NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF STODDARD SOLVENT IIC

(CAS NO. 64742-88-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

September 2004

NTP TR 519

NIH Publication No. 04-4453

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 and Prevention. 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.

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Technical Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Perspectives (EHP) http://ehp.niehs.nih.gov (866-541-3841 or 919-653-2590). In addition, printed copies of these reports are available from EHP as supplies last. A listing of all the NTP Technical Reports printed since 1982 appears on the inside back cover.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF STODDARD SOLVENT IIC

(CAS NO. 64742-88-7)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

September 2004

NTP TR 519

NIH Publication No. 04-4453

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

CONTRIBUTORS

National Toxicology Program

Evaluated and interpreted results and reported findings

R.S. Chhabra, Ph.D., Study Scientist
D.E. Malarkey, D.V.M., Ph.D., Study Pathologist
D.W. Bristol, Ph.D.
J.R. Bucher, Ph.D.
J.R. Hailey, D.V.M.
J.K. Haseman, Ph.D.
R.A. Herbert, D.V.M., Ph.D.
R.R. Maronpot, D.V.M.
J.C. Peckham, D.V.M., M.S., Ph.D.
J.H. Roycroft, Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
K.L. Witt, M.S., ILS, Inc.

Battelle Northwest Operations

Conducted studies and evaluated pathology findings

B.J. Chou, D.V.M., Ph.D., Principal Investigator (2-week and 3-month studies)
J.A. Dill, Ph.D., Principal Investigator (2-year studies)
S.L. Grumbein, D.V.M., Ph.D.
B.K. Hayden
R.A. Miller, D.V.M., Ph.D.
R.A. Renne, D.V.M.
R.B. Westerberg, Ph.D.

Experimental Pathology Laboratories, Inc.

Provided pathology review

J.F. Hardisty, D.V.M., Principal Investigator
N. Allison, D.V.M.
J.C. Peckham, D.V.M., M.S., Ph.D.
K.J. Cimon, D.V.M., M.S.
G. Willson, B.V.M. & S.

Dynamac Corporation

Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group

Evaluated slides and prepared pathology report on rats (August 15 and October 8, 2002)

A. Suttie, B.V.Sc., Ph.D., Chairperson
ILS, Inc.
K.J. Cimon, D.V.M., M.S.
Experimental Pathology Laboratories, Inc.
J.R. Hailey, D.V.M.
National Toxicology Program
M.A. Hanes, D.V.M.
Duke University
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
G.D. Hill, D.V.M., Ph.D.
National Toxicology Program
A. Nyska, D.V.M.
National Toxicology Program
J.C. Peckham, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.
H.G. Wall, D.V.M., Ph.D.
GlaxoSmithKline
G. Willson, B.V.M. & S.
Experimental Pathology Laboratories, Inc.

Evaluated slides and prepared pathology report on mice (June 13, 2002)

A. Suttie, B.V.Sc., Ph.D., Chairperson
ILS, Inc.
N. Allison, D.V.M.
Experimental Pathology Laboratories, Inc.
S.V. Ching, D.V.M., Ph.D.
SVC Associates, Inc.
K.J. Cimon, D.V.M., M.S.
Experimental Pathology Laboratories, Inc.
J.R. Hailey, D.V.M.
National Toxicology Program
M.A. Hanes, D.V.M.
Duke University
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
G.D. Hill, D.V.M., Ph.D.
National Toxicology Program
A. Nyska, D.V.M.
National Toxicology Program

Analytical Sciences, Inc.

Provided statistical analyses

P.W. Crockett, Ph.D., Principal Investigator
L.J. Betz, M.S.
K.P. McGowan, M.B.A.
J.T. Scott, M.S.

Biotechnical Services, Inc.

Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
P.A. Gideon, B.A.
L.M. Harper, B.S.
E.S. Paal, M.S.J.
D.C. Serbus, Ph.D.
R.A. Willis, B.A., B.S.

CONTENTS

SUMMARY

Background

White spirit (also called mineral spirit) is a complex mixture of solvents derived from oil. The most widely used white spirit in the paint industry is called Stoddard solvent, and it is also used as a dry cleaning agent and as a solvent for cleaning and degreasing. We studied Stoddard solvent IIC to determine if it caused cancer in rats or mice.

Methods

We exposed groups of 50 male and female rats and mice to air containing Stoddard solvent six hours per day for two years. Male rats were exposed to 138, 550, or 1,100 milligrams of Stoddard solvent per cubic meter of air; female rats and male and female mice were exposed to 550, 1,100, or 2,200 mg/m^3. Similar groups of 50 animals were exposed to clean air in the same inhalation chambers 6 hours per day as the untreated control groups. Tissues from more than 40 sites were examined for every animal.

Results

There were more deaths in male and female rats exposed to the highest concentration of Stoddard solvent than in other animal groups. There were no differences in survival of mice exposed to the solvent. Male rats exposed to Stoddard solvent IIC had higher rates of tumors of the adrenal gland, and female mice exposed to Stoddard solvent IIC had slightly increased rates of liver adenomas.

Conclusions

We conclude that Stoddard solvent IIC caused cancer of the adrenal gland in male rats. An increase in liver tumors in female mice may have been related to exposure to Stoddard solvent IIC. There was no evidence that Stoddard solvent increased tumor rates in female rats or male mice.

ABSTRACT

Stoddard Solvent IIC

CAS No. 64742-88-7

Synonyms: Medium aliphatic solvent naphtha (petroleum); white spirit

Stoddard solvent (white spirit/mineral spirit) is the most widely used solvent in the paint industry. It is used as a dry cleaning agent; as an extraction, cleaning, and degreasing solvent; and as a solvent in aerosols, paints, wood preservatives, asphalt products, lacquers, and varnishes. Stoddard solvent IIC was nominated by the International Union, United Auto Workers, for carcinogenicity testing because of the large volume used in industrial and other settings. Male and female F344/N rats and B6C3F$_1$ mice were exposed to Stoddard solvent IIC (greater than 99% pure) by inhalation for 2 weeks, 3 months, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and mouse peripheral blood erythrocytes.

2-Week Study in Rats

Groups of five male and five female rats were exposed to Stoddard solvent IIC by inhalation at concentrations of 0, 138, 275, 550, 1,100, or 2,200 mg/m^3, 6 hours per day, 5 days per week for 16 days. All rats survived to the end of the study, and mean body weights of all exposed groups were similar to those of the chamber controls. Liver weights of males exposed to 550 mg/m^3 or greater and of females exposed to 275 mg/m^3 or greater were increased. Minimal diffuse cytoplasmic vacuolization of hepatocytes of the liver occurred in all females exposed to 2,200 mg/m^3.

2-Week Study in Mice

Groups of five male and five female mice were exposed to Stoddard solvent IIC by inhalation at concentrations of 0, 138, 275, 550, 1,100, or 2,200 mg/m^3, 6 hours per day, 5 days per week for 17 days. All mice survived to the end of the study, and mean body weights of all exposed groups were similar to those of the chamber controls. Liver weights of males and females exposed to 275 mg/m^3 or greater were significantly increased. Cytomegaly of the liver occurred in all males and females exposed to 2,200 mg/m^3.

3-Month Study in Rats

Groups of 10 male and 10 female rats were exposed to Stoddard solvent IIC by inhalation at concentrations of 0, 138, 275, 550, 1,100, or 2,200 mg/m^3, 6 hours per day, 5 days per week for 14 weeks. All rats survived to the end of the study, and the final mean body weight of females exposed to 275 mg/m^3 was greater than that of the chamber controls. The relative kidney, liver, and testis weights of all exposed groups of males and the absolute kidney weights of males exposed to 550 mg/m^3 or greater were increased. The sperm motility of 550 mg/m^3 or greater males was significantly decreased. The incidences of renal tubule granular casts were significantly increased in males exposed to 550 mg/m^3 or greater, and the severities of renal tubule hyaline droplet accumulation, granular casts, and regeneration increased with increasing exposure concentration in males. The incidences of goblet cell hypertrophy of the nasal respiratory epithelium in males and females exposed to 2,200 mg/m^3 were significantly increased. Sperm motility was decreased in males exposed to 550 mg/m^3 or greater.

3-Month Study in Mice

Groups of 10 male and 10 female mice were exposed to Stoddard solvent IIC by inhalation at concentrations of 0, 138, 275, 550, 1,100, or 2,200 mg/m^3, 6 hours per day, 5 days per week for 14 weeks. Mean body weights of exposed groups were similar to those of the chamber controls, but liver weights of males exposed to 2,200 mg/m^3 were significantly increased. The sperm motility of 2,200 mg/m^3 males was significantly decreased. This reduction in sperm motility, while statistically significant, is probably of modest importance as studies in mice have found that fertility is unaffected by motility decreases of less than 40%. The incidences of hematopoietic cell proliferation of the spleen in all exposed groups of females were greater than that in the chamber controls.

2-Year Study in Rats

Groups of 50 male and 50 female rats were exposed to Stoddard solvent IIC by inhalation at concentrations of 0, 138 (males), 550, 1,100, or 2,200 (females) mg/m^3, 6 hours per day, 5 days per week for 104 to 105 weeks. Additional groups of 10 males and 10 females were exposed to the same concentrations for 3 months for renal toxicity analyses. Survival in the top exposure concentration groups of males and females was significantly less than that of the chamber controls. Mean body weights of exposed males and females were similar to those of the chamber controls.

Cell proliferation analyses were performed in the left kidney of males and females after 3 months of exposure. The mean numbers of labeled cells and the labeling indices in males exposed to 550 and 1,100 mg/m^3 were significantly increased. The amount of α2u-globulin in the right kidney of males increased with increasing exposure concentration. Also, the incidences of granular casts and cortical tubule degeneration and regeneration were generally increased in exposed males, as was the severity of hyaline droplets. These effects did not occur in females.

At 2 years, the incidences of benign and benign or malignant pheochromocytoma (combined) of the adrenal medulla occurred with positive trends in males, and the incidences in the 550 and 1,100 mg/m^3 groups were significantly increased. Due to increased incidences of renal tubule hyperplasia in males at 2 years, extended kidney evaluations were conducted; a slightly increased incidence of renal tubule adenoma occurred in the 1,100 mg/m^3 group. Nonneoplastic lesions related to Stoddard solvent IIC exposure occurred in the kidney of males.

2-Year Study in Mice

Groups of 50 male and 50 female mice were exposed to Stoddard solvent IIC by inhalation at concentrations of 0, 550, 1,100, or 2,200 mg/m^3, 6 hours per day, 5 days per week for 105 weeks. Survival of exposed mice was similar to that of the chamber controls. Mean body weights of exposed females were greater than those of the chamber controls. The incidences of hepatocellular adenoma occurred with a positive trend in females, and the incidence of multiple hepatocellular adenoma in females exposed to 2,200 mg/m^3 was significantly increased. However, the incidences of hepatocellular adenoma or carcinoma (combined) and hepatocellular carcinoma alone in exposed males and females were not significantly increased.

Genetic Toxicology

Stoddard solvent IIC was tested for mutagenicity in *Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535, with and without S9 metabolic activation enzymes; all results were negative. *In vivo*, the frequency of micronucleated erythrocytes was assessed in peripheral blood samples from male and female B6C3F$_1$ mice after 3 months of inhalation exposure to Stoddard solvent IIC, and results were negative.

Conclusions

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity* of Stoddard solvent IIC in male F344/N rats based on increased incidences of adrenal medulla neoplasms; the slightly increased incidences of renal tubule adenoma may have been related to Stoddard solvent IIC exposure. There was *no evidence of carcinogenic activity* of Stoddard solvent IIC in female F344/N rats exposed to 550, 1,100, or 2,200 mg/m^3. There was *no evidence of carcinogenic activity* of Stoddard solvent IIC in male B6C3F$_1$ mice exposed to 550, 1,100, or 2,200 mg/m^3. There was *equivocal evidence of carcinogenic activity* of Stoddard solvent IIC in female B6C3F$_1$ mice based on

increased incidences of hepatocellular adenoma; this slight increase was associated with increased body weight in exposed females.

Exposure of male rats to Stoddard solvent IIC resulted in nonneoplastic lesions of the kidney characteristic of α2u-globulin accumulation.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A Summary of the Technical Reports Review Subcommittee comment and the public discussion on this Technical Report appears on page 13.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Stoddard Solvent IIC

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in air	Chamber control, 138, 550, or 1,100 mg/m^3	Chamber control, 550, 1,100, or 2,200 mg/m^3	Chamber control, 550, 1,100, or 2,200 mg/m^3	Chamber control, 550, 1,100, or 2,200 mg/m^3
Survival rates	29/50, 19/50, 21/50, 16/50	36/50, 30/50, 32/50, 25/50	34/50, 32/50, 27/50, 32/50	36/50, 34/50, 27/50, 34/50
Body weights	Exposed groups similar to the chamber control group	Exposed groups similar to the chamber control group	Exposed groups similar to the chamber control group	Exposed groups greater than the chamber control group
Nonneoplastic effects	Kidney: renal tubule hyperplasia (0/50, 1/50, 8/50, 23/50); transitional epithelial hyperplasia (0/50, 2/50, 8/50, 5/50); papilla mineralization (1/50, 8/50, 30/50, 39/50); severity of chronic nephropathy (2.0, 2.3, 2.5, 2.8)	None	None	None
Neoplastic effects	Adrenal medulla: benign pheochromocytoma (5/50, 9/50, 13/50, 17/50); benign or malignant pheochromocytoma (6/50, 9/50, 13/50, 19/50)	None	None	None
Equivocal findings	Kidney: (standard and extended evaluation combined) renal tubule adenoma (3/50, 2/50, 3/50, 7/50)	None	None	Liver: hepatocellular adenoma (9/50, 12/50, 15/50, 18/50)
Level of evidence of carcinogenic activity	Some evidence	No evidence	No evidence	Equivocal evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535, with and without S9			
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo:*	Negative in males and females			

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.

For studies showing multiple chemical-related neoplastic effects that if considered individually would be assigned to different levels of evidence categories, the following convention has been adopted to convey completely the study results. In a study with clear evidence of carcinogenic activity at some tissue sites, other responses that alone might be deemed some evidence are indicated as "were also related" to chemical exposure. In studies with clear or some evidence of carcinogenic activity, other responses that alone might be termed equivocal evidence are indicated as "may have been" related to chemical exposure.

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 Stoddard solvent IIC on May 22, 2003, 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.

Mary Anna Thrall, D.V.M., Chairperson
Department of Pathology
College of Veterinary Medicine and Biomedical Sciences
Colorado State University
Fort Collins, CO

Kim Boekelheide, M.D., Ph.D., Principal Reviewer
Division of Biology and Medicine
Department of Pathology and Laboratory Medicine
Brown University
Providence, RI

Hillary M. Carpenter, III, Ph.D., Principal Reviewer
Minnesota Department of Health
St. Paul, MN

Michael R. Elwell, D.V.M., Ph.D.
Pfizer Global Research and Development
Groton, CT

Walter W. Piegorsch, Ph.D.
Department of Statistics
University of South Carolina
Columbia, SC

Stephen M. Roberts, Ph.D.
Department of Physiological Sciences
College of Veterinary Medicine
University of Florida
Gainesville, FL

Richard D. Storer, M.P.H., Ph.D.
Department of Genetic and Cellular Toxicology
Merck Research Laboratories
West Point, PA

Mary Vore, Ph.D., Principal Reviewer
Graduate Center for Toxicology
University of Kentucky
Lexington, KY

Cheryl Lyn Walker, Ph.D.
M.D. Anderson Cancer Center
The University of Texas
Smithville, TX

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On May 22, 2003, the draft Technical Report on the toxicology and carcinogenesis studies of Stoddard solvent IIC 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. R.S. Chhabra, NIEHS, introduced the toxicology and carcinogenesis studies of Stoddard solvent IIC by discussing the uses, human exposure, and nomination rationale for the chemical and the designs and results of the 2-week, 3-month, and 2-year inhalation studies. The proposed conclusions were *some evidence of carcinogenic activity* in male F344/N rats based on increased incidences of adrenal medulla neoplasms. The slightly increased incidences of renal tubule adenoma may have been exposure related in male F344/N rats. There was *no evidence of carcinogenic activity* in female F344/N rats exposed to 550, 1,100, or 2,200 mg/m^3 Stoddard solvent IIC. There was *no evidence of carcinogenic activity* in male B6C3F$_1$ mice exposed to 550, 1,100, or 2,200 mg/m^3 Stoddard solvent IIC. There was *equivocal evidence of carcinogenic activity* in female B6C3F$_1$ mice based on increased incidences of hepatocellular adenoma. The slight increase was associated with increased body weight in exposed female B6C3F$_1$ mice.

Dr. Vore, the first principal reviewer, stated that the study design was adequate with the highest dose physically possible being used. Dr. Vore agreed with the proposed conclusions.

Dr. Carpenter, the second principal reviewer, inquired about the specificity or variability of toxicity assessment for a solvent that is a mixture of over 80 compounds. Dr. Chhabra stated that the composition of the mixture is well defined and the overall solvent fits within a narrow range of physical specification.

Dr. Boekelheide, the third principal reviewer, suggested that the observation of sperm motility alterations in both species be given more attention. Dr. Chhabra noted that the changes were fairly small but more would be added to the discussion.

Dr. A. Medeiros, from the American Chemical Council's Hydrocarbons Solvents Panel, suggested that the formation of adrenal gland pheochromocytomas in male mice may have been a secondary effect of the observed α2u-globulin induced kidney nephropathy and cited concurrent increases in pheochromocytomas and nephropathy from a review of some NTP studies. Dr. J.K. Haseman, NIEHS, replied that a logistic regression analysis performed on the same data set provided only a very weak correlation between the two lesions, whereas dose and survival did affect the incidences of both lesions after adjustment for other factors.

Dr. Vore moved and Dr. Carpenter seconded that the conclusions be accepted as written. The motion was approved unanimously with eight votes.

INTRODUCTION

Stoddard Solvent IIC

CAS No. 64742-88-7

Synonyms: Medium aliphatic solvent naphtha (petroleum); white spirit

Chemical and Physical Properties

White spirit (also called mineral spirit) is a complex petrochemical solvent mixture of saturated aliphatic and alicyclic C_7 to C_{12} hydrocarbons with a boiling range of 130° to 220° C (WHO, 1996). A variety of crude oil starting materials and production processes are used in the refining of white spirit and several Types and Classes of the solvent have been defined according to the boiling range, flash point, and aromatic content of the resulting product. The most widely used white spirit (Type 1; boiling range of 149° to 208° C and a flash point of at least 38° C) is generally called Stoddard solvent in the United States (*Merck Index,* 1996). Stoddard solvent IIC is a white spirit that consists of a clear liquid mixture of petroleum distillates with little or no odor, a boiling point range of 177° to 213° C, a flash point of at least 61° C, an aromatic content of 0% to 2%, and a density (at 15.6° C) of 0.768 to 0.800 (ASTM, 1995). Because the scientific literature contains information on many different kinds of white spirit, mineral spirit, and Stoddard solvent mixtures, in this Technical Report, each mixture will be defined by its boiling point range and/or hydrocarbon class content whenever possible.

Production, Use, and Human Exposure

The various Types and Classes of white spirit are produced from straight-run naphtha and straight-run kerosene, two refinery streams obtained from the distillation of crude oil; fractional distillation of these products is followed by hydrodesulfurization, solvent extraction, and/or hydrogenation to obtain mixtures with specified physicochemical characteristics (WHO, 1996). White spirit is in high demand, as 9.22×10^8 kg of various white spirit solvents were produced in the United States in 1985 (IARC, 1989). Production estimates for Stoddard solvent IIC were not found in the literature.

White spirit is used as a dry cleaning agent; as an extraction, cleaning, and degreasing solvent; and as a solvent in aerosols, paints, wood preservatives, asphalt products, lacquers, and varnishes (WHO, 1996). White spirit is the most widely used solvent in the paint industry, and approximately 45% of the white spirit sold in the United States in 1985 was used in paints and coatings (IARC, 1989).

A large portion of manufactured white spirit is released to the atmosphere due to its extensive use as a solvent, dry cleaning agent, degreasing agent, and volatile ingredient of paints, varnishes, and lacquers; both the general population and workers in occupationally exposed environments may thus be regularly exposed (ATSDR, 1995). Oberg (1968) measured the concentration of white spirit (Stoddard solvent) in dry cleaning plants in Detroit. Peak exposures at plants using high-flash (60° C) Stoddard solvent did not exceed 1,200 mg/m^3 air, and the 8-hour average exposure was calculated to be 90 mg/m^3. Air samples collected from the inhalation zone of 14 house painters during 19 days of work revealed short-term peak and geometric mean exposures of 4,038 and 929 mg white spirit vapor/m^3, respectively (Cohr and Stokholm, 1979). Riala *et al.* (1984) estimated that the yearly inhalation dose in the 1960s and

early 1970s for the average painter amounted to 0.53 kg of white spirit (240 mg/m^3 for daily 8-hour continuous exposures). Painters working after 1977 were found to have been exposed to a somewhat lower yearly dose of 0.32 kg white spirit (daily 8-hour exposures to 150 mg/m^3). Car washers were exposed to time-weighted average concentrations of 5 to 465 or 45 to 805 mg/m^3 white spirit when washing automobiles or heavy vehicles, respectively; both Type 1 (boiling range 145° to 200° C) and high-flash white spirit (boiling range 185° to 200° C) were used by these workers (Niemelä *et al.,* 1987). White spirit vapor concentrations ranged from 270 to 6,140 mg/m^3 in six typical brush-painting scenarios that varied according to ventilation, room volume, temperature, size of painted area, etc. (Hansen, 1988). For a single painter using paint products containing 23.5% or 32% white spirit in six outside and 25 inside brush-painting scenarios, Gill *et al.* (1991a) measured time-weighted average exposures of 18 to 136 and 37 to 372 mg/m^3 for the outdoor and indoor scenarios, respectively.

The National Institute for Occupational Safety and Health (NIOSH) has extensively surveyed occupational exposures to white spirit (Stoddard solvent/mineral spirit) and has reported the following concentrations in the breathing zone of laborers: maintenance painters, 33 to 761 mg/m^3; workers in airline hangers, 363 to 8,860 mg/m^3; workers in screen-cleaning processes, 137 to 385 mg/m^3; workers operating a parts washer for automobile parts, 43 to 594 mg/m^3; manufacturers of catapult cylinders, 2,615 mg/m^3 when spraying solvents and up to 275 mg/m^3 when painting; ski boot finishers, 345 to 451 mg/m^3; and telephone cable assemblers, 79 to 244 mg/m^3 (NIOSH, 1973; 1975a,b,c,d,e; 1980).

Biodegradation is expected to be the primary fate for Stoddard solvent deposited in soil or water, and the rate and extent of the process is dependent on the ambient temperature, the availability of a hydrocarbon-metabolizing population of microorganisms, and the concentration of the white spirit contamination (ATSDR, 1995). Schmitt *et al.* (1991) measured white spirit concentrations as high as 500 mg/L and 3,500 mg/kg in the soil water and soil immediately below a site contaminated by underground storage tanks. These authors reported 99% removal of the white spirit to a concentration less than the limit of detection within 4 months when using a biological treatment for bioremediation. Low water solubility and moderate vapor pressure suggest that volatilization and subsequent photooxidation contribute to atmospheric abiotic degradation of Stoddard solvent (USAF, 1989). White spirit has been identified in at least seven of the nearly 1,300 hazardous waste sites on the U.S. Environmental Protection Agency National Priority List, but it is not known if the substance has been released into the environment from these sites (ATSDR, 1995).

Although no human exposure limits have been established for Stoddard solvent IIC, several have been published for Stoddard solvent (CAS No. 8052-41-3). Specifically, the American Conference of Governmental Industrial Hygienists (2002) recommends a threshold limit value time-weighted average (TWA) of 525 mg/m^3 (100 ppm) for Stoddard solvent. NIOSH (1997) established an Immediately Dangerous to Life or Health concentration for Stoddard solvent of 20,000 mg/m^3. In addition, NIOSH set a recommended exposure limit TWA for Stoddard solvent of 350 mg/m^3 (for up to a 10-hour work day) with a 15-minute ceiling that is not to exceed 1,800 mg/m^3 during the work day. The Occupational Safety and Health Administration set the permissible exposure limit TWA for Stoddard solvent at 2,900 mg/m^3 (NIOSH, 1997). The National Occupational Exposure Survey (1981-1983) reported that approximately 1,922,000 workers were potentially exposed to Stoddard solvent in the United States (NIOSH, 1990).

Absorption, Distribution, and Excretion

Experimental Animals

Verkkala *et al.* (1984) reported that 260, 210, and 240 mg of three different white spirits containing 0.3%, 11.7%, and 17% aromatics (respectively) were absorbed in rats following 3 hours of dermal exposure to an unspecified dose of the solvents. Lam *et al.* (1992) exposed groups of five rats to white spirit (boiling range, 148° to 200° C; 20% aromatic hydrocarbons) at concentrations of 0, 2,290, or 4,580 mg/m^3 air by inhalation, 6 hours per day, 5 days per week for 3 weeks. The total aromatic and aliphatic hydrocarbon fraction concentrations in the brain were approximately two and threefold greater, respectively, in rats exposed to 4,580 mg/m^3 than in those exposed to 2,290 mg/m^3, indicating that accumulation of hydrocarbons may occur following long-term exposure to high concentrations of white spirit. After 3 weeks of inhalation exposure (6 hours per day, 5 days per week), the fat:brain:blood concentration

coefficients for total white spirit were approximately 250:3:1 in male rats exposed to 2,400 or 4,800 mg/m^3 dearomatized white spirit (Löf *et al.,* 1999).

