
Female						
Necropsy body wt	196 ± 4	192 ± 3	190 ± 2	192 ± 2	197 ± 4	196 ± 4
Heart						
Absolute	0.724 ± 0.020	0.716 ± 0.016	0.698 ± 0.010	0.728 ± 0.017	0.732 ± 0.016	0.705 ± 0.017
Relative	3.69 ± 0.05	3.74 ± 0.11	3.68 ± 0.06	3.80 ± 0.07	3.73 ± 0.08	3.60 ± 0.10
R. Kidney						
Absolute	0.874 ± 0.032	0.852 ± 0.021	0.851 ± 0.016	0.840 ± 0.015	0.882 ± 0.028	0.890 ± 0.015
Relative	4.45 ± 0.11	4.44 ± 0.08	4.49 ± 0.08	4.39 ± 0.07	4.48 ± 0.08	4.55 ± 0.10
Liver						
Absolute	8.007 ± 0.292	7.769 ± 0.222	7.757 ± 0.235	7.877 ± 0.230	7.624 ± 0.160	8.096 ± 0.253
Relative	40.88 ± 1.30	40.51 ± 1.03	40.90 ± 1.20	41.08 ± 0.92	38.79 ± 0.40	41.24 ± 0.98
Lung						
Absolute	0.997 ± 0.036	1.061 ± 0.029	0.958 ± 0.015	1.037 ± 0.044	0.987 ± 0.018	0.994 ± 0.022
Relative	5.09 ± 0.14	5.54 ± 0.17	5.06 ± 0.10	5.41 ± 0.22	5.04 ± 0.13	5.07 ± 0.09
Thymus						
Absolute	0.244 ± 0.016	0.250 ± 0.017	0.231 ± 0.014	0.229 ± 0.011	0.257 ± 0.015	0.237 ± 0.012
Relative	1.24 ± 0.07	1.30 ± 0.09	1.22 ± 0.07	1.20 ± 0.06	1.31 ± 0.07	1.21 ± 0.07

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE F3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 17-Day Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	5 mg/mL	15 mg/mL	44 mg/mL	133 mg/mL	400 mg/mL
n	5	5	5	5	5	5
Male						
Necropsy body wt	25.4 ± 0.8	24.8 ± 1.8	26.1 ± 0.7	25.0 ± 0.3	25.6 ± 0.4	26.4 ± 0.3
Heart						
Absolute	0.140 ± 0.014	0.126 ± 0.010	0.132 ± 0.002	0.132 ± 0.013	0.128 ± 0.004	0.144 ± 0.007
Relative	5.49 ± 0.48	5.10 ± 0.27	5.06 ± 0.09	5.28 ± 0.50	5.00 ± 0.13	5.45 ± 0.22
R. Kidney						
Absolute	0.268 ± 0.019	0.258 ± 0.025	0.282 ± 0.006	0.264 ± 0.015	0.294 ± 0.011	0.292 ± 0.012
Relative	10.50 ± 0.48	10.32 ± 0.35	10.83 ± 0.32	10.56 ± 0.52	11.48 ± 0.39	11.05 ± 0.40
Liver						
Absolute	1.200 ± 0.058	1.216 ± 0.136	1.462 ± 0.068*	1.430 ± 0.045*	1.406 ± 0.038	1.746 ± 0.071**
Relative	47.12 ± 1.11	48.33 ± 2.78	55.93 ± 1.49**	57.29 ± 1.64**	54.93 ± 1.41**	66.10 ± 2.36**
Lung						
Absolute	0.178 ± 0.012	0.166 ± 0.010	0.172 ± 0.002	0.164 ± 0.020	0.166 ± 0.009	0.172 ± 0.007
Relative	6.99 ± 0.39	6.78 ± 0.48	6.61 ± 0.20	6.56 ± 0.79	6.49 ± 0.33	6.51 ± 0.26
R. Testis						
Absolute	0.105 ± 0.003	0.103 ± 0.003	0.100 ± 0.002	0.098 ± 0.004	0.101 ± 0.003	0.104 ± 0.003
Relative	4.14 ± 0.09	4.24 ± 0.33	3.82 ± 0.07	3.91 ± 0.13	3.94 ± 0.09	3.92 ± 0.09
Thymus						
Absolute	0.042 ± 0.003	0.047 ± 0.010	0.044 ± 0.006	0.046 ± 0.005	0.049 ± 0.003	0.053 ± 0.005
Relative	1.66 ± 0.06	1.81 ± 0.32	1.69 ± 0.23	1.83 ± 0.20	1.92 ± 0.12	2.01 ± 0.18
Female						
Necropsy body wt	20.9 ± 0.4	20.2 ± 0.3	20.8 ± 0.5	20.8 ± 0.5	21.0 ± 0.3	21.3 ± 0.2
Heart						
Absolute	0.108 ± 0.004	0.114 ± 0.007	0.116 ± 0.007	0.122 ± 0.009	0.112 ± 0.004	0.138 ± 0.012*
Relative	5.17 ± 0.22	5.63 ± 0.33	5.58 ± 0.37	5.85 ± 0.29	5.34 ± 0.19	6.46 ± 0.53
R. Kidney						
Absolute	0.182 ± 0.006	0.172 ± 0.007	0.204 ± 0.004	0.196 ± 0.011	0.196 ± 0.010	0.210 ± 0.012
Relative	8.70 ± 0.21	8.51 ± 0.31	9.81 ± 0.32	9.42 ± 0.33	9.37 ± 0.57	9.84 ± 0.55
Liver						
Absolute	1.132 ± 0.046	1.098 ± 0.041	1.212 ± 0.025	1.234 ± 0.060	1.250 ± 0.051	1.418 ± 0.054**
Relative	54.07 ± 1.70	54.24 ± 1.33	58.24 ± 1.33	59.32 ± 1.78	59.52 ± 1.87*	66.43 ± 2.33**
Lung						
Absolute	0.152 ± 0.004	0.158 ± 0.012	0.174 ± 0.015	0.164 ± 0.014	0.158 ± 0.011	0.204 ± 0.016*
Relative	7.27 ± 0.19	7.81 ± 0.56	8.39 ± 0.79	7.86 ± 0.52	7.54 ± 0.55	9.58 ± 0.82
Thymus						
Absolute	0.085 ± 0.004	0.072 ± 0.008	0.068 ± 0.005	0.080 ± 0.002	0.085 ± 0.003	0.080 ± 0.004
Relative	4.08 ± 0.21	3.56 ± 0.37	3.26 ± 0.27	3.86 ± 0.08	4.05 ± 0.16	3.76 ± 0.21

* Significantly different ($P \leq 0.05$) from the control group by Williams' or Dunnett's test
** $P \leq 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

TABLE F4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 14-Week Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	5 mg/mL	15 mg/mL	44 mg/mL	133 mg/mL	400 mg/mL
Male						
n	10	10	10	10	10	10
Necropsy body wt	36.0 ± 0.6	32.9 ± 0.8*	35.6 ± 0.7	36.7 ± 0.6	35.5 ± 0.7	37.4 ± 0.7
Heart						
Absolute	0.173 ± 0.006	0.161 ± 0.004	0.172 ± 0.005	0.171 ± 0.005	0.166 ± 0.007	0.170 ± 0.004
Relative	4.81 ± 0.14	4.92 ± 0.15	4.86 ± 0.20	4.66 ± 0.11	4.70 ± 0.23	4.56 ± 0.10
R. Kidney						
Absolute	0.329 ± 0.010	0.354 ± 0.008	0.363 ± 0.008*	0.375 ± 0.011**	0.352 ± 0.008	0.370 ± 0.009**
Relative	9.16 ± 0.26	10.82 ± 0.33**	10.22 ± 0.20*	10.21 ± 0.23*	9.96 ± 0.36	9.93 ± 0.26
Liver						
Absolute	1.698 ± 0.046	1.575 ± 0.045	1.682 ± 0.034	1.741 ± 0.054	1.644 ± 0.021	1.748 ± 0.051
Relative	47.24 ± 1.12	48.10 ± 1.63	47.33 ± 0.53	47.37 ± 1.18	46.38 ± 0.72	46.76 ± 0.75
Lung						
Absolute	0.191 ± 0.011	0.178 ± 0.006	0.192 ± 0.009	0.194 ± 0.008	0.190 ± 0.008	0.184 ± 0.006
Relative	5.32 ± 0.30	5.45 ± 0.24	5.41 ± 0.25	5.29 ± 0.23	5.37 ± 0.24	4.93 ± 0.14
R. Testis						
Absolute	0.126 ± 0.003	0.124 ± 0.002	0.122 ± 0.002	0.124 ± 0.002	0.120 ± 0.002	0.124 ± 0.002
Relative	3.49 ± 0.08	3.79 ± 0.06	3.43 ± 0.08	3.39 ± 0.07	3.38 ± 0.09	3.34 ± 0.06
Thymus						
Absolute	0.046 ± 0.002	0.034 ± 0.002**	0.044 ± 0.002	0.044 ± 0.002	0.042 ± 0.002	0.046 ± 0.002
Relative	1.27 ± 0.06	1.03 ± 0.07*	1.23 ± 0.07	1.19 ± 0.06	1.18 ± 0.06	1.22 ± 0.03
Female						
n	10	9	9	10	9	10
Necropsy body wt	30.6 ± 0.8	30.2 ± 0.6	30.8 ± 0.7	32.5 ± 0.7	30.7 ± 0.6	30.1 ± 0.8
Heart						
Absolute	0.137 ± 0.002	0.137 ± 0.004	0.132 ± 0.002	0.139 ± 0.003	0.143 ± 0.006	0.138 ± 0.004
Relative	4.49 ± 0.10	4.54 ± 0.14	4.30 ± 0.08	4.29 ± 0.10	4.67 ± 0.15	4.60 ± 0.12
R. Kidney						
Absolute	0.237 ± 0.004	0.239 ± 0.004	0.236 ± 0.006	0.238 ± 0.005	0.228 ± 0.004	0.234 ± 0.004
Relative	7.77 ± 0.16	7.94 ± 0.16	7.65 ± 0.16	7.36 ± 0.23	7.44 ± 0.17	7.81 ± 0.17
Liver						
Absolute	1.474 ± 0.038	1.484 ± 0.028	1.418 ± 0.036	1.384 ± 0.022	1.462 ± 0.056	1.442 ± 0.035
Relative	48.19 ± 0.74	49.31 ± 0.92	46.02 ± 0.81	42.70 ± 0.80**	47.59 ± 1.28	48.11 ± 1.14
Lung						
Absolute	0.184 ± 0.006	0.184 ± 0.005	0.170 ± 0.007	0.176 ± 0.006	0.183 ± 0.003	0.173 ± 0.004
Relative	6.03 ± 0.20	6.13 ± 0.17	5.52 ± 0.23	5.43 ± 0.20	5.99 ± 0.13	5.79 ± 0.19
Thymus						
Absolute	0.057 ± 0.002	0.049 ± 0.002	0.053 ± 0.002	0.052 ± 0.003	0.053 ± 0.004	0.051 ± 0.001
Relative	1.86 ± 0.04	1.63 ± 0.05	1.73 ± 0.07	1.61 ± 0.09	1.74 ± 0.11	1.71 ± 0.05

* Significantly different ($P \le 0.05$) from the control group by Williams' or Dunnett's test
** $P \le 0.01$
[a] Organ weights (absolute weights) and body weights are given in grams; organ-weight-to-body-weight ratios (relative weights) are given as mg organ weight/g body weight (mean ± standard error).