Humans

Inhalation exposure of human volunteers to white spirit (1,250 or 2,500 mg/m^3; boiling range, 150° to 200° C; 83% aliphatics and alicyclics, 17% aromatics) for 30 minutes during rest or exercise indicated that it is readily absorbed, the concentration of aliphatics and aromatics in alveolar air increases with exposure concentration and the rate of respiration due to exercise, and the concentrations in venous and arterial blood accurately reflect the exposure level (Astrand *et al.,* 1975). At the end of the exposure periods, an approximate 2:1 ratio of aliphatics to aromatics in alveolar air was observed. Rapid absorption of white spirit (17% aromatics) was also reported in a study of 21 human volunteers exposed by inhalation to 204, 600, 1,200, or 2,400 mg/m^3; steady state in alveolar air was obtained after 20 minutes of exposure at rest and after 1.5 hours during work (Stokholm and Cohr, 1979a). In this study, the steady-state ratio of alveolar aliphatics to aromatics was approximately 3:1; in blood, where steady state was not achieved even after 7 hours of exposure, the ratio of these hydrocarbon classes ranged from 5:1 to 6:1. Minor blood accumulation of white spirit (99% aliphatics) from 2.00 mg/L on day 1 to 2.54 mg/L on day 5 was reported during 5 days of inhalation exposure (6 hours per day) of seven volunteers to 600 mg/m^3 (Pedersen *et al.,* 1984). In a later study by the same investigators, groups of 12 human volunteers were given single 6-hour inhalation exposures to 600 mg/m^3 white spirit mixtures containing either aliphatics, alicyclics, and 18% aromatics; aliphatics, alicyclics, and less than 0.1% aromatics; or essentially all (98.9%) aliphatics (Pedersen and Cohr, 1984a). Absorption of the first two types of white spirit were similar (blood concentrations of 3.1 and 3.2 mg/L respectively), but the group exposed to essentially all aliphatic alkanes had a significantly lower blood concentration of 2.3 mg/L. Gill *et al.* (1991b) exposed four human volunteers to 575 mg/m^3 white spirit (Carless 100F, a "typical" white spirit) by inhalation for 4 hours and reported an uptake of 55% to 60% of the dose.

In the study by Astrand *et al.* (1975), the *in vivo* blood:air partition coefficients for the aliphatic and aromatic fractions of white spirit never exceeded 10 or 50, respectively (calculated by Hass and Prior, 1986) although it should be noted that equilibrium between alveolar air and blood was not achieved in this study. Distribution of white spirit (99% aliphatics) was demonstrated in seven volunteers exposed to 600 mg/m^3, 6 hours per day for 5 days by inhalation (Pedersen *et al.,* 1984, 1987). Using a mathematical fit to a three-compartment model, a fat:blood partition coefficient of 47 was calculated for white spirit and the redistribution phase was estimated to be 20 hours. In the brain, steady-state maximum and minimum concentrations of 5 and 0.6 mg/kg, respectively, were calculated.

Pulmonary excretion of white spirit vapor was measured in expired alveolar air of six volunteers after 7 hours of inhalation exposure to 300 or 600 mg/m^3 white spirit (17% aromatics) by Stokholm and Cohr (1979a). Ten minutes after exposure ended, the expiratory concentrations of the aliphatic and aromatic fractions were approximately 12% of the exposure concentrations, and 16 hours later the concentrations in expired air were 2% and 4%, respectively, of the initial concentrations of the two fractions. Elimination of white spirit (99% aliphatics, 1% cyclic aliphatics) from the blood was studied in two groups of seven and eight volunteers given either 5 consecutive days of 6-hour inhalation exposure or a single 3-hour inhalation exposure to 600 mg/m^3 (Pedersen *et al.,* 1987). In both scenarios, after exposure ceased there was a brief phase of rapid elimination from blood followed by a long phase with a slow elimination half-life of 46 hours. The half-life of white spirit in fat was calculated to be 46 to 48 hours. Gill *et al.* (1991b) found that white spirit (Carless 100F) was rapidly cleared from the blood of four volunteers exposed by inhalation to 575 mg/m^3 for 4 hours, declining from maximum concentrations ranging from 1.37 to 1.60 mg/L to below the limit of detection (0.5 mg/L) within 40 minutes after exposure ended. Pfäffli *et al.* (1985) reported that the amount of dimethylbenzoic acid isomers in urine of car washers (inhalation exposure concentrations were described as 5 to 465 mg white spirit/m^3 by Niemelä *et al.,* 1987) was linearly related to the subjects' exposure to the white spirit that contained 11% aromatics. These benzoic acids were formed by the oxidation of trimethylbenzenes that were approximately 1% of this solvent mixture.

TOXICITY

Experimental Animals

White spirit has been found to have low acute toxicity in animals. Groups of 15 or 16 male 5-week old Harlan-Wistar rats were exposed by inhalation for 8 hours to 2,400, 4,600, or 8,200 mg/m^3 white spirit

(Stoddard solvent; 48% aliphatics, 38% cyclic aliphatics, 14% aromatics) (Carpenter *et al.,* 1975a). One 8,200 mg/m^3 rat died, and symptoms such as slight loss of coordination, eye irritation, and bloody nasal exudate were reported. Rats exposed to 2,400 mg/m^3 did not show any signs of toxicity during exposure or during a 14-day follow-up period. In additional experiments in this study, all four cats exposed by inhalation to 10,000 mg/m^3 Stoddard solvent died during a 7.5-hour exposure following the development of decreased reactivity to light, tremors, and clonic convulsions; a dog exposed to 8,000 mg/m^3 for 8 hours suffered from eye irritation, increased salivation, tremors, and clonic spasms. At 4,000 mg/m^3, no signs of toxicity were noted in dogs. In addition, three of six male Swiss-Webster mice given a 1-minute 10,000 mg/m^3 inhalation exposure to this solvent developed respiratory depression that exceeded a 50% rate decline; a similar decrease was not seen in mice briefly exposed to 4,400 mg/m^3.

In a later multispecies study using a similar design from the same laboratory (Carpenter *et al.,* 1975b), rats were exposed to 500, 1,250, 2,500, 5,000, or 10,000 mg/m^3 dearomatized white spirit (high flash white spirit; 61% aliphatics, 36% cyclic aliphatics, 3% aromatics). In this study, two 10,000 mg/m^3 rats died, and rats exposed to this concentration showed slight loss of coordination and irritation of the skin. Due to condensation, a vapor concentration of 2,900 mg/m^3 was actually measured for this group. No toxic effects were noted in animals exposed to 500 mg/m^3 (due to condensation, the measured concentration for this group was 270 mg/m^3). Four cats exposed by inhalation to 10,000 mg/m^3 of this high flash solvent showed no signs of poisoning, but a dog exposed to 1,700 mg/m^3 exhibited lacrimation. In mice, inhalation of 350 or 1,200 mg/m^3 for 1 minute produced no respiratory tract irritation or change in respiratory rate. In an acute inhalation study in Sprague-Dawley rats (API, 1987a), groups of five males and five females were exposed to 5,500 mg/m^3 white spirit for 4 hours (Stoddard solvent; boiling range, 160° to 199° C, 14.5% aromatics). All rats survived, and clinical signs included languid behavior and squinted eyes.

No deaths or toxic signs were reported (Coombs *et al.,* 1977) in male or female rats gavaged with 1, 2, 4, or 8 mg white spirit (boiling range, 157° to 198° C; 17% aromatics)/kg body weight; 4-hour inhalation exposures of greater than 14,000 mg/m^3 (solvent qualities unspecified) resulted in restlessness, but no deaths. Although no deaths occurred during 14 days of observation, hypoactivity and ataxia were noted in five animals following gavage administration of 5.0 g/kg white spirit (Stoddard solvent; 14.5% aromatics) to five male and five female Sprague-Dawley rats (API, 1986a). Also in this study, groups of four male and four female New Zealand White rabbits were dermally dosed for 24 hours with 2.0 or 3.0 g/kg white spirit (Stoddard solvent; 14.5% aromatics) applied under a bandage over 10% of their body surface; all dosing surfaces were shaved, and the shaved skin was abraded in two animals in each group. All rabbits exhibited loss of appetite and hypoactivity on the first day after dosing. Thickening and reddening of application-site skin occurred in 2.0 g/kg rabbits, and one 2.0 g/kg female with abraded skin died 3 days after exposure.

Rats were administered 0, 2,400, or 4,800 mg/m^3 aromatic white spirit (qualities unspecified) by inhalation, 6 hours per day, 7 days per week for 3 weeks (Steensgaard *et al.,* 1996). During the first week of exposure, animals showed signs of irritation of mucous membranes and appeared to be sedated, but both effects gradually diminished during the second week of exposure. In a large multispecies inhalation study by Rector *et al.* (1966), groups of 14 to 18 male and female Long-Evans and Sprague-Dawley rats, 14 to 59 guinea pigs, three to five New Zealand White rabbits, three squirrel monkeys, and two beagle dogs were exposed continuously for 90 days to 114 to 1,271 mg/m^3 white spirit (boiling range, 140° to 190° C; 80% to 86% aliphatics and cyclic alkanes, 1% alkenes, 13% to 19% aromatics). A significant increase in mortality was seen in guinea pigs at exposure concentrations of 363 mg/m^3 or greater, but mortality was not increased in any other species tested. No signs of toxicity were noted during the exposure period except for occasional slight diarrhea and nasal discharge in guinea pigs. Lung irritation and congestion were commonly observed in all species at necropsy; the severity of lung irritation was exposure-concentration related, and congestion occurred primarily in animals exposed to 1,271 mg/m^3. Mild to moderate vacuolar changes were seen in hepatic cells of guinea pigs exposed to 363 mg/m^3 or greater. Similar effects were seen in the liver of guinea pigs exposed by inhalation to 892 mg/m^3 white spirit (19% to 20% aromatics) for 90 days (Jenkins *et al.,* 1971).

Carpenter *et al.* (1975a) exposed groups of 25 male Harlan-Wistar rats and four beagle dogs to 0, 480, 1,100, or 1,900 mg/m^3 white spirit (Stoddard solvent; boiling range, 152° to 194° C; 47.7% aliphatics, 37.6% cyclic

aliphatics, 14.7% aromatics) by inhalation, 6 hours per day, 5 days per week for up to 13 weeks. After 13 weeks, marked renal tubule regeneration was observed in four of nine rats exposed to 1,900 mg/m^3 and in two of nine rats exposed to 1,100 mg/m^3. Renal tubule dilatation with eosinophilic debris was also observed in six of nine rats exposed to 1,900 mg/m^3 and in three of nine rats exposed to 1,100 mg/m^3. Similar renal lesions were also noted in some rats killed after only 8 weeks of exposure. In a subsequent study using a similar design, slight renal tubular degeneration was noted in 14 of 35 rats (but not in dogs) exposed by inhalation to 0, 49, 100, or 230 mg/m^3 dearomatized white spirit (140° Flash Aliphatic Solvent); however, because the lesion was noted in control and exposed groups, it was not considered solvent related (Carpenter *et al.,* 1975b).

In an inhalation study conducted by Blair *et al.* (1979), groups of 18 male and 18 female Wistar rats were exposed to 2,000, 4,000, or 7,500 mg/m^3 Low Aromatic White Spirit (LAWS), 6 hours per day, 5 days per week for 13 weeks. Slight lethargy was noted in the 7,500 mg/m^3 groups 30 minutes after the cessation of exposure. A single exposure to LAWS caused low grade anemia and mild degenerative changes in the kidneys of all exposed groups of males; hyaline droplets were typically found in the proximal tubular epithelium of the outer cortex. Liver weights were significantly increased in exposed groups of females but there were no accompanying histopathologic lesions.

Riley *et al.* (1984) exposed a group of six female rats to 214 mg/m^3 white spirit vapor (boiling range, 150° to 195° C; 61% aliphatics, 20% cyclic aliphatics, 19% aromatics), 4 hours per day for 4 consecutive days. Respiratory tract lesions in the exposed animals included loss of cilia, hyperplasia of mucosal and basal cells, squamous cell metaplasia, and inflammatory cell infiltrate in the nasal cavity, trachea, and larynx.

Groups of 36 3-month old and 14 15-month old male rats were exposed by inhalation to 0, 2,290, or 4,580 mg/m^3 white spirit (boiling range, 148° to 200° C; 20% aromatics), 6 hours per day, 5 days per week for 6 months followed by an exposure-free, 4-month recovery period (Ostergaard *et al.,* 1993). Animals showed signs of discomfort during the initial exposure period. Mucosal irritation, bloody nasal discharge, and lacrimation were observed. Body weights were reduced in the 4,580 mg/m^3 groups, but the deficits were ameliorated during the recovery period. Water consumption was monitored in the 3-month old animals, and it was significantly increased in both exposed groups. Significant increases in plasma urea and creatinine concentrations and decreases in serum alanine aminotransferase activity were noted in the exposed groups.

Minor irritation and a low irritation index of 1.55 were reported for 0.5 mL white spirit (Stoddard solvent) in New Zealand White rabbits following a 24-hour occlusive exposure (Nethercott *et al.,* 1980). In another test for primary dermal irritation, 0.5 mL of Stoddard solvent (14.5% aromatics) was applied to the shaved (abraded and not abraded) skin of six male New Zealand White rabbits (API, 1986a). Following 24 hours of occlusion, the exposure caused moderate to severe erythema and edema; after 72 hours, a primary dermal irritation index of 4.5 was calculated. One hour after application of 0.1 mL of this solvent to the eyes, one of six rabbits showed mild injection and swelling of the conjunctiva, which disappeared after 24 hours. These investigators also reported mild to moderate irritation from this solvent after conducting a Buehler test using a 75% solution of the solvent in paraffin oil for the three sensitizing doses and a 25% solution for the challenge dose. In a subsequent study, 6-hour occlusive dermal doses of 200, 1,000, or 2,000 mg/kg Stoddard solvent were given to groups of 10 New Zealand White rabbits 3 times weekly for 4 weeks (API, 1986b). Moderate and severe irritation of the occluded skin was seen in 200 and 2,000 mg/kg rabbits, respectively. Body weight gain was significantly reduced in 2,000 mg/kg males and females and in 1,000 mg/kg females. Females dosed with 2,000 mg/kg developed liver lesions described as white streaks or foci with a granular surface.

Semi-occluded 4-hour application of LAWS 15/20A to six New Zealand White rabbits caused moderate irritation and slight edema that regressed in one of the animals 14 days after the exposure (Gardener, 1989). White spirit and trichloroethylene were found to be the two most potent dermal irritants of 14 organic solvents following thrice-daily application of 10 µL of the solutions to the shaved skin of Dunkin Hartley guinea pigs for 3 days (Anderson *et al.,* 1986). White spirit induced macroscopic responses, dermal thickness increases, and extent of dermal cell involvement similar to those of a 2% positive control solution of sodium lauryl sulfate. Thickening and cracking of the skin and patchy hair loss were observed from days 7 to 14 when hydrogenated white spirit/naphtha (boiling range, 134° to 217° C;

86.8% aliphatics and cyclic aliphatics, 12.9% aromatics) was applied to the skin of 20 mice three times per week for up to 4 weeks (Ingram *et al.,* 1993). Epidermal necrosis was seen within one day after the second treatment; after day 7, repeated cycles of necrosis and healing were indicated by epidermal necrosis, ulceration, eschar formation, vesiculation, and epidermal hyperplasia.

Groups of 35 male and 35 female Sprague-Dawley rats were exposed by inhalation to 1,970 or 5,610 mg/m^3 dearomatized white spirit (boiling range, 155° to 193° C; 58% aliphatics, 42% cyclic aliphatics, <0.5% aromatics), 6 hours per day, 5 days per week for 12 weeks (Phillips and Egan, 1984). No deaths occurred and weight gain was reduced sporadically only in 5,610 mg/m^3 males. Significant increases in absolute and relative kidney weights were found in all exposed groups after 4, 8, and 12 weeks of exposure, and histopathologic examination revealed the presence of regenerative epithelium in the cortex and dilated tubules filled with proteinaceous casts in the corticomedullary areas of the kidney; dilation was focal with 5% to 10% of the tubules affected. Closer examination of this kidney toxicity was later reported by Phillips and Cockrell (1984) following inhalation exposure of groups of 50 male and 50 female Sprague-Dawley and Fisher rats to 0, 570, or 4,580 mg/m^3 white spirit (boiling range, 156° to 204° C; 55% aliphatics, 27% cyclic aliphatics, 18% aromatics), 6 hours per day, 5 days per week for 8 weeks. At 8 weeks, exposure-concentration related increases in urine volume (with decreased osmolality) and concentrations of glucose and protein were noted. A marked increase in the number of epithelial cells in urine was also observed. Male Fisher rats were more significantly affected than male Sprague-Dawley rats. Structural changes found in the kidneys of animals killed at 4 weeks were identical to those reported by Phillips and Egan (1984). Significant increases in absolute and relative kidney weights have also been reported in exposed groups following inhalation exposure to 0, 2,290, or 4,580 mg/m^3 white spirit (boiling range, 148° to 200° C; 20% aromatics), 6 hours per day, 7 days per week for 3 weeks (Lam *et al.,* 1994). The relative kidney weight changes were exposure-concentration dependent.

Using a behavioral test battery that measured changes in activity, coordination, grip strength, and discrimination performance, only minor behavioral changes were observed in groups of eight male Wistar rats exposed by inhalation to 0, 1,200, 2,400, or 4,800 mg/m^3 white spirit vapor (boiling range, 158° to 193° C; 44% aliphatics, 36% cyclic aliphatics, 18% aromatics), 8 hours per day for 3 consecutive days or 26 weeks (Kulig, 1989). Tail nerve conduction velocity was significantly reduced in 4,800 mg/m^3 rats. Ostergaard *et al.* (1993) exposed groups of 36 3-month old and 14 15-month old male Wistar rats to 0, 2,290, or 4,580 mg/m^3 white spirit vapor (boiling range, 148° to 200° C; 80% aliphatics and cyclic aliphatics, 20% aromatics), 6 hours per day, 5 days per week for 6 months. This inhalation exposure caused no significant differences between exposed and control groups at the end of a 2-month recovery period for general functional behaviors and passive avoidance, eight-arm radial maze, and Morris maze cognitive tests. However, whole brain content of the neurotransmitters dopamine and 5-hydroxytryptamine were significantly increased after 4 months of recovery. In a subsequent report, permanent reductions in dark-period motor activity were seen in exposed groups of male Wistar rats 2 months after the end of inhalation exposure to 0, 2,339, or 4,679 mg/m^3 dearomatized white spirit type 3 (boiling range, 145° to 200° C; <0.4% aromatics), 6 hours per day, 5 days per week for 6 months (Lund *et al.,* 1996). Although learning and memory functions at this point were not affected by exposure as measured by behavioral tests, exposure-concentration related increases in the amplitudes of the early-latency peaks of flash-, somatosensory-, and auditory-evoked potentials led to the conclusion that dearomatized white spirit induced possibly irreversible central nervous system effects in the rat.

Brain enzyme activities in male Wistar rats were measured by Savolainen and Pfäffli (1982) after exposure to white spirit vapor (boiling range, 152° to 182° C; 61% aliphatics, 27.3% cyclic aliphatics, 11.7% aromatics) at concentrations of 575, 2,875, or 5,750 mg/m^3 for 6 hours per day, 5 days per week for 4 to 17 weeks. At 8 weeks, an exposure-concentration dependent decrease in cerebellar succinate dehydrogenase activity was measured. Glial cell proliferation was proposed to have occurred by week 12 because creatine kinase activity had increased at this time point and an increase in the specific activity in the glial cell fraction was not seen. Muscle cell membranes were presumed to be affected by the solvent exposure because sialic and uronic acid concentrations were decreased in proportion to phospholipids or total membrane protein. The 17-week virtual no-effect level was determined to be 575 mg/m^3. Central nervous system synaptosomal calcium uptake, ATPase

activity, and membrane fluidity were measured in the brains of rats after single 18-hour inhalation exposures to 0, 3,000 or 6,000 mg/m^3 white spirit (qualities not specified) (Edelfors and Ravn-Jonsen, 1985, 1992). Compared to control rats, calcium uptake was increased in 3,000 mg/m^3 animals and decreased in 6,000 mg/m^3 animals. Ca^{++}/Mg^{++}-ATPase activity was decreased after 20 minutes of buffered exposure to 12% to 50% saturating concentrations of the dearomatized white spirit *in vitro*. Membrane fluidity (measured by fluorescence polarization) was slightly reduced by exposure to the solvent.

Exposure-concentration related increases in whole-brain content of noradrenaline, dopamine, and 5-hydroxytryptamine were reported in groups of five male Wistar rats following inhalation exposure to 0, 2,290, or 4,580 mg/m^3 white spirit (boiling range, 148° to 200° C; 20% v/v aromatics), 6 hours per day, 5 days per week for 3 weeks (Lam *et al.,* 1992). Compared to controls, the yield of synaptosomal protein per gram of brain tissue was reduced by 3 weeks of inhalation exposure to white spirit in a study using the same experimental design (Lam *et al.,* 1995); this finding was repeated when the duration of the exposure was extended to 6 months and the measurement was made after a 4-month exposure-free recovery period. In this study, synaptosomal 5-hydroxytryptamine uptake and synaptosomal concentrations of noradrenaline, dopamine, and 5-hydroxytryptamine were significantly increased in both exposure groups after 3 weeks and 6 months. In addition, relative synaptosomal 5-hydroxytryptamine content and butyrylcholinesterase activity (compared to whole brain content/activity) were significantly increased in animals exposed to 4,580 mg/m^3 for 3 weeks.

When groups of 10 male Wistar rats were exposed by inhalation to dearomatized white spirit (boiling range, 145° to 200° C; <0.4% aromatics) at concentrations of 0, 2,290, or 4,580 mg/m^3 for 6 hours per day, 7 days per week for 3 weeks, exposure-concentration related increases were seen in the concentrations of reduced glutathione in P2 fractions of the cerebrum (Lam *et al.*, 1994). Although glutamine synthetase activities were not significantly affected by solvent exposure, the rate of generation of reactive oxygen species in P2 fractions of the hippocampus was significantly increased in 4,580 mg/m^3 animals. The authors concluded that solvent exposure yielded oxidative stress in the brain. Depression of P2 glutamine synthetase activity in the liver and the rate of generation of reactive oxygen species in P2 fractions of the kidney in 4,580 mg/m^3 animals suggested that dearomatized white spirit induced oxidative stress in these two organs as well. In contrast, glutathione concentrations have also been reported to be unchanged in P2 fractions of the frontal cortex and hippocampus in groups of 5- or 14-month old male Wistar rats exposed by inhalation to 2,290 or 4,580 mg/m^3 white spirit (boiling range, 150° to 220° C; 14% to 20% aromatics), 6 hours per day, 7 days per week for 3 weeks (Bondy *et al.,* 1995). Hippocampal P2 glutamine synthetase activities were increased in both exposed groups of young rats and in 4,580 mg/m^3 aged rats, suggesting that glial activation was being induced by white spirit. Decreased P2-fraction concentrations of glutathione and glutamine synthetase activities in the liver and kidney of exposed rats suggested that prooxidant events were occurring in these two organs but not in the brain. The kidney effects were more severe in the aged animals.

Humans

Severe lesions and ulcerations in the mucous membranes of the esophagus and gastrointestinal tract have been reported after ingestion of approximately 500 mL white spirit (Paris *et al.,* 1978); an aspirated dose of 30 mL may be fatal (McDermott, 1975). A 42-year old woman who experienced near-fatal poisoning from white spirit in paint and lacquer suffered cardiac arrest, ventricular fibrillation, pulmonary edema, hemolytic anemia, and metabolic abnormalities after painting for several hours in a closed room with poor ventilation (Nierenberg *et al.,* 1991). Similarly, a 60-year old man developed malaise with headache, anorexia, and coughing after painting in an unventilated bathroom for 1 hour with a paint containing white spirit (Atkinson *et al.,* 1989); during recovery in the hospital, he evidenced bone marrow suppression and liver cell damage attributed to the solvent exposure. Five cases of ulcerative and erythematous lesions of the genitals and buttocks of workers wearing coveralls still moist from dry-cleaning with white spirit (Stoddard solvent) were reported by Nethercott *et al.* (1980); six additional cases of cutaneous irritation after skin contact (vesicles, crusts, erythema, and desquamation) were also discussed.

In an early case report, a healthy 26-year old man developed liver swelling, jaundice, weakness, dermatitis, anemia, gastrointestinal disorders, bloody stools, albuminuria, and glucosuria after 3 months of heavy skin and inhalation exposure to white spirit (Stoddard solvent) at his job in a dry-cleaning facility (Braunstein and Schenectady, 1940). Complete recovery occurred when

he was removed from the exposure and hospitalized. Diffuse petechiae, aplastic anemia, and profound bone marrow depression developed in a 41-year old man frequently exposed to white spirit (Stoddard solvent) for 16 years as a heavy equipment mechanic (Prager and Peters, 1970); the patient died of aplastic anemia 11 months after diagnosis. Other cases have also attributed lethal or nonlethal aplastic anemia to white spirit (Stoddard solvent) exposure (Kegels, 1958; Scott *et al.,* 1959).

As determined in a questionnaire study, dermal exposure to white spirit (18% aromatics) caused skin disorders of the hands (dry, rough skin surface with fissures) in 11% of 148 exposed people compared to a spontaneous incidence of 4% in 71 controls (Björn *et al.,* 1983). A dose-response relationship was observed, as heavily exposed workers (exposure exceeding 4 hours per day) reported these effects more often. A 16-year old girl developed antibody-mediated glomerulonephritis after 5 days at a job where she sprayed ball bearings with white spirit (D'Apice *et al.,* 1978). Similar kidney toxicity was reported in the case of a 29-year old man who developed renal failure involving diffuse glomerulonephritis and focal necrosis after 1 year of floor cleaning with white spirit (Stoddard solvent); the cleaning was performed without the use of protective equipment for up to 6 hours each day (Daniell *et al.,* 1988).