APPENDIX G
HEMATOLOGY
AND CLINICAL CHEMISTRY RESULTS

TABLE G1
Hematology Data for Male Rats in the 14-Week Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	5 mg/mL	15 mg/mL	44 mg/mL	133 mg/mL	400 mg/mL
n						
Day 5	7	10	9	10	8	6
Day 21	10	10	9	10	10	9
Week 14	10	10	10	10	10	10
Hematocrit (%)						
Day 5	44.7 ± 0.6	42.7 ± 0.5	43.1 ± 0.6	43.4 ± 0.3	43.8 ± 0.7	42.6 ± 0.7
Day 21	45.6 ± 1.1	46.4 ± 0.3	44.2 ± 2.3	48.0 ± 0.5	45.9 ± 0.4	45.8 ± 0.5
Week 14	47.7 ± 0.5	47.5 ± 0.5	47.0 ± 0.5	46.8 ± 0.3	47.4 ± 0.3	46.7 ± 0.6
Hemoglobin (g/dL)						
Day 5	14.9 ± 0.2	14.3 ± 0.2	14.4 ± 0.3	14.6 ± 0.1	14.7 ± 0.2	14.2 ± 0.1
Day 21	15.0 ± 0.3	15.2 ± 0.1	14.6 ± 0.8	15.9 ± 0.2	15.2 ± 0.1	15.1 ± 0.2
Week 14	15.7 ± 0.2	15.6 ± 0.2	15.5 ± 0.1	15.6 ± 0.1	15.5 ± 0.1	15.5 ± 0.1
Erythrocytes ($10^6/\mu L$)						
Day 5	7.51 ± 0.08	7.14 ± 0.06	7.38 ± 0.14	7.37 ± 0.06	7.34 ± 0.19	6.98 ± 0.16*
Day 21	8.09 ± 0.16	8.24 ± 0.07	7.96 ± 0.39	8.55 ± 0.09	8.19 ± 0.14	8.05 ± 0.09
Week 14	9.63 ± 0.08	9.67 ± 0.09	9.41 ± 0.09	9.45 ± 0.08	9.49 ± 0.07	9.42 ± 0.13
Reticulocytes ($10^6/\mu L$)						
Day 5	0.03 ± 0.01[b]	0.03 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.04 ± 0.01	0.02 ± 0.00
Day 21	0.07 ± 0.02	0.06 ± 0.01	0.08 ± 0.02	0.09 ± 0.01	0.06 ± 0.02	0.08 ± 0.01
Week 14	0.02 ± 0.00	0.01 ± 0.00	0.02 ± 0.00	0.01 ± 0.00	0.01 ± 0.00	0.01 ± 0.00
Mean cell volume (fL)						
Day 5	59.6 ± 0.7	59.9 ± 0.6	58.3 ± 0.4	58.9 ± 0.5	59.9 ± 0.7	61.0 ± 0.6
Day 21	56.5 ± 0.5	56.5 ± 0.4	55.3 ± 0.6	56.1 ± 0.3	56.1 ± 0.6	57.1 ± 0.4
Week 14	49.5 ± 0.2	49.1 ± 0.2	49.9 ± 0.2	49.4 ± 0.2	50.1 ± 0.2	49.6 ± 0.2
Mean cell hemoglobin (pg)						
Day 5	19.9 ± 0.3	20.0 ± 0.3	19.5 ± 0.1	19.8 ± 0.2	20.0 ± 0.4	20.4 ± 0.4
Day 21	18.5 ± 0.2	18.5 ± 0.1	18.2 ± 0.2	18.5 ± 0.2	18.6 ± 0.2	18.8 ± 0.2
Week 14	16.3 ± 0.1	16.1 ± 0.1	16.5 ± 0.1	16.5 ± 0.1	16.3 ± 0.1	16.5 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 5	33.4 ± 0.2	33.4 ± 0.2	33.3 ± 0.3	33.6 ± 0.2	33.5 ± 0.3	33.4 ± 0.3
Day 21	32.8 ± 0.2	32.7 ± 0.2	32.9 ± 0.3	33.0 ± 0.2	33.1 ± 0.2	33.0 ± 0.3
Week 14	32.9 ± 0.2	32.7 ± 0.1	33.0 ± 0.2	33.4 ± 0.2	32.7 ± 0.2	33.2 ± 0.3
Platelets ($10^3/\mu L$)						
Day 5	987.7 ± 33.4	980.4 ± 33.3	959.8 ± 37.7	984.8 ± 63.7	914.3 ± 48.4	878.3 ± 15.9*
Day 21	746.2 ± 55.3	743.9 ± 55.0	843.8 ± 121	817.7 ± 21.8	708.1 ± 37.5	835.0 ± 30.7
Week 14	702.9 ± 17.1	729.9 ± 21.2	699.1 ± 18.0	699.9 ± 18.1	715.2 ± 8.6	678.3 ± 12.2
Leukocytes ($10^3/\mu L$)						
Day 5	4.93 ± 0.81	3.91 ± 0.31	3.67 ± 0.44	4.08 ± 0.20	3.70 ± 0.51	3.58 ± 0.45
Day 21	5.72 ± 0.34	4.78 ± 0.47	6.47 ± 1.26	6.92 ± 0.30	5.61 ± 0.56	6.57 ± 0.55
Week 14	8.49 ± 0.38	8.78 ± 0.29	8.59 ± 0.30	9.86 ± 0.47	8.96 ± 0.17	9.02 ± 0.34
Segmented neutrophils ($10^3/\mu L$)						
Day 5	0.64 ± 0.18	0.54 ± 0.05	0.48 ± 0.08	0.42 ± 0.06	0.55 ± 0.10	0.47 ± 0.10
Day 21	0.59 ± 0.10	0.61 ± 0.15	0.74 ± 0.23	0.47 ± 0.04	0.69 ± 0.09	0.63 ± 0.11
Week 14	1.33 ± 0.09	1.12 ± 0.11	1.00 ± 0.05	1.08 ± 0.11	1.11 ± 0.10	1.28 ± 0.13
Lymphocytes ($10^3/\mu L$)						
Day 5	4.21 ± 0.67	3.36 ± 0.27	3.13 ± 0.40	3.65 ± 0.19	3.14 ± 0.43	3.12 ± 0.40
Day 21	5.06 ± 0.24	4.16 ± 0.44	5.67 ± 1.02	6.40 ± 0.31	4.88 ± 0.48	5.87 ± 0.51
Week 14	6.64 ± 0.30	6.99 ± 0.26	7.08 ± 0.30	8.04 ± 0.49	7.17 ± 0.10	7.09 ± 0.30
Monocytes ($10^3/\mu L$)						
Week 14	0.46 ± 0.08	0.56 ± 0.08	0.42 ± 0.07	0.58 ± 0.06	0.55 ± 0.06	0.56 ± 0.08
Eosinophils ($10^3/\mu L$)						
Day 5	0.04 ± 0.03	0.03 ± 0.02	0.02 ± 0.02	0.02 ± 0.01	0.00 ± 0.00	0.02 ± 0.02
Day 21	0.06 ± 0.04	0.03 ± 0.02	0.06 ± 0.03	0.06 ± 0.02	0.05 ± 0.02	0.07 ± 0.02
Week 14	0.09 ± 0.03	0.12 ± 0.04	0.11 ± 0.04	0.15 ± 0.03	0.15 ± 0.05	0.09 ± 0.04

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=6

TABLE G2
Hematology Data for Female Rats in the 14-Week Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	5 mg/mL	15 mg/mL	44 mg/mL	133 mg/mL	400 mg/mL
n						
Day 5	6	10	7	10	8	8
Day 21	10	10	10	10	10	10
Week 14	10	10	10	10	10	10
Hematocrit (%)						
Day 5	45.5 ± 0.8	43.6 ± 0.7	43.9 ± 0.5	44.8 ± 0.4	44.3 ± 0.9	43.0 ± 0.7
Day 21	46.3 ± 0.7	46.3 ± 0.4	46.6 ± 0.7	46.6 ± 0.5	44.7 ± 0.8	46.2 ± 0.5
Week 14	46.3 ± 0.4	46.7 ± 0.4	47.6 ± 0.4	46.8 ± 0.4	46.9 ± 0.4	46.4 ± 0.3
Hemoglobin (g/dL)						
Day 5	14.8 ± 0.2	14.5 ± 0.3	14.6 ± 0.2	14.8 ± 0.2	14.5 ± 0.3	14.4 ± 0.3
Day 21	15.5 ± 0.2	15.5 ± 0.2	15.4 ± 0.2	15.5 ± 0.2	15.0 ± 0.2	15.4 ± 0.2
Week 14	15.3 ± 0.1	15.4 ± 0.1	15.6 ± 0.1	15.4 ± 0.1	15.4 ± 0.1	15.4 ± 0.2
Erythrocytes ($10^6/\mu L$)						
Day 5	7.83 ± 0.17	7.38 ± 0.13	7.51 ± 0.11	7.49 ± 0.07	7.50 ± 0.16	7.32 ± 0.11
Day 21	7.97 ± 0.13	7.96 ± 0.09	8.02 ± 0.13	7.96 ± 0.11	7.78 ± 0.11	8.02 ± 0.10
Week 14	8.65 ± 0.07	8.71 ± 0.07	8.91 ± 0.06*	8.78 ± 0.07	8.77 ± 0.07	8.67 ± 0.06
Reticulocytes ($10^6/\mu L$)						
Day 5	0.12 ± 0.01	0.15 ± 0.01	0.12 ± 0.02	0.08 ± 0.01	0.08 ± 0.01	0.12 ± 0.02
Day 21	0.07 ± 0.01	0.07 ± 0.01	0.10 ± 0.02	0.11 ± 0.02*	0.10 ± 0.01*	0.10 ± 0.01*
Week 14	0.05 ± 0.02	0.03 ± 0.01	0.02 ± 0.00	0.03 ± 0.01	0.04 ± 0.01	0.04 ± 0.01
Mean cell volume (fL)						
Day 5	58.2 ± 0.5	59.1 ± 0.6	58.6 ± 0.5	59.9 ± 0.6	59.3 ± 0.5	58.8 ± 0.6
Day 21	58.1 ± 0.4	58.3 ± 0.4	58.2 ± 0.3	58.5 ± 0.4	57.5 ± 0.5	57.7 ± 0.4
Week 14	53.6 ± 0.2	53.6 ± 0.2	53.5 ± 0.2	53.3 ± 0.2	53.5 ± 0.2	53.3 ± 0.2
Mean cell hemoglobin (pg)						
Day 5	19.0 ± 0.2	19.6 ± 0.3	19.5 ± 0.1	19.7 ± 0.2	19.4 ± 0.2	19.7 ± 0.3
Day 21	19.5 ± 0.1	19.5 ± 0.1	19.2 ± 0.2	19.5 ± 0.1	19.3 ± 0.2	19.2 ± 0.1
Week 14	17.7 ± 0.1	17.7 ± 0.1	17.5 ± 0.1	17.6 ± 0.1	17.6 ± 0.1	17.8 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 5	32.6 ± 0.2	33.2 ± 0.3	33.3 ± 0.2	33.0 ± 0.2	32.7 ± 0.2	33.5 ± 0.2*
Day 21	33.5 ± 0.2	33.5 ± 0.3	33.1 ± 0.2	33.3 ± 0.3	33.6 ± 0.2	33.4 ± 0.3
Week 14	32.9 ± 0.2	33.0 ± 0.2	32.8 ± 0.2	33.0 ± 0.2	32.9 ± 0.3	33.3 ± 0.1
Platelets ($10^3/\mu L$)						
Day 5	802.8 ± 28.4	925.2 ± 42.0	846.1 ± 13.8	863.9 ± 20.0	893.9 ± 26.5	877.1 ± 15.7
Day 21	700.1 ± 30.5	742.3 ± 36.1	748.3 ± 32.8	837.2 ± 12.2**	792.9 ± 29.5*	831.7 ± 17.0**
Week 14	752.9 ± 31.4	699.2 ± 8.4	713.5 ± 10.5	705.7 ± 16.4	715.5 ± 16.1	708.2 ± 16.6
Leukocytes ($10^3/\mu L$)						
Day 5	3.77 ± 0.77	4.38 ± 0.49	4.14 ± 0.61	4.16 ± 0.66	4.16 ± 0.57	4.39 ± 0.54
Day 21	3.94 ± 0.46	4.46 ± 0.48	3.29 ± 0.28	4.37 ± 0.51	4.81 ± 0.52	4.42 ± 0.44
Week 14	6.16 ± 0.47	5.42 ± 0.45	5.68 ± 0.45	5.41 ± 0.48	6.02 ± 0.43	6.16 ± 0.37
Segmented neutrophils ($10^3/\mu L$)						
Day 5	0.47 ± 0.09	0.28 ± 0.04	0.49 ± 0.14	0.45 ± 0.12	0.61 ± 0.10	0.54 ± 0.13
Day 21	0.39 ± 0.07	0.56 ± 0.12	0.32 ± 0.03	0.35 ± 0.06	0.53 ± 0.08	0.58 ± 0.10
Week 14	0.86 ± 0.21	0.63 ± 0.09	0.74 ± 0.14	0.71 ± 0.10	0.74 ± 0.12	0.82 ± 0.09
Lymphocytes ($10^3/\mu L$)						
Day 5	3.27 ± 0.69	4.04 ± 0.49	3.64 ± 0.48	3.69 ± 0.57	3.53 ± 0.48	3.85 ± 0.44
Day 21	3.49 ± 0.40	3.90 ± 0.41	2.96 ± 0.26	4.01 ± 0.46	4.25 ± 0.48	3.80 ± 0.38
Week 14	5.23 ± 0.34	4.73 ± 0.38	4.90 ± 0.39	4.68 ± 0.41	5.17 ± 0.42	5.25 ± 0.32
Monocytes ($10^3/\mu L$)						
Week 14	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.02
Eosinophils ($10^3/\mu L$)						
Day 5	0.07 ± 0.03	0.03 ± 0.02	0.03 ± 0.02	0.02 ± 0.01	0.04 ± 0.02	0.04 ± 0.02
Day 21	0.04 ± 0.02	0.02 ± 0.01	0.00 ± 0.00	0.00 ± 0.00	0.02 ± 0.01	0.03 ± 0.02
Week 14	0.07 ± 0.03	0.06 ± 0.03	0.05 ± 0.02	0.04 ± 0.02	0.09 ± 0.03	0.07 ± 0.02

* Significantly different ($P \le 0.05$) from the control group by Dunn's or Shirley's test
** $P \le 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

TABLE G3
Clinical Chemistry Data for Male Rats in the 14-Week Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	5 mg/mL	15 mg/mL	44 mg/mL	133 mg/mL	400 mg/mL
n						
Day 5	10	10	10	10	10	9
Day 21	10	10	10	10	10	9
Week 14	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 5	28.0 ± 1.2	23.6 ± 0.6**	26.0 ± 0.8	25.7 ± 0.8	24.6 ± 0.7	24.3 ± 0.9
Day 21	25.9 ± 1.0	25.9 ± 1.0	25.8 ± 1.4	25.5 ± 0.4	25.6 ± 1.2	24.4 ± 1.0
Week 14	23.4 ± 0.6	23.9 ± 0.7	23.3 ± 0.6	23.2 ± 0.4	23.0 ± 0.7	23.5 ± 0.7
Creatinine (mg/dL)						
Day 5	0.41 ± 0.02	0.46 ± 0.02	0.43 ± 0.02	0.44 ± 0.04	0.46 ± 0.02	0.41 ± 0.03
Day 21	0.62 ± 0.03	0.60 ± 0.02	0.61 ± 0.02	0.61 ± 0.02	0.60 ± 0.02	0.56 ± 0.05
Week 14	0.50 ± 0.02	0.50 ± 0.02	0.49 ± 0.02	0.50 ± 0.01	0.50 ± 0.01	0.47 ± 0.03
Total protein (g/dL)						
Day 5	6.0 ± 0.1	6.0 ± 0.1	6.1 ± 0.2	6.1 ± 0.1	6.0 ± 0.1	5.8 ± 0.1
Day 21	6.3 ± 0.1	6.3 ± 0.2	5.9 ± 0.2	6.6 ± 0.1	6.1 ± 0.1	6.2 ± 0.1
Week 14	6.9 ± 0.1	7.0 ± 0.1	6.8 ± 0.1	6.8 ± 0.1	7.0 ± 0.1	6.8 ± 0.1
Albumin (g/dL)						
Day 5	3.6 ± 0.1	3.5 ± 0.1	3.7 ± 0.1	3.6 ± 0.1	3.6 ± 0.1	3.6 ± 0.0
Day 21	3.6 ± 0.1	3.6 ± 0.1	3.5 ± 0.1	3.7 ± 0.1	3.6 ± 0.1	3.5 ± 0.1
Week 14	3.9 ± 0.1	4.0 ± 0.1	3.9 ± 0.1	3.9 ± 0.1	3.9 ± 0.1	3.8 ± 0.1
Alanine aminotransferase (IU/L)						
Day 5	41 ± 1	45 ± 1	42 ± 1	48 ± 2**	47 ± 2**	45 ± 1*
Day 21	59 ± 7	55 ± 3	52 ± 2	52 ± 3	52 ± 2	47 ± 2
Week 14	52 ± 2	59 ± 5	52 ± 1	54 ± 2	51 ± 1	55 ± 3
Alkaline phosphatase (IU/L)						
Day 5	579 ± 26	617 ± 25	569 ± 22	593 ± 13	615 ± 25	595 ± 12
Day 21	468 ± 19	471 ± 18	459 ± 17	464 ± 8	460 ± 16	457 ± 13
Week 14	258 ± 9	274 ± 12	270 ± 7	272 ± 9	276 ± 8	267 ± 9
Creatine kinase (IU/L)						
Day 5	531 ± 38	407 ± 56	428 ± 73	608 ± 177	612 ± 149	373 ± 46
Day 21	334 ± 61	296 ± 39	296 ± 38	445 ± 117	291 ± 31	272 ± 25
Week 14	287 ± 30	228 ± 31	276 ± 37	264 ± 58	202 ± 26	231 ± 62
Sorbitol dehydrogenase (IU/L)						
Day 5	6 ± 0	6 ± 0	5 ± 0	7 ± 1	6 ± 1	6 ± 1
Day 21	7 ± 1	6 ± 0	6 ± 0	7 ± 1	6 ± 1	6 ± 0
Week 14	8 ± 0	11 ± 2	9 ± 1	8 ± 0	7 ± 0	9 ± 1
Bile acids (μmol/L)						
Day 5	19.3 ± 3.0	18.4 ± 2.9	18.3 ± 3.0	28.6 ± 3.1	19.2 ± 5.0	23.1 ± 3.4
Day 21	18.9 ± 2.7	28.8 ± 6.8	28.4 ± 5.1	25.7 ± 3.6	26.2 ± 3.7	28.6 ± 3.5
Week 14	30.0 ± 5.3	18.2 ± 2.6	21.9 ± 4.9	21.3 ± 3.1	23.2 ± 4.3	21.4 ± 3.2

* Significantly different ($P \leq 0.05$) from the control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.