Eye irritation and lacrimation were reported by Carpenter *et al.* (1975a) in six volunteers after 15 minutes of inhalation exposure to 2,700 mg/m^3 white spirit vapor (Stoddard solvent; 48% aliphatics, 38% cyclic aliphatics, 14% aromatics); two of these six volunteers experienced slight dizziness. At 850 mg/m^3, only one person reported slight eye irritation, and no irritation was detected at 140 mg/m^3. Hastings *et al.* (1984) found that 25 volunteers exposed to white spirit (Stoddard solvent; 35% aliphatics, 40% cyclic aliphatics, 25% aromatics) at 600 mg/m^3 for 30 minutes reported mild irritation of the nose (31% versus 15% in the control group) and eyes (36% versus 24% in the control group).

Stokholm and Cohr (1979b,c) exposed nine student volunteers to 0, 204, 600, 1,200, or 2,400 mg/m^3 and six students and nine painters to 0, 300, or 600 mg/m^3 white spirit (17% aromatics) by inhalation for 7 hours. Eye irritation was the most sensitive measure of effect; there was a significant exposure-concentration relationship in the house painter cohort and the student cohort exposed to concentrations up to 2,400 mg/m^3, and the house painters were more sensitive to the effect. In addition, an exposure-concentration relationship for irritation of the nose was noted in students exposed to 600 to 2,400 mg/m^3. In a subsequent elaboration on these studies, headache, tiredness, and giddiness were found to be increased in relationship to exposure concentration in the students exposed up to 2,400 mg/m^3, and headache was increased in the group of 600 mg/m^3 painters (Cohr *et al.,* 1980). Altered vestibular-cerebellar reflexes were seen in the 600, 1,200, and 2,400 mg/m^3 student groups but not in the 600 mg/m^3 painter group. Conversely, short-term memory was significantly impaired in 300 mg/m^3 house painters but not in students exposed to concentrations as high as 2,400 mg/m^3. Gamberale *et al.* (1975) reported that perceptual speed, reaction time, short-term memory, numerical ability, and manual dexterity were not adversely affected by a 30-minute exposure of 14 human volunteers to white spirit vapor (83% aliphatics and cyclic aliphatics, 17% aromatics) at 0, 625, 1,250, 1,875, or 2,500 mg/m^3; however, a 50-minute exposure to 4,000 mg/m^3 resulted in impaired short-term memory and perceptual speed. Serum creatine kinase activity was significantly increased and follicle stimulating hormone concentration was significantly decreased in a clinical study of seven student volunteers exposed by inhalation to 600 mg/m^3 white spirit (99% aliphatics), 6 hours per day for 5 days (Pedersen and Cohr, 1984b).

Because of the high occupational exposure to organic solvents in alkyd paints, painters represent the human population group with the highest likely exposure to white spirit, and despite the general lack of chemical identification or quantification for their exposures, a review of solvent toxicity in this subpopulation is warranted. As reviewed by Arlien-Soborg (1985), common acute symptoms reported by painters include irritation of the eyes, nose, and throat; nausea; headache; "drunkenness", dizziness, and fatigue; and loss of taste and appetite. These symptoms often disappear during exposure-free periods on weekends and holidays, but over the years the symptom-free periods become shorter and a chronic syndrome develops. With chronic exposure, memory impairment, irritability, apathy, anxiety, depression, abdominal pain, impotence, and blurred vision symptoms are added to the list. Although it is somewhat speculative to attribute all of these effects to a nonspecific and usually unquantitated solvent exposure, a positive association in epidemiological studies has been demonstrated between neuropsychological disorders and long-term exposure of painters to white spirit (Axelson

et al., 1976; Mikkelsen, 1980; Lindström *et al.,* 1984; Brackbill *et al.,* 1990).

Arlien-Soborg *et al.* (1979) found 39 of 50 painters who used white spirit as a solvent in paints to be intellectually impaired in a neuropsychological test battery after their referral to an occupational medical clinic because of suspected chronic brain syndrome. This patient group had a mean exposure of 27 years to mainly white spirit as a solvent in paints. These investigators later reported that similar impairment was seen in 57 of 81 tested house painters who had been mainly exposed to white spirit for a mean of 25.3 years (Arlien-Soborg *et al.,* 1981). In both of these studies, computerized tomography indicated brain atrophy in approximately 50% of the patients. Study of a smaller group of nine intellectually-impaired house painters indicated significantly reduced cerebral blood flow in painters exposed mainly to white spirit for a mean of 22 years compared to a group of 11 unexposed controls (Arlien-Soborg *et al.,* 1982). A 2-year follow-up study of 26 of the 50 patients initially examined by Arlien-Soborg *et al.* (1979) noted considerable improvement in the incidences of headache, dizziness, and irritability at 2 years, but no significant change in neurological status, neuropsychological impairment, or cerebral atrophy (Bruhn *et al.,* 1981).

Neuropsychological tests of figure classification, psychomotor coordination, memory, and reaction time were all significantly worse in white-spirit exposed painters (mean exposure 14.2 years) in a cross-sectional study of 52 age-matched pairs of painters and control industrial workers (Blume *et al.,* 1975; Hane *et al.,* 1977). Questionnaire responses from 42 of these pairs in a follow-up study indicated that there was a significant increase in irritability, impaired memory, and depression in the painters after 5 years but no change in these symptoms in the controls (Agrell *et al.,* 1980). The results of this follow-up study and those reported by Bruhn *et al.* (1981) indicate that symptoms of white spirit exposure do partially ameliorate with time after cessation of exposure, but the abnormal neuropsychological findings remain unchanged, suggesting that the brain disorder is neither fully nor partially reversible.

In a historical follow-up study of 2,601 painters (who received approximately 75% of their total solvent exposure as white spirit) and 1,790 bricklayers, the painters were determined to have a statistically significant relative risk factor of 3.4 for being awarded disability pensions because of presenile dementia (Mikkelsen, 1980). In a cross-sectional study questionnaire-based comparison of 72 house painters (mean white spirit exposure 20.2 years; 240 mg/m^3 mean daily exposure during working hours) with 77 reinforcement workers, Seppäläinen and Lindström (1982) reported that more painters suffered from nausea, "drunkenness," irritated mucous membranes, paresthesia, vertigo, and anosmia. A subsequent study of 219 similarly exposed house painters and 229 reinforcement workers led Lindström and Wickström (1983) to conclude that white spirit exposure impaired performance on four of the eight intelligence and psychomotor performance tests; short-term visual memory and simple reaction time were the most affected functions.

In a large cross-sectional study, a group of 85 painters (75% of total solvent exposure was white spirit; mean exposure 32.5 years; 240 mg/m^3 mean daily exposure during working hours) was sorted according to individual history of "high," "medium," and "low" cumulative solvent consumption and compared to a group of 85 bricklayers using tests of neuropsychological, neurological, and neurophysiological performance (Mikkelsen *et al.,* 1988). Significantly increased odds ratios for the development of dementia were seen in the two highest consumption groups of painters, and a strong correlation was seen between cumulative consumption and total number of abnormal neurological test scores (motor performance, coordination, reflexes, and sensitivity). As measured by computerized tomography, three of 11 neurophysiological parameters were altered by solvent exposure. An average no-observed-effect-level of 240 mg/m^3 for 13 years was estimated from these studies.

Bazylewicz-Walczak *et al.* (1990) utilized a cross-sectional design to compare the performance of a group of 226 rubber footwear industry workers (500 mg/m^3 mean white spirit exposure in the last 13 years) with that of a group of 102 unexposed hosiery plant workers on a battery of 12 neuropsychological tests. The performance of exposed footwear workers was significantly worse than that of the unexposed controls for four of the seven tests for intellectual functioning and three of the five tests for psychomotor performance. When the exposed population was sorted by individual exposure history, variables such as simple and complex reaction time and coordination were found to deteriorate with duration of exposure.

A cross-sectional study of 90 pairs of age-matched brush painters and unexposed controls utilizing a symptom and psychiatric state questionnaire and a neuropsychological

test battery was reported by Spurgeon *et al.* (1990, 1992). In this study, the solvent exposure was primarily white spirit at an average estimated concentration of 300 mg/m^3 for 2 days per week. To aid in the analysis, the exposed cohort was subdivided into four subgroups based on duration of exposure. Although there was no indication of a white spirit-related increase in psychiatric symptoms, significantly impaired performance was observed in the symbol-digit substitution test in the brush painters, and it was concluded that there was some evidence for effects of solvent exposure on cognitive functioning after long-term exposure.

Reproductive and Developmental Toxicity

Experimental Animals

Daily 6-hour inhalation exposure of pregnant rats (group sizes unspecified) to 600 or 1,800 mg/m^3 white spirit (qualities unspecified) on days 6 to 15 of gestation yielded no exposure-related alterations of implantation, number of live fetuses, fetal resorption, fetal size, sex distribution, or soft tissue development (Biodynamics, 1979; Phillips and Egan, 1981). Groups of 26 or 27 female rats were exposed by inhalation to white spirit (Stoddard solvent; boiling range, 157° to 204° C; 43% aliphatics, 33% cyclic aliphatics, 24% aromatics) at concentrations of 0, 600, or 2,400 mg/m^3 for 6 hours per day on days 6 to 15 of gestation (API, 1983). No maternal toxicity or differences in litter size or average fetal weight were seen between the groups. A low incidence of unspecified skeletal variation was noted in each of the exposed groups, and the effects were considered expressions of retarded growth rather than malformations. Maternal toxicity (eye irritation and decreased weight gain) was observed when pregnant Wistar rats were exposed by inhalation to 5,700 mg/m^3 white spirit (qualities unspecified), 6 hours per day on days 3 to 20 of gestation (Jakobsen *et al.,* 1986). In the fetuses, average body weight was significantly reduced by solvent exposure, and increased incidences of delayed ossification and supernumerary ribs were noted.

Edelfors *et al.* (1999) administered 0, 2,400, or 4,800 mg/m^3 white spirit (qualities unspecified) to female rats by inhalation 6 hours per day, on days 7 to 20 of gestation. The authors reported that long-lasting and possibly irreversible changes in calcium homeostasis were induced by prenatal exposure because synaptosomal cytosolic calcium concentrations were found to be significantly increased in the brains of exposed female offspring 35 days after birth. Daily 6-hour exposures of rat dams to 4,800 mg/m^3 white spirit (qualities unspecified) during gestation days 7 to 20 yielded impaired Morris maze performance in the offspring 2 and 5 months after birth (Hass *et al.,* 2001). These authors concluded that prenatal exposure to white spirit induced long-lasting learning and memory deficits in rats.

Humans

No reproductive or developmental toxicity studies of defined types of white spirit or Stoddard solvent in humans were found in a review of the literature.

Carcinogenicity

Experimental Animals

No carcinogenicity studies of defined types of white spirit or Stoddard solvent in experimental animals were found in a review of the literature. However, unleaded gasoline, which has a chemical composition similar to formulations of Stoddard solvent with high aromatic content, produced renal tumors in male rats and hepatocellular tumors in female mice in chronic inhalation studies (Kitchen, 1984; MacFarland, 1984).

Humans

Duh and Asal (1984) reported excess kidney and lung cancer in a standardized mortality odds ratio analysis of laundry and dry cleaning workers in Oklahoma. Increased proportionate mortality ratios for respiratory cancer of 1.42 (44 deaths, $P<0.05$) and for pancreatic cancer of 1.96 (12 deaths, $P<0.05$) were reported for a cohort-mortality study with 4,000 dry cleaning workers; similar results were obtained from the subset of workers (approximately 60% of the cohort) who were exposed solely to white spirit (Stoddard solvent) (Petrone *et al.,* 1987). Spirtas *et al.* (1991) found no statistically significant increased risk of non-Hodgkin's lymphoma or multiple myeloma in small groups of aircraft maintenance workers exposed to white spirit (Stoddard solvent). In a comprehensive evaluation of cancer epidemiology data pertaining to workers in the paint manufacturing industry and in painters themselves, the International Agency for Research on Cancer (1989) has reported a consistent excess of all cancers and of lung cancers in particular (approximately 20% and 40% above the national averages, respectively) especially in the larger cohort studies. Less consistent but increased risks for these populations were noted for cancers of the esophagus, stomach, and bladder, and some studies reported excess leukemia and cancers of the buccal cavity and larynx.

Genetic Toxicity

White spirit (Stoddard solvent; boiling range, 157° to 204° C; 19% aromatics) was not mutagenic (0.001 to 5 g/plate and 3.38 to 25 µL/mL in suspension) in *Salmonella typhimurium* strain TA98, TA100, TA1535, TA1537, or TA1538 with or without induced rat liver S9 enzymes (API, 1984a); these concentrations of white spirit also failed to induce a mutagenic response in *Saccharomyces cerevisiae* D4 with and without metabolic activation. These investigators also found this solvent to be nonmutagenic in an L5178Y $TK^{+/-}$ mouse lymphoma assay (0.005 to 0.1 µL/mL, with and without metabolic activation) and to not increase chromosomal abnormalities in the bone marrow of Sprague-Dawley rats following single or repeated (5 days) intraperitoneal injections of 0.087, 0.289, or 0.868 mL/kg. However, in subsequent mouse lymphoma cell studies of a similar white spirit (Stoddard solvent; boiling range, 161° to 199° C; 14.5% aromatics) the solvent was positive over the concentration range 0.0125 to 0.1 µL/mL, both with and without metabolic activation (API, 1987b). No cytogenetic damage was reported in micronucleus tests conducted with BALB/c mice exposed to white spirit (initial boiling point, 160° C; 15% aromatics) by intraperitoneal injection (0.01, 0.05, or 0.1 mL) or inhalation (50 g/m^3) (Gochet *et al.,* 1984). No effects on implantation rates, implantation efficiency, or fetal deaths were observed in a dominant lethal test in which male rats were exposed by inhalation to 600 or 1,200 mg/m^3 white spirit (qualities unspecified), 6 hours per day, 5 days per week for 8 weeks (Phillips and Egan, 1981). A similar lack of mutagenic effect on male germ cells was observed in dominant lethal tests with rats and mice dosed intraperitoneally or subcutaneously with 1 mL/kg white spirit (Stoddard solvent) or 140° Flash Aliphatic Solvent (API, 1984b).

Study Rationale

Stoddard solvent IIC ("high flash" and low aromatic grade) was nominated for carcinogenicity testing by the International Union, United Auto Workers. Because of the large volume of Stoddard solvent used in industrial and other settings, the potential for human exposure is considerable. Nevertheless, no long-term carcinogenicity studies have been conducted on any type of Stoddard solvent. Inhalation was chosen as the route of administration for these studies because it is the primary route of exposure in humans. Because 2,200 mg/m^3 was determined to be the maximum concentration that could be generated without aerosolization, 2,200 mg/m^3 was selected as the highest concentration for use in the current studies.

MATERIALS AND METHODS

Procurement and Characterization of Stoddard Solvent IIC

Stoddard solvent IIC was obtained from Shell Chemical Company (Houston, TX) in one lot (00106808). Lot 00106808 was used in the 2-week, 3-month, and 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and the study laboratory. Stability analyses were conducted by the study laboratory. Reports on analyses performed in support of the Stoddard solvent IIC studies are on file at the National Institute of Environmental Health Sciences.

Lot 00106808 of the chemical, a clear liquid, was identified as Stoddard solvent IIC by the analytical chemistry laboratory using infrared and nuclear magnetic resonance proton and carbon-13 spectroscopy, gas chromatography with mass spectrometry (GC/MS), aromatic content, boiling range, and flash point. Identity was confirmed by the study laboratory using GC/MS and aromatic content. Infrared and nuclear magnetic resonance spectra were consistent with a mixture of saturated hydrocarbons. Spectra by GC/MS were consistent with National Bureau of Standards Library spectra for hydrocarbons with 10 to 14 carbons; spectra by a second GC/MS system were consistent with the NIST/EPA/NIH Mass Spectral Library Database (NIST, 1994) for a mixture of *n*-paraffins, isoparaffins, or cycloparaffins with 10 to 13 carbons. Aromatic content was determined by GC at the analytical chemistry laboratory and at the study laboratory. The observed aromatic contents of 0.93% and 0.58% were consistent with the designation of the chemical as a Class C material (ASTM, 1995). The determined boiling range of 184.7° to 206.1° C was consistent with designation of the chemical as a Type II material. The observed flash point of 60.2° C was slightly lower than the 61° C minimal ASTM specification for a Type II material. The difference was attributed to the use of a different instrument from that specified in the ASTM standard.

The purity of lot 00106808 was determined by the study laboratory using GC. Gas chromatography indicated approximately 80 peaks with areas greater than 0.1% of the total peak area and approximately 30 peaks with areas greater than 1% of the total peak area. In these assays, concentrations of decane, undecane, and dodecane were determined by comparison to bracketing standards and yielded estimates of 1.70%, 19.3%, and 5.73% by weight for the three chemicals, respectively. Decalin contamination in lot 00106808 was determined by the analytical chemistry laboratory using GC; approximately 0.56% decalin was detected.

To ensure stability, the bulk chemical was stored in its original shipping containers (55-gallon metal drums) under a nitrogen headspace at controlled room temperature (15° to 30° C). Stability of the bulk chemical was monitored by the study laboratory relative to frozen reference (–20° C, amber vials with a nitrogen headspace) standards during the 2-week, 3-month, and 2-year studies using GC. Weight percents of decane, undecane, and dodecane were determined using GC. No degradation of the bulk chemical was detected.

Vapor Generation and Exposure System

Stoddard solvent IIC was pumped through a preheater and then into the top of a heated glass column filled with glass beads to increase the surface area for evaporation. Heated nitrogen entering the column from below vaporized the chemical as it conveyed it out of the generator. Generator output was controlled by the delivery rate of the chemical metering pump.

Because the vapor leaving the generator was above room temperature, the transport line to the exposure room was heated to prevent condensation. In the exposure room, the vapor was mixed with additional heated air before it entered a short vapor distribution manifold. Concentration in the manifold was determined by the chemical pump rate, nitrogen flow rate, and dilution air

flow rate. All three components were monitored by the exposure operator. The pressure in the distribution manifold was kept fixed to ensure constant flows through the manifold and into the chambers.

Electronically actuated metering valves controlled flow to each chamber. In the 2-year studies, a compressed air vacuum pump was attached to the delivery line and was used for fine control of vapor delivery to the 138 mg/m^3 chamber. An exposure shutoff valve, mounted in series with each chamber metering valve, stopped vapor delivery to each chamber. Vapor was diverted to the exposure chamber exhaust until the generation system was stable and exposures were initiated. To begin the exposures, the exposure valves were opened to allow the flow of vapor through chamber metering valves and into individual temperature-controlled delivery lines to the exposure chamber. The vapor was then injected into the chamber inlet duct where it was further diluted with conditioned chamber air to achieve the desired exposure concentration.

The study laboratory designed the inhalation exposure chamber (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m^3. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used during the 2-week and 3-month studies and a condensation particle counter (Model 3022A, TSI Inc., St. Paul, MN) was used during the 2-year studies with and without animals in the exposure chambers to ensure that Stoddard solvent IIC vapor, and not aerosol, was produced. There were no appreciable or consistent differences between particle measurements before or during the exposure period.

Vapor Concentration Monitoring

The Stoddard solvent IIC concentrations in the exposure chambers were monitored by an online gas chromatograph. Samples were drawn from each exposure chamber approximately every 24 minutes using a 12-port stream select valve (VALCO Instruments Company, Houston, TX). The online gas chromatograph was checked throughout the day for instrument drift against an on-line standard of an approximately 400 mg/m^3 mixture of the *n*-paraffins decane, undecane, and dodecane in nitrogen supplied by a diffusion tube standard generator (Model 491, Kin-Tek, La Marque, TX). The on-line gas chromatograph was calibrated monthly or when excessive calibration drift was detected by a comparison of chamber concentration data to data from grab samples, which were collected with charcoal sampling tubes (ORBO-101, Supelco, Bellefonte, PA). Grab samples were extracted with hexanes containing nonane as an internal standard and analyzed by an off-line gas chromatograph. Known volumes of chamber atmosphere from each chamber were sampled at a constant flow rate ensured by a calibrated critical orifice. The off-line gas chromatograph was calibrated with gravimetrically prepared standards of Stoddard solvent IIC and an internal standard (nonane) in hexanes.

The composition of Stoddard solvent IIC in the 2,200 mg/m^3 exposure chamber was monitored by a second on-line gas chromatograph in the 3-month and 2-year studies. Samples were drawn from the exposure chamber five or six times during each 6-hour exposure period using a 12-port stream select valve. The on-line gas chromatograph was checked against the on-line standard after exposure termination. The composition monitor provided enhanced chromatographic separation of the components and allowed reporting of the relative amounts of the major *n*-paraffins of Stoddard solvent IIC. Mean results for decane, undecane, and dodecane of 100.1%, 100.0%, and 99.9%, respectively, during the 2-year studies indicated that the composition of Stoddard solvent IIC did not change significantly during exposure.

Chamber Atmosphere Characterization

Buildup and decay rates for chamber vapor concentrations were determined with animals present in the chambers. At a chamber airflow rate of 15 air changes per hour, the theoretical value for the time to achieve 90% of the target concentration after the beginning of vapor generation (T_{90}) and the time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated (T_{10}) was approximately 12.5 minutes. Based on experimental data, a T_{90} value of 12 minutes was selected for all studies.

The uniformity and persistence of Stoddard solvent IIC vapor concentrations in the inhalation exposure chambers and Stoddard solvent IIC degradation products were evaluated throughout the study using GC. Chamber concentration uniformity was maintained; no evidence of

degradation was found, and no extraneous peaks were seen. Stoddard solvent IIC was stable for 273 days in the generator reservoir.

2-Week Studies

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY). On receipt, the rats and mice were approximately 4 weeks old. Animals were quarantined for 12 days and were approximately 6 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 control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix L). Groups of five male and five female rats and mice were exposed to Stoddard solvent IIC at concentrations of 0, 138, 275, 550, 1,100, or 2,200 mg/m^3, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 16 (rats) or 17 (mice) days. Feed was available *ad libitum* except during exposure periods; water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded daily. The 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.

Necropsies were performed on all rats and mice. The heart, right kidney, liver, lung, right testis, and thymus were weighed. Histopathologic examinations were performed on all rats and mice. Table 1 lists the tissues and organs examined.

3-Month Studies

The 3-month studies were conducted to evaluate the cumulative toxic effects of repeated exposure to Stoddard solvent IIC and to determine the appropriate exposure concentrations to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services. On receipt, the rats and mice were 3 to 4 weeks old. Animals were quarantined for 13 (males) or 14 (females) days and were 5 to 6 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 control rats and mice using the protocols of the NTP Sentinel Animal Program (Appendix L).

Groups of 10 male and 10 female rats and mice were exposed to Stoddard solvent IIC at concentrations of 0, 138, 275, 550, 1,100, or 2,200 mg/m^3, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 14 weeks. Feed was available *ad libitum* except during exposure periods; water was available *ad libitum*. Rats and mice were housed individually. Clinical findings were recorded weekly for rats and mice. The core study 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.

Animals were anesthetized with carbon dioxide, and blood was collected from the retroorbital sinus of clinical pathology rats on days 3 and 23 and from core study rats at the end of the study for hematology and clinical chemistry analyses. Blood was collected from the supraorbital sinus of mice at the end of the study for hematology analyses. The animals were anesthetized with a mixture of carbon dioxide in room air. Samples for hematology analyses were placed in microcollection tubes containing potassium EDTA; samples for clinical chemistry evaluations were placed in similar tubes containing a separator gel and without coagulant. Packed cell volume; hemoglobin concentration; erythrocyte, platelet, and leukocyte counts; mean cell volume; mean cell hemoglobin; and mean cell hemoglobin concentration were determined with a Roche Cobas Helios (Roche Diagnostics, Branchburg, NJ). Manual hematocrit values were determined using a Damon/IEC MB microcentrifuge (International Equipment Company, Needham Heights, MA) and capillary reader (Damon IEC) for comparison to Cobas values for packed cell volume. A Miller disc was used to determine reticulocyte counts from smears prepared with blood stained with new methylene blue. Due to the small blood volumes obtained on days 3 and 23 from rats, leukocyte differentials were counted manually from blood smears prepared and stained using a Wescor Aerospray 7100 slide stainer (Wescor, Inc., Logan, UT). Leukocyte differential counts in rats at terminal sacrifice were performed using the Roche Cobas Helios. For clinical chemistry analyses, serum samples were analyzed using Roche Cobas Fara methodologies. The parameters measured are listed in Table 1.

At the end of the 3-month studies, samples were collected for sperm count and motility and vaginal cytology evaluations on core study rats and mice exposed to 0, 550, 1,100, or 2,200 mg/m^3. The parameters evaluated are listed in Table 1. For 12 consecutive days prior to scheduled terminal sacrifice, females were subjected to vaginal lavage; the vaginal fluid and cells obtained were placed on a slide and stained with toluidine blue. Relative numbers of leukocytes, nucleated epithelial cells, and large squamous epithelial cells were determined and used to ascertain estrous cycle stage (i.e., diestrus, proestrus, estrus, and metestrus). Male animals were evaluated for sperm count and motility. The left testis and left epididymis were isolated and weighed, and the left testis was frozen in liquid nitrogen. Modified Tyrode's buffer (mice) or 80 µL of test yolk (rats) was applied to slides on a 37° C slide warmer and a small incision was made at the distal border of the cauda epididymis. The sperm effluxing from the incision were dispersed in the buffer on the slides, and the numbers of motile and nonmotile spermatozoa were counted for five fields per slide by two observers. Following completion of sperm motility estimates, each left cauda epididymis was placed in 37° C buffered saline solution and finely minced. After 15 minutes of incubation, an aliquot of the sperm suspension was placed in a tube and the sperm killed by heat or formalin for determination of sperm density. To quantify spermatogenesis, the testicular spermatid head count was determined by removing the tunica albuginea and homogenizing the left testis in phosphate-buffered saline containing 10% dimethyl sulfoxide. Homogenization-resistant spermatid nuclei were counted with a hemacytometer.