TABLE G4
Clinical Chemistry Data for Female Rats in the 14-Week Dermal Study of Sodium Xylenesulfonate[a]

	Vehicle Control	5 mg/mL	15 mg/mL	44 mg/mL	133 mg/mL	400 mg/mL
n	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 5	25.3 ± 0.7	25.8 ± 0.8	26.7 ± 0.5	27.0 ± 0.5	26.4 ± 0.5	27.1 ± 1.0
Day 21	27.3 ± 1.1	26.7 ± 0.8	28.1 ± 0.9	26.1 ± 0.8	27.2 ± 0.6	26.1 ± 0.6
Week 14	23.7 ± 1.0	23.3 ± 0.8	23.9 ± 1.1	25.0 ± 0.6	25.0 ± 0.8	24.9 ± 0.8
Creatinine (mg/dL)						
Day 5	0.42 ± 0.03	0.42 ± 0.04	0.47 ± 0.02	0.49 ± 0.03[b]	0.45 ± 0.02	0.37 ± 0.05
Day 21	0.59 ± 0.02	0.58 ± 0.02	0.63 ± 0.02	0.58 ± 0.02	0.56 ± 0.03	0.58 ± 0.02
Week 14	0.44 ± 0.02	0.44 ± 0.03	0.47 ± 0.02	0.48 ± 0.01	0.45 ± 0.01	0.48 ± 0.02
Total protein (g/dL)						
Day 5	5.7 ± 0.1	5.6 ± 0.1	5.8 ± 0.1	5.7 ± 0.1	5.8 ± 0.1	5.7 ± 0.1
Day 21	6.0 ± 0.2	6.1 ± 0.1	6.2 ± 0.1	6.1 ± 0.2	5.9 ± 0.1	6.2 ± 0.1
Week 14	6.4 ± 0.1	6.4 ± 0.1	6.5 ± 0.0	6.5 ± 0.1	6.5 ± 0.1	6.4 ± 0.1
Albumin (g/dL)						
Day 5	3.6 ± 0.0	3.5 ± 0.1	3.7 ± 0.1	3.6 ± 0.1	3.7 ± 0.1	3.5 ± 0.0
Day 21	3.6 ± 0.0	3.5 ± 0.1	3.6 ± 0.1	3.5 ± 0.1	3.4 ± 0.1	3.6 ± 0.1
Week 14	3.7 ± 0.1	3.7 ± 0.1	3.8 ± 0.1	3.8 ± 0.1	3.8 ± 0.1	3.8 ± 0.1
Alanine aminotransferase (IU/L)						
Day 5	43 ± 2	42 ± 1	42 ± 1	41 ± 2	43 ± 2	41 ± 1
Day 21	49 ± 2	46 ± 2	45 ± 2	43 ± 2	46 ± 2	45 ± 2
Week 14	45 ± 2	44 ± 1	47 ± 1	46 ± 1	47 ± 2	50 ± 3
Alkaline phosphatase (IU/L)						
Day 5	508 ± 12	509 ± 12	536 ± 17	514 ± 12	469 ± 15	500 ± 12
Day 21	437 ± 13	408 ± 13	423 ± 6	439 ± 8	387 ± 15	422 ± 12
Week 14	274 ± 8	285 ± 8	285 ± 12	285 ± 10	290 ± 14	294 ± 10
Creatine kinase (IU/L)						
Day 5	449 ± 57	423 ± 40	441 ± 72	419 ± 38	345 ± 25[b]	563 ± 83
Day 21	463 ± 20	407 ± 39	463 ± 44	436 ± 31	548 ± 58	475 ± 47
Week 14	230 ± 42	223 ± 38	291 ± 74	219 ± 19	281 ± 72	335 ± 110
Sorbitol dehydrogenase (IU/L)						
Day 5	3 ± 0	4 ± 0	4 ± 0	4 ± 1	4 ± 1	4 ± 0
Day 21	4 ± 0	4 ± 0	4 ± 0	4 ± 0	3 ± 0	4 ± 0
Week 14	6 ± 0	6 ± 0	6 ± 0	5 ± 0	6 ± 0	6 ± 0
Bile acids (μmol/L)						
Day 5	32.0 ± 4.9	28.6 ± 4.8	32.0 ± 8.2	22.0 ± 3.5	31.5 ± 5.5	22.9 ± 3.3
Day 21	20.0 ± 3.8	20.3 ± 4.7	25.1 ± 4.7	26.8 ± 4.7	17.3 ± 1.4	22.4 ± 3.0
Week 14	22.3 ± 3.8	20.6 ± 4.5	23.2 ± 4.8	21.6 ± 4.0	15.9 ± 2.9	27.1 ± 3.4

[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9

APPENDIX H
CHEMICAL CHARACTERIZATION AND DOSE FORMULATION STUDIES

CHEMICAL CHARACTERIZATION AND DOSE FORMULATION

PROCUREMENT AND CHARACTERIZATION OF SODIUM XYLENESULFONATE

Sodium xylenesulfonate was obtained from Ruetgers Nease Chemical Company (State College, PA) in one lot (R092085), which was used for the 17-day, 14-week, and 2-year studies. Identity, purity, and stability studies were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO). Reports on analyses performed in support of the sodium xylenesulfonate studies are on file at the National Institutes of Environmental Health Sciences.

The chemical, a white powder, was identified as sodium xylenesulfonate by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectra were consistent with those expected for the structure; infrared and nuclear magnetic resonance spectra were consistent with the literature spectra (*Sadtler Standard Spectra*) for sodium xylenesulfonate (Figures H1 and H2).

The purity was determined by elemental analysis, Karl Fischer water analysis, functional group titration, thin-layer chromatography (TLC), and high-performance liquid chromatography (HPLC). Functional group titration for ionic sulfate was performed by dissolving the sodium xylenesulfonate sample in a water:acetone solution and titrating with 0.01 N barium perchlorate solution. The titration was monitored visually with Sulfonazo III indicator. TLC was performed on Silica Gel 60 F-254 plates with two solvent systems: 1) chloroform:methanol (50:50) and 2) acetone:water (90:10). 2-Naphthalenesulfonic acid was used as a reference standard. Plates were examined under visible and under ultraviolet light (254 nm) and iodine vapor. Plates were also inspected under visible and ultraviolet light (254 nm and 366 nm) after a spray of silver nitrate/sodium fluorescein. HPLC was performed with a Waters μBondapak phenyl column at a flow of 1 mL/min with UV detection at 254 nm. Two isocratic solvent systems were used consisting of (A) 0.005 M tetrabutylammonium hydroxide in water with the pH adjusted to 7 with phosphoric acid and (B) 0.005 M tetrabutylammonium hydroxide in methanol with an identical volume of phosphoric acid added. The solvent ratio used in system 1 was 70:30 (A:B) and, in system 2, 40:60.

Elemental analyses for carbon and hydrogen were in agreement with the theoretical values for sodium xylene sulfonate. Calculated on the basis of 5.15% water and 3.82% sodium sulfate, results for sulfur were slightly higher than theoretical values and results for sodium were slightly lower than theoretical values. Karl Fischer water analysis indicated 5.15% $\pm$ 0.07% water. Functional group titration indicated 3.82% $\pm$ 0.04% sodium sulfate. TLC by system 1 indicated a major spot and a slight trace impurity. TLC by system 2 indicated a major spot only. HPLC by system A indicated a major peak and five impurities with areas totalling 39.2% relative to the major peak; system B indicated an additional impurity with a peak area of 9.6% relative to the major peak.

Under these chromatographic conditions, sodium 2,4- and 2,5-xylenesulfonate coelute with the major peak. Evidence for sodium ethyl benzenesulfonate being present as a component in the material can be seen in the nuclear magnetic resonance spectrum, (i.e., triplet at 1.14 ppm [$CH_2\mathbf{CH_3}$] and quartet at approximately 2.5 ppm [$\mathbf{CH_2}CH_3$]) due to the ethyl group of ethyl benzenesulfonate.

Concomitant HPLC analyses of lot R092085 with lot 3835 (not used in these studies) indicated a purity of approximately 115% for lot R092085 relative to lot 3835.

Stability studies of lot 3835 were performed by the analytical chemistry laboratory. To ensure stability of the bulk chemical during the 17-day and 14-week studies, sodium xylenesulfonate was stored in glass bottles

with Teflon®-lined caps or double bagged in metal drums at room temperature in the dark. During the 2-year studies the bulk chemical was stored in amber glass bottles at room temperature in the dark.

PREPARATION AND ANALYSIS OF DOSE FORMULATIONS

The dose formulations for the 17-day studies were prepared twice during the study by stirring the appropriate quantities of sodium xylenesulfonate to solution in deionized water and were then brought to the desired concentration by the further addition of deionized water. The dose formulations for the 14-week studies were prepared every 2 weeks by mixing the appropriate amount of sodium xylenesulfonate with 50% ethanol (in deionized water) which was then brought to the desired concentration by the further addition of 50% ethanol. The 5 and 15 mg/mL doses were stirred to solution and the 44, 133, and 400 mg/mL doses were stirred to suspension. Dose formulations in the 2-year studies of sodium xylenesulfonate were prepared every 2 to 3 weeks by mixing the appropriate weight of sodium xylenesulfonate in deionized water. A suspension was formed by shaking, and then the mixture was brought to the desired concentrations of ethanol and sodium xylenesulfonate by the addition of 95% ethanol. The resulting suspension was the required dose in 50% ethanol. Dose formulations in the 17-day, 14-week, and 2-year studies were stored at room temperature in glass bottles with Teflon®-lined lids in the dark for up to 3 weeks (17-day and 14-week studies) or for 3 to 4 weeks (2-year studies).

Stability studies of 4 mg/mL dose formulations (in deionized water and in 50% ethanol) were conducted by the analytical chemistry laboratory. Aliquots (20 mL) of the solutions were analyzed by HPLC with a Zorbax C_8 column, a mobile phase of cetyltrimethylammonium bromide (10 mg/mL water): methanol (50:50 for dosed water; 25:75 for ethanol formulations), a flow rate of 1 mL/min, and benzoic acid as an internal standard; detection was at 254 nm. Stability was confirmed for at least 3 weeks when stored in the dark at room temperature in sealed glass vials and for 3 hours at room temperature open to air and light.

Homogeneity studies of the dose formulations used in the 2-year studies and a limited stability study of the 75 mg/mL dose formulation used in the 2-year studies were performed by the study laboratory using the same HPLC system as in the previous dose stability study. Homogeneity was confirmed; the 75 mg/mL concentration was stable for 29 days when stored at room temperature, protected from light.

Periodic analyses of the dose formulations of sodium xylenesulfonate were conducted by the study laboratory with HPLC. During the 17-day studies, doses were analyzed at the beginning of the studies (Table H2). During the 14-week studies, doses were analyzed at the beginning, midpoint, and end of the studies (Table H3). During the 2-year studies, dose formulations were analyzed at the beginning of the studies and every 7 to 10 weeks thereafter (Table H4). Although the results of a preliminary mixing trial for the 5 and 400 mg/mL concentrations used in the 17-day studies were within 10% of the target concentrations, the first set of dose formulations were 12% to 14% greater than the target concentrations due to a mixing error. These formulations were remixed and were all within 10% of the target concentrations (Table H2). Animal-room samples for the 17-day studies were also within 10% of the target concentrations. During the 14-week studies, all of the dose formulations and all of the animal room samples were within 10% of the target concentrations. In the 2-year studies, all of the dose formulations and all but two of the animal room samples were within 10% of the target concentrations. For the 14-week studies, two referee analyses performed by the analytical chemistry laboratory indicated good agreement with the results of the study laboratory (Table H5).

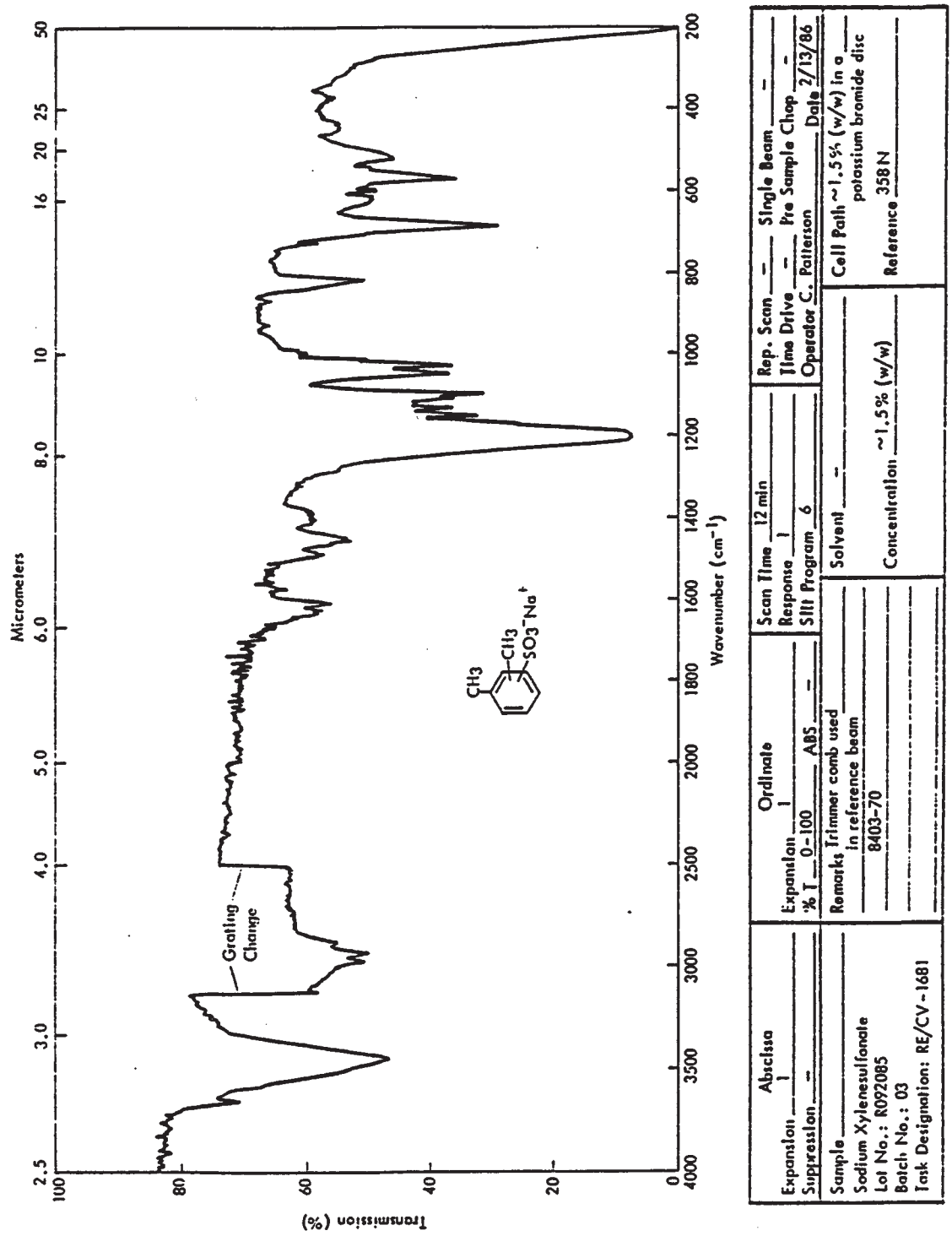

FIGURE H1
Infrared Absorption Spectrum of Sodium Xylenesulfonate

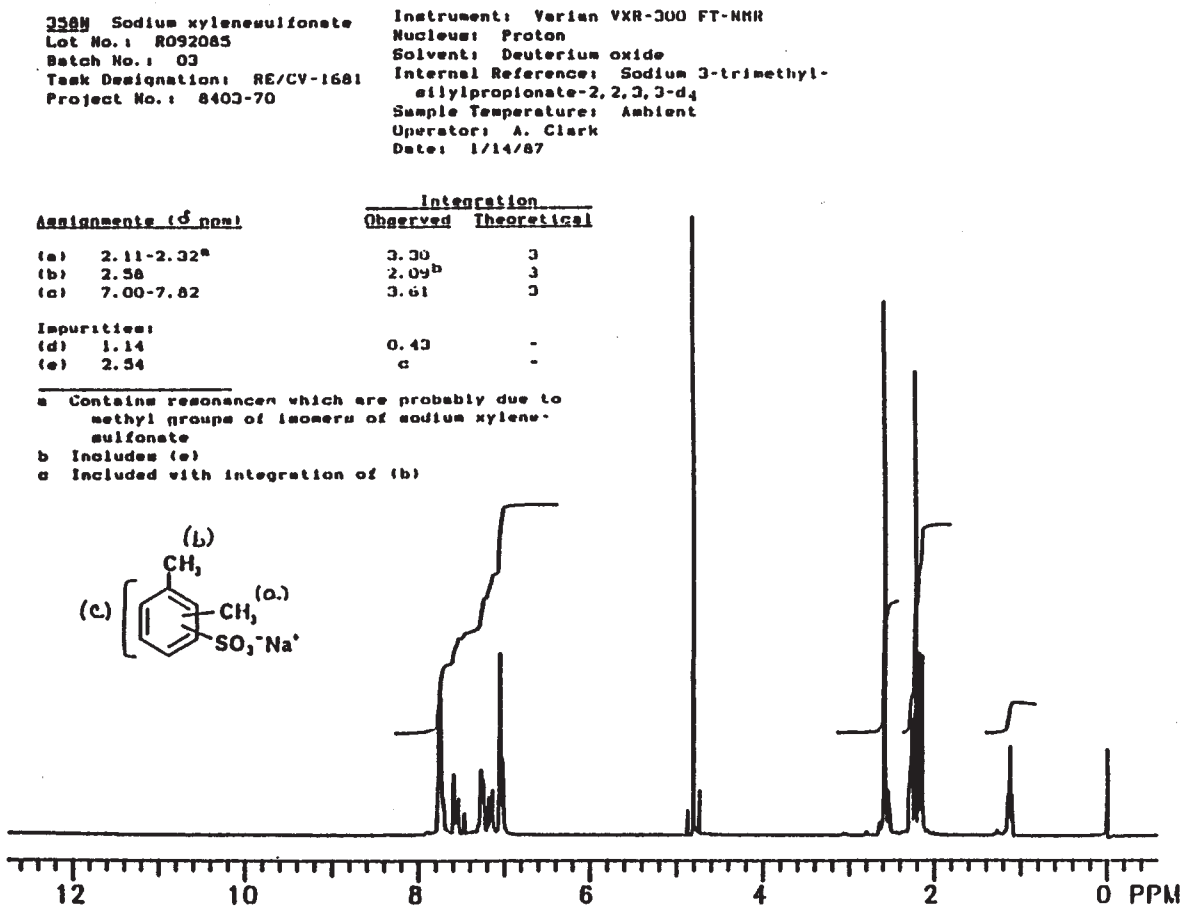

FIGURE H2
Nuclear Magnetic Resonance Spectrum of Sodium Xylenesulfonate

TABLE H1
Preparation and Storage of Dose Formulations in the Dermal Studies of Sodium Xylenesulfonate

17-Day Studies	14-Week Studies	2-Year Studies
Preparation		
The required weight of sodium xylenesulfonate was stirred to solution in deionized water. The solution was brought to the desired concentrations by the further addition of deionized water.	The required weight of sodium xylenesulfonate was mixed with 50% ethanol (in deionized water). The formulation was brought to the desired concentration by the further addition of 50% ethanol. The 5 and 15 mg/mL doses were stirred to solution while the 44, 133, and 400 mg/mL doses were stirred to suspension.	The required weight of sodium xylenesulfonate was mixed with deionized water by shaking. The resulting suspension was then brought to the desired concentration of ethanol (50%) and sodium xylenesulfonate by the addition of 95% ethanol.
Chemical Lot Number		
R092085	R092085	R092085
Maximum Storage Time		
20 days	20 days	3 to 4 weeks
Storage Conditions		
Stored at room temperature in the dark	Same as 17-day studies	Same as 17-day studies
Study Laboratory		
Southern Research Institute (Birmingham, AL)	Southern Research Institute (Birmingham, AL)	Battelle Columbus Laboratories (Columbus, OH)
Referee Laboratory		
None	Midwest Research Institute (Kansas City, MO)	None

TABLE H2
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 17-Day Dermal Studies of Sodium Xylenesulfonate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	% Difference from Target
5 June 1987[b]	8-9 June 1987	5	5.14	+3
		400	412	+3
15 July 1987	16 July 1988	5	5.66	+13
		15	16.9	+13
		44	49.1	+12
		133	152	+14
		400	452	+13
17 July 1987[c]	20 July 1987	5	4.94	-1
		15	15.0	0
		44	44.4	+1
		133	134	+1
		400	408	+2
17 July 1987	28-29 July 1987[d]	5	5.05	+1
		15	15.3	+2
		44	45.2	+3
		133	138	+4
		400	414	+4
17 July 1987	28-29 July 1987[e]	5	5.17	+3
		15	15.2	+1
		44	45.0	+2
		133	136	+2
		400	412	+3

[a] Results of duplicate analyses. Dosing volume=300 μL for rats and 100 μL for mice.
[b] Preliminary mixing trial; not used for dosing
[c] Results of remix
[d] Animal room samples for rats
[e] Animal room samples for mice

TABLE H3
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Dermal Studies of Sodium Xylenesulfonate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	% Difference from Target
10 February 1988	11-12 February 1988	5	5.12	+2
		15	15.3	+2
		44	44.6	+1
		133	134	+1
		400	425	+6
	29 February - 2 March 1988[b]	5	5.09	+2
		15	15.2	+1
		44	44.0	0
		133	132	−1
		400	406	+2
23 March 1988	23-25 March 1988	5	5.02	0
		15	14.8	−1
		44	43.9	0
		133	135	+2
		400	410	+3
	12-13 April 1988[b]	5	5.08	+2
		15	14.8	−1
		44	43.9	0
		133	133	0
		400	410	+3
4 May 1988	6-9 May 1988	5	4.96	−1
		15	15.2	+1
		44	43.9	0
		133	132	−1
		400	406	+2
	26-27 May 1988[b]	5	5.01	0
		15	15.1	+1
		44	43.8	0
		133	132	−1
		400	398	0

[a] Results of duplicate analyses. Dosing volume=300 μL for rats and 100 μL for mice.
[b] Animal room sample

TABLE H4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Sodium Xylenesulfonate

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration[a] (mg/mL)	% Difference from Target
Rats				
26 November 1990	28 November 1990	75	74.2	−1
		150	146	−3
		300	296	−1
26 November 1990[b]	13 December 1990	75	76.1	+1
		150	150	0
		300	303	+1
Rats and Mice				
6 December 1990	14 December 1990	75	74.8	0
		150	150	0
		300	293	−2
6 December 1990[c]	4 January 1991	75	75.0	0
		150	152	+1
		300	296	−1
14 February 1991	18 February 1991	75	76.3	+2
		150	155	+3
		300	299	0
11 April 1991	30 April 1991	75	79.5	+6
		150	154	+3
		300	317	+6
11 April 1991[b]	30 April 1991	75	79.1	+5
		150	157	+5
		300	312	+4
11 April 1991[c]	11 April 1991	75	78.5	+5
		150	159	+6
		300	308	+3
6 June 1991	11 June 1991	75	77.6	+3
		150	155	+3
		300	301	0
1 August 1991	2 August 1991	75	76.9	+3
		150	155	+3
		300	309	+3
26 September 1991	27 September 1991	75	74.4	−1
		150	146	−3
		300	298	−1
26 September 1991[b]	28 October 1991	75	78.1	+4
		150	155	+3
		300	308	+3

TABLE H4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Sodium Xylenesulfonate (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Rats and Mice (continued)				
26 September 1991[c]	28 October 1991	75	78.4	+5
		150	154	+3
		300	309	+3
21 November 1991	22 November 1991	75	77.1	+3
		150	154	+3
		300	302	+1
16 January 1992	17 January 1992	75	76.5	+2
		150	152	+1
		300	298	-1
12 March 1992	12 March 1992	75	76.3	+2
		150	152	+1
		300	302	+1
12 March 1992[b]	9-10 April 1992	75	78.8	+5
		150	162	+8
		300	306	+2
12 March 1992[c]	9-10 April 1992	75	79.6	+6
		150	156	+4
		300	306	+2
7 May 1992	8 May 1992	75	76.5	+2
		150	153	+2
		300	305	+2
2 July 1992	6 July 1992	75	77.4	+3
		150	152	+1
		300	301	0
20 August 1992	21 August 1992	75	75.6	+1
		150	156	+4
		300	308	+3
20 August 1992[b]	21-22 September 1992	75	77.3	+3
		150	157	+5
		300	312	+4
20 August 1992[c]	21-22 September 1992	75	79.9	+7
		150	171	+14
		300	333	+11

TABLE H4
Results of Analyses of Dose Formulations Administered to Rats and Mice in the 2-Year Dermal Studies of Sodium Xylenesulfonate (continued)

Date Prepared	Date Analyzed	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	% Difference from Target
Rats and Mice (continued)				
22 October 1992	26-27 October 1992	75	79.7	+6
		150	153	+2
		300	326	+9

[a] Results of duplicate analyses. Dosing volume for rats was 85 to 357 μL; 60 mg/kg = 75 mg/mL; 120 mg/kg = 150 mg/mL; 240 mg/kg = 300 mg/mL; dosing volume for mice was 46 to 128 μL; 182 mg/kg = 75 mg/mL; 364 mg/kg = 150 mg/mL; 727 mg/kg = 300 mg/mL.
[b] Animal room samples for rats
[c] Animal room samples for mice

TABLE H5
Results of Referee Analyses of Dose Formulations Administered to Rats and Mice in the 14-Week Dermal Studies of Sodium Xylenesulfonate

Date Prepared	Target Concentration (mg/mL)	Determined Concentration (mg/mL)	
		Study Laboratory[a]	Referee Laboratory[b]
10 February 1988	133	134	132 ± 1
23 March 1988	15.0	14.8	14.8 ± 0.0

[a] Results of duplicate analyses
[b] Results of triplicate analyses (mean ± standard error)

APPENDIX I
DOSES, BODY WEIGHTS, AND DOSE CONCENTRATIONS

TABLE I1
Doses, Body Weights, and Dose Concentrations for Rats in the 17-Day Dermal Study of Sodium Xylenesulfonate

Dose (mg/mL)	Dose Volume (μL)	Average Body Weight (kg)	Dose Concentration (mg/kg)
Male			
0	300	0.145	0 #
5	300	0.150	10 #
15	300	0.150	30 #
44	300	0.140	94 #
133	300	0.151	264 #
400	300	0.149	808 #
Female			
0	300	0.114	0 #
5	300	0.117	13 #
15	300	0.118	38 #
44	300	0.113	117 #
133	300	0.120	334 #
400	300	0.116	1,035 #

TABLE I2
Doses, Body Weights, and Dose Concentrations for Mice in the 17-Day Dermal Study of Sodium Xylenesulfonate

Dose (mg/mL)	Dose Volume (μL)	Average Body Weight (kg)	Dose Concentration (mg/kg)
Male			
0	100	0.025	0 #
5	100	0.025	20 #
15	100	0.025	61 #
44	100	0.024	187 #
133	100	0.025	532 #
400	100	0.025	1,633 #
Female			
0	100	0.020	0 #
5	100	0.019	26 #
15	100	0.020	77 #
44	100	0.020	220 #
133	100	0.020	682 #
400	100	0.020	2,051 #

TABLE I3
Doses, Body Weights, and Dose Concentrations for Rats in the 14-Week Dermal Study of Sodium Xylenesulfonate

Dose (mg/mL)	Dose Volume (mL)	Weeks 1 to 4		Weeks 4 to 8		Weeks 8 to 14	
		Avg Wt (kg)	Dose Concentration (mg/kg)	Avg Wt (kg)	Dose Concentration (mg/kg)	Avg Wt (kg)	Dose Concentration (mg/kg)
Male							
0	300	0.192	0	0.265	0	0.322	0
5	300	0.189	8	0.266	6	0.323	5
15	300	0.179	25	0.259	17	0.322	14
44	300	0.178	74	0.255	52	0.308	43
133	300	0.180	222	0.255	157	0.316	126
400	300	0.179	670	0.254	472	0.319	376
Female							
0	300	0.130	0	0.164	0	0.187	0
5	300	0.123	12	0.158	10	0.181	8
15	300	0.121	37	0.156	29	0.180	25
44	300	0.122	108	0.160	83	0.183	72
133	300	0.128	312	0.163	245	0.188	212
400	300	0.128	938	0.163	736	0.186	645