Necropsies were performed on all core study animals. The heart, right kidney, liver, lung, 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 4 to 6 µm, and stained with hematoxylin and eosin. Complete histopathologic examinations were performed on 0 and 2,200 mg/m^3 core study rats and mice; the kidney (rats), larynx, lung, nose, spleen (female mice), and trachea were examined in the remaining exposure groups. Table 1 lists the tissues and organs routinely examined.

2-Year Studies

Study Design

Groups of 50 male and 50 female rats and mice were exposed to Stoddard solvent IIC at concentrations of 0, 138 (male rats), 550, 1,100, or 2,200 (mice and female rats) mg/m^3, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 105 weeks. Additional groups of 10 male and 10 female rats were exposed to the same concentrations for 13 weeks for renal toxicity analyses.

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services for use in the 2-year studies. Core study rats were quarantined for 11 days and renal toxicity study rats for 12 days before the beginning of the studies; mice were quarantined for 13 days. Five male and five female rats and mice were randomly selected for parasite evaluation and gross observation of disease. 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 L).

Animal Maintenance

Rats and mice were housed individually. Feed was available *ad libitum* except during exposure periods; water was available *ad libitum*. Chambers and racks were rotated weekly. Further details of animal maintenance are given in Table 1. Information on feed composition and contaminants is provided in Appendix K.

Renal Toxicity Study

Osmotic pumps containing 30 mg/mL bromodeoxyuridine (BrdU) were implanted subcutaneously in the renal toxicity study rats on the Sunday before the 13th week of exposure; the animals were sacrificed on Friday of the 13th week. The duodenum, kidneys, and the portion of the tail with identification were removed from each rat; the remaining carcass was discarded. The kidneys were weighed, and α2u-globulin concentration and cell proliferation analyses were performed. For α2u-globulin assessment, the right kidney was frozen in liquid

nitrogen and stored at –70° C pending analysis. After thawing, a volume of sodium/potassium phosphate buffer (pH 7.2) equivalent to twice the recorded fresh weight of the sample was added, and the sample was homogenized using a tissue homogenizer (Tekmar Co., Cincinnati, OH). The homogenate was centrifuged at 3,000 g for 15 minutes at 4° C, and the supernatant was drawn off and stored at –70° C. The protein content of each supernatant was measured in a 1:50 dilution in PBS-Tween using a pyrogallol red assay.

Homogenates were analyzed for α2u-globulin using a competitive indirect ELISA technique. Ascites fluid containing anti-α2u-globulin monoclonal antibodies was provided by Dr. Susan J. Borghoff. The amount of α2u-globulin was measured by comparing the relative fluorescent signal intensity in the study samples to that observed with known amounts of α2u-globulin present in calibration standards. Calibration standards and ELISA control standards (negative and positive) were plated in predetermined wells on 96-well microtiter plates. Calibration standards and study samples were assayed in triplicate.

For cell proliferation analyses, the left kidney (bisected longitudinally) and a piece of duodenum were removed, fixed in 10% neutral buffered formalin for 24 hours and then transferred to 70% ethanol for 24 hours. The tissues were then processed, embedded in paraffin, and stained immunohistochemically. Cell proliferation assessment was done using a 20× objective and ocular grid; labeled and unlabeled tubular nuclei were counted from each kidney. The duodenum section was examined first for positive BrdU staining in crypts. Then counting started at the second grid in from the outer edge of the cortex of the kidney. After one grid was counted, the slide was moved toward the medulla and every other field encountered by the grid was counted. If 2,000 proximal tubular nuclei were reached before the entire grid had been counted, the remainder of the grid was counted. If 2,000 proximal tubular nuclei were not counted by the time the outer medulla was reached, the slide was moved two grids laterally and the counting process resumed at the second grid in from the edge of the cortex.

In addition to the cell proliferation assessment, sections of the left kidney and duodenum were stained with hematoxylin and eosin and with Mallory-Heidenhain stains. These sections were evaluated microscopically for evidence of renal toxicity.

Clinical Examinations and Pathology

All animals were observed twice daily. Animals were weighed at the beginning of the studies. Clinical findings and body weights were recorded every 4 weeks from week 5 through 89 and every 2 weeks from week 92 to the end of the studies.

Complete necropsies and microscopic examinations were performed on all core study rats and mice. At necropsy, all organs and tissues were examined for grossly visible lesions, and all major tissues were fixed and preserved in 10% neutral buffered formalin, processed and trimmed, embedded in paraffin, sectioned to a thickness of 4 to 6 µm, and stained with hematoxylin and eosin for microscopic examination. For all paired organs (e.g., adrenal gland, kidney, ovary), samples from each organ were examined. To perform an extended evaluation of renal tubular proliferative lesions, additional sections of both kidneys in the residual formalin-fixed wet tissues from each male rat were imbedded in separate paraffin blocks and step sectioned at 1 mm intervals. Three (left kidney) or four (right kidney) sections were examined from each kidney. 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 evaluated slides from all tumors and all potential target organs, which included the adrenal medulla, heart, kidney, liver, nose, preputial gland, and spleen in male rats; the clitoral gland, liver, mammary gland, and nose in female rats; the liver and skin in male and female mice, and the small intestine in male mice.

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 pathologists, 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. 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).

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Stoddard Solvent IIC

2-Week Studies	3-Month Studies	2-Year Studies
Study Laboratory		
Battelle Northwest Operations (Richland, WA)	Battelle Toxicology Northwest (Richland, WA)	Battelle Toxicology Northwest (Richland, WA)
Strain and Species		
F344/N rats $B6C3F_1$ mice	F344/N rats $B6C3F_1$ mice	F344/N rats $B6C3F_1$ mice
Animal Source		
Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)	Taconic Laboratory Animals and Services (Germantown, NY)
Time Held Before Studies		
12 days	Male rats and mice: 13 days Female rats and mice: 14 days	Rats: 11 (core study) or 12 (renal toxicity study) days Mice: 13 days
Average Age When Studies Began		
6 weeks	5 to 6 weeks	6 weeks
Date of First Exposure		
November 9, 1997	Male rats and mice: February 9, 1998 Female rats and mice: February 10, 1998	Rats: January 18 (core study) or 19 (renal toxicity study), 1999 Mice: December 21, 1998
Duration of Exposure		
6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 16 (rats) or 17 (mice) days	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 14 weeks	6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 104 to 105 weeks
Date of Last Exposure		
Rats: November 24, 1997 Mice: November 25, 1997	Rats: May 11 (males) or 12 (females), 1998 Mice: May 13 (males) or 14 (females), 1998	Rats: January 17, 2001 Mice: December 20, 2000
Necropsy Dates		
Rats: November 25, 1997 Mice: November 26, 1997	Rats: May 12 (males) or 13 (females), 1998 Mice: May 14 (males) or 15 (females), 1998	Rats: January 15-18, 2001 Mice: December 18-19 (males) or 19-21 (females), 2000
Average Age at Necropsy		
8 weeks	18 to 19 weeks	110 weeks
Size of Study Groups		
5 males and 5 females	10 males and 10 females	Core study: 50 males and 50 females Renal toxicity: 10 males and 10 females
Method of Distribution		
Animals were distributed randomly into groups of approximately equal initial mean body weights.	Same as 2-week studies	Same as 2-week studies
Animals per Cage		
1	1	1

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Stoddard Solvent IIC

2-Week Studies	3-Month Studies	2-Year Studies
Method of Animal Identification		
Tail tattoo	Tail tattoo	Tail tattoo
Diet		
Irradiated NTP-2000 open formula pelleted diet (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure periods, changed weekly	Same as 2-week studies	Same as 2-week studies
Water		
Tap water (Richland municipal supply) via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*	Same as 2-week studies	Same as 2-week studies
Cages		
Stainless steel wire-bottom (Hazleton System Inc., Aberdeen, MD), changed weekly	Same as 2-week studies	Stainless steel wire-bottom (Lab Products, Inc., Seaford, DE), changed weekly
Chamber Air Supply Filters		
Single HEPA (Northland Filter System International, Mechanicville, NY), charcoal (RSE, Inc., New Baltimore, MI), Purafil (Environmental Systems, Lynnwood, WA)	Same as 2-week studies	Single HEPA (Environmental Filter, Santa Rosa, CA), charcoal (RSE, Inc., New Baltimore, MI), Purafil (Environmental Systems, Lynnwood, WA)
Chambers		
Stainless steel with excreta pan suspended below each cage unit (Lab Products, Inc., Aberdeen, MD), changed weekly	Same as 2-week studies	Same as 2-week studies
Chamber Environment		
Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour	Temperature: 72° ± 3° F Relative humidity: 50% ± 15% Room fluorescent light: 12 hours/day Chamber air changes: 15/hour
Exposure Concentrations		
0, 138, 275, 550, 1,100, or 2,200 mg/m^3	0, 138, 275, 550, 1,100, or 2,200 mg/m^3	0, 138 (male rats), 550, 1,100, or 2,200 mg/m^3 (female rats and male and female mice)
Type and Frequency of Observation		
Observed twice daily; animals were weighed initially, weekly, and at the end of the studies; clinical findings were recorded daily.	Observed twice daily; core study animals were weighed initially, weekly, and at the end of the studies; clinical findings were recorded weekly and at the end of the studies.	Observed twice daily; body weights were recorded on day 1, and clinical findings and body weights were recorded every 4 weeks from week 5 through 89 and every 2 weeks from week 92 to the end of the studies.
Method of Sacrifice		
Carbon dioxide asphyxiation	Same as 2-week studies	Same as 2-week studies
Necropsy		
Necropsies were performed on all animals. Organs weighed were the heart, right kidney, liver, lung, right testis, and thymus.	Necropsies were performed on all core study animals. Organs weighed were the heart, right kidney, liver, lung, right testis, and thymus.	Necropsies were performed on all core study animals.

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Stoddard Solvent IIC

2-Week Studies	3-Month Studies	2-Year Studies
Clinical Pathology		
None	Blood was collected from the retroorbital sinus of clinical pathology rats on days 3 and 23 and from core study rats at the end of the study for hematology and clinical chemistry; blood was collected from the supraorbital sinus of mice at the end of the study for hematology. ***Hematology:*** hematocrit; packed cell volume; hemoglobin; erythrocyte, reticulocyte, platelet, and leukocyte counts; reticulocyte, erythrocyte, and nucleated erythocyte/leukocyte ratios; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; and leukocyte differentials ***Clinical chemistry:*** urea nitrogen, creatinine, total protein, albumin, globulin; albumin/globulin ratio, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, bile acids, and hemolysis	None
Histopathology		
In addition to gross lesions and tissue masses, the following tissues were examined in all rats and mice: kidney, larynx, liver, lungs, sciatic nerve, and trachea.	Complete histopathology was performed on 0 and 2,200 mg/m^3 core study rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gall bladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung with mainstem bronchi, lymph nodes (mandibular, mesenteric, bronchial, and mediastinal), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus. The larynx, lung, nose, and trachea of rats and mice; kidney of rats; and spleen of female mice were also examined in the remaining exposure groups.	Complete histopathology was performed on all core study rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, eye, gall bladder (mice), harderian gland, heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular, mesenteric, bronchial, and mediastinal), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, skin, spinal cord, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

TABLE 1
Experimental Design and Materials and Methods in the Inhalation Studies of Stoddard Solvent IIC

2-Week Studies	3-Month Studies	2-Year Studies
Sperm Motility and Vaginal Cytology		
None	At the end of the studies, sperm samples were collected from male core study animals in the 0, 550, 1,100, and 2,200 mg/m^3 groups for sperm count and motility evaluations. The following parameters were evaluated: spermatid heads per testis, per gram testis, per cauda and per gram cauda, and epididymal spermatozoal motility. The left cauda, left epididymis, and left testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from core study females exposed to 0, 550, 1,100, or 2,200 mg/m^3 for vaginal cytology evaluations. The percentage of time spent in the various estrous cycle stages and estrous cycle length were evaluated.	None
Renal Toxicity Study		
None	None	At 13 weeks, concentrations of α2u-globulin and soluble protein were measured in the right kidney of renal toxicity study rats; left kidneys were used for assessment of cell proliferation indices and histopathologic examination.

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 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 are presented in Tables A1, A5, B1, B4, C1, C5, D1, and D5 as the numbers of animals bearing such lesions at a specific anatomic site and the numbers 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., harderian gland, intestine, mammary gland, and skin) 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. This survival-adjusted rate (based on the Poly-3 method described below) accounts for differential mortality by assigning a reduced risk of neoplasm, proportional to the third power of the fraction of time on study, to animals that do not reach terminal sacrifice.

Analysis of Neoplasm and Nonneoplastic Lesion Incidences

The Poly-k test (Bailer and Portier, 1988; Portier and Bailer, 1989; Piegorsch and Bailer, 1997) was used to assess neoplasm and nonneoplastic lesion prevalence. This test is a survival-adjusted quantal-response procedure that modifies the Cochran-Armitage linear trend test to take survival differences into account. More specifically, this method modifies the denominator in the quantal estimate of lesion incidence to approximate more closely the total number of animal years at risk. For analysis of a given site, each animal is assigned a risk weight. This value is one if the animal had a lesion at that site or if it survived until terminal sacrifice; if the animal died prior to terminal sacrifice and did not have a lesion at that site, its risk weight is the fraction of the entire study time that it survived, raised to the kth power.

This method yields a lesion prevalence rate that depends only upon the choice of a shape parameter for a Weibull hazard function describing cumulative lesion incidence over time (Bailer and Portier, 1988). Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. This value was recommended by Bailer and Portier (1988) following an evaluation of neoplasm onset time distributions for a variety of site-specific neoplasms in control F344 rats and B6C3F$_1$ mice (Portier *et al.,* 1986). Bailer and Portier (1988) showed that the Poly-3 test gave valid results if the true value of k was anywhere in the range from 1 to 5. A further advantage of the Poly-3 method is that it does not require lesion lethality assumptions. Variation introduced by the use of risk weights, which reflect differential mortality, was accommodated by adjusting the variance of the Poly-3 statistic as recommended by Bieler and Williams (1993).

Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Continuity-corrected Poly-3 tests were used in the analysis of lesion incidence, and reported P values are one sided. The significance of lower incidences or decreasing trends in lesions is represented as 1– P with the letter N added (e.g., P=0.99 is presented as P=0.01N).

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 historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Hematology, clinical chemistry, renal toxicity, spermatid, and epididymal spermatozoal data, which have typically skewed distributions, were analyzed using the nonparametric multiple comparison methods of Shirley (1977) (as modified by Williams, 1986) 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 statistical 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 with the Mann-Whitney U test (Hollander and Wolfe, 1973). Because vaginal cytology data are proportions (the proportion of the observation period that an animal was in a given estrous stage), an arcsine transformation was used to bring the data into closer conformance with a normality assumption. Treatment effects were investigated by applying a multivariate analysis of variance (Morrison, 1976) to the transformed data to test for simultaneous equality of measurements across exposure concentrations.

Historical Control Data

The concurrent control group represents the most valid comparison to the treated groups and is the only control group analyzed statistically in NTP bioassays. However, historical control data are often helpful in interpreting potential treatment-related effects, particularly for uncommon or rare neoplasm types. For meaningful comparisons, the conditions for studies in the historical database must be generally similar. One significant factor affecting the background incidence of neoplasms at a variety of sites is diet. In 1995, the NTP incorporated a new diet (NTP-2000) that contains less protein and more fiber and fat than the NIH-07 diet previously used in toxicity and carcinogenicity studies (Rao, 1996, 1997). The current NTP historical database contains all 21 studies that use the NTP-2000 diet with histopathology findings completed up to the present. A second potential source of variability is route of administration. In general, the historical database for a given study will include studies using the same route of administration, and the overall incidences of neoplasms for all routes of administration are included for comparison.

Quality Assurance Methods

The 3-month 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 covered completeness and accuracy of the pathology data, pathology specimens, final pathology tables, and a draft of this NTP Technical Report. 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, and all comments were resolved or otherwise addressed during the preparation of this Technical Report.

Genetic Toxicology

The genetic toxicity of Stoddard solvent IIC was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium* and increases in the frequency of micronucleated erythrocytes in mouse peripheral blood. The protocols for these studies and the results are given in Appendix E.

The genetic toxicity studies have evolved from an earlier effort by the NTP to develop a comprehensive database permitting a critical anticipation of a chemical's carcinogenicity in experimental animals based on numerous considerations, including the molecular structure of the chemical and its observed effects in short-term *in vitro* and *in vivo* genetic toxicity tests (structure-activity relationships). The short-term tests were originally developed to clarify proposed mechanisms of chemical-induced DNA damage based on the relationship between electrophilicity and mutagenicity (Miller and Miller, 1977) and the somatic mutation theory of cancer (Straus, 1981; Crawford, 1985). However, it should be noted that not all cancers arise through genotoxic mechanisms.

DNA reactivity combined with *Salmonella* mutagenicity is highly correlated with induction of carcinogenicity in multiple species/sexes of rodents and at multiple tissue sites (Ashby and Tennant, 1991). A positive response in the *Salmonella* test was shown to be the most predictive *in vitro* indicator for rodent carcinogenicity (89% of the *Salmonella* mutagens are rodent carcinogens) (Tennant *et al.,* 1987; Zeiger *et al.,* 1990). Additionally, no battery of tests that included the *Salmonella* test improved the predictivity of the *Salmonella* test alone. However, these other tests can provide useful information on the types of DNA and chromosomal damage induced by the chemical under investigation.

The predictivity for carcinogenicity of a positive response in acute *in vivo* bone marrow chromosome aberration or micronucleus tests appears to be less than that in the *Salmonella* test (Shelby *et al.,* 1993; Shelby and Witt, 1995). However, clearly positive results in long-term peripheral blood micronucleus tests have high predictivity for rodent carcinogenicity (Witt *et al.,* 2000); negative results in this assay do not correlate well with either negative or positive results in rodent carcinogenicity studies. Because of the theoretical and observed associations between induced genetic damage and adverse effects in somatic and germ cells, the determination of *in vivo* genetic effects is important to the overall understanding of the risks associated with exposure to a particular chemical. Most organic chemicals that are identified by the International Agency for Research on Cancer as human carcinogens, other than hormones, are genotoxic. The vast majority of these are detected by both the *Salmonella* assay and rodent bone marrow cytogenetics tests (Shelby, 1988; Shelby and Zeiger, 1990).

RESULTS

RATS

2-WEEK STUDY

All rats survived to the end of the study, and final mean body weights and body weight gains of all exposed groups were similar to those of the chamber control groups (Table 2). There were no clinical findings related to Stoddard solvent IIC exposure.

Absolute and relative liver weights of 550 mg/m^3 males, relative liver weights of 1,100 and 2,200 mg/m^3 males, and absolute and relative liver weights of 275 mg/m^3 or greater females were significantly increased (Table H1); relative kidney weights of exposed females were also increased. Minimal diffuse cytoplasmic vacuolization of hepatocytes of the liver occurred in one chamber control female and in all 2,200 mg/m^3 females (data not presented).

Exposure Concentration Selection Rationale: Because there were no effects of Stoddard solvent IIC on survival or body weights of male and female rats in the 2-week study, exposure concentrations selected for the 3-month inhalation study were 0, 138, 275, 550, 1,100, and 2,200 mg/m^3.

TABLE 2
Survival and Body Weights of Rats in the 2-Week Inhalation Study of Stoddard Solvent IIC

Concentration (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	73 ± 1	144 ± 3	71 ± 2	
138	5/5	72 ± 1	141 ± 4	69 ± 4	98
275	5/5	73 ± 1	144 ± 2	71 ± 3	100
550	5/5	75 ± 2	147 ± 2	72 ± 2	102
1,100	5/5	72 ± 1	146 ± 3	75 ± 3	102
2,200	5/5	72 ± 1	145 ± 2	73 ± 2	101
Female					
0	5/5	69 ± 1	116 ± 1	47 ± 2	
138	5/5	69 ± 1	116 ± 4	47 ± 3	100
275	5/5	66 ± 2	116 ± 2	50 ± 2	99
550	5/5	69 ± 1	117 ± 2	49 ± 1	101
1,100	5/5	68 ± 2	115 ± 2	47 ± 2	99
2,200	5/5	68 ± 1	115 ± 3	47 ± 1	99

[a] Number of animals surviving at 2 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test.

3-Month Study

All rats survived to the end of the study (Table 3). The final mean body weight of 275 mg/m^3 females was greater than that of the chamber controls. There were no clinical findings related to Stoddard solvent IIC exposure.

Clinical pathology data for rats are listed in Table F1. An exposure concentration-related decrease in alanine aminotransferase activity occurred in males and females at most time points. These changes may reflect a change in enzyme metabolism/catabolism or release by the liver or enzyme inhibition. At day 3, a transient increase in total serum bile acid concentration occurred in exposed females; by day 23, concentrations were similar to that of the chamber controls. In males, a minimal decrease in the erythron, evidenced by small decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts, occurred at study termination in the 2,200 mg/m^3 group; the decrease in the erythron was a minimal effect and was not considered toxicologically relevant. At day 3, transient, minimal increases in creatinine (males and females), total protein (males), and albumin (males) concentrations occurred in the 550 mg/m^3 or greater groups. The increases were likely related to a transient decrease in circulating plasma volume and were not considered significant.

The relative kidney, liver, and testis weights of all exposed groups of males and the absolute kidney weights of 550 mg/m^3 or greater males were significantly increased (Table H2). The sperm motility of 550 mg/m^3 or greater males was significantly decreased (Table I1).

Table 3
Survival and Body Weights of Rats in the 3-Month Inhalation Study of Stoddard Solvent IIC

Concentration (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	76 ± 3	324 ± 7	248 ± 7	
138	10/10	75 ± 3	318 ± 6	243 ± 5	98
275	10/10	80 ± 3	322 ± 4	243 ± 5	100
550	10/10	80 ± 3	322 ± 6	241 ± 6	99
1,100	10/10	75 ± 2	322 ± 6	247 ± 5	99
2,200	10/10	76 ± 3	305 ± 6	229 ± 6	94
Female					
0	10/10	71 ± 4	170 ± 4	99 ± 3	
138	10/10	74 ± 4	183 ± 2	109 ± 4	107
275	10/10	74 ± 4	189 ± 4**	114 ± 5	111
550	10/10	73 ± 3	177 ± 4	104 ± 4	104
1,100	10/10	72 ± 3	183 ± 4	111 ± 5	107
2,200	10/10	68 ± 4	178 ± 3	109 ± 4	104

** Significantly different (P≤0.01) from the chamber control group by Dunnett's test
[a] Number of animals surviving at 3 months/number initially in group
[b] Weights and weight changes are given as mean ± standard error.

Gross observations at necropsy included pale capsular surface of the kidney in 1,100 and 2,200 mg/m^3 males. The incidences of renal tubule granular casts were significantly increased in 550 mg/m^3 or greater males (Table 4). The severities of granular casts, renal tubule hyaline droplet accumulation, and regeneration increased with increasing exposure concentration, and these lesions are consistent with α2u-globulin nephropathy in male rats. Hyaline droplets were rounded or occasionally angular, eosinophilic cytoplasmic deposits in renal tubule epithelial cells of the cortex and were accompanied by granular casts and tubular regeneration. Renal tubule regeneration was characterized by cortical tubular epithelial cells that were uniformly basophilic, cuboidal to flattened, and variably surrounded by thickened basement membranes. Granular casts consisted of compact, lightly eosinophilic, granular debris that filled the enlarged lumens of medullary renal tubules. Granular casts and renal tubule regeneration are considered secondary to injury caused by the formation of hyaline droplets.

The incidences of goblet cell hypertrophy of the nasal respiratory epithelium in 2,200 mg/m^3 males and females and 1,100 mg/m^3 females were significantly increased (Table 4). This lesion was characterized by larger and more abundant goblet cells covering the nasal septum in Level I and surrounding the vomeronasal organ in Level II.

Exposure Concentration Selection Rationale: In male rats, granular casts in renal medullary tubules, hyaline droplets in cortical tubules, and cortical tubule regenerative hyperplasia were caused by Stoddard solvent IIC exposure. Granular casts and tubule regeneration are indicative of renal tubule epithelium damage. Based on the severity of these changes in male rats exposed to 2,200 mg/m^3 and the likelihood that progression of the renal lesions would exacerbate the typical age-related onset of nephropathy in male Fischer rats, exposure concentrations selected for the 2-year study in male rats were 0, 138, 550, and 1,100 mg/m^3; 0, 550, 1,100, and 2,200 mg/m^3 were selected for female rats because few effects occurred in females at exposure concentrations up to 2,200 mg/m^3 in the 3-month study.

TABLE 4
Incidences of Selected Nonneoplastic Lesions in Rats in the 3-Month Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Male						
Kidney[a]	10	10	10	10	10	10
Medulla, Renal Tubule, Casts Granular[b]	0	0	1 (1.0)[c]	4* (1.0)	10** (1.7)	10** (3.0)
Renal Tubule, Accumulation, Hyaline Droplet	10 (1.3)	10 (2.4)	10 (3.1)	10 (3.1)	10 (3.6)	10 (3.6)
Cortex, Renal Tubule, Regeneration	8 (1.0)	8 (1.1)	10 (1.1)	10 (1.5)	10 (1.7)	10 (1.9)
Nose	10	10	10	10	9	10
Goblet Cell, Respiratory Epithelium, Hypertrophy	2 (1.0)	2 (1.0)	2 (1.0)	2 (1.0)	4 (1.5)	7* (1.9)
Female						
Nose	10	10	10	10	10	10
Goblet Cell, Respiratory Epithelium, Hypertrophy	0	1 (2.0)	1 (1.0)	0	4* (1.0)	9** (1.7)

* Significantly different (P≤0.05) from the chamber control group by the Fisher exact test
** P≤0.01
[a] Number of animals with tissue examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

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 138 and 1,100 mg/m^3 males and 2,200 mg/m^3 females was significantly less than that of the chamber controls.