TABLE I4
Doses, Body Weights, and Dose Concentrations for Mice in the 14-Week Dermal Study of Sodium Xylenesulfonate

Dose (mg/mL)	Dose Volume (mL)	Weeks 1 to 4		Weeks 4 to 8		Weeks 8 to 14	
		Avg Wt (kg)	Dose Concentration (mg/kg)	Avg Wt (kg)	Dose Concentration (mg/kg)	Avg Wt (kg)	Dose Concentration (mg/kg)
Male							
0	100	0.027	0	0.030	0	0.034	0
5	100	0.027	19	0.029	17	0.033	15
15	100	0.027	56	0.030	50	0.034	44
44	100	0.028	157	0.031	142	0.035	126
133	100	0.027	493	0.030	443	0.034	391
400	100	0.028	1,429	0.031	1,290	0.035	1,143
Female							
0	100	0.021	0	0.025	0	0.029	0
5	100	0.021	24	0.025	20	0.028	18
15	100	0.021	71	0.025	60	0.029	52
44	100	0.022	200	0.026	169	0.030	147
133	100	0.022	605	0.025	532	0.028	475
400	100	0.022	1,818	0.025	1,600	0.028	1,429

TABLE I5
Doses, Body Weights, and Dose Concentrations for Rats in the 2-Year Dermal Study of Sodium Xylenesulfonate

Dose (mg/mL)	Dose Volume (μL)	Average Body Weight Range (kg)	Dose Concentration (mg/kg)
Male			
0	102 – 357	0.127 – 0.439	0
75	101 – 357	0.127 – 0.438	60
150	102 – 349	0.128 – 0.437	120
300	102 – 345	0.127 – 0.432	240
Female			
0	86 – 232	0.108 – 0.289	0
75	86 – 230	0.107 – 0.288	60
150	85 – 232	0.107 – 0.290	120
300	86 – 217	0.107 – 0.271	240

TABLE I6
Doses, Body Weights, and Dose Concentrations for Mice in the 2-Year Dermal Study of Sodium Xylenesulfonate

Dose (mg/mL)	Dose Volume (μL)	Average Body Weight Range (kg)	Dose Concentration (mg/kg)
Male			
0	58 – 116	0.024 – 0.047	0
75	57 – 114	0.024 – 0.047	182
150	58 – 113	0.024 – 0.047	364
300	57 – 116	0.024 – 0.048	727
Female			
0	46 – 128	0.019 – 0.051	0
75	46 – 128	0.019 – 0.052	182
150	46 – 122	0.019 – 0.050	364
300	46 – 128	0.019 – 0.053	727

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

TABLE J1
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 were ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE J2
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 J3
Nutrient Composition of NIH-07 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	23.45 ± 0.52	22.2 – 24.3	23
Crude fat (% by weight)	5.34 ± 0.19	5.00 – 5.90	23
Crude fiber (% by weight)	3.37 ± 0.34	2.60 – 4.30	23
Ash (% by weight)	6.46 ± 0.18	6.12 – 6.81	23
Amino Acids (% of total diet)			
Arginine	1.280 ± 0.083	1.110 – 1.390	11
Cystine	0.308 ± 0.071	1.181 – 0.400	11
Glycine	1.158 ± 0.048	1.060 – 1.220	11
Histidine	0.584 ± 0.027	0.531 – 0.630	11
Isoleucine	0.917 ± 0.033	0.867 – 0.965	11
Leucine	1.975 ± 0.051	1.850 – 2.040	11
Lysine	1.274 ± 0.049	1.200 – 1.370	11
Methionine	0.437 ± 0.109	0.306 – 0.699	11
Phenylalanine	0.999 ± 0.120	0.665 – 1.110	11
Threonine	0.904 ± 0.058	0.824 – 0.985	11
Tryptophan	0.218 ± 0.153	0.107 – 0.671	11
Tyrosine	0.685 ± 0.094	0.564 – 0.794	11
Valine	1.086 ± 0.055	0.962 – 1.170	11
Essential Fatty Acids (% of total diet)			
Linoleic	2.407 ± 0.227	1.830 – 2.570	10
Linolenic	0.259 ± 0.065	0.100 – 0.320	10
Vitamins			
Vitamin A (IU/kg)	6,780 ± 1,363	5,730 – 11,450	23
Vitamin D (IU/kg)	4,450 ± 1,382	3,000 – 6,300	4
α-Tocopherol (ppm)	36.12 ± 9.15	22.5 – 48.9	10
Thiamine (ppm)	17.48 ± 2.06	14.0 – 22.0	23
Riboflavin (ppm)	7.83 ± 0.923	6.10 – 9.00	11
Niacin (ppm)	98.64 ± 25.51	65.0 – 150.0	10
Pantothenic acid (ppm)	30.55 ± 3.52	23.0 – 34.6	11
Pyridoxine (ppm)	9.11 ± 2.53	5.60 – 14.0	11
Folic acid (ppm)	2.46 ± 0.63	1.80 – 3.70	11
Biotin (ppm)	0.268 ± 0.047	0.190 – 0.354	11
Vitamin B_{12} (ppb)	40.5 ± 19.1	10.6 – 65.0	11
Choline (ppm)	2,991 ± 382	2,300 – 3,430	10
Minerals			
Calcium (%)	1.17 ± 0.09	1.00 – 1.49	23
Phosphorus (%)	0.92 ± 0.05	0.760 – 1.00	23
Potassium (%)	0.886 ± 0.063	0.772 – 0.971	9
Chloride (%)	0.529 ± 0.087	0.380 – 0.635	9
Sodium (%)	0.316 ± 0.033	0.258 – 0.371	11
Magnesium (%)	0.166 ± 0.010	0.148 – 0.181	11
Sulfur (%)	0.272 ± 0.059	0.208 – 0.420	10
Iron (ppm)	350.5 ± 87.3	255.0 – 523.0	11
Manganese (ppm)	92.48 ± 5.14	81.7 – 99.4	11
Zinc (ppm)	59.33 ± 10.2	46.1 – 81.6	11
Copper (ppm)	11.81 ± 2.50	8.09 – 15.4	11
Iodine (ppm)	3.54 ± 1.19	1.52 – 5.83	10
Chromium (ppm)	1.66 ± 0.46	0.85 – 2.09	11
Cobalt (ppm)	0.76 ± 0.23	0.49 – 1.15	7

TABLE J4
Contaminant Levels in NIH-07 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.48 ± 0.17	0.10 – 0.70	23
Cadmium (ppm)	0.14 ± 0.07	0.04 – 0.20	23
Lead (ppm)	0.36 ± 0.25	0.10 – 1.00	23
Mercury (ppm)	0.02 ± 0.00	0.02 – 0.03	23
Selenium (ppm)	0.32 ± 0.11	0.05 – 0.04	23
Aflatoxins (ppb)	<5.0		23
Nitrate nitrogen (ppm)[c]	8.07 ± 4.02	2.90 – 17.0	23
Nitrite nitrogen (ppm)[c]	0.15 ± 0.07	0.10 – 0.30	23
BHA (ppm)[d]	1.48 ± 0.95	1.00 – 5.00	23
BHT (ppm)[d]	1.35 ± 0.88	1.00 – 5.00	23
Aerobic plate count (CFU/g)	102,443 ± 168,151	4,100 – 710,000	23
Coliform (MPN/g)	3.1 ± 0.3	3.0 – 4.0	23
Escherichia coli (MPN/g)	<3.0		23
Salmonella (MPN/g)	Negative		23
Total nitrosoamines (ppb)[e]	7.53 ± 1.84	4.70 – 11.40	23
N-Nitrosodimethylamine (ppb)[e]	5.58 ± 1.22	2.90 – 8.20	23
N-Nitrosopyrrolidine (ppb)[e]	1.96 ± 1.04	1.00 – 4.30	23
Pesticides (ppm)			
α-BHC	<0.01		23
β-BHC	<0.02		23
γ-BHC	<0.01		23
δ-BHC	<0.01		23
Heptachlor	<0.01		23
Aldrin	<0.01		23
Heptachlor epoxide	<0.01		23
DDE	<0.01		23
DDD	<0.01		23
DDT	<0.01		23
HCB	<0.01		23
Mirex	<0.01		23
Methoxychlor	<0.05		23
Dieldrin	<0.01		23
Endrin	<0.01		23
Telodrin	<0.01		23
Chlordane	<0.05		23
Toxaphene	<0.10		23
Estimated PCBs	<0.20		23
Ronnel	<0.01		23
Ethion	<0.02		23
Trithion	<0.05		23
Diazinon	<0.10		23
Methyl parathion	<0.02		23
Ethyl parathion	<0.02		23
Malathion	0.23 ± 0.24	0.05 – 0.97	23
Endosulfan I	<0.01		23
Endosulfan II	<0.01		23
Endosulfan sulfate	<0.03		23

[a] CFU = colony-forming units, MPN = most probable number, BHC = hexachlorocyclohexane or benezene hexachloride
[b] For values less than the limit of detection, the detection limit is given as the mean.
[c] Sources of contamination: alfalfa, grains, and fish meal
[d] Sources of contamination: soy oil and fish meal
[e] All values were corrected for percent recovery.

APPENDIX K
SENTINEL ANIMAL PROGRAM

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 rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are all 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.

Serum samples were collected from randomly selected rats and mice during the 14-week and 2-year studies. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to Microbiological Associates Inc. (Bethesda, MD), for determination of antibody titers. The laboratory serology methods and viral agents for which testing was performed are tabulated below; the times at which the blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
14-Week Study	
ELISA	
PVM (pneumonia virus of mice)	14 weeks
RCV/SDA	
(rat coronavirus/sialodacryoadenitis virus)	14 weeks
Sendai	14 weeks
Hemagglutination Inhibition	
H-1 (Toolan's H-1 virus)	14 weeks
KRV (Kilham rat virus)	14 weeks
2-Year Study	
ELISA	
Mycoplasma arthritidis	24 months
Mycoplasma pulmonis	24 months
PVM	Quarantine, 6, 12, 18, and 24 months
RCV/SDA	Quarantine, 6, 12, 18, and 24 months
Sendai	Quarantine, 6, 12, 18, and 24 months
Hemagglutination Inhibition	
H-1	Quarantine, 6, 12, 18, and 24 months
KRV	Quarantine, 6, 12, 18, and 24 months

MICE

14-Week Study

ELISA	
Ectromelia virus	14 weeks
GDVII (mouse encephalomyelitis virus)	14 weeks
LCM (lymphocytic choriomeningitis virus)	14 weeks
MVM (minute virus of mice)	14 weeks
Mouse adenoma virus	14 weeks
MHV (mouse hepatitis virus)	14 weeks
PVM	14 weeks
Sendai	14 weeks
Immunofluorescence Assay	
EDIM (epizootic diarrhea of infant mice)	14 weeks
Reovirus 3	14 weeks
Hemagglutination Inhibition	
K (papovavirus)	14 weeks
Polyoma virus	14 weeks

2-Year Study

ELISA	
Ectromelia virus	Quarantine, 6, 12, 18, and 24 months
EDIM	Quarantine, 12, 18, and 24 months
GDVII	Quarantine, 6, 12, 18, and 24 months
LCM	Quarantine, 6, 12, 18, and 24 months
Mouse adenoma virus-FL	Quarantine, 6, 12, 18, and 24 months
MHV	Quarantine, 6, 12, 18, and 24 months
M. arthritidis	24 months
M. pulmonis	24 months
PVM	Quarantine, 6, 12, 18, and 24 months
Reovirus 3 #	Quarantine, 6, 12, 18, and 24 months
Sendai	Quarantine, 6, 12, 18, and 24 months
Immunofluorescence Assay	
EDIM	6, 12, and 18 months
LCM	18 months
Mouse adenoma virus-FL	18 months
MHV	12 and 18 months
Reovirus 3	12 and 18 months
Hemagglutination Inhibition	
K	Quarantine, 6, 12, 18, and 24 months
MVM	Quarantine, 6, 12, 18, and 24 months
Polyoma virus	Quarantine, 6, 12, 18, and 24 months

Results of serology tests are presented in Table K1.

TABLE K1
Murine Virus Antibody Determinations for Rats and Mice in the 14-Week and 2-Year Dermal Studies of Sodium Xylenesulfonate

Interval	Incidence of Antibody in Sentinel Animals	Positive Serologic Reaction for
14-Week Studies		
Rats		
Study termination	0/10	None positive
Mice		
Study termination	0/10	None positive
2-Year Studies		
Rats		
Quarantine	0/10	None positive
6 Months	0/10	None positive
12 Months	0/9	None positive
18 Months	0/7	None positive
24 Months	2/10	*M. arthritidis*[a]
Mice		
Quarantine	0/9	None positive
6 Months	0/10	None positive
12 Months	1/10	Reovirus 3
18 Months	0/9	None positive
24 Months	2/10	*M. arthritidis*[a]

[a] Further evaluation of samples positive for *M. arthritidis* by immunoblot and Western blot procedures indicated that the positive titers may have been due to cross reaction with antibiotics of nonpathogenic *Mycoplasma* or other agents. Only sporadic samples were positive, and there were no clinical findings or histopathologic changes of *M. athritidis* infection in rats or mice with positive titers. Accordingly, sporadic *M. arthritidis*-positive titers were considered to be false positives.

APPENDIX L
IMPACT OF *HELICOBACTER HEPATICUS* INFECTION IN B6C3F$_1$ MICE FROM 12 NTP 2-YEAR CARCINOGENESIS STUDIES

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IMPACT OF *HELICOBACTER HEPATICUS* INFECTION IN B6C3F$_1$ MICE FROM 12 NTP 2-YEAR CARCINOGENESIS STUDIES

ABSTRACT

Male and female B6C3F$_1$ mice from 12 NTP 2-year carcinogenesis studies were found to be infected with *Helicobacter hepaticus*. Many of the male mice from nine of these studies ("affected" studies) had an associated hepatitis. The current evaluations were performed in an attempt to determine if the data from the *H. hepaticus*-affected NTP B6C3F$_1$ mouse studies were compromised and unsuitable for cancer hazard identification. The incidences of neoplasms of the liver (both hepatocellular neoplasms and hemangiosarcoma), but not of other organs in control male B6C3F$_1$ mice, were found to be increased in affected studies compared to control males from unaffected studies. The increased incidence of hepatocellular neoplasms was observed in those males exhibiting *H. hepaticus*-associated hepatitis. Other observations further differentiated control male mice from affected and unaffected studies. H-*ras* codon 61 CAA-to-AAA mutations were less common in liver neoplasms in males from affected studies compared to historical and unaffected study controls. In addition, increases in cell proliferation rates and apoptosis were observed in the livers of male mice with *H. hepaticus*-associated hepatitis. These data support the hypothesis that the increased incidence of liver neoplasms is associated with *H. hepaticus* and that hepatitis may be important in the pathogenesis. Therefore, interpretation of carcinogenic effects in the liver of B6C3F$_1$ mice may be confounded if there is *H. hepaticus*-associated hepatitis.