Body Weights and Clinical Findings

Mean body weights of exposed groups of males and females were similar to those of the chamber control groups throughout the study (Figure 2; Tables 6 and 7). There were no clinical findings related to Stoddard solvent IIC exposure.

TABLE 5
Survival of Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

Male	**Chamber Control**	**138 mg/m^3**	**550 mg/m^3**	**1,100 mg/m^3**
Animals initially in study	50	50	50	50
Moribund	18	27	21	27
Natural deaths	3	4	8	7
Animals surviving to study termination	29	19	21	16
Percent probability of survival at end of study[a]	58	38	42	32
Mean survival (days)[b]	701	659	676	666
Survival analysis[c]	P=0.057	P=0.014	P=0.125	P=0.007

Female	**Chamber Control**	**550 mg/m^3**	**1,100 mg/m^3**	**2,200 mg/m^3**
Animals initially in study	50	50	50	50
Moribund	12	19	15	23
Natural deaths	2	1	3	2
Animals surviving to study termination	36	30	32	25
Percent probability of survival at end of study	72	60	64	50
Mean survival (days)	696	693	697	670
Survival analysis	P=0.037	P=0.331	P=0.576	P=0.040

[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 chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns.

TABLE 6
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

Weeks on Study	Chamber Control		138 mg/m^3			550 mg/m^3			1,100 mg/m^3		
	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	105	50	103	98	50	104	99	50	104	99	50
5	225	50	227	101	50	231	103	50	229	102	50
9	292	50	297	102	50	299	102	50	295	101	50
13	337	50	339	101	50	343	102	50	337	100	50
17	367	50	365	100	50	369	101	50	364	99	50
21	388	50	386	100	50	393	101	50	388	100	50
25	410	50	406	99	50	411	100	50	408	99	50
29	424	50	420	99	50	428	101	50	423	100	50
33	438	50	432	99	50	440	100	50	435	100	50
37	450	50	446	99	50	452	101	50	450	100	50
41	460	50	455	99	50	462	101	50	459	100	50
45	471	50	464	99	50	472	100	50	469	100	50
49	477	50	472	99	50	480	101	50	478	100	50
53	483	50	480	99	50	487	101	50	485	100	50
57	494	50	485	98	50	495	100	49	492	100	50
61	502	50	494	99	48	501	100	49	496	99	50
65	505	50	498	99	48	508	101	49	498	99	49
69	511	49	503	99	47	512	100	49	501	98	48
73	519	49	510	98	47	517	100	49	503	97	48
77	523	49	511	98	47	521	100	47	509	97	46
81	524	49	511	98	46	524	100	43	503	96	44
85	531	48	513	97	42	528	99	42	505	95	41
89	534	45	505	95	41	531	99	40	510	96	38
92	531	44	495	93	35	526	99	38	504	95	37
94	526	44	498	95	29	531	101	36	508	97	33
96	516	42	496	96	25	523	101	36	502	97	32
98	522	38	507	97	20	526	101	33	502	96	27
100	523	35	504	96	20	519	99	31	502	96	23
102	522	34	502	96	20	517	99	27	497	95	20
104	521	30	496	95	20	509	98	22	503	97	16
Mean for weeks											
1-13	240		242	101		244	102		241	100	
14-52	432		427	99		434	100		430	100	
53-104	517		500	97		516	100		501	97	

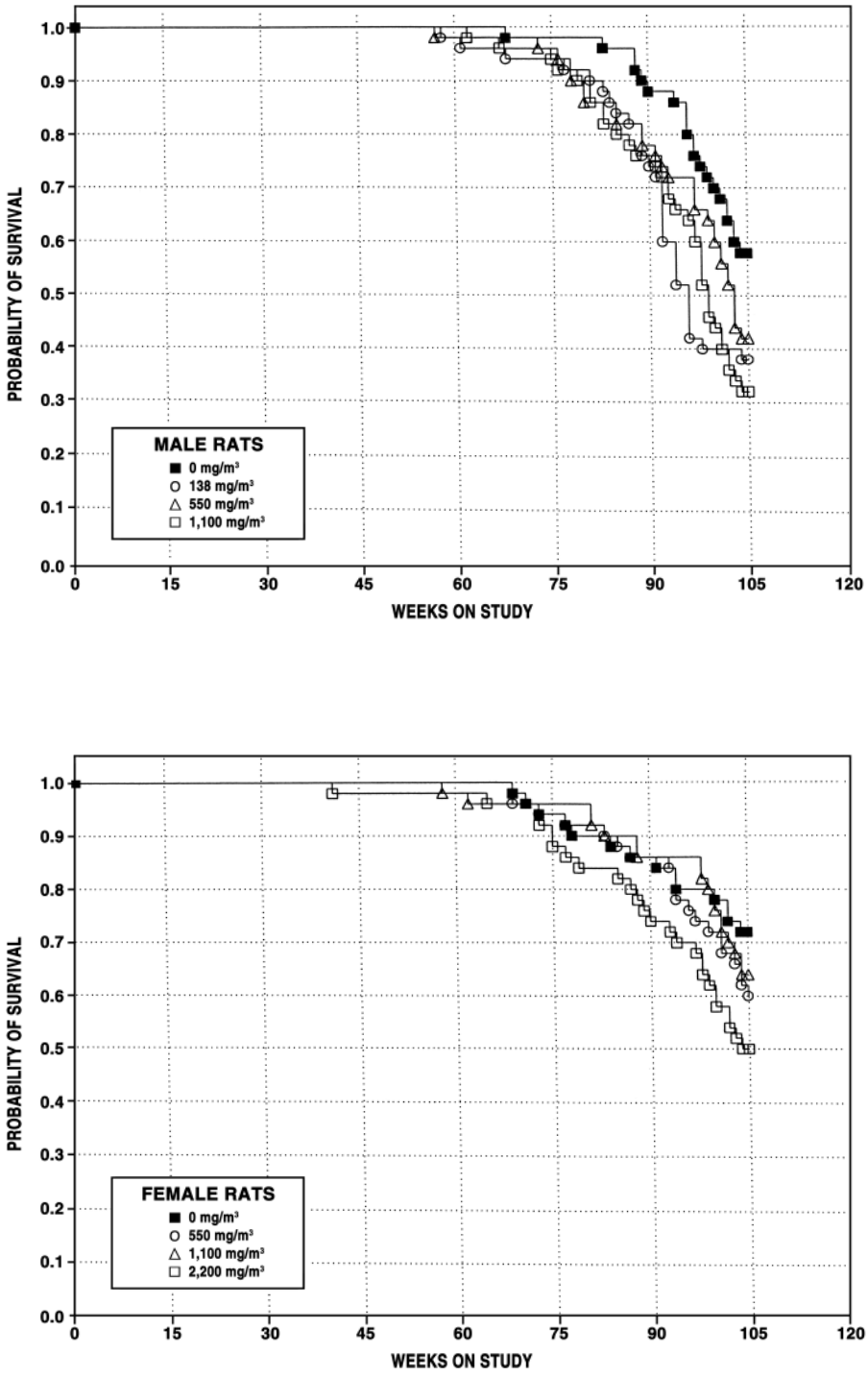

FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Stoddard Solvent IIC by Inhalation for 2 Years

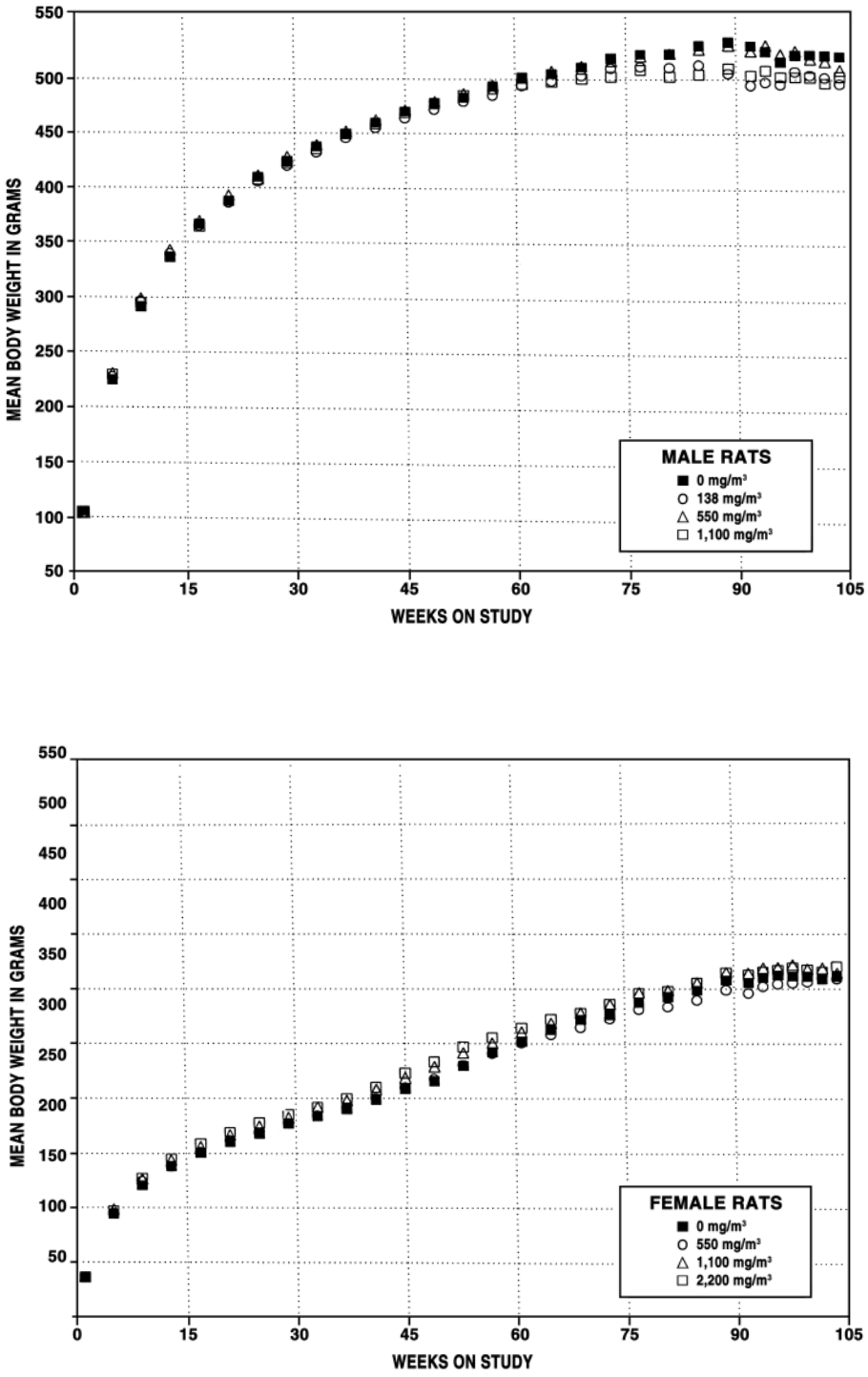

FIGURE 2
Growth Curves for Male and Female Rats Exposed to Stoddard Solvent IIC by Inhalation for 2 Years

TABLE 7
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

Weeks on Study	Chamber Control		550 mg/m^3			1,100 mg/m^3			2,200 mg/m^3		
	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	87	50	87	100	50	87	100	50	87	100	50
5	145	50	145	100	50	149	103	50	147	102	50
9	171	50	174	102	50	176	103	50	177	104	50
13	188	50	188	100	50	194	103	50	195	104	50
17	201	50	201	100	50	206	103	50	209	104	50
21	211	50	212	101	50	217	103	50	219	104	50
25	218	50	218	100	50	225	103	50	228	104	50
29	227	50	228	100	50	233	102	50	236	104	50
33	234	50	235	100	50	242	104	50	242	103	50
37	241	50	242	101	50	249	103	50	250	104	50
41	249	50	250	101	50	258	104	50	260	105	50
45	259	50	260	100	50	269	104	50	273	105	49
49	266	50	268	101	50	279	105	50	283	107	49
53	280	50	280	100	50	292	104	50	297	106	49
57	292	50	291	100	50	300	103	50	306	105	49
61	302	50	301	100	50	311	103	49	314	104	49
65	313	50	308	99	50	319	102	48	322	103	48
69	322	50	315	98	50	328	102	48	328	102	48
73	326	48	323	99	47	336	103	48	337	103	47
77	338	47	331	98	47	347	103	48	346	103	44
81	343	45	333	97	46	349	102	47	348	102	42
85	349	44	340	97	45	356	102	45	356	102	41
89	358	43	349	98	43	365	102	43	365	102	39
92	356	42	346	97	43	365	102	43	363	102	37
94	361	42	352	98	41	369	102	43	366	102	36
96	363	40	355	98	39	370	102	43	368	101	35
98	362	40	356	98	37	372	103	41	370	102	32
100	362	40	356	99	36	369	102	39	368	102	29
102	360	39	360	100	34	369	103	35	366	102	29
104	362	36	359	99	33	365	101	33	371	103	25
Mean for weeks											
1-13	148		149	101		152	103		152	103	
14-52	234		235	100		242	103		244	104	
53-104	338		333	99		346	102		347	103	

Renal Toxicity Study

In the satellite groups, cell proliferation analyses were performed on the left kidney of males and females after 3 months of exposure (Table G1). The mean numbers of labeled cells and the labeling indices in 550 and 1,100 mg/m^3 males were significantly increased. The labeling index in 1,100 mg/m^3 males was significantly greater than that in the 550 mg/m^3 group, suggesting an exposure concentration-related increase in renal cell proliferation in exposed males. No significant differences in labeling indices were noted in females; however, the labeling indices in all exposed groups of females were lower than that in the male chamber control group.

Concentrations of soluble protein and α2u-globulin were measured in the right kidney of males and females (Table G1). The concentration of soluble protein in kidney homogenates was increased in 138 mg/m^3 males and 2,200 mg/m^3 females; however, there were no exposure concentration-related increases in males or in other groups of females. The amount of α2u-globulin was normalized to either soluble protein concentration or kidney weight. In males, the amount of α2u-globulin increased with increasing exposure concentration; the amounts of α2u-globulin in 550 and 1,100 mg/m^3 males were significantly greater than that in the chamber controls. The concentration of α2u-globulin (nmol/g kidney) was increased in 2,200 mg/m^3 females.

Microscopic lesions occurred in male left kidneys at 3 months (Table 8). Hyaline droplets occurred in all chamber control and all exposed males; the severity increased with increasing exposure concentration. The incidences of granular casts in 550 and 1,100 mg/m^3 males, cortical tubule degeneration in 1,100 mg/m^3 males, and cortical tubule regeneration in 550 and 1,100 mg/m^3 males were significantly increased. Though apparent with the hematoxylin and eosin stain, hyaline droplets were most visible in the sections stained with Mallory-Heidenhain. The droplets were bright pink to magenta and were within proximal convoluted tubules. Granular casts were characterized by distended tubular lumens filled with cellular debris and proteinaceous material and are indicative of cell death and believed to result from epithelial cells damaged by excessive accumulations of α2u-globulin. The hyaline droplets and granular casts are consistent with α2u-globulin nephropathy. Degeneration was a minimal lesion of the cortical tubular epithelium characterized by pyknotic nuclei, shrunken eosinophilic cytoplasm, and loss of cell membranes and may have been a component of the α2u-globulin nephropathy. Regeneration was characterized by tubules lined by the epithelial cells with basophilic cytoplasm and enlarged nuclei. Regeneration of renal tubule epithelium is an early component of chronic progressive nephropathy, a common spontaneous syndrome in F344/N rats, particularly in males.

TABLE 8
Incidences of Nonneoplastic Lesions of the Kidney in Male Rats Exposed to Stoddard Solvent IIC for 3 Months

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Number Examined Microscopically	10	10	10	10
Hyaline Droplets[a]	10 (1.1)[b]	10 (1.9)	10 (2.6)	10 (2.9)
Granular Casts	0	0	8**(1.0)	10**(1.7)
Cortical Tubule Degeneration	0	0	2 (1.0)	6**(1.0)
Cortical Tubule Regeneration	3 (1.0)	4 (1.0)	9**(1.2)	10**(1.7)

** Significantly different (P≤0.01) from the chamber control group by the Fisher exact test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of neoplasms and nonneoplastic lesions of the adrenal medulla, clitoral and preputial glands, kidney, and nose. Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary neoplasms that occurred with an incidence of at least 5% in at least one animal group, and historical incidences for the neoplasms mentioned in this section are presented in Appendix A for male rats and Appendix B for female rats.

Adrenal Medulla: The incidences of benign and benign or malignant pheochromocytoma (combined) occurred with positive trends in males, and the incidences in the 550 and 1,100 mg/m^3 groups were significantly increased (Tables 9 and A3). The incidences of benign pheochromocytoma in 550 and 1,100 mg/m^3 males and benign or malignant pheochromocytoma in 1,100 mg/m^3 males exceeded the historical ranges in chamber controls (Tables 9 and A4). Benign pheochromocytomas were characterized by a proliferating mass of adrenal medullary cells that compressed adjacent tissue. Malignant pheochromocytomas were generally larger with invasion of or beyond the adrenal capsule.

The incidence of hyperplasia of the adrenal medulla in 550 mg/m^3 males was significantly increased (Tables 9 and A5). Medullary hyperplasia was characterized by an increase in basophilia of medullary cells that sometimes accompanied increased size and minimal compression of the adjacent tissue.

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Adrenal Medulla in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Number Examined Microscopically	50	50	50	50
Hyperplasia[a]	12 (2.5)[b]	14 (2.6)	23**(2.6)	15 (2.2)
Benign Pheochromocytoma, Bilateral	0	1	1	4
Benign Pheochromocytoma (includes bilateral)[c]				
Overall rate[d]	5/50 (10%)	9/50 (18%)	13/50 (26%)	17/50 (34%)
Adjusted rate[e]	11.0%	22.9%	29.9%	41.6%
Terminal rate[f]	3/29 (10%)	5/19 (26%)	5/21 (24%)	7/16 (44%)
First incidence (days)	626	605	541	652
Poly-3 test[g]	P<0.001	P=0.117	P=0.022	P<0.001
Malignant Pheochromocytoma	1	0	0	2
Benign or Malignant Pheochromocytoma[h]				
Overall rate	6/50 (12%)	9/50 (18%)	13/50 (26%)	19/50 (38%)
Adjusted rate	13.1%	22.9%	29.9%	45.8%
Terminal rate	3/29 (10%)	5/19 (26%)	5/21 (24%)	7/16 (44%)
First incidence (days)	626	605	541	565
Poly-3 test	P<0.001	P=0.185	P=0.044	P<0.001

** Significantly different (P≤0.01) from the chamber control group by the Poly-3 test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year inhalation studies with chamber controls given NTP-2000 diet (mean ± standard deviation): 42/298 (14.1% ± 6.7%), range 8%-24%
[d] Number of animals with neoplasm per number of animals with adrenal medulla examined microscopically
[e] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[f] Observed incidence at terminal kill
[g] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[h] Historical incidence: 48/298 (16.1% ± 7.0%), range 10%-28%

Clitoral and Preputial Glands: The incidences of adenoma and adenoma or carcinoma (combined) of the clitoral gland occurred with positive trends in females (Tables 10 and B3). The incidences of adenoma in the 1,100 and 2,200 mg/m^3 groups and adenoma or carcinoma (combined) in the 2,200 mg/m^3 group were significantly increased. However, the incidences were within the historical ranges in chamber controls for adenoma [20/295 (7% ± 6%), range 0%-17%] and adenoma or carcinoma (combined) [24/295 (8% ± 6%), range 2%-19%]. The incidence of adenoma or carcinoma (combined) of the preputial gland in 550 mg/m^3 males was significantly increased; however, the incidence was within the historical range [11/298 (4% ± 5%), range 0%-13%] (Tables 10 and A3). The incidences of clitoral and preputial gland hyperplasia were not significantly increased (Tables 10, A5, and B4). Proliferative lesions of the clitoral and preputial glands comprise a morphologic continuum from hyperplasia (a preneoplastic lesion) to adenoma and carcinoma. These lesions are separated based on cytologic features and the degree of altered growth patterns. Clitoral and preputial gland hyperplasia was characterized by an increased number of sebaceous cells with normal cell orientation and morphology forming crowded large acini, often associated with cyst formation. In hyperplasia, the cell cytoplasm is more basophilic and less vacuolated. Because the incidence of clitoral gland adenoma in chamber control females was low (0%) compared to historical chamber controls (6.8%), the incidences in exposed females were within the historical control range, and because of the absence of exposure-related hyperplasia and carcinoma, the increased incidences of clitoral gland adenoma were not considered chemical related. The increased incidence of preputial gland adenoma or carcinoma (combined) was also not exposure related.

TABLE 10
Incidences of Neoplasms and Nonneoplastic Lesions of the Clitoral and Preputial Glands in Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

Female	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Clitoral Gland[a]	49	50	50	50
Hyperplasia[b]	2 (2.0)[c]	3 (3.0)	3 (2.0)	1 (2.0)
Adenoma[d]				
Overall rate[e]	0/49 (0%)	3/50 (6%)	5/50 (10%)	6/50 (12%)
Adjusted rate[f]	0.0%	6.8%	11.1%	14.6%
Terminal rate[g]	0/35 (0%)	3/30 (10%)	4/32 (13%)	4/25 (16%)
First incidence (days)	—[i]	730 (T)	682	606
Poly-3 test[h]	P=0.011	P=0.119	P=0.033	P=0.012
Carcinoma	1	2	1	1
Adenoma or Carcinoma[j]				
Overall rate	1/49 (2%)	5/50 (10%)	6/50 (12%)	7/50 (14%)
Adjusted rate	2.3%	11.4%	13.3%	16.9%
Terminal rate	1/35 (3%)	5/30 (17%)	5/32 (16%)	4/25 (16%)
First incidence (days)	730 (T)	730 (T)	682	606
Poly-3 test	P=0.029	P=0.102	P=0.060	P=0.024

Male	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Preputial Gland	50	50	50	50
Hyperplasia	1 (3.0)	1 (4.0)	0	2 (2.5)
Adenoma	0	1	2	1
Carcinoma	0	1	3	0
Adenoma or Carcinoma[k]	0	2	5*	1

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with clitoral or preputial gland examined microscopically
[b] Number of animals with lesion
[c] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[d] Historical incidence for 2-year inhalation studies with chamber controls given NTP-2000 diet (mean ± standard deviation): 20/295 (6.8% ± 6.1%), range 0%-17%
[e] Number of animals with neoplasm per number of animals with tissue examined microscopically
[f] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[g] Observed incidence at terminal kill
[h] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[i] Not applicable; no neoplasms in animal group
[j] Historical incidence: 24/295 (8.2% ± 5.9%), range 2%-19%
[k] Historical incidence: 11/298 (3.8% ± 5.0%), range 0%-13%

Kidney: In the standard evaluation of a single hematoxylin and eosin stained section of the left and right kidney, the incidences of mild to moderate renal tubule and transitional epithelial hyperplasia in 550 and 1,100 mg/m^3 males were significantly increased (Tables 11 and A4). The incidences of renal tubule adenoma and renal tubule carcinoma in exposed groups of male rats were similar to those in the chamber controls at the standard evaluation. Renal tubule hyperplasia, adenoma, and carcinoma are thought to represent a continuum in the progression of proliferative lesions of the renal tubule epithelium. Because there were increased incidences of renal tubule hyperplasia (a preneoplastic lesion) in male rats, additional kidney sections were evaluated, and additional renal tubule hyperplasias and adenomas were identified. In the extended evaluation, the significantly increased incidences of renal tubule hyperplasia in 550 and 1,100 mg/m^3 males were confirmed. In the extended evaluation, the incidence of renal tubule adenoma was greater in 1,100 mg/m^3 males than in the chamber controls, however, the increase was not significant (Table 11); the incidences of renal tubule carcinoma in exposed groups of males were similar to that in the chamber control group.

Renal tubule hyperplasia was generally focal solid or cystic masses composed of tubules that were dilated two to four times normal diameter and were lined by increased numbers of epithelial tubule cells that partially or totally filled the tubule lumen. Renal tubule adenomas were large, discrete lesions that ranged from greater than five tubule diameters to 1 mm or more in size. They often consisted of a solid mass of large, relatively normal appearing, closely packed tubular epithelial cells. Cells within adenomas were mildly to moderately pleomorphic, sometimes had vacuolated cytoplasm, and tended to form complex patterns, particularly slightly dilated microtubular structures. Renal tubule carcinomas were differentiated from adenomas in that they usually were larger, were less discrete, had a prominent vascular supply, and had more anaplasia and cellular atypia. These carcinomas also were characterized by vesiculated nuclei with prominent nucleoli and increased numbers of mitotic figures.

Transitional epithelial hyperplasia was characterized by small papillary fronds or masses of normal appearing transitional epithelial cells that were several layers thick and lined the renal papilla. Transitional epithelial hyperplasia overlying the renal papilla frequently accompanies severe nephropathy, and the increased incidences of epithelial hyperplasia in the current study may reflect the enhanced nephropathy.

In males, the severity of chronic nephropathy of the kidney and the incidences and severity of mineralization increased with increasing exposure concentration. Nephropathy is an age-related disease process characterized by a spectrum of lesions, including varying degrees of tubular dilation; proteinaceous tubular casts; atrophy, degeneration, regeneration, and hypertrophy of the tubular epithelium; thickening of tubular and glomerular basement membranes; glomerulosclerosis; interstitial fibrosis; and varying numbers and aggregates of mononuclear inflammatory cells within the interstitium. Minimal nephropathy was characterized by a few scattered foci of tubular regeneration. These regenerative tubules had increased numbers of more intensely stained basophilic cells. Basement membranes, both in glomeruli and around tubules, were slightly thickened. As nephropathy became more severe, tubular dilatation, proteinaceous casts, and interstitial fibrosis were evident. Mineralization was characterized by the presence of lamellated intraluminal or intracellular concretions within the collecting tubules of the renal papilla usually forming linear deposits. Mineralization of the renal medulla oriented in a linear fashion is characteristic of α2u-globulin inducers in 2-year studies, as is exacerbated nephropathy.