INTRODUCTION

Helicobacter-Induced Diseases

Since the bacterium *H. pylori* was isolated from humans in 1983, numerous *Helicobacter* species have been identified in several laboratory and domestic animal species. Their pathogenicity varies, with some species inducing significant disease while others appear merely to colonize the gastrointestinal tract. *H. pylori* is known to cause chronic gastritis and peptic ulcers in humans (Marshall and Warren, 1984; Graham, 1989; Lee *et al.*, 1993) and, more recently, has been linked to adenocarcinoma and mucosa-associated lymphoma of the stomach (Fox *et al.*, 1989; Nomura *et al.*, 1991; Parsonnet *et al.*, 1991; Wotherspoon *et al.*, 1993). Based on epidemiological and pathology findings, the International Agency for Research on Cancer (1994) has classified *H. pylori* as a group 1 carcinogen in humans. *H. hepaticus* is associated with an increase in liver neoplasm incidences in A/JCr mice (Ward *et al.*, 1994a; Fox *et al.*, 1996).

H. hepaticus commonly colonizes the gastrointestinal tract of many strains of mice from many sources (Fox *et al.*, 1994; Ward *et al.*, 1994b; Shames *et al.*, 1995). It has been shown to be pathogenic, with hepatitis highly prevalent in some strains of mice (A/JCr, BALB/cAnNCr, C3H/HeNCr, SJL/NCr, and SCID/NCr) (Ward *et al.*, 1994b). Intestinal colonization does not necessarily result in subsequent hepatitis, and the conditions that lead to migration of the organism from the intestine to the liver have not been determined. *H. hepaticus* appears to reside primarily within the bile canaliculi. Male mice were reported to have a greater incidence and severity of hepatitis than female mice, and this finding occurred in NTP studies as well. The recently identified *H. bilis*, like *H. hepaticus*, colonizes the biliary tract, liver, and intestine of mice. While *H. bilis* has been identified in animals with chronic hepatitis, whether it caused the hepatitis is not known (Fox *et al.*, 1995).

The pathogenesis of *H. hepaticus*-induced disease has not been fully characterized. In susceptible strains of mice, *H. hepaticus* can cause acute, focal, nonsuppurative, necrotizing hepatitis, which progresses to chronic, active hepatitis characterized by minimal necrosis, hepatocytomegaly, oval cell hyperplasia, and

cholangitis. *H. hepaticus* has been found to possess high levels of urease (Fox *et al.*, 1994). *H. hepaticus* is often isolated from the cecum and colon but is not necessarily isolated from the liver of A/JCr mice, even though these animals develop severe hepatitis. Culture supernatants from several strains of *H. hepaticus* and several other *Helicobacter* species were shown to cause cytopathic effects in a rodent hepatocyte cell line (Taylor *et al.*, 1995). Ward *et al.* (1996) suggested that autoimmunity may play a role in the progressive hepatitis and carcinogenesis in livers infected with *H. hepaticus*.

NTP Infectious Disease Surveillance

In 1993, during the histological evaluation of an NTP 2-year study, pathologists identified a constellation of liver lesions (hepatitis) in control and treated male mice that was consistent with what would later be described in mice infected with *H. hepaticus* (Ward *et al.*, 1993, 1994a; Fox *et al.*, 1994). Subsequently, pathology results from all mouse studies begun since 1984 (67 two-year studies) were reviewed for diagnoses of the characteristic hepatitis; the lesions were identified in nine studies (NTP, 1998a,b,c,d,e,f). Silver stains revealed helical bacteria consistent with *Helicobacter* present in the liver of male mice in the nine studies.

Every reasonable measure is taken to prevent the occurrence of infectious diseases during NTP 2-year carcinogenicity studies. When infections occasionally occur, care is taken to identify the causal agent and its source, measures are taken to ensure that animals in later studies will not be infected, and the potential impact on biological parameters (primarily neoplastic endpoints) important in interpretation of the study is determined. To date, animals (control and treated) from a few studies have had a mild pulmonary inflammatory response presumed to be caused by an infectious agent. In other studies, there have been utero-ovarian infections with *Klebsiella* sp. (Rao *et al.*, 1987) and fungal infections of the nasal cavity. For scientifically valid reasons, interpretation of chemical-related effects was not considered significantly compromised in any of these studies. Unlike the previous infections, *H. hepaticus* involves the liver, the major metabolic organ, and has been associated with an increase in incidences of liver neoplasms in the A/JCr mouse (Ward *et al.*, 1994a). Therefore, when the contemporary epizootic of *H. hepaticus* infection in the United States affected several NTP studies, use of the data for hazard identification was questioned. The first step was to determine the extent of the infection within NTP studies and then evaluate the impact the infection had on biological parameters important in interpretation of the carcinogenic potential of test chemicals.

MATERIALS AND METHODS

Histologic Examination

Studies in which mice were potentially infected with *H. hepaticus* were identified by reviewing the summary pathology tables for characteristic diagnoses: oval and/or biliary epithelial hyperplasia, hepatocyte enlargement (often diagnosed as karyomegaly), chronic inflammation, and regenerative hyperplasia. All 13-week and 2-year studies begun by the NTP since 1984 and for which complete pathology data were available (67 two-year studies) were examined. Eight contemporary studies in which the characteristic lesions were not identified from pathology tables were randomly selected for histologic reevaluation. Slides containing sections of hematoxylin- and eosin-stained livers from 20 to 25 control and 20 to 25 high-dose male mice from each of seven 2-year studies and one 13-week study (10 animals from each group) were reexamined microscopically for the presence of hepatitis potentially related to *H. hepaticus* infection. Hepatitis consistent with that observed with *H. hepaticus* infection was not observed in any of these studies.

Liver sections from five or more animals from each of nine 2-year studies in which hepatitis was observed were prepared using the Warthin-Starry silver stain or Steiner's modification to identify silver-positive helical bacteria.

PCR-RFLP Detection of *Helicobacter* DNA

Assays based on polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) were conducted at the NIEHS (Malarkey *et al.*, 1997) and the University of Missouri Research Animal Diagnostic and Investigative Laboratory (MU-RADIL) (Riley *et al.*, 1996) on liver tissue from approximately 20 animals from each of 32 NTP 2-year studies (including the nine affected studies) and three NTP 13-week studies. The majority of these studies were selected because they were begun at approximately the same time (1988-1990) as the nine affected studies. Also, two earlier studies (1984-1985; mouse life-span and *p*-nitroaniline studies) and one later study (1993; methyleugenol) were selected. The mouse life-span study was designed to evaluate the incidences of spontaneous changes associated with age; therefore, there is no NTP Technical Report. Pathology peer review is not complete for the methyleugenol study, and the NTP Technical Report (NTP, 1998g) has not been completed. Frozen tissue was available from 22 of these studies, while only formalin-fixed tissue was available for the remaining ten 2-year studies and the three 13-week studies. Most of the assays were conducted by MU-RADIL, which used *Helicobacter* genus-specific primers; MU-RADIL used restriction endonucleases on a subset of positives to determine if the species was *H. hepaticus*. DNA was isolated from frozen liver samples with a QIAamp Tissue Kit (Qiagen Inc., Chatsworth, CA) according to the manufacturer's recommendations or routine phenol/chloroform extraction (Malarkey *et al.*, 1997). DNA content and purity were determined spectrophotometrically by measuring the A_{260}/A_{280} optical density ratio. To isolate DNA from paraffin-embedded samples, five 10-μm sections were washed twice with 1 mL xylene and twice with 500 μL ethanol. Tissues were then dried within a vacuum centrifuge prior to DNA isolation as described above. Routine measures were taken to avoid contamination at every step from tissue collection to PCR amplification, and concurrently run controls without DNA were consistently negative.

Statistical Analyses

Multiple regression procedures were used to compare control neoplasm rates in the nine affected studies with the 26 unaffected contemporary studies which had no histologic evidence of *H. hepaticus*-associated liver disease. While frozen liver tissue was unavailable from 13 of these 26 studies, none showed the hepatitis indicative of *H. hepaticus* and thus were assumed to be unaffected. Potential confounding factors such as body weight, date study was begun, route of administration, and animal supplier were included as covariables in the statistical analysis.

Analysis for H-*ras* Codon 61 CAA-to-AAA Mutations

For analyses of formalin-fixed tissue, three to five unstained serial sections (10 μm thick) were cut from paraffin blocks containing hepatocellular adenomas or carcinomas. Paraffin-embedded tissues were deparaffinized and rehydrated prior to being digested with proteinase k overnight at 55° C to isolate DNA. Frozen tissues were digested with 10 mg/mL pronase in 1% sodium dodecyl sulfate in TNE buffer (10 mM TRIS, 150 mM NaCl, and 2 mM EDTA; pH 7.5) overnight at 37° C; DNA was isolated by phenol chloroform extraction and precipitated with ethanol (Marmur, 1961; Sills *et al.*, 1995).

Nested primers were used for amplification of exon 2 of H-*ras* by PCR. The outer primers were 5'-CCA CTA AGC CTG TTG TGT TTT GCA G-3' (forward primer) and 5'-CTG TAC TGA TGG ATG TCC TCG AAG GA-3' (reverse primer). The inner primers (second round of amplification) were 5'-GAC ATC TTA GAC ACA GCA GTT-3' (forward primer) and 5'-GGT GTT GTT GAT GGC AAA TAC-3' (reverse primer). Although the normal sequence of codon 60 is GCT, the forward PCR primer is made with a T at the penultimate 3' base to create the restriction site for Mse1.

A nonradioactive RFLP method was employed to identify CAA-to-AAA mutations in the H-*ras* gene at codon 61 in liver neoplasms (Lee and Drinkwater, 1995). This was based on Mse1 enzyme restriction cutting only the sequence 5'-TTAA-3'. Thus, Mse1 will detect C→A conversion mutation at the first position of codon 61.

Analysis of PCNA and Apoptosis

Detailed methods are included in a report by Nyska *et al.* (1997). Cell proliferation was assessed in nonneoplastic areas of the liver, kidney, and lung by determining a PCNA S-phase labeling index (the percentage of cells in S phase). The identification of apoptotic cells was based on morphologic criteria (Garewal *et al.*, 1996; Goldsworthy *et al.*, 1996) and confirmed immunohistochemically by the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end labeling (TUNEL) procedure (Gavrieli *et al.*, 1992).

RESULTS AND DISCUSSION

Identification of *H. hepaticus* Infection in NTP Studies

Determining the extent of *H. hepaticus* infection involved a three-pronged approach of histologic evaluation, silver stains, and PCR-RFLP based assays; all were necessary because of the limitations identified for each. In NTP studies, and as reported in other studies (Ward *et al.*, 1994b), there were no obvious clinical signs of infection, and the only significant histologic lesion (hepatitis) was observed in the liver, primarily in males. Therefore, summary pathology tables were reviewed to identify studies that may have been affected by *H. hepaticus*-associated hepatitis. Male mice from nine studies were identified (Table L1) as having the hepatitis. Eight of the nine studies were begun during a time span of about 6 months (July 1990 to January 1991), while the other study was begun much earlier (October 1988). The hepatitis was not observed in any 13-week studies. Use of histologic evaluation for identification of infected animals has limitations, however. It is somewhat insensitive, as *H. hepaticus* has been cultured and identified by PCR-RFLP methods within livers of animals with no histological evidence of infection (Fox *et al.*, 1998). This may be explained in part by the limited sampling (two liver sections) and the sometimes focal nature of *H. hepaticus*-associated hepatitis. Also, while in the more severely affected animals the hepatitis appears somewhat characteristic, component lesions of the hepatitis are not pathognomonic, and, when the hepatitis is subtle in 2-year old animals, it is more difficult to recognize or attribute to *H. hepaticus*.

Within affected studies, the incidences of the hepatitis in male mice varied from 16% to 78% (Table L1). While generally mild to moderate, the hepatitis varied in severity from barely detectable in some animals to extensive liver involvement and regeneration in others. Only a few females were identified as having the characteristic hepatitis (Table L1). In general, the incidences and severities of *H. hepaticus*-associated hepatitis were similar between control and treated groups. This constellation of nonneoplastic liver lesions, while not pathognomonic, was certainly suggestive of an *H. hepaticus* infection, particularly when observed in control animals. Characteristic lesions included proliferation of oval and/or biliary epithelial cells, hepatocyte enlargement (diagnosed as karyomegaly), and chronic inflammation. In many instances, areas of regenerative hyperplasia were identified within diseased liver.

Helicobacter spp. are not usually observed on routine histologic examination of hematoxylin and eosin-stained sections of liver. The methods for confirmation of infection with *Helicobacter* include Warthin-Starry silver stain or Steiner's modification (Garvey *et al.*, 1985) of this stain for direct microscopic observation of the organisms in tissue; however, this can be a relatively insensitive technique when few organisms are present. In most instances, histologic differentiation between *Helicobacter* species is not possible. Speciation can usually be accomplished with electron microscopy, but this technique is both time consuming and labor intensive. Microbiologic culture of feces, cecal smears, and fresh or frozen liver is also possible. Currently, assays involving amplification of the DNA of the organism using PCR are the most rapid and perhaps the most sensitive methods of detection, and the use of restriction endonucleases has allowed a determination of the species present. PCR-based methods also can be used on feces, cecal contents, or liver homogenates and are most sensitive when using fresh or frozen tissue (Riley *et al.*, 1996; Malarkey *et al.*, 1997).

Using Warthin-Starry silver stains or Steiner's modification on the livers of five or more animals per study, helical bacteria (*Helicobacter*) were identified in animals from the nine affected studies. In some animals, helical bacteria were numerous, suggesting a heavy bacterial burden in these infected animals. However, even in these animals with abundant organisms, few to none were observed in proliferative hepatic lesions such as foci and neoplasms. Helical bacteria were not identified in approximately 25% of males with moderate hepatitis and were rarely identified in males without hepatitis or in females. The absence of identification of helical organisms by silver stains does not preclude infection, nor does the presence of organisms confirm *H. hepaticus*. Based upon current knowledge, however, the characteristic liver lesions in $B6C3F_1$ mice, coupled with the presence of silver-positive helical organisms, are highly suggestive of *H. hepaticus* infection.

As the NTP evaluation evolved, PCR-based assays were developed that appeared more sensitive than histologic evaluation and silver stains for identification and speciation of *Helicobacter*. Therefore, PCR-RFLP-based assays were used to confirm the presence of pathogenic *Helicobacter* (primarily *H. hepaticus*) within the nine affected studies and to determine whether there was *H. hepaticus* infection in other NTP studies. Unfortunately, none of the PCR-based assays had been specifically developed for, or proven reliable for use with, formalin-fixed tissue. Frozen tissue was available from a limited number of animals from a limited number of NTP studies, including only three of the nine affected studies. Furthermore, available frozen liver was almost always limited to tissue from a neoplasm, and, based upon results obtained with silver stains, organisms are generally not readily observed within proliferative hepatic lesions, even when organisms are abundant in adjacent liver tissue. Because the availability of frozen tissue was limited, a PCR-RFLP-based assay was developed and evaluated (Malarkey *et al.*, 1997) for use with frozen or formalin-fixed tissue.

The NIEHS and MU-RADIL laboratories conducted PCR-RFLP-based assays on 32 NTP 2-year studies and three NTP 13-week studies (data not shown); frozen tissues from 22 of the 2-year studies were available. All three bioassays in which hepatitis was identified and for which frozen tissue was available were positive for *H. hepaticus* by the PCR-RFLP-based assays (Table L2). At a third laboratory, *H. hepaticus* was also cultured from the liver tissue of animals in one of these studies (Fox *et al.*, 1998). Formalin-fixed tissues from two of the three studies were evaluated and were also positive; these tissues had been fixed in formalin for less than 48 hours. In the other six affected studies, for which only formalin-fixed tissue was available, *H. hepaticus* was identified in only 1 of 120 animals (Table L2). This decreased sensitivity was considered to be related to the prolonged formalin fixation (Malarkey *et al.*, 1997) rather than proof of an absence of *H. hepaticus*. The presence or absence of *H. hepaticus* apparently cannot be confirmed with current PCR-RFLP-based assays in liver that has been fixed in formalin for long periods (weeks or months). In the three 13-week studies with formalin-fixed tissue, only 1 of 30 animals was positive for *H. hepaticus*.

Within the three affected, PCR-RFLP-positive 2-year studies, *H. hepaticus* was often identified by PCR in frozen livers of mice that had no overt hepatitis. In fact, based upon the combined data from two studies (including PCR results from three laboratories), of 57 animals without characteristic liver lesions, 13 of 24 male mice (54%) and 17 of 33 female mice (52%) were positive for *H. hepaticus*. Furthermore, *H. hepaticus* was identified by PCR in frozen liver of several animals from three "unaffected" studies in which hepatitis typical of that associated with *H. hepaticus* was not observed (Table L2). Apparent variability occurs between various strains of mice and between individual mice from affected studies in developing hepatitis in response to *H. hepaticus* infection. One would assume that, within affected studies, most or all animals have been exposed to the organism, and even animals resistant to developing hepatitis may have organisms within the liver. This assumption is supported by the fact that animals without hepatitis are often positive with PCR-RFLP-based assays. Therefore, although alternative explanations are possible, the three PCR-RFLP-positive studies in which liver lesions are absent are assumed to be true positives. In fact, helical organisms were identified with a silver stain in one animal from one of these studies (Malarkey *et al.*, 1997). Therefore, in addition to assessing the affect of *H. hepaticus* in the nine affected 2-year

studies, the significance of a positive PCR-RFLP assay for *H. hepaticus* in the absence of liver lesions is also an important question.

Inconsistent Results with PCR-Based Methods

As with any technique, the PCR-RFLP-based assays have limitations even when used to assay fresh and frozen tissue. One assessment of the variability in results of PCR and serologic analyses for *Helicobacter* among three commercial laboratories revealed significant inconsistencies (Dew *et al.*, 1997). Others (J.M. Ward and J. Thigpen, personal communications) have obtained similarly inconsistent results when sending replicate samples to different laboratories. Though the number of samples evaluated by both the NIEHS and MU-RADIL laboratories was limited, there was good, but not complete, correlation of PCR-RFLP results. Also, within the affected studies, the PCR assays were not positive in some animals with liver disease. This result may be explained, in part, by the fact that the only frozen tissues available were neoplasms; as described above, neoplasms are expected to have fewer organisms.

Analysis of *H. hepaticus*-Affected and Unaffected Studies for Incidence of Common Neoplasms

To determine whether the incidences of various neoplasms were different between control groups from affected and unaffected studies, the nine affected studies were compared to 26 unaffected studies begun at relatively similar times (Table L3). There were no statistically significant differences in body weight or survival among the affected and unaffected studies. The neoplasms evaluated represent those that occurred at high enough incidences in various organs for statistically significant differences to be detected. Using multiple regression procedures, male mice in the nine affected studies were demonstrated to have a significantly ($P < 0.05$) increased incidence of only two neoplasm types, both of which were in the liver (hepatocellular neoplasms and hemangiosarcoma), when compared to the unaffected studies. Because of these differences, there was also a corresponding significant difference in the overall incidence of malignant neoplasms (all sites) as well as in the overall proportion of neoplasm-bearing animals. No other tissue site showed a significant difference in the incidence of neoplasms. For female mice, the slightly increased incidence of hepatocellular neoplasms observed in the affected studies was not statistically significant.

This seemingly simple analysis is complicated by several potential confounding variables. There have been coordinate, time-related increases in body weight and in the incidence of liver neoplasms in mice in NTP studies (Haseman, 1992). Table L4 presents the liver neoplasm incidences in relation to the dates the studies began and clearly shows the increases in liver neoplasm incidences and body weights (Seilkop, 1995). In assessing differences in neoplasm incidences between *H. hepaticus*-affected and unaffected studies, the most relevant comparison would be between studies begun at approximately the same time. The starts of 20 of the 26 unaffected studies were clustered near the early part of the time frame (April 1988 to June 1990), while the starts of the affected studies were clustered toward the later end, with eight of the nine studies begun between July 1990 and January 1991; incidences of liver neoplasms in these later studies are expected to be higher based on trends in body weight alone. While the slightly increased incidences of liver neoplasms observed in female control mice in the nine affected studies is likely due to clustering in time, clearly, this alone cannot account for the increased liver neoplasm incidences observed in control male mice in the affected studies (Table L3).

Ideally, unaffected studies used in the above comparison should not only be free of histologic evidence of infection with *H. hepaticus* but should be confirmed as negative by PCR assays. Thirteen of these 26 studies could not be confirmed as negative by PCR because frozen tissue was not available; however, *H. hepaticus*-associated hepatitis was not present in any of the 26 studies. Because these and other data reported to date suggest that hepatitis is associated with neoplasm development in the liver, it seems reasonable to include those 13 studies, unconfirmed by PCR, in this analysis. The majority of the 13 studies confirmed as negative by PCR were begun much earlier than the clearly affected studies, and, therefore, comparing them alone to the nine affected studies is not reasonable. Although not presented

here, a number of comparisons were made with various groupings of studies based on the degree of confidence in their infection status. Although the outcomes of the various comparisons varied somewhat, incidences of hepatocellular neoplasms and hemangiosarcomas of the liver were consistently increased in control male mice from affected studies compared to control males from unaffected studies. Significantly increased liver neoplasm incidences generally were not observed in females. Importantly, the following data corroborate the findings and association with *H. hepaticus* identified in these analyses.

Analysis of Hepatitis-Positive and Hepatitis-Negative Mice for Liver Neoplasm Incidence

Several infectious agents known to be associated with increased incidences of neoplasms cause chronic inflammation in the target tissue or organ. It is commonly hypothesized that this inflammatory process may cause or contribute to the development of neoplasms. One approach to address this was to stratify the mice from the affected studies according to the severity of hepatitis and examine liver neoplasm incidences in relation to these groupings. Thus, animals within the nine affected studies were placed into three groups: 1) animals with mild to moderate hepatitis considered related to *H. hepaticus* infection (+), 2) animals with minimal to mild hepatitis that may have been associated with *H. hepaticus* (±), and 3) animals with no hepatitis that was considered to be associated with *H. hepaticus* (–). Within these groupings, the incidence of liver neoplasms was significantly increased ($P < 0.05$) in males with mild to moderate *H. hepaticus*-associated hepatitis (+) when compared to animals without such hepatitis (Table L5). The neoplasm incidence in animals with minimal lesions (±) was also increased. The liver neoplasm incidence in males without hepatitis (58%) was similar to the incidence (54.8%) in males from the 26 unaffected studies (Table L3). This analysis clearly suggests an association of *H. hepaticus*-associated hepatitis with increased liver neoplasm incidences. Females showed a similar trend, albeit not significant; however, these comparisons are weak because of the low numbers of females with hepatitis.

Analysis of H-*ras* Oncogene Mutations in Liver Neoplasms in Mice from Affected and Unaffected Studies

Liver neoplasms commonly occur in control $B6C3F_1$ mice in 2-year studies. In the historical database of 333 male and female mice with liver neoplasms, 106 (32%) had H-*ras* codon 61 CAA-to-AAA mutations (Maronpot *et al.*, 1995). This historical control database is composed primarily of male data; however, adequate numbers of females have been assayed, and there was no significant difference in the incidences of CAA-to-AAA mutations between males and females.

In an attempt to examine further whether *H. hepaticus* infection had an effect on the development of hepatocellular neoplasms, neoplasms from control male mice from selected affected (NTP, 1998a,b,c) and unaffected (NTP, 1993, 1998h) studies were evaluated for H-*ras* codon 61 CAA-to-AAA mutations (Table L6). Only 6% (2/33) of the hepatocellular neoplasms from control males with hepatitis from three affected studies had this mutation. This percentage is significantly ($P < 0.01$) less than the 32% (11/34) observed in males from the two unaffected studies and less than the 32% (106/333) that occurred in historical control animals. In addition, neoplasms from males without hepatitis from the affected, PCR-positive triethanolamine study (NTP, 1998a) and the unaffected, PCR-positive methyleugenol study (NTP, 1998g) were evaluated; the incidences of mutations in those groups were 3/14 (21%) and 2/17 (12%), respectively.

Neoplasms from control female mice (none had hepatitis) from affected and unaffected studies were evaluated for the CAA-to-AAA mutation (Table L6). The mutation rate was low in both the affected studies (1/25; 4%) and the unaffected study (1/11; 9%) when compared to the 32% observed in the historical control groups.

The finding of a different H-*ras* mutation profile in neoplasms of male mice from affected studies tends to support the association of increased neoplasm incidences with *H. hepaticus,* although there is no mechanistic

understanding behind this observation. In a study of *H. hepaticus*-infected A/JCr mice, *ras* mutations were not detected in the 25 hepatocellular neoplasms analyzed using a PCR/single-strand conformation polymorphism assay (Sipowicz *et al.*, 1997). Because of the low spontaneous rate of liver neoplasms in the A/JCr mouse, there are few or no conclusive data on *ras* mutations in uninfected animals, however. Point mutations at codons 12, 13, and 61 of the Ki-, Ha- and N-*ras* genes were not identified in 45 early gastric carcinomas in humans, whether or not *H. pylori* was present (Craanen *et al.*, 1995). If the increased incidence of hepatocellular neoplasms is associated with hepatitis, as many suspect, then one would expect the neoplasms from animals without hepatitis to have a similar mutational profile as that of the historical controls. The data do not provide a clear answer, because the hepatitis-free males from the affected triethanolamine study (NTP, 1998a) and the males from the methyleugenol study (NTP, 1998g), which were positive by PCR but lacked hepatitis, had mutation frequencies between those of the unaffected controls and the hepatitis-positive mice. Furthermore, mutations in neoplasms from females, none of which had hepatitis, from two affected and one unaffected study were very low compared to the historical controls. These findings were unexpected, and their significance is not understood.

H. hepaticus-Associated Alterations in Cell Kinetics

Studies evaluating cell kinetics were completed to explore further the link between hepatitis and the increased incidence of liver neoplasms (Table L7; Nyska *et al.*, 1997). One of the major objectives was to determine whether there were differences between PCNA labeling indices in the livers of animals with hepatitis from three affected studies, cobalt sulfate heptahydrate, chloroprene, and triethanolamine (NTP, 1998a,b,c), compared to animals without hepatitis, whether from the same three affected studies or from an unaffected study, 1-trans-delta^9-tetrahydrocannabinol (NTP, 1996). Male mice with hepatitis from the three affected studies had a significantly increased ($P < 0.001$) labeling index, with a 24-fold increase over males from the unaffected study and a sixfold increase over males without hepatitis from the same three affected studies (Table L7). The labeling index increase in these mice was substantial and was considered biologically significant. Male mice without hepatitis from the three affected studies had a significantly greater labeling index (increased fourfold) than male mice from the unaffected study (Table L7). The significance of this finding is uncertain, as differences of a similar magnitude were observed in other comparisons. For example, the labeling index of females from the unaffected 1-trans-delta^9-tetrahydrocannabinol study (Table L7; NTP, 1996) was increased fivefold over females from the PCR-positive, hepatitis-negative scopolamine hydrobromide trihydrate study (NTP, 1997). Such differences may be within the limits of normal variability for 2-year-old animals.

A second objective of the cell proliferation studies of the liver was to determine if labeling indices were increased in animals from the PCR-positive, hepatitis-negative methyleugenol (NTP, 1998g), scopolamine hydrobromide trihydrate (NTP, 1997), and mouse life-span studies compared to an unaffected PCR-negative and hepatitis-negative 1-trans-delta^9-tetrahydrocannabinol study (NTP, 1996). The scopolamine hydrobromide trihydrate study was evaluated and included in the study by Nyska *et al.* (1997), while the methyleugenol and mouse life-span studies were completed later and are included in Table L7. The labeling indices of males from two of these three studies were almost identical to those of males from the unaffected study. However, the labeling index of males from the mouse life-span study is increased approximately fivefold over that of males from the unaffected study as well as fivefold over the labeling indices of males from the two like studies of scopolamine hydrobromide trihydrate and methyleugenol. This finding suggests that the increase observed in the mouse life-span study is not attributable to the presence of *H. hepaticus,* as two other studies also positive for *H. hepaticus* did not show a similar increase.

The cell proliferation data for the liver from NTP studies are consistent with data from a study by Fox *et al.* (1996) in which cell proliferation indices were evaluated at 8, 10, and 13 months in the A/JCr mouse, which is generally believed to be more susceptible to *H. hepaticus*-associated hepatitis than the B6C3F$_1$ mouse. In the study by Fox *et al.* (1996), cell proliferation rates were significantly increased at all time points in males. Some increases were observed in females in that study but did not reach statistical

significance. An increased incidence of hepatocellular neoplasms was observed only in the males. Though liver lesions were observed in females in that study, they were less severe than those in males.

In addition to the liver, cell proliferation indices (PCNA) were evaluated in the kidneys and lungs of male and female mice in affected studies versus those in unaffected studies (Nyska *et al.*, 1997). No apparent effect of *H. hepaticus* infection or the presence of hepatitis on PCNA indices was observed for the kidneys or lungs.