Nose: The incidences of olfactory epithelial hyaline degeneration were significantly increased in 138 mg/m^3 males (chamber control, 2/50; 138 mg/m^3, 8/50; 550 mg/m^3, 2/50; 1,100 mg/m^3, 3/50) and in 2,200 mg/m^3 females (chamber control, 12/49; 550 mg/m^3, 18/50; 1,100 mg/m^3, 15/49; 2,200 mg/m^3, 28/50) (Tables A5 and B4). Hyaline degeneration was characterized by large eosinophilic globules that filled the cytoplasm of olfactory epithelial cells. This degeneration is a common age-related change in the nasal passages of rats that is often exacerbated during inhalation studies. Because of the variation in the incidences of degeneration in the current study, the biological significance of Stoddard solvent IIC exposure is unclear.

TABLE 11
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Number Examined Microscopically	50	50	50	50
Single Sections (Standard Evaluation)				
Renal Tubule, Hyperplasia[a]	0	1 (3.0)[b]	8**(2.3)	23**(2.4)
Pelvis, Transitional Epithelium, Hyperplasia	0	2 (2.0)	8**(2.1)	5* (3.0)
Nephropathy, Chronic	50 (2.0)	49 (2.3)	50 (2.5)	50 (2.8)
Papilla, Mineralization	1 (1.0)	8**(1.1)	30**(1.9)	39**(2.2)
Renal Tubule Adenoma	0	0	1	0
Renal Tubule Carcinoma	1	0	0	1
Step Sections (Extended Evaluation)				
Renal Tubule, Hyperplasia	4	3	19**	17**
Pelvis, Transitional Epithelium, Hyperplasia	0	0	0	2
Renal Tubule Adenoma (includes multiple)				
Overall rate[c]	3/50 (6%)	2/50 (4%)	2/50 (4%)	7/50 (14%)
Adjusted rate[d]	6.6%	5.1%	4.8%	17.5%
Terminal rate[e]	1/29 (3%)	0/19 (0%)	1/21 (5%)	1/16 (6%)
First incidence (days)	621	636	673	667
Poly-3 test[f]	P=0.041	P=0.569N	P=0.541N	P=0.110
Renal Tubule Carcinoma	1	0	0	0
Pelvis, Transitional Epithelium, Carcinoma	0	0	1	0
Single Sections and Step Sections (Combined)				
Renal Tubule, Hyperplasia	4	4	25**	27**
Pelvis, Transitional Epithelium, Hyperplasia	0	2	8**	6*
Renal Tubule Adenoma (includes multiple)				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	7/50 (14%)
Adjusted rate	6.6%	5.1%	7.1%	17.5%
Terminal rate	1/29 (3%)	0/19 (0%)	1/21 (5%)	1/16 (6%)
First incidence (days)	621	636	509	667
Poly-3 test	P=0.039	P=0.569N	P=0.628	P=0.110
Renal Tubule Carcinoma	1	0	0	1
Pelvis, Transitional Epithelium, Carcinoma	0	0	1	0

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
** $P \leq 0.01$
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Number of animals with neoplasm per number of animals with kidney examined microscopically
[d] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[e] Observed incidence at terminal kill
[f] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.

MICE

2-WEEK STUDY

All mice survived to the end of the study, and final mean body weights and body weight gains of all exposed groups were similar to those of the chamber control groups (Table 12). There were no clinical findings related to Stoddard solvent IIC exposure.

Liver weights of 275 mg/m^3 or greater males and females and relative kidney weights of 1,100 and 2,200 mg/m^3 females were significantly increased (Table H3). Cytomegaly of the liver occurred in all 2,200 mg/m^3 males and females (data not presented).

Exposure Concentration Selection Rationale: Because there were no effects of Stoddard solvent IIC on survival or body weights of male and female mice in the 2-week study, exposure concentrations selected for the 3-month inhalation study were 0, 138, 275, 550, 1,100, and 2,200 mg/m^3.

TABLE 12
Survival and Body Weights of Mice in the 2-Week Inhalation Study of Stoddard Solvent IIC

Concentration (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	5/5	23.0 ± 0.2	27.9 ± 0.3	4.9 ± 0.2	
138	5/5	23.2 ± 0.2	27.2 ± 0.3	4.1 ± 0.4	98
275	5/5	22.6 ± 0.2	26.9 ± 0.5	4.3 ± 0.3	96
550	5/5	22.9 ± 0.3	26.9 ± 0.6	4.0 ± 0.4	97
1,100	5/5	22.9 ± 0.3	27.9 ± 0.4	5.0 ± 0.3	100
2,200	5/5	22.9 ± 0.3	27.1 ± 0.5	4.2 ± 0.4	97
Female					
0	5/5	19.4 ± 0.4	23.0 ± 0.4	3.7 ± 0.4	
138	5/5	19.4 ± 0.3	22.6 ± 0.5	3.3 ± 0.4	98
275	5/5	19.6 ± 0.4	23.7 ± 0.6	4.0 ± 0.3	103
550	5/5	19.2 ± 0.3	22.4 ± 0.5	3.2 ± 0.4	97
1,100	5/5	19.2 ± 0.2	22.7 ± 0.5	3.5 ± 0.5	98
2,200	5/5	19.5 ± 0.2	23.2 ± 0.3	3.8 ± 0.5	101

[a] Number of animals surviving at 2 weeks/number initially in group
[b] Weights and weight changes are given as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test.

3-Month Study

One 138 mg/m^3 male was killed moribund during week 6; all other mice survived to the end of the study (Table 13). Final mean body weights and body weight gains of exposed groups were similar to those of the chamber control groups. Clinical findings included thinness in exposed groups of males; however, surviving mice appeared normal by the end of the study.

There were no hematologic changes in males or females exposed to Stoddard solvent IIC for 3 months (Table F2).

Liver weights of 2,200 mg/m^3 males were significantly increased (Table H4). The sperm motility of 2,200 mg/m^3 males was significantly decreased (Table I3).

The incidences of hematopoietic cell proliferation of the spleen were significantly greater in all exposed groups of females than in the chamber controls (chamber control, 1/10; 138 mg/m^3, 8/10; 275 mg/m^3, 7/10; 550 mg/m^3, 7/10; 1,100 mg/m^3, 9/9; 2,200 mg/m^3, 9/10). This lesion was characterized by the presence of random foci of dense, basophilic, round nuclei consistent with red blood cell precursors in the splenic parenchyma.

Exposure Concentration Selection Rationale: The only biologically significant findings related to exposure in the 3-month study were increases in liver weights of 2,200 mg/m^3 males; however, there were no corresponding histopathologic lesions. Furthermore, there were no exposure-related effects on survival or body weights. Therefore, the exposure concentrations selected for the 2-year inhalation study were 0, 550, 1,100, and 2,200 mg/m^3.

Table 13
Survival and Body Weights of Mice in the 3-Month Inhalation Study of Stoddard Solvent IIC

Concentration (mg/m^3)	Survival[a]	Mean Body Weight[b] (g)			Final Weight Relative to Controls (%)
		Initial	Final	Change	
Male					
0	10/10	23.2 ± 0.3	38.0 ± 0.5	14.8 ± 0.5	
138	9/10[c]	23.4 ± 0.3	37.5 ± 0.5	14.3 ± 0.5	99
275	10/10	23.5 ± 0.3	38.4 ± 0.6	15.0 ± 0.5	101
550	10/10	23.2 ± 0.3	37.9 ± 0.6	14.7 ± 0.6	100
1,100	10/10	23.7 ± 0.3	38.6 ± 1.0	14.9 ± 0.9	101
2,200	10/10	23.6 ± 0.4	37.2 ± 0.8	13.6 ± 0.5	98
Female					
0	10/10	19.6 ± 0.3	31.9 ± 1.0	12.3 ± 1.0	
138	10/10	19.3 ± 0.4	29.5 ± 0.6	10.3 ± 0.4	93
275	10/10	19.2 ± 0.3	31.8 ± 1.3	12.6 ± 1.2	100
550	10/10	19.6 ± 0.2	31.7 ± 0.7	12.1 ± 0.7	100
1,100	10/10	19.7 ± 0.2	32.3 ± 1.2	12.6 ± 1.2	101
2,200	10/10	19.9 ± 0.3	33.3 ± 0.8	13.4 ± 0.7	105

[a] Number of animals surviving at 3 months/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. Differences from the chamber control group are not significant by Dunnett's test.
[c] Week of death: 6

2-YEAR STUDY

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 14 and in the Kaplan-Meier survival curves (Figure 3). Survival of exposed groups of mice was similar to that of the chamber control groups.

Body Weights and Clinical Findings

Mean body weights of exposed groups of males were similar to those of the chamber controls throughout the study. Mean body weights of 550 and 1,100 mg/m^3 females were generally greater than those of the chamber controls after week 17 of the study, and those of 2,200 mg/m^3 females were greater during the second year of the study. (Figure 4; Tables 15 and 16). Clinical findings included ulcer/abscess of the ventral torso in chamber control and exposed males.

TABLE 14
Survival of Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Male				
Animals initially in study	50	50	50	50
Accidental death[a]	0	0	1	0
Moribund	7	9	16	13
Natural deaths	9	9	6	5
Animals surviving to study termination	34	32	27	32
Percent probability of survival at end of study[b]	68	64	55	64
Mean survival (days)[c]	690	686	667	682
Survival analysis[d]	P=0.690	P=0.860	P=0.320	P=0.791
Female				
Animals initially in study	50	50	50	50
Moribund	6	11	11	10
Natural deaths	8	5	12	6
Animals surviving to study termination	36	34	27	34
Percent probability of survival at end of study	72	68	54	68
Mean survival (days)	701	688	680	693
Survival analysis	P=0.757	P=0.715	P=0.104	P=0.845

[a] Censored from survival analyses
[b] Kaplan-Meier determinations
[c] Mean of all deaths (uncensored, censored, and terminal sacrifice).
[d] The result of the life table trend test (Tarone, 1975) is in the chamber control column, and the results of the life table pairwise comparisons (Cox, 1972) with the chamber controls are in the exposed group columns.

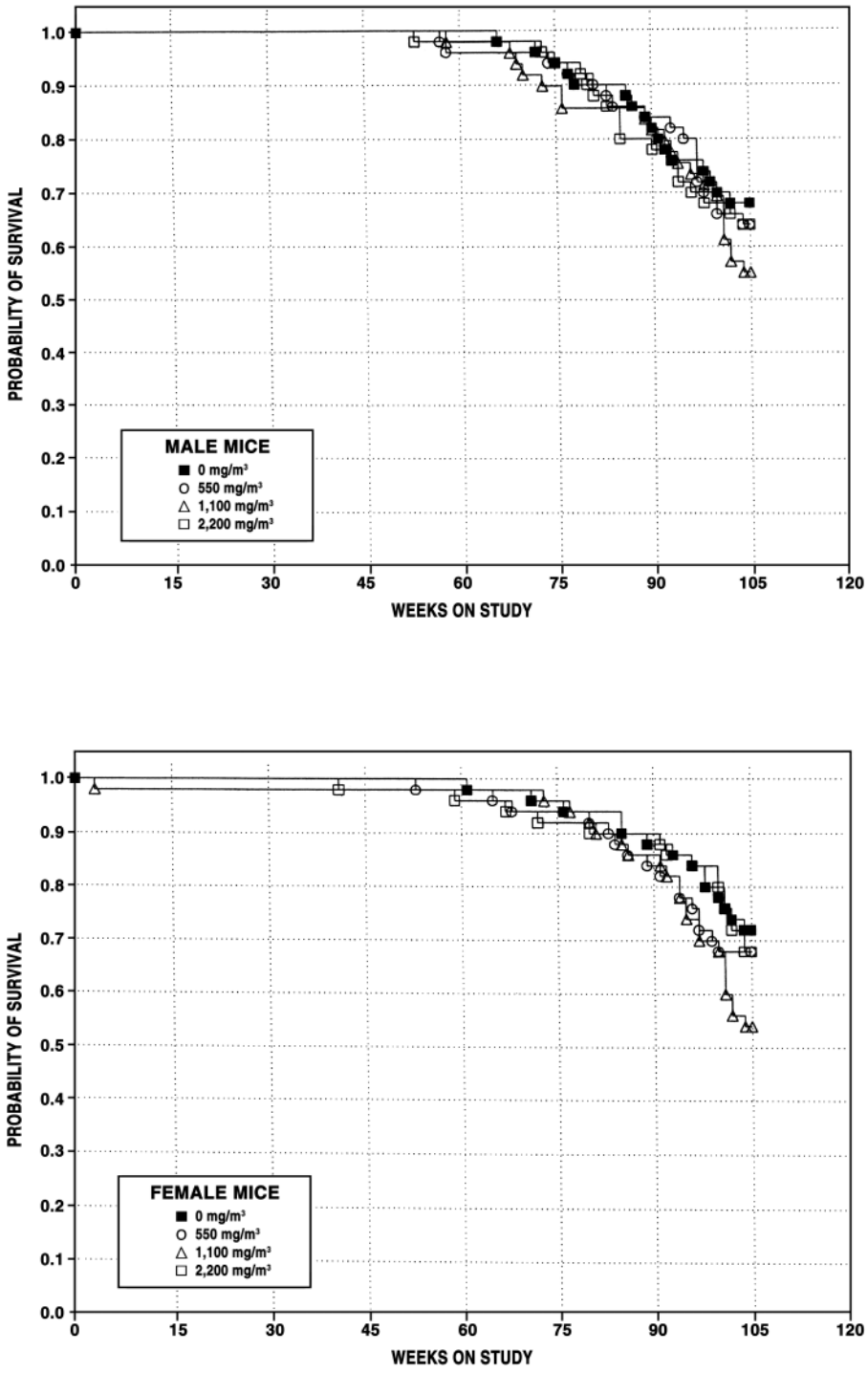

FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Stoddard Solvent IIC by Inhalation for 2 Years

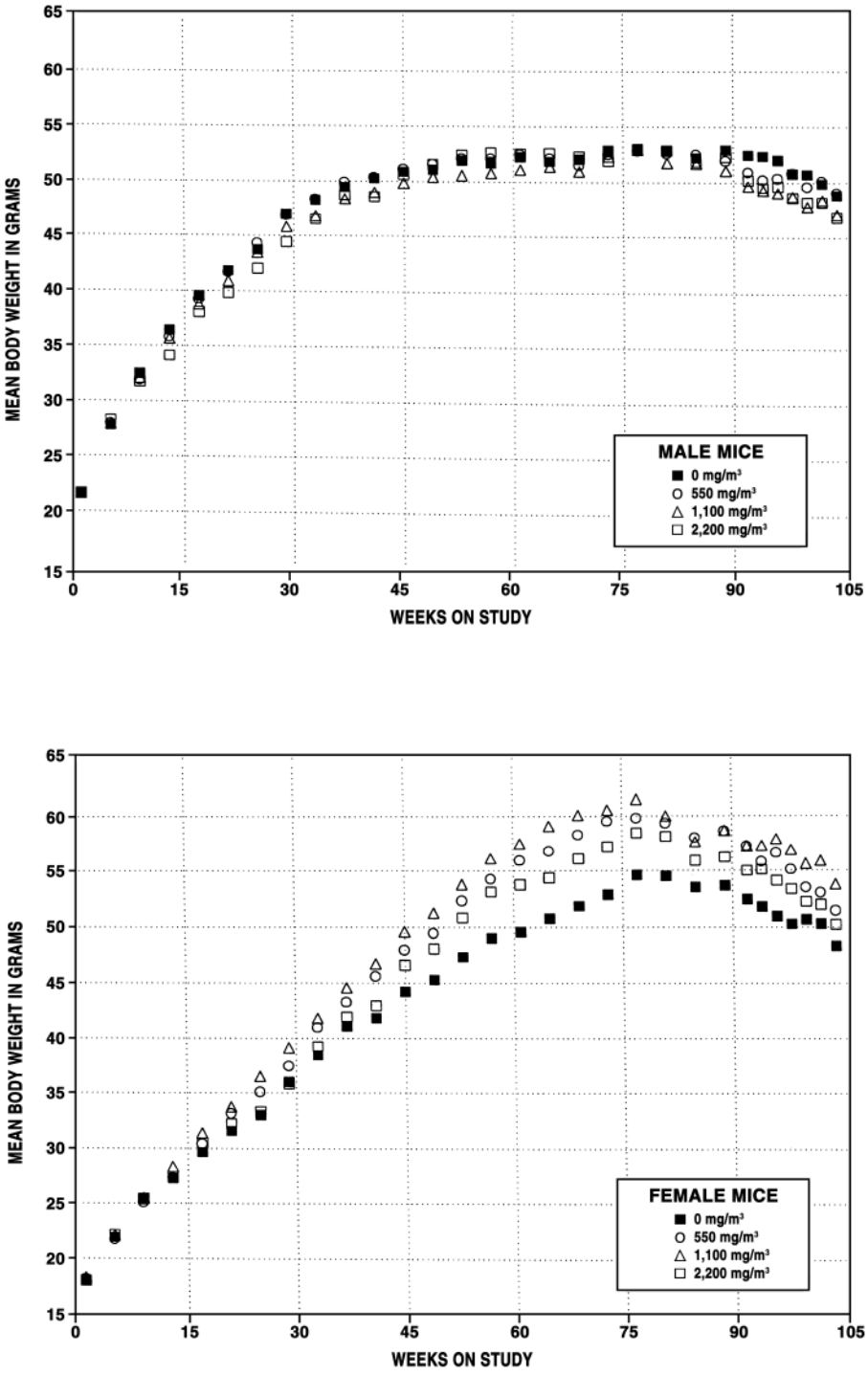

FIGURE 4
Growth Curves for Male and Female Mice Exposed to Stoddard Solvent IIC by Inhalation for 2 Years

TABLE 15
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

Weeks on Study	Chamber Control		550 mg/m^3			1,100 mg/m^3			2,200 mg/m^3		
	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	21.7	50	21.5	99	50	21.6	100	50	21.6	100	50
5	27.8	50	28.0	101	50	27.9	100	50	28.3	102	50
9	32.5	50	31.9	98	50	32.1	99	50	31.8	98	50
13	36.4	50	35.9	99	50	35.7	98	49	34.1	94	50
17	39.5	50	39.3	100	50	38.8	98	49	38.1	97	50
21	41.8	50	41.7	100	50	40.9	98	49	39.8	95	50
25	43.7	50	44.3	101	50	43.5	100	49	42.1	96	50
29	47.0	50	46.9	100	50	45.8	97	49	44.4	95	50
33	48.3	50	48.4	100	50	46.8	97	49	46.5	96	50
37	49.5	50	50.0	101	50	48.4	98	49	48.7	98	50
41	50.3	50	50.4	100	50	49.0	97	49	48.6	97	50
45	50.9	50	51.1	100	50	49.9	98	49	50.6	99	50
49	51.1	50	51.6	101	50	50.4	99	49	51.6	101	50
53	52.0	50	52.1	100	50	50.6	97	49	52.4	101	49
57	51.7	50	52.1	101	50	50.8	98	49	52.7	102	49
61	52.3	50	52.5	100	48	51.1	98	48	52.6	101	49
65	51.9	50	52.2	101	48	51.4	99	48	52.6	101	49
69	52.1	49	51.6	99	48	51.0	98	47	52.3	100	49
73	52.9	48	52.6	99	48	52.4	99	45	51.9	98	49
77	52.9	47	52.9	100	47	53.0	100	42	53.0	100	47
81	52.8	45	52.6	100	46	51.8	98	42	52.9	100	45
85	52.3	45	52.6	101	43	51.7	99	42	51.9	99	43
89	53.0	41	52.0	98	43	51.1	96	41	52.3	99	40
92	52.5	40	51.0	97	42	49.7	95	40	50.2	96	39
94	52.4	38	50.3	96	41	49.3	94	38	49.5	95	38
96	52.1	38	50.4	97	40	49.1	94	37	49.7	95	36
98	50.8	38	50.9	100	36	48.7	96	36	48.6	96	35
100	50.7	35	49.6	98	35	47.8	94	35	48.2	95	34
102	49.9	35	50.1	100	33	48.4	97	30	48.2	97	34
104	48.9	34	49.1	100	33	47.1	96	28	46.8	96	33
Mean for weeks											
1-13	29.6		29.3	99		29.3	99		29.0	98	
14-52	46.9		47.1	100		45.9	98		45.6	97	
53-104	51.8		51.4	99		50.3	97		50.9	98	

TABLE 16
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

Weeks on Study	Chamber Control		550 mg/m^3			1,100 mg/m^3			2,200 mg/m^3		
	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	18.0	50	18.2	101	50	18.3	102	50	17.9	99	50
5	21.9	50	21.7	99	50	22.1	101	49	22.1	101	50
9	25.4	50	25.1	99	50	25.6	101	49	25.5	100	50
13	27.3	50	27.4	100	50	28.4	104	49	27.4	100	50
17	29.7	50	30.4	102	50	31.4	106	49	30.5	103	50
21	31.6	50	33.2	105	50	33.8	107	49	32.2	102	50
25	33.0	50	35.1	106	50	36.5	111	49	33.3	101	50
29	36.0	50	37.5	104	50	39.1	109	49	35.8	99	50
33	38.5	50	41.0	107	50	41.8	109	49	39.2	102	50
37	41.1	50	43.3	105	50	44.6	109	49	42.0	102	50
41	41.9	50	45.7	109	50	46.8	112	49	43.0	103	50
45	44.2	50	48.0	109	50	49.6	112	49	46.6	105	49
49	45.3	50	49.5	109	50	51.3	113	49	48.1	106	49
53	47.4	50	52.4	111	50	53.8	114	49	50.9	107	49
57	49.0	50	54.3	111	49	56.1	115	49	53.1	108	49
61	49.6	50	56.0	113	49	57.5	116	49	53.8	109	48
65	50.8	49	56.8	112	49	59.1	116	49	54.4	107	48
69	51.9	49	58.3	112	47	60.1	116	49	56.1	108	47
73	52.9	48	59.6	113	47	60.5	114	49	57.2	108	46
77	54.6	47	59.8	110	47	61.5	113	48	58.5	107	46
81	54.5	47	59.4	109	46	60.0	110	46	58.2	107	45
85	53.5	47	58.0	108	44	57.7	108	45	55.9	105	45
89	53.7	45	58.6	109	43	58.7	109	43	56.2	105	45
92	52.5	44	57.3	109	41	57.3	109	42	55.0	105	44
94	51.8	43	55.8	108	41	57.3	111	40	55.1	106	43
96	51.0	43	56.7	111	38	57.9	114	37	54.1	106	43
98	50.3	42	55.2	110	36	56.9	113	35	53.4	106	42
100	50.7	39	53.5	106	35	55.7	110	35	52.2	103	41
102	50.3	37	53.1	106	34	55.9	111	29	52.0	103	36
104	48.3	37	51.5	107	34	53.8	111	28	50.2	104	36
Mean for weeks											
1-13	23.2		23.1	100		23.6	102		23.2	100	
14-52	37.9		40.4	107		41.7	110		39.0	103	
53-104	51.3		56.3	110		57.6	112		54.5	106	

Pathology and Statistical Analyses

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

Liver: The incidences of hepatocellular adenoma occurred with a positive trend in females, and the incidences of multiple hepatocellular adenoma in 2,200 mg/m^3 males and females were significantly increased; however, the incidences of adenoma or carcinoma (combined) and carcinoma alone in exposed males and females were not significantly increased (Tables 17, C3, and D3). The increased incidence of multiple hepatocellular adenoma in 2,200 mg/m^3 males was not considered related to Stoddard solvent IIC exposure because the incidences of all adenomas (including multiple) were not significantly increased in the exposed groups. The incidences of hepatocellular adenoma in 550 and 2,200 mg/m^3 males and 1,100 and 2,200 mg/m^3 females and of hepatocellular adenoma or carcinoma (combined) in 550 mg/m^3 males and 2,200 mg/m^3 females exceeded the historical ranges in chamber controls (Tables 17, C4, and D4); the incidences in chamber control males and 1,100 mg/m^3 females were at the upper end of the historical ranges. The adenomas were discrete masses with distinct borders that caused compression of the surrounding normal hepatic parenchyma. Adenomas were usually composed of hepatocytes that appeared similar to those seen in eosinophilic foci, except that in adenomas the normal lobular architecture was not apparent, and plates of neoplastic hepatocytes intersected the surrounding normal hepatocytes at sharp angles rather than merging with them as foci. Carcinomas were discrete masses that generally had irregular borders due to localized areas of growth of neoplastic hepatocytes into the surrounding normal parenchyma. The neoplastic hepatocytes often were somewhat atypical, but the major distinguishing features of carcinomas were the presence of abnormal patterns of growth. The most common abnormal growth pattern was formation of trabeculae of neoplastic hepatocytes that were three or more cell layers thick, while less commonly, the neoplastic cells formed glandular structures or solid masses.

The incidences of eosinophilic and basophilic focus of the liver in 1,100 mg/m^3 males and of eosinophilic focus in 2,200 mg/m^3 females were significantly increased (Tables 17, C5, and D5). Eosinophilic and basophilic foci were small to moderately large lesions composed of somewhat enlarged hepatocytes with eosinophilic or basophilic cytoplasm. The hepatocytes were arranged in normal hepatic cords that merged with the surrounding normal hepatocytes; some degree of compression was present in some larger foci.

Lung: The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) were decreased in exposed males, and the decrease in the 550 mg/m^3 group was significant (chamber control, 13/50; 550 mg/m^3, 4/49; 1,100 mg/m^3, 6/50; 2,200 mg/m^3, 6/50; Table C3). The incidence in the chamber controls was at the lower end of the historical range in chamber controls, and the incidences in the exposed groups were less than the historical range [85/250 (34% ± 7%), range 26%-44%]. It was uncertain if these decreased incidences were related to Stoddard solvent IIC exposure.

GENETIC TOXICOLOGY

Stoddard solvent IIC, tested over a concentration range of 33 to 10,000 ug/plate, was not mutagenic in *Salmonella typhimurium* tester strains TA97, TA98, TA100, or TA1535 with or without S9 metabolic activation enzymes (Table E1). *In vivo*, the frequency of micronucleated erythrocytes was assessed in peripheral blood samples obtained from male and female B6C3F$_1$ mice after 3 months of inhalation exposure to Stoddard solvent IIC over a concentration range of 138 to 2,200 mg/m^3; results of this test showed no indication of induced chromosomal damage in the form of micronuclei in either male or female mice (Table E2). Furthermore, there were no significant alterations in the percentages of polychromatic erythrocytes in either male or female mice over the concentration range tested, indicating an absence of notable toxicity to the bone marrow.

TABLE 17
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Male				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus[a]	5 (1.8)[b]	7 (2.1)	14* (2.2)	9 (1.9)
Basophilic Focus	9 (2.3)	13 (2.3)	17* (2.4)	11 (2.5)
Hepatocellular Adenoma, Multiple	10	12	7	18*
Hepatocellular Adenoma (includes multiple)[c]	23	28	21	29
Hepatocellular Carcinoma (includes multiple)	16	15	17	10
Hepatocellular Adenoma or Carcinoma[d]	34	37	30	32[e]
Female				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus	4 (2.3)	9 (2.5)	6 (2.5)	11* (2.2)
Hepatocellular Adenoma, Multiple	0	3	4	7*
Hepatocellular Adenoma (includes multiple)[f]				
Overall rate[g]	9/50 (18%)	12/50 (24%)	15/50 (30%)	18/50 (36%)
Adjusted rate[h]	19.5%	27.3%	33.8%	38.8%
Terminal rate[i]	5/36 (14%)	11/34 (32%)	7/27 (26%)	13/34 (38%)
First incidence (days)	590	578	600	465
Poly-3 test[j]	P=0.023	P=0.264	P=0.095	P=0.032
Hepatocellular Carcinoma (includes multiple)	6	7	5	6
Hepatocellular Adenoma or Carcinoma[k]				
Overall rate	13/50 (26%)	17/50 (34%)	18/50 (36%)	21/50 (42%)
Adjusted rate	28.0%	37.9%	40.3%	45.2%
Terminal rate	8/36 (22%)	13/34 (38%)	9/27 (33%)	15/34 (44%)
First incidence (days)	590	578	600	465
Poly-3 test	P=0.059	P=0.217	P=0.154	P=0.063

* Significantly different ($P \leq 0.05$) from the chamber control group by the Poly-3 test
[a] Number of animals with lesion
[b] Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked
[c] Historical incidence for 2-year inhalation studies with chamber controls given NTP-2000 diet (mean ± standard deviation): 95/250 (38.0% ± 6.8%), range 30%-46%
[d] Historical incidence: 139/250 (55.6% ± 7.3%), range 50%-68%
[e] A single incidence of hepatoblastoma occurred in an animal that also had a carcinoma.
[f] Historical incidence: 48/248 (19.4% ± 6.9%), range 12%-29%
[g] Number of animals with neoplasm per number of animals with liver examined microscopically
[h] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[i] Observed incidence at terminal kill
[j] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.
[k] Historical incidence: 72/248 (29.0% ± 6.8%), range 22%-37%

DISCUSSION AND CONCLUSIONS

Stoddard solvent is a mixture of numerous hydrocarbons derived from refining crude oil. It is a multipurpose petroleum solvent; a solvent in liquid photocopier toners; an agent in dry cleaning and paint, coating, and wax thinners; and is used in paints, printing inks, and adhesives (ACGIH, 1991). The Stoddard solvent mixture has three major components: linear and branched alkanes (paraffins) (30%-50%); cycloalkanes (30%-40%); and aromatic hydrocarbons (0%-20%). There are various types of Stoddard solvents with varying flash points and composition of linear alkanes, cycloalkanes, and aromatic hydrocarbons. There are four types of mineral spirit (Stoddard solvent): Type I, regular; Type II, high flash point; Type III, odorless; and Type IV, low dry point (ASTM, 1995). Stoddard solvent type IIC (high flash point, low aromatic grade) was nominated to the NTP by the International Union, United Auto Workers, for toxicity and carcinogenicity inhalation testing in rats and mice. The NTP conducted 2-week, 3-month, and 2-year inhalation studies of Stoddard solvent IIC vapors; the highest exposure concentration was 2,200 mg/m^3, which was the maximum vapor concentration that could be obtained.

In general, the current studies confirmed previous findings on Stoddard solvent IIC toxicity. Most of the studies found in the literature for short- and long-term toxicity identified the kidney and liver as the major target organs (Carpenter *et al.,* 1975a; Blair *et al.,* 1979; WHO, 1996).

In the current 3-month studies, species- and sex-specific differences were observed in exposure-related effects. Kidney effects occurred only in male rats; exposure-related kidney weight changes correlated with pathologic kidney changes. The most obvious lesion induced by Stoddard solvent IIC was granular casts in medullary tubules, which occurred in all 1,100 and 2,200 mg/m^3 males. Hyaline droplets in cortical tubules occurred in all male rats, and the severities of granular casts and hyaline droplets increased with increasing exposure concentration. The histopathologic changes indicated that exposure to Stoddard solvent IIC induced nephropathy in male rats.

Male and female rats were exposed to Stoddard solvent IIC for 3 months and evaluated for renal toxicity as part of the 2-year study. Results from cell proliferation indices and α2u-globulin assays were consistent with the increased incidences of hyaline droplets in the 3-month toxicity study. The morphologic characteristics of the chemical-induced lesions were similar to those of α2u-globulin nephropathies reported in male rats exposed to a diverse group of chemicals, including Stoddard solvent IIC (Phillips and Cockrell, 1984; Phillips and Egan, 1984; Hard *et al.,* 1993; Rodgers and Baetcke, 1993).

Clinical pathology data from the 3-month rat study suggested an exposure concentration-related decrease (50% or less) in serum alanine aminotransferase activity in males and females at most time points and could indicate an alteration in enzyme metabolism/catabolism or release by the liver or enzyme inhibition. Ostergaard *et al.* (1993) reported similar decreases in rats exposed to Stoddard solvent. In males from the current 3-month study, a minimal decrease in the erythron, evidenced by small decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts, occurred at study termination in the 2,200 mg/m^3 group; the decrease in the erythron had a minimal effect and was not considered toxicologically relevant. However, occupational and consumer use of Stoddard-type solvents has caused aplastic anemia in humans (ACGIH, 1991), suggesting species differences.

Other adverse effects noted in the 3-month rat study were epididymal sperm motility decreases in males exposed to 550 mg/m^3 or greater. In the 2-year studies, doses that produced decreased motility in the 3-month studies did not cause morphologic effects in the testis. In the absence of any other microscopic effects on the testes, it was difficult to interpret this finding. Furthermore, there are no adequate studies in laboratory animals and humans (WHO, 1996) that would support these exposure-related decreases. However, there are some human studies that suggest that exposure to organic solvents might be a risk factor for male fertility (Cherry *et al.*, 2001).

The observed decreases in sperm motility for both rats and mice suggest that Stoddard Solvent IIC is a reproductive toxicant with biochemical effects in mature sperm, or in epididymal function leading to alterations in sperm maturation, since sperm motility was decreased in the absence of any changes in any other reproductive endpoints (Chapin and Heindel, 1993). However, these reductions in sperm motility, while statistically significant, are probably of modest importance relative to fertility. The latest meta-analysis of 80 multigenerational studies in mice in the Reproductive Assessment by Continuous Breeding database found that fertility was unaffected until motility fell to 40% moving sperm (Chapin *et al.*, 1997).

In mice, Stoddard solvent IIC toxicity was limited to the liver. In the 2-week study, increased liver weights occurred in 275 mg/m^3 or greater males and females. In the 3-month study, exposure-related increased liver weights occurred in males exposed to 2,200 mg/m^3. However, there were no liver lesions that could be correlated with the increased liver weights.

No Stoddard solvent IIC toxicity studies have been reported in mice. However, the pattern of Stoddard solvent IIC toxicity observed in the current 3-month studies in rats and mice resembles that for decalin (NTP, 2004a) and propylene glycol mono-*t*-butyl ether (NTP, 2004b), two hydrocarbon solvents that induce α2u-globulin in male rat kidneys. For all three chemicals, the major target organs after 3 months of exposure were the kidney in male rats and the liver in mice.

Chronic exposure to Stoddard solvent IIC by inhalation resulted in significant reductions in survival of exposed male and female rats. However, overall effects on mean body weights and clinical findings in the surviving males and females were minimal.

After exposure to Stoddard solvent IIC for 105 weeks, the most significant exposure-related pathologic finding in rats was a spectrum of renal lesions in males that included increased incidences of cortical tubule hyperplasia, linear mineralization of the renal papilla, hyperplasia of the transitional epithelium lining the renal pelvis, and exacerbation of chronic nephropathy. This spectrum of lesions was characteristic of renal toxicity related to chronic accumulation of α2u-globulin in cortical tubule epithelium. There has been an association between α2u-globulin-mediated nephropathy and induction of kidney neoplasms for some chemicals. The association between chemically induced α2u-globulin nephropathy and renal carcinogenesis for certain hydrocarbons has led to the theory that the carcinogenicity of these compounds is unique to male rats and that it only occurs at exposure concentrations sufficient to cause hyaline (protein) droplet nephropathy (Swenberg *et al.,* 1989; Borghoff *et al.,* 1990; Short, 1993; Swenberg, 1993; Swenberg and Lehman-McKeeman, 1999). However, an alternate theory suggests that α2u-globulin might serve as a vector to increase the delivery of a toxicant (or protoxicant) to proximal tubule cells (Melnick, 1992). The plausibility of this theory was demonstrated in the physiological model by Melnick and Kohn (1999).

In the current 2-year rat study, there was evidence of renal tubule toxicity and a subsequent proliferative effect of Stoddard solvent IIC exposure on renal tubule epithelium in males; however, the occurrence of renal neoplasms was low. The routine histopathologic evaluation of the male kidneys did not reveal a difference in renal neoplasm incidences between the chamber control and exposed groups. However, an extended evaluation revealed a slightly increased incidence of adenoma in the 1,100 mg/m^3 group. The incidences of renal tubule adenoma or carcinoma (combined) were 14% in the 1,100 mg/m^3 group and 8% in the chamber control group when the original and step sections were combined, suggesting that these neoplasms may have been induced by Stoddard solvent IIC exposure. This relationship was further supported by the marked exposure-related toxic/proliferative effects on renal cortical epithelium that was shown in the nonneoplastic histopathology data.

The incidences of benign pheochromocytoma in 550 and 1,100 mg/m^3 male rats and benign or malignant pheochromocytoma (combined) in 1,100 mg/m^3 male rats exceeded the historical chamber control ranges, suggesting that exposure to Stoddard solvent IIC caused the increased incidences of these adrenal medulla neoplasms. Nyska *et al.* (1999) investigated the correlation between the severity of nephropathy and the incidence of pheochromocytoma in male F344/N rats based on data from the NTP feed and inhalation studies (NIH-07 diet), and reported significant relationships between the two variables for the feed ($P<0.05$) and inhalation ($P<0.01$) controls. Because Stoddard solvent IIC apparently affected both nephropathy severity and the pheochromocytoma incidences, a similar correlation analysis was performed for the current study data. However, the correlation was weak and not statistically significant. Thus, the increase in the incidences of pheochromocytoma was

not explained by a concomitant increase in the severity of nephropathy.

In the current 2-year study in mice, exposure to Stoddard solvent IIC for 2 years at concentrations up to 2,200 mg/m^3 did not result in significant in-life carcinogenicity. The mice could have tolerated higher concentrations, but the exposure concentrations were limited by the maximum attainable vapor generation of Stoddard solvent IIC. There appeared to be chemical-related mean body weight increases in exposed females; the body weights of 1,100 mg/m^3 females were greater from week 17 until the end of the study. Chronic exposure did not cause significant microscopic lesions while possibly exposure-related increases occurred in the incidences of hepatocellular adenoma and eosinophilic foci of the liver. In females, there was a slightly increased incidence of hepatocellular adenoma in exposed groups. Liver tumors in B6C3F$_1$ mice are known to be sensitive to body weight changes (Rao *et al.,* 1987; Seilkop, 1995). Haseman *et al.* (1997), using data from the NTP historical control database (NIH-07 diet), derived a predictive model that estimates liver tumor occurrence based on 52-week body weights and age at death. Application of this model to the current Stoddard solvent IIC 2-year mouse data suggests that the slight increase in the incidences of liver neoplasms in exposed females was due primarily to the increased body weights. Additional statistical analyses using individual animal body weight and liver neoplasm data for females confirmed this correlation and its impact on the increased incidences of liver neoplasms in the exposed groups.

Stoddard solvent IIC was not mutagenic in microbial or mammalian systems in the current studies. The marginal carcinogenic effects related to kidney neoplasms in rats and liver neoplasms in mice may have been related to Stoddard solvent IIC exposure. The increased incidences of adrenal pheochromocytoma that occurred in male rats are rarely observed in humans and other animals (Nyska *et al.,* 1999). The WHO (1996) evaluation of several epidemiologic studies in workers (painters, metal machinists, construction workers, and dry cleaners) who were potentially exposed to Stoddard solvent IIC suggested that those studies were insufficient to demonstrate a causal association with Stoddard solvent IIC. Similarly, the case control findings and studies on early markers of nephrotoxicity are conflicting; however, the indications are that painters have a higher risk of primary glomerulonephritis and renal dysfunction.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity* of Stoddard solvent IIC in male F344/N rats based on increased incidences of adrenal medulla neoplasms; the slightly increased incidences of renal tubule adenoma may have been related to Stoddard solvent IIC exposure. There was *no evidence of carcinogenic activity* of Stoddard solvent IIC in female F344/N rats exposed to 550, 1,100, or 2,200 mg/m^3. There was *no evidence of carcinogenic activity* of Stoddard solvent IIC in male B6C3F$_1$ mice exposed to 550, 1,100, or 2,200 mg/m^3. There was *equivocal evidence of carcinogenic activity* of Stoddard solvent IIC in female B6C3F$_1$ mice based on increased incidences of hepatocellular adenoma; this slight increase was associated with increased body weight in exposed females.

Exposure of male rats to Stoddard solvent IIC resulted in nonneoplastic lesions of the kidney characteristic of α2u-globulin accumulation.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 11. A Summary of the Technical Reports Review Subcommittee comment and the public discussion on this Technical Report appears on page 13.

REFERENCES

Agency for Toxic Substances and Disease Registry (ATSDR) (1995). Toxicological profile for Stoddard solvent (CAS# 8052-41-3). U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, Atlanta, GA.

Agrell, A., Hane, M., and Hogstedt, C. (1980). A five year follow-up of subjective symptoms among house painters [in Swedish, English summary]. *Lakartidningen* **77**, 440-442.

American Conference of Governmental Industrial Hygienists (ACGIH) (1991). *Documentation of the Threshold Limit Values and Biological Exposure Indices,* p. 1428. Cincinnati, OH.

American Conference of Governmental Industrial Hygienists (ACGIH) (2002). *2002 TLVs® and BEIs®. Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices,* p. 53. Cincinnati, OH.

American Petroleum Institute (API) (1983). *Teratology Study in Rats, Stoddard Solvent - Final Report* (Microfiche FYI-AX-0183-0232). Litton Bionetics, Inc., Project No. 20698-2. API, Washington, DC (cited in WHO, 1996).

American Petroleum Institute (API) (1984a). *Mutagenicity Evaluation of Stoddard Solvent* (API Medical Research Publication No. 26-60010) (Microfiche FYI-OTS-0684-0313). Litton Bionetics, Inc., API, Washington, DC (cited in WHO, 1996).

American Petroleum Institute (API) (1984b). *Mutagenicity Study of Thirteen Petroleum Fractions* (Microfiche FYI-OTS-0584-0313). The Hine Laboratories, Inc., Project No. U-150-14/EA-1. API, Washington, DC (cited in WHO, 1996).

American Petroleum Institute (API) (1986a). *Acute Oral Toxicity Study in Rats. Acute Dermal Toxicity Study in Rabbits. Primary Dermal Irritation Study in Rabbits. Primary Eye Irritation Study in Rabbits. Dermal Sensitizing Study in Guinea Pigs. Final Report: API 85-01, Stoddard Solvent* (CAS 8052-41-3) (Microfiche addendum #5, FYI-AX-0586-0371). Hazleton Laboratories America, Inc., Study No. 51000252. API, Washington, DC (cited in WHO, 1996).

American Petroleum Institute (API) (1986b). *28-Day Dermal Toxicity Study of API 85-01 in Rabbits* (Microfiche FYI-AX-0287-533). Tegeris Project No. 85023/1. API, Washington, DC (cited in WHO, 1996).

American Petroleum Institute (API) (1987a). *Acute Inhalation Toxicity Evaluation of a Petroleum Derived Hydrocarbon in Rats: API 85-01, Stoddard Solvent* (CAS 8052-41-3). Final Report (Microfiche FYI-AX-0987-0411). Hazleton Laboratories America, Inc., Project No. 22235-14. API, Washington, DC (cited in WHO, 1996).

American Petroleum Institute (API) (1987b). *Mutagenicity of API 85-01, Stoddard Solvent (CAS 8052-41-3) in a Mouse Lymphoma Mutation Assay. Final Report* (Microfiche FYI-AX-0187-0531). Litton Bionetics, Inc., Project No. 20989. API, Washington, DC (cited in WHO, 1996).

American Society for Testing and Materials (ASTM) (1995). D 235 Standard specification for mineral spirits (petroleum spirits) (hydrocarbon dry cleaning solvent). In *Annual Book of ASTM Standards,* Vol. 05.01. ASTM, Philadelphia, PA.

Anderson, C., Sundberg, K., and Groth, O. (1986). Animal model for assessment of skin irritancy. *Contact Dermatitis* **15**, 143-151.

Arlien-Soborg, P. (1985). Chronic effects of organic solvents on the central nervous system and diagnostic criteria. In *Chronic Effects of Organic Solvents on the Central Nervous System and Diagnostic Criteria* (Environmental Health Series No. 5), pp. 197-218. Report of the Joint WHO/Nordic Council of Ministers Working Group, World Health Organization, Regional Office for Europe, Copenhagen.

Arlien-Soborg, P., Bruhn, P., Gyldensted, C., and Melgaard, B. (1979). Chronic painters' syndrome. Chronic toxic encephalopathy in house painters. *Acta Neurol. Scand.* **60**, 149-156.

Arlien-Soborg, P., Zilstorff, K., Grandjean, B., and Pedersen, L.M. (1981). Vestibular dysfunction in occupational chronic solvent intoxication. *Clin. Otolaryngol.* **6**, 285-290.

Arlien-Soborg, P., Henriksen, L., Gade, A., Gyldensted, C., and Paulson, O.B. (1982). Cerebral blood flow in chronic toxic encephalopathy in house painters exposed to organic solvents. *Acta Neurol. Scand.* **66**, 34-41.

Ashby, J., and Tennant, R.W. (1991). Definitive relationships among chemical structure, carcinogenicity and mutagenicity for 301 chemicals tested by the U.S. NTP. *Mutat. Res.* **257,** 229-306.

Astrand. I., Kilbom, A., and Övrum, P. (1975). Exposure to white spirit. I. Concentration in alveolar air and blood during rest and exercise. *Scand. J. Work Environ. Health* **1**, 15-30.

Atkinson, L., Ince, P., Smith, N.M., and Taylor, R. (1989). Toxic reaction to inhaled paint fumes. *Postgrad. Med. J.* **65**, 559-562.

Axelson, O., Hane, M., and Hogstedt, C. (1976). A case-referent study on neuropsychiatric disorders among workers exposed to solvents. *Scand. J. Work Environ. Health* **2**, 14-20.

Bailer, A.J., and Portier, C.J. (1988). Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. *Biometrics* **44,** 417-431.

Bazylewicz-Walczak, B., Marszal-Wisniewska, M., and Siuda, A. (1990). The psychological effects of chronic exposure to white spirit in rubber industry workers. *Pol. J. Occup. Med.* **3**, 117-127.

Bieler, G.S., and Williams, R.L. (1993). Ratio estimates, the delta method, and quantal response tests for increased carcinogenicity. *Biometrics* **49,** 793-801.

Biodynamics, Inc. (1979). A segment II teratology study in rats following inhalation exposure to Varsel 40 (Exxon Project No. 78-7093). Study conducted for Exxon Corporation.

Björn, A., Järvholm, B., and Lavenius, B. (1983). Rough and dry skin and respiratory symptoms among workers exposed to petroleum naphtha [in Swedish]. *Lakartidningen* **80**, 1676-1678.

Blair, D., Clark, D.G., and Linnett, S.L. (1979). The inhalation toxicology of LAWS (low aromatic white spirit) to rats following 13 week's exposure (Group Research Report No. TLGR.79.141). Shell Toxicology Laboratory, Sittingbourne, Kent, Great Britain.

Blume, J., Hane, M., Sundell, L., and Ydreborg, B. (1975). Mental function changes among house painters [in Swedish, English summary]. *Lakartidningen* **72**, 702-706.

Bondy, S.C., Lam, H.R., Ostergaard, G., Guo, S.X., and Ladefoged, O. (1995). Changes in markers of oxidative status in brain, liver and kidney of young and aged rats following exposure to aromatic white spirit. *Arch. Toxicol.* **69**, 410-414.

Boorman, G.A., Montgomery, C.A., Jr., Eustis, S.L., Wolfe, M.J., McConnell, E.E., and Hardisty, J.F. (1985). Quality assurance in pathology for rodent carcinogenicity studies. In *Handbook of Carcinogen Testing* (H.A. Milman and E.K. Weisburger, Eds.), pp. 345-357. Noyes Publications, Park Ridge, NJ.

Borghoff, S.J., Short, B.G., and Swenberg, J.A. (1990). Biochemical mechanisms and pathobiology of α_{2u}-globulin nephropathy. *Annu. Rev. Pharmacol. Toxicol.* **30**, 349-367.

Brackbill, R.M., Maizlish, N., and Fischbach, T. (1990). Risk of neuropsychiatric disability among painters in the United States. *Scand. J. Work Environ. Health* **16**, 182-188.

Braunstein, L.E., and Schenectady, N.Y. (1940). Subacute yellow atrophy of the liver due to "solvent." *J. Am. Med. Assoc.* **114**, 136-138.

Bruhn, P., Arlien-Soborg, P., Gyldensted, C., and Christensen, E.L. (1981). Prognosis in chronic toxic encephalopathy. A two-year follow-up study in 26 house painters with occupational encephalopathy. *Acta Neurol. Scand.* **64**, 259-272.

Carpenter, C.P., Kinkead, E.R., Geary, D.L., Jr., Sullivan, L.J., and King, J.M. (1975a). Petroleum hydrocarbon toxicity studies. III. Animal and human response to vapors of Stoddard solvent. *Toxicol. Appl. Pharmacol.* **32**, 282-297.

Carpenter, C.P., Kinkead, E.R., Geary, D.L., Jr., Sullivan, L.J., and King, J.M. (1975b). Petroleum hydrocarbon toxicity studies. VIII. Animal and human response to vapors of "140 Flash Aliphatic Solvent." *Toxicol. Appl. Pharmacol.* **34**, 413-429.

Chapin, R.E., and Heindel, J.J. (1993). Introduction. *In Male Reproductive Toxicology* (R.E. Chapin and J.J. Heindel, Eds.), pp. 5-7. Academic Press, New York.

Chapin, R.E., Sloane, R.A., and Haseman, J.K. (1997). The relationships among reproductive endpoints in Swiss mice, using the Reproductive Assessment by Continuous Breeding database. *Fundam. Appl. Toxicol.* **38**, 129-142.

Cherry, N., Labrèche, F., Collins, J., and Tulandi, T. (2001). Occupational exposure to solvents and male infertility. *Occup. Environ. Med.* **58**, 635-640.

Code of Federal Regulations (CFR) **21,** Part 58.

Cohr, K.-H., and Stokholm, J. (1979). Concentrations in alveolar air and venous blood during house painting. In *Exposure of Humans to White Spirit IV.,* Report No. 3/1979, pp. 27-51 [in Danish, English summary]. Danish National Labour Inspection Service, Danish National Institute of Occupational Health, Copenhagen, Denmark.

Cohr, K.-H., Stokholm, J., and Bruhn, P. (1980). Neurologic response to white spirit exposure. *Dev. Toxicol. Environ. Sci.* **8**, 95-102.

Coombs, A.D., Blair, D., Doak, S.M., and Carter, B.I. (1977). The acute toxicity of LAWS (Research Report No. M(T)-3-77). Shell Toxicology Laboratory, Sittingbourne, Kent, Great Britain.

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

Crawford, B.D. (1985). Perspectives on the somatic mutation model of carcinogenesis. In *Advances in Modern Environmental Toxicology. Mechanisms and Toxicity of Chemical Carcinogens and Mutagens* (M.A. Mehlman, W.G. Flamm, and R.J. Lorentzen, Eds.), pp. 13-59. Princeton Scientific Publishing Co., Inc., Princeton, NJ.