Apoptosis (programmed cell death) is another important parameter in evaluations of cell kinetics. The apoptotic index in the liver of male mice with hepatitis from an affected study, cobalt sulfate heptahydrate (NTP, 1998b), was significantly ($P < 0.01$) greater than that observed in males from the unaffected 1-trans-delta^9-tetrahydrocannabinol study and the PCR-positive, hepatitis-negative scopolamine hydrobromide trihydrate study (Nyska *et al.*, 1997). For females, there were no significant differences among the three studies.

Two 13-week studies which were begun during the same time as the nine affected studies were randomly selected for evaluation of PCNA indices. *H. hepaticus* was not identified in either of the studies by PCR-RFLP; however, as with all NTP 13-week studies, only tissue fixed in formalin for an unspecified period was available. Because of this, no true negative control group was available; therefore, the labeling index of these 19- to 20-week-old animals was compared to values cited in the literature (Eldridge and Goldsworthy, 1996) for 20-week-old B6C3F$_1$ mice. The labeling index in the NTP studies clearly was not increased (data not shown).

The Impact of *H. hepaticus* on the Interpretation of 2-Year Carcinogenesis Studies

Increases in the incidences of neoplasms are associated with a number of infectious agents. The chronic inflammation caused by these agents has been hypothesized to be important in the pathogenesis of the increased neoplasm incidences (e.g., gastric cancer associated with *H. pylori*). The increased incidences of liver neoplasms in male mice from the nine affected NTP studies were observed in the animals with *H. hepaticus*-associated hepatitis. Neoplasms from males with hepatitis tended to have an H-*ras* mutation profile different from that of animals from unaffected studies. Further, cell replication rates at 2 years were significantly higher in males with hepatitis compared to those in males without hepatitis. The data suggest that *H. hepaticus*-associated hepatitis is associated with the increased incidences of liver neoplasms in the male B6C3F$_1$ mouse. Therefore, the most important consideration in evaluating the impact of *H. hepaticus* infection on the interpretation of study results appears to be the presence or absence of significant hepatitis.

For any carcinogenicity study, data within and specific to the individual study provide the greatest basis for an accurate interpretation. However, it is prudent to consider and evaluate all data or information which may affect the interpretation. Based upon the data presented in this and other reports, general guidelines emerge that may be useful in interpreting potential chemical-associated carcinogenic effects in *H. hepaticus*-infected B6C3F$_1$ mice. In a study with sufficient evidence of *H. hepaticus*-associated hepatitis ($> 10\%$ of the animals having the characteristic hepatitis may be a reasonable guideline), interpretation of increased incidences of liver neoplasms (hepatocellular neoplasms and hemangiosarcoma) of male mice is considered to be potentially confounded.

Altered chemical uptake and metabolism, due to the intestinal load of *H. hepaticus* and to *H. hepaticus*-associated liver disease, respectively, are possible reasons for considering that the male mouse response to chemical administration at sites other than the liver should also be considered confounded. Data do not currently exist that definitively answer this question. In this group of nine studies, however, there is no evidence to suggest that affected mice responded to chemical treatment in organs other than the liver in a manner different from mice in nonaffected studies. Within each study, there was excellent concordance in chemical-associated neoplasms between the male mice and the females, which had little or no hepatitis

(Table L8). Furthermore, analyses indicate that *H. hepaticus* is not associated with neoplastic responses outside the liver; incidences of neoplasms at sites other than the liver were not different between control groups from affected and unaffected studies (Table L3). Cell replication rates in two major organs (lung and kidney) also were not increased in control groups from affected studies compared to those from unaffected studies.

One of the more difficult issues to address is whether interpretation of a treatment-related increase in liver neoplasm incidences in the female mouse is confounded when *H. hepaticus*-associated hepatitis is present within the male mice in the study. Most evidence to date links hepatitis with the increased liver neoplasm incidences observed in males, and female B6C3F$_1$ mice in affected studies do not have significant hepatitis at 2 years. The lack of hepatitis in females, however, is based on an analysis in which only late time points were evaluated histologically. Therefore, it is conceivable that hepatitis along with increased cell proliferation could have occurred earlier and resolved by 18 months to 2 years. Data collected to date, however, suggest that *H. hepaticus*-associated hepatitis is a late-developing and persistent disease in the B6C3F$_1$ mouse. *H. hepaticus*-associated hepatitis has never been observed in any NTP 13-week studies, including five begun during the same 6-month time span as eight of the nine affected 2-year studies. Also, within affected 2-year studies, more males (51%) that were 18 to 24 months of age had hepatitis than those (34%) that were 12 to 18 months of age. This is consistent with a report by Ward *et al.* (1994b) that *H. hepaticus*-associated liver lesions are not observed at early time points in the B6C3F$_1$ mouse.

Nonetheless, within affected studies, female control mice did have a slightly elevated incidence of liver neoplasms when compared to control mice from unaffected studies, and the data derived from the H-*ras* mutation frequency analysis were inconclusive. The possibility that *H. hepaticus*-infected female mice from affected studies may respond differently to a liver carcinogen than mice from unaffected studies cannot be eliminated at this time. However, because within an affected study hepatitis is observed only rarely in females, until definitive data suggest otherwise, it is concluded that the interpretation of an apparent chemical-induced neoplastic effect in the liver of female mice is not confounded. To censor the few females with *H. hepaticus*-associated hepatitis from any statistical analyses of hepatocellular neoplasms would be prudent. Studies in the ostensibly more sensitive A/JCr mouse (Fox *et al.*, 1996) also showed significant increases in neoplasm incidences and cell proliferation rates in the liver of *H. hepaticus*-infected males, but not females.

Another concern is how to interpret possible chemical-related effects in a study in which the status of *H. hepaticus* infection cannot be determined by PCR-RFLP because only tissues fixed in formalin for more than 48 hours are available. While histologic evaluation is inadequate to identify infection, it appears adequate for identifying hepatitis severe enough to alter the outcome of the study. Therefore, in the absence of significant histologic evidence of *H. hepaticus*-associated hepatitis, the outcome of a 2-year study should not be considered potentially compromised.

The causality between *H. hepaticus* infection and neoplasia has not been proven in the B6C3F$_1$ mouse in these studies, nor has the mechanism of this association been determined; further studies are needed. However, sufficient information exists to make reasonable scientific judgments relative to the interpretation of data from the nine 2-year carcinogenicity studies in the B6C3F$_1$ mouse. Refinements to the above interpretive positions may occur if warranted by future information.

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TABLE L1
Incidence of *Helicobacter hepaticus*-Associated Hepatitis in Control B6C3F$_1$ Mice from Nine NTP 2-Year Studies[a]

Study	Incidence of Hepatitis (%)	
	Males	Females
Sodium xylenesulfonate	78	4
AZT/5,000 U α-interferon A/D	76	4
Cobalt sulfate heptahydrate	72	8
AZT/500 U α-interferon A/D	66	0
Chloroprene	54	0
Theophylline	32	0
α-Interferon A/D	22	4
Triethanolamine	20	0
AZT	16	2
Average	48	2

[a] Includes regeneration and mild to marked (excludes minimal) chronic inflammation, karyomegaly, oval cell hyperplasia, and bile duct hyperplasia. AZT=3′-azido-3′-deoxythymidine

TABLE L2
Identification of *Helicobacter hepaticus* with PCR-RFLP-Based Assays in Control B6C3F$_1$ Mice from 32 NTP 2-Year Studies and Three NTP 13-Week Studies[a]

Type of Sample	Total Studies	*H. hepaticus*-Positive Studies[b]	
		Affected Studies	Unaffected Studies
13-Week Studies			
Formalin-fixed liver	3	—	1/3[c]
2-Year Studies			
Frozen liver	22	3/3	3/19
Formalin-fixed liver	10	1/6[c]	0/4

[a] PCR-RFLP=polymerase chain reaction-restriction fragment length polymorphism
[b] Number of *H. hepaticus*-positive studies/number of affected or unaffected studies. Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.
[c] Only one animal in the positive study was positive for *H. hepaticus*.

TABLE L3
Comparison of Neoplasm Incidences in Control B6C3F$_1$ Mice from *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies

	Males		Females	
	Affected Studies[a]	Unaffected Studies	Affected Studies	Unaffected Studies
Number of studies	9	26	9	26
Survival (%)	64	71	68	68
12-Month body wt (g)	48.0	48.3	48.1	47.0
Neoplasm incidence (%)				
Liver	71.3*	54.8	50.3	40.5
Lung	26.6	23.2	7.6	10.3
Pituitary gland	0.4	0.8	14.7	14.3
Harderian gland	5.6	6.1	6.0	4.9
Lymphoma	6.9	6.3	16.2	15.5
Circulatory system	9.8	6.0	5.3	4.7
liver only	7.1*	2.5	—	—
All benign	61.8	57.2	59.1	54.6
All malignant	61.3*	40.9	50.0	44.2
All neoplasms	88.0*	77.4	82.7	75.4

* Significantly different ($P \leq 0.05$) from the unaffected studies
[a] Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.

TABLE L4
Liver Neoplasm Incidences and Body Weights of Control B6C3F$_1$ Mice in Relation to Study Start Dates of *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies[a]

Study Start Date	Liver Neoplasm Incidence (%)		Mean Body Weight (g)	
	Affected Studies[a]	Unaffected Studies	Affected Studies	Unaffected Studies
Male				
April to September 1988	—	43.8 (8)[b]	—	46.2 (8)
October 1988	62.0 (1)	—	48.3 (1)	—
November 1988 to September 1989	—	52.6 (7)	—	48.7 (7)
October 1989 to June 1990	—	61.2 (5)	—	48.9 (5)
July 1990 to January 1991	72.5 (8)	66.2 (4)	48.0 (8)	49.0 (4)
February 1991 to April 1992	—	68.0 (2)	—	52.8 (2)
Average	71.3	54.8	48.0	48.3
Female				
April to September 1988	—	31.1 (8)	—	44.8 (8)
October 1988	46.0 (1)	—	46.4 (1)	—
November 1988 to September 1989	—	39.9 (7)	—	47.2 (7)
October 1989 to June 1990	—	38.6 (5)	—	45.9 (5)
July 1990 to January 1991	50.9 (8)	54.2 (4)	48.3 (8)	48.0 (4)
February 1991 to April 1992	—	58.0 (2)	—	55.6 (2)
Average	50.3	40.5	48.1	47.0

[a] Includes nine affected studies (those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice) and 26 unaffected studies
[b] Number of studies is given in parentheses.

TABLE L5
Association of Liver Neoplasm Incidence and Severity of *Helicobacter hepaticus*-Associated Hepatitis in Control B6C3F$_1$ Mice from Nine Affected NTP 2-Year Studies[a]

Severity of Hepatitis	Liver Neoplasm Incidence	
	Males	Females
Absent	101/175 (58%)	196/396 (49%)
Minimal	44/57 (77%)	23/42 (55%)
Mild/moderate	176/218 (81%)	7/11 (64%)
Significance of association	P < 0.05	NS[b]

[a] Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.
[b] NS=not significant

TABLE L6
H-*ras* Codon 61 AAA Mutations in Spontaneous Liver Neoplasms in Control B6C3F$_1$ Mice from *Helicobacter hepaticus*-Affected and Unaffected NTP 2-Year Studies

Study	Affected[a]	H-*ras* AAA Mutations
Male		
Cobalt sulfate heptahydrate	+	0/10 (0%)
Chloroprene	+	1/13 (8%)
Triethanolamine	+	1/10 (10%)
Oxazepam	—	7/18 (39%)
Diethanolamine	—	4/16 (25%)
Historical control database		106/333 (32%)
Female		
Chloroprene	+	0/10 (0%)
Triethanolamine	+	1/15 (7%)
Diethanolamine	—	1/11 (9%)
Historical control database		106/333 (32%)

[a] +=affected; —=not affected. Affected studies are those in which hepatitis typical of that associated with *H. hepaticus* infection occurred in many male mice.

TABLE L7
Proliferating Cell Nuclear Antigen Labeling Indices in the Liver of Control B6C3F$_1$ Mice[a]

	Hepatitis	No. of Animals	PCNA Labeling Index[b]	Average PCNA Labeling Index[c]
Male				
Cobalt sulfate heptahydrate[d]	+	15	0.535 ± 0.129	
Chloroprene[d]	+	12	1.452 ± 0.386	
Triethanolamine[d]	+	9	1.215 ± 0.374	1.011
Cobalt sulfate heptahydrate	—	7	0.175 ± 0.117	
Chloroprene	—	10	0.296 ± 0.124	
Triethanolamine	—	12	0.100 ± 0.042	0.186
1-Trans-delta^9-tetrahydrocannabinol[e]	—	15	0.042 ± 0.011	
Scopolamine hydrobromide trihydrate[f]	—	14	0.043 ± 0.012	
Methyleugenol[f]	—	14	0.077 ± 0.020	
Mouse life-span study[f]	—	15	0.217 ± 0.880	
Female				
Cobalt sulfate heptahydrate	+	5	0.161 ± 0.062	
Cobalt sulfate heptahydrate	—	17	0.055 ± 0.015	
Chloroprene	—	12	0.154 ± 0.050	
Triethanolamine	—	12	0.138 ± 0.053	0.108
1-Trans-delta^9-tetrahydrocannabinol	—	13	0.156 ± 0.047	
Scopolamine hydrobromide trihydrate	—	15	0.032 ± 0.009	

[a] A portion of these data are presented in Nyska *et al.* (1997). +=hepatitis present; —=no hepatitis present
[b] Mean ± standard error; PCNA=proliferating cell nuclear antigen
[c] Average of the mean labeling indices for animals from all three studies
[d] Affected study (one in which hepatitis typical of that associated with *H. hepaticus* occurred in many male mice)
[e] Unaffected study (one in which the typical hepatitis did not occur in mice)
[f] Unaffected study with no typical hepatitis, but positive for *H. hepaticus* by polymerase chain reaction-restriction fragment length polymorphism-based assay

TABLE L8
Summary of Target Sites of Carcinogenicity in B6C3F$_1$ Mice from NTP 2-Year Studies with *Helicobacter hepaticus*-Associated Hepatitis

	Males	Females
Chloroprene	Lung Circulatory system[a] Harderian gland Forestomach Kidney	Lung Circulatory system Harderian gland Forestomach Liver Skin Mesentery Zymbal's gland Mammary gland
Cobalt sulfate heptahydrate[b]	Lung	Lung
Triethanolamine	Liver	Liver
AZT[c]	None	Vagina
Sodium xylenesulfonate	None	None
Theophylline	None	None

[a] Hemangioma and hemangiosarcoma of the liver were excluded from the analysis in males.
[b] An apparent treatment-related increase in the incidence of hemangiosarcoma of the liver was discounted in male mice because of the presence of *H. hepaticus*.
[c] AZT=3′-azido-3′-deoxythymidine. Includes four studies: AZT; α-interferon A/D; AZT/500 U α-interferon A/D; and AZT/5,000 U α-interferon A/D