Daniell, W.E., Couser, W.G., and Rosenstock, L. (1988). Occupational solvent exposure and glomerulonephritis. A case report and review of the literature. *J. Am. Med. Assoc.* **259**, 2280-2283.

D'Apice, A.J., Kincaid-Smith, P., Becker, G.H., Loughhead, M.G., Freeman, J.W., and Sands, J.M. (1978). Goodpasture's syndrome in identical twins. *Ann. Intern. Med.* **88**, 61-62.

Dixon, W.J., and Massey, F.J., Jr. (1951). *Introduction to Statistical Analysis,* 2nd ed., pp. 276-278, 412. McGraw-Hill Book Company, Inc., New York.

Duh, R.-W., and Asal, N.R. (1984). Mortality among laundry and dry cleaning workers in Oklahoma. *Am. J. Public Health* **74**, 1278-1280.

Dunn, O.J. (1964). Multiple comparisons using rank sums. *Technometrics* **6,** 241-252.

Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *J. Am. Stat. Assoc.* **50,** 1096-1121.

Edelfors, S., and Ravn-Jonsen, A. (1985). Calcium uptake in rat brain synaptosomes after short-term exposure to organic solvents: A pilot study. *Acta Pharmacol. Toxicol. (Copenh.)* **56**, 431-434.

Edelfors, S., and Ravn-Jonsen, A. (1992). Effect of organic solvents on nervous cell membrane as measured by changes in the (Ca2+/Mg2+) ATPase activity and fluidity of synaptosomal membrane. *Pharmacol. Toxicol.* **70**, 181-187.

Edelfors, S., Hass, U., and Ravn-Jonsen, A. (1999). The effect of in vitro exposure to white spirit on [Ca2+i] in synaptosomes from rats exposed prenatally to white spirit. *Pharmacol. Toxicol.* **84**, 197-200.

Gamberale, F., Annwall, G., and Hultengren, M. (1975). Exposure to white spirit. II. Psychological functions. *Scand. J. Work Environ. Health* **1**, 31-39.

Gardener, J.R. (1989). LAWS 15/20A: Skin irritancy (Group Research Report No. SBGR.89.148). Shell Research Ltd., Sittingbourne, Kent, Great Britain.

Gill, R., Osselton, M.D., Broad, J.E., and Ramsey, J.D. (1991a). The response of evidential breath alcohol testing instruments with subjects exposed to organic solvents and gases. III. White spirit exposure during domestic painting. *Med. Sci. Law* **31**, 214-220.

Gill, R., Warner, H.E., Broster, C.G., Osselton, M.D., Ramsey, J.D., Wilson, H.K., and Wilcox, A.H. (1991b). The response of evidential breath alcohol testing instruments with subjects exposed to organic solvents and gases. II. White spirit and nonane. *Med. Sci. Law* **31**, 201-213.

Gochet, B., de Meester, C., Léonard, A., and Deknudt, G. (1984). Lack of mutagenic activity of white spirit. *Int. Arch. Occup. Environ. Health* **53**, 359-364.

Hane, M., Axelson, O., Blume, J., Högstedt, C., Sundell, L., and Ydreborg, B. (1977). Psychological function changes among house painters. *Scand. J. Work Environ. Health* **3**, 91-99.

Hansen, T.B. (1988). Organic solvents in household goods (Environmental Project No. 101) [in Danish]. Danish Environmental Protection Agency, Copenhagen.

Hard, G.C., Rodgers, I.S., Baetcke, K.P., Richards, W.L., McGaughy, R.E., and Valcovic, L.R. (1993). Hazard evaluation of chemicals that cause accumulation of α_{2u}-globulin, hyaline droplet nephropathy, and tubule neoplasia in the kidneys of male rats. *Environ. Health Perspect.* **99**, 313-349.

Haseman, J.K., Young, E., Eustis, S.L., and Hailey, J.R. (1997). Body weight-tumor incidence correlations in long-term rodent carcinogenicity studies. *Toxicol. Pathol.* **25**, 256-263.

Hass, U., and Prior, M.B. (1986). *Nordic Expert Group for Documentation of Occupational Exposure Limits: 64. White Spirit* (Work and Health: Scientific Publication Series 1986:1) [in Swedish]. National Institute of Occupational Health, Solna, Sweden.

Hass, U., Ladefoged, O., Lam, H.R., Ostergaard, G., Lund, S.P., and Simonsen, L. (2001). Behavioural effects in rats after prenatal exposure to dearomatized white spirit. *Pharmacol. Toxicol.* **89**, 201-207.

Hastings, L., Cooper, G.P., and Burg, W. (1984). Human sensory response to selected petroleum hydrocarbons. In *Advances in Modern Environmental Toxicology. Applied Toxicology of Petroleum Hydrocarbons* (H.N. MacFarland, C.E. Holdsworth, J.A. MacGregor, R.W. Call, and M.L. Lane, Eds.), pp. 255-270. Princeton Scientific Publishers, Inc., Princeton, NJ.

Hollander, M., and Wolfe, D.A. (1973). *Nonparametric Statistical Methods,* pp. 120-123. John Wiley and Sons, New York.

Ingram, A.J., King, D.J., Grasso, P., and Sharratt, M. (1993). The early changes in mouse skin following topical application of a range of middle distillate oil products. *J. Appl. Toxicol.* **13**, 247-257.

Integrated Laboratory Systems (ILS) (1990). Micronucleus Data Management and Statistical Analysis Software, Version 1.4. ILS, P.O. Box 13501, Research Triangle Park, NC 27707.

International Agency for Research on Cancer (IARC) (1989). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting,* Vol. 47. IARC, Lyon, France.

Jakobsen, B.M., Hass, U., Jull, F., and Kjaergaard, S. (1986). Prenatal toxicity of white spirit inhalation in the rat. *Teratology* **34**, 415.

Jenkins, L.J., Jr., Coon, R.A., Lyon, J.P., and Siegel, J. (1971). Effect on experimental animals of long-term inhalation exposure to mineral spirits. II. Dietary, sex and strain influences in guinea pigs. *Toxicol. Appl. Pharmacol.* **18**, 53-59.

Jonckheere, A.R. (1954). A distribution-free *k*-sample test against ordered alternatives. *Biometrika* **41,** 133-145.

Kaplan, E.L., and Meier, P. (1958). Nonparametric estimation from incomplete observations. *J. Am. Stat. Assoc.* **53,** 457-481.

Kegels (1958). Un cas d'anémie aplastique d'origine professionelle probable par le white spirit. *Arch. Belg. Med. Soc.* **16**, 161-174.

Kitchen, D.N. (1984). Neoplastic renal effects of unleaded gasoline in Fischer 344 rats. In *Advances in Modern Environmental Toxicology. Renal Effects of Petroleum Hydrocarbons* (M.A. Mehlman, G.P. Hemstreet, J.J. Thorpe, and N.K. Weaver, Eds.). Princeton Scientific Publishers, Inc., Princeton, NJ.

Kulig, B.M. (1989). The effects of white spirits on neurobehavioral functioning in the rat (unpublished report). TNO Medical/Biological Laboratory, Rijswijk, The Netherlands.

Lam, H.R., Löf, A., and Ladefoged, O. (1992). Brain concentrations of white spirit components and neurotransmitters following a three week inhalation exposure of rats. *Pharmacol. Toxicol.* **70**, 394-396.

Lam, H.R., Ostergaard, G., Guo, S.X., Ladefoged, O., and Bondy, S.C. (1994). Three weeks' exposure of rats to dearomatized white spirit modifies indices of oxidative stress in brain, kidney, and liver. *Biochem. Pharmacol.* **47**, 651-657.

Lam, H.R., Ostergaard, G., and Ladefoged, O. (1995). Three weeks' and six months' exposure to aromatic white spirit affect synaptosomal neurochemistry in rats. *Toxicol. Lett.* **80**, 39-48.

Lindström, K., and Wickström, G. (1983). Psychological function changes among maintenance house painters exposed to low levels of organic solvent mixtures. *Acta Psychiatr. Scand. Suppl.* **303**, 81-91.

Lindström, K., Riihimäki, H., and Hänninen, K. (1984). Occupational solvent exposure and neuropsychiatric disorders. *Scand. J. Work Environ. Health* **10**, 321-323.

Löf, A., Lam, H.R., Gullstrand, E., Ostergaard, G., and Ladefoged, O. (1999). Distribution of dearomatised white spirit in brain, blood, and fat tissue after repeated exposure of rats. *Pharmacol. Toxicol.* **85**, 92-97.

Lund, S.P., Simonsen, L., Hass, U., Ladefoged, O., Lam, H.R., and Ostergaard, G. (1996). Dearomatized white spirit inhalation exposure causes long-lasting neurophysiological changes in rats. *Neurotoxicol. Teratol.* **18**, 67-76.

McConnell, E.E., Solleveld, H.A., Swenberg, J.A., and Boorman, G.A. (1986). Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. *JNCI* **76,** 283-289.

McDermott, H.J. (1975). Stoddard solvent (mineral spirits, white spirits). Hygienic guide series. *Am. Ind. Hyg. Assoc. J.* **36**, 553-558.

MacFarland, H.N. (1984). Xenobiotic induced kidney lesions: Hydrocarbons. The 90-day and 2-year gasoline studies. In *Advances in Modern Environmental Toxicology. Renal Effects of Petroleum Hydrocarbons* (M.A. Mehlman, G.P. Hemstreet, J.J. Thorpe, and N.K. Weaver, Eds.). Princeton Scientific Publishers, Inc., Princeton, NJ.

MacGregor, J.T., Wehr, C.M., Henika, P.R., and Shelby, M.D. (1990). The *in vivo* erythrocyte micronucleus test: Measurement at steady state increases assay efficiency and permits integration with toxicity studies. *Fundam. Appl. Toxicol.* **14**, 513-522.

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

Melnick, R.L. (1992). An alternative hypothesis on the role of chemically induced protein droplet (alpha 2u-globulin) nephropathy in renal carcinogenesis. *Regul. Toxicol. Pharmacol.* **16**, 111-125.

Melnick, R.L., and Kohn, M.C. (1999). Possible mechanisms of induction of renal tubule cell neoplasms in rats associated with α_{2u}-globulin: Role of protein accumulation versus ligand delivery to the kidney. *IARC Sci. Pub.* **147**, 119.

The Merck Index (1996). 12th ed. (S. Budavari, Ed.), pp. 1060-1061. Merck & Company Inc., Whitehouse Station, NJ.

Mikkelsen, S. (1980). A cohort study of disability pension and death among painters with special regard to disabling presenile dementia as an occupational disease. *Scand. J. Soc. Med. Suppl.* **16**, 34-43.

Mikkelsen, S., Jorgensen, M., Browne, E., and Gyldensted, C. (1988). Mixed solvent exposure and organic brain damage. A study of painters. *Acta Neurol. Scand.* **78**, 1-143.

Miller, J.A., and Miller, E.C. (1977). Ultimate chemical carcinogens as reactive mutagenic electrophiles. In *Origins of Human Cancer* (H.H. Hiatt, J.D. Watson, and J.A. Winsten, Eds.), pp. 605-627. Cold Spring Harbor Laboratory, Cold Spring Harbor, NY.

Morrison, D.F. (1976). *Multivariate Statistical Methods,* 2nd ed., pp. 170-179. McGraw-Hill Book Company, New York.

National Institute for Occupational Safety and Health (NIOSH) (1973). Health hazard evaluation determination report No. 72-67-87: Westinghouse Electric Corporation-Lamp division, Bloomfield, New Jersey. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Cincinnati, OH.

National Institute for Occupational Safety and Health (NIOSH) (1975a). Health hazard evaluation determination report No. 74-138-208: Frontier Airlines, Denver, Colorado. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Cincinnati, OH.

National Institute for Occupational Safety and Health (NIOSH) (1975b). Health hazard evaluation determination report No. 75-90-236: Russell Corporation, Alexander City, Alabama. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Cincinnati, OH.

National Institute for Occupational Safety and Health (NIOSH) (1975c). Health hazard evaluation determination report No. 74-144-211: Safeguard Automotive Company, Baltimore, Maryland. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Cincinnati, OH.

National Institute for Occupational Safety and Health (NIOSH) (1975d). Health hazard evaluation determination report No. 75-26-245: Babcock and Wilcox Company, Canton, Ohio. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Cincinnati, OH.

National Institute for Occupational Safety and Health (NIOSH) (1975e). Health hazard evaluation determination report No. 74-148-239: Lange Company, Broomfield, Colorado. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Cincinnati, OH.

National Institute for Occupational Safety and Health (NIOSH) (1980). Health hazard evaluation determination report No. HE/79-142-697: Mountain Bell, Denver, Colorado. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, Cincinnati, OH.

National Institute for Occupational Safety and Health (NIOSH) (1990). National Occupational Exposure Survey (1981-1983), unpublished provisional data as of July 1, 1990. NIOSH, Cincinnati, OH.

National Institute for Occupational Safety and Health (NIOSH) (1997). NIOSH Pocket Guide to Chemical Hazards, p. 286. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, Cincinnati, OH.

National Institute of Standards and Technology (NIST) (1994). Mass Spectral Database. Standard Reference Database 1A. Standard Reference Data Program. National Institute of Standards and Technology. Gaithersburg, MD.

National Toxicology Program (NTP) (2004a). NTP Technical Report on the Toxicology and Carcinogenesis Studies of Decalin (CAS No. 91-17-8) in F344/N Rats and B6C3F_1 Mice (Inhalation Studies). Technical Report Series No. 513. NIH Publication No. 04-4447. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. (in press)

National Toxicology Program (NTP) (2004b). NTP Technical Report on the Toxicology and Carcinogenesis Studies of Propylene Glycol Mono-*t*-Butyl Ether (CAS No. 57018-52-7) in F344/N Rats and B6C3F$_1$ Mice and a Toxicology Study of Propylene Glycol Mono-*t*-Butyl Ether in Male NBR Rats (Inhalation Studies). Technical Report Series No. 515. NIH Publication No. 04-4449. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

Nethercott, J.R., Pierce, J.M., Likwornick, G., and Murray, A.H. (1980). Genital ulceration due to Stoddard solvent. *J. Occup. Med.* **22**, 549-552.

Niemelä, R., Pfäffli, P., and Härkönen, H. (1987). Ventilation and organic solvent exposure during car washing. *Scand. J. Work Environ. Health* **13**, 424-430.

Nierenberg, D.W., Horowitz, M.B., Harris, K.M., and James, D.H. (1991). Mineral spirits inhalation associated with hemolysis, pulmonary edema, and ventricular fibrillation. *Arch. Intern. Med.* **151**, 1437-1440.

Nyska, A., Haseman, J.K., Hailey, J.R., Smetana, S., and Maronpot, R.R. (1999). The association between severe nephropathy and pheochromocytoma in the male F344 rat – the National Toxicology Program experience. *Toxicol. Pathol.* **27**, 456-462.

Oberg, M. (1968). A survey of the petroleum solvent inhalation exposure in Detroit dry cleaning plants. *Am. Ind. Hyg. Assoc. J.* **29**, 547-550.

Ostergaard, G., Lam, H.R., Ladefoged, O., and Arlien-Soborg, P. (1993). Effects of six months' white spirit inhalation exposure in adult and old rats. *Pharmacol. Toxicol.* **72**, 34-39.

Paris, J., Ribet, M., and Busi, P. (1978). Esophagogastric lesions following ingestion of white spirit [in French]. *Sem. Hop. Paris* **54**, 151-153.

Pedersen, L.M., and Cohr, K.-H. (1984a). Biochemical pattern in experimental exposure of humans to white spirit. I. The effects of a 6 hours single dose. *Acta Pharmacol. Toxicol. (Copenh.)* **55**, 317-324.

Pedersen, L.M., and Cohr, K.-H. (1984b). Biochemical pattern in experimental exposure of humans to white spirit. II. The effects of repetitive exposures. *Acta Pharmacol. Toxicol. (Copenh.)* **55**, 325-330.

Pedersen, L.M., Larsen, K., and Cohr, K.-H. (1984). Kinetics of white spirit in human fat and blood during short-term experimental exposure. *Acta Pharmacol. Toxicol. (Copenh.)* **55**, 308-316.

Pedersen, L.M., Rasmussen, S., and Cohr, K.-H. (1987). Further evaluation of the kinetics of white spirit in human volunteers. *Pharmacol. Toxicol.* **60**, 135-139.

Petrone, R., Asal, N., and Coleman, R. (1987). Cancer mortality among petroleum solvent-exposed Oklahoma dry cleaners. *Am. J. Epidemiol.* **126**, 743.

Pfäffli, P., Härkönen, H., and Savolainen, H. (1985). Urinary dimethylbenzoic acid excretion as an indicator of occupational exposure to white spirit. *J. Chromatogr.* **337**, 146-150.

Phillips, R.D., and Cockrell, B.Y. (1984). Effect of certain light hydrocarbons on kidney function and structure in male rats. In *Advances in Modern Environmental Toxicology - Vol. III: Renal Effects of Petroleum Hydrocarbons,* (M.A. Mehlman, G.P. Hemstreet, J.J. Thorpe, and N.K. Weaver, Eds.), pp. 89-105. Princeton Scientific Publishers, Inc., Princeton, NJ.

Phillips, R.D., and Egan, G.F. (1981). Teratogenic and dominant lethal investigation of two hydrocarbon solvents. *Toxicologist* **1**, 15.

Phillips, R.D., and Egan, G.F. (1984). Subchronic inhalation exposure of dearomatized white spirit and C_{10}-C_{11} isoparaffinic hydrocarbon in Sprague-Dawley rats. *Fundam. Appl. Toxicol.* **4**, 808-818.

Piegorsch, W.W., and Bailer, A.J. (1997). *Statistics for Environmental Biology and Toxicology,* Section 6.3.2. Chapman and Hall, London.

Portier, C.J., and Bailer, A.J. (1989). Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam. Appl. Toxicol.* **12,** 731-737.

Portier, C.J., Hedges, J.C., and Hoel, D.G. (1986). Age-specific models of mortality and tumor onset for historical control animals in the National Toxicology Program's carcinogenicity experiments. *Cancer Res.* **46,** 4372-4378.

Prager, D., and Peters, C. (1970). Development of aplastic anemia and the exposure to Stoddard solvent. *Blood* **35**, 286-287.

Rao, G.N. (1996). New diet (NTP-2000) for rats in the National Toxicology Program toxicity and carcinogenicity studies. *Fundam. Appl. Toxicol.* **32**, 102-108.

Rao, G.N. (1997). New nonpurified diet (NTP-2000) for rodents in the National Toxicology Program's toxicology and carcinogenesis studies. *J. Nutr.* **127,** 842s-846s.

Rao, G.N., Piegorsch, W.W., and Haseman, J.K. (1987). Influence of body weight on the incidence of spontaneous tumors in rats and mice of long-term studies. *Am. J. Clin. Nutr.* **45**, 252-260.

Rector, D.E., Steadman, B.L., Jones, R.A., and Siegel, J. (1966). Effects on experimental animals of long-term inhalation exposure to mineral spirits. *Toxicol. Appl. Pharmacol.* **9**, 257-268.

Riala, R., Kalliokoski, P., Pyy, L., and Wickström, G. (1984). Solvent exposure in construction and maintenance painting. *Scand. J. Work Environ. Health* **10**, 263-266.

Riley, A.J., Collings., A.J., Browne, N.A., and Grasso, P. (1984). Response of the upper respiratory tract of the rat to white spirit vapour. *Toxicol. Lett.* **22**, 125-131.

Rodgers, I.S., and Baetcke, K.P. (1993). Interpretation of male rat renal tubule tumors. *Environ. Health Perspect. Suppl.* **101**, 45-52.

Savolainen, H., and Pfäffli, P. (1982). Neurochemical effects of extended exposure to white spirit vapour at three concentration levels. *Chem. Biol. Interact.* **39**, 101-110.

Schmitt, E.K., Lieberman, M.T., Caplan, J.A., Blaes, D., Keating, P., and Richards, W. (1991). Bioremediation of soil and groundwater contaminated with Stoddard solvent and mop oil using the PetroClean bioremediation system. In *In situ Bioreclamation: Proceedings of an International Symposium on In situ and On-site Bioreclamation, San Diego, California, March, 1991,* (R.E. Hinchee and R.F. Olfenbuttel, Eds.), Vol. 2, Ch. 45, pp. 581-599. Butterworth-Heinemann, Stoneham, MA.

Scott, L.J., Cartwright, E., and Wintrobe, M.M. (1959). Acquired aplastic anemia: An analysis of thirty-nine cases and review of the pertinent literature. *Medicine* **38**, 119-172.

Seilkop, S.K. (1995). The effect of body weight on tumor incidence and carcinogenicity testing in B6C3F1 mice and F344 rats. *Fundam. Appl. Toxicol.* **24**, 247-259.

Seppäläinen, A.M., and Lindström, K. (1982). Neurophysiological findings among house painters exposed to solvents. *Scand. J. Work Environ. Health* **8**, 131-135.

Shelby, M.D. (1988). The genetic toxicity of human carcinogens and its implications. *Mutat. Res.* **204**, 3-15.

Shelby, M.D., and Witt, K.L. (1995). Comparison of results from mouse bone marrow chromosome aberration and micronucleus tests. *Environ. Mol. Mutagen.* **25,** 302-313.

Shelby, M.D., and Zeiger, E. (1990). Activity of human carcinogens in the *Salmonella* and rodent bone-marrow cytogenetics tests. *Mutat. Res.* **234**, 257-261.

Shelby, M.D., Erexson, G.L., Hook, G.J., and Tice, R.R. (1993). Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. *Environ. Mol. Mutagen.* **21**, 160-179.

Shirley, E. (1977). A non-parametric equivalent of Williams' test for contrasting increasing dose levels of a treatment. *Biometrics* **33**, 386-389.

Short, B.G. (1993). Cell proliferation and renal carcinogenesis. *Environ. Health Perspect.* **101**, 115-120.

Spirtas, R., Stewart, P.A., Lee, J.S., Marano, D.E., Forbes, C.D., Grauman, D.J., Pettigrew, H.M., Blair, A., Hoover, R.N., and Cohen, J.L. (1991). Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. *Br. J. Ind. Med.* **48**, 515-530.

Spurgeon, A., Gray, C.N., and Sims, J. (1990). An investigation of the possible chronic neuropsychological effects of long-term occupational exposure to organic solvents (unpublished report). Institute of Occupational Health, University of Birmingham, Birmingham, AL.

Spurgeon, A., Gray, C.N., Sims, J., Calvert, I., Levy, L.S., Harvey, P.G., and Harrington, J.M. (1992). Neurobehavioral effects of long-term occupational exposure to organic solvents: Two comparable studies. *Am. J. Ind. Med.* **22**, 325-335.

Steensgaard, A., Ostergaard, G., Jensen, C.V., Lam, H.R., Topp, S., Ladefoged, O., Arlien-Soborg, P., and Henriksen, O. (1996). Effect on the content of *n*-acetylaspartate, total creatine, choline containing compounds, and lactate in the hippocampus of rats exposed to aromatic white spirit for three weeks measured by NMR spectroscopy. *Neurotoxicology* **17**, 785-792.

Stokholm, J., and Cohr, K.-H. (1979a). Concentrations in alveolar air and venous blood during experimental exposure. In *Exposure of Humans to White Spirit III.,* Report No. 3/1979, pp. 7-25 [in Danish, English summary]. Danish National Labour Inspection Service, Danish National Institute of Occupational Health, Copenhagen, Denmark.

Stokholm, J., and Cohr, K.-H. (1979b). Methods and materials. In *Exposure of Humans to White Spirit I.,* Report No. 2/1979, pp. 9-22 [in Danish, English summary]. Danish National Labour Inspection Service, Danish National Institute of Occupational Health, Copenhagen, Denmark.

Stokholm, J., and Cohr, K.-H. (1979c). Effects on the mucosae and the nervous system as measured by symptoms and clinical examinations. In *Exposure of Humans to White Spirit V.,* Report No. 4/1979, pp. 7-29 [in Danish, English summary]. Danish National Labour Inspection Service, Danish National Institute of Occupational Health, Copenhagen, Denmark.

Straus, D.S. (1981). Somatic mutation, cellular differentiation, and cancer causation. *JNCI* **67**, 233-241.

Swenberg, J.A. (1993). Alpha 2u-globulin nephropathy: Review of the cellular and molecular mechanisms involved and their implications for human risk assessment. *Environ. Health Perspect.* **101**, 39-44.

Swenberg, J.A., and Lehman-McKeeman, L.D. (1999). α_2-Urinary globulin-associated nephropathy as a mechanism of renal tubule cell carcinogenesis in male rats. *IARC Sci. Pub.* **147**, 95-118.

Swenberg, J.A., Short, B., Borghoff, S., Strasser, J., and Charbonneau, M. (1989). The comparative pathobiology of α_{2u}-globulin nephropathy. *Toxicol. Appl. Pharmacol.* **97**, 35-46.

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

Tennant, R.W., Margolin, B.H., Shelby, M.D., Zeiger, E., Haseman, J.K., Spalding, J., Caspary, W., Resnick, M., Stasiewicz, S., Anderson, B., and Minor, R. (1987). Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. *Science* **236**, 933-941.

United States Air Force (USAF) (1989). Stoddard solvent. In *The Installation Restoration Program Toxicology Guide,* Vol. 4 (Contract No. DE-AC05-84OR21400). Air Force Systems Command, Aerospace Medical Division, Harry G. Armstrong Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Dayton, OH.

Verkkala, E., Pfäffli, P., and Savolainen, H. (1984). Comparison of local neurotoxicity of three white spirit formulations by percutaneous exposure of rat tail nerve. *Toxicol. Lett.* **21**, 293-299.

Williams, D.A. (1971). A test for differences between treatment means when several dose levels are compared with a zero dose control. *Biometrics* **27**, 103-117.

Williams, D.A. (1972). The comparison of several dose levels with a zero dose control. *Biometrics* **28**, 519-531.

Williams, D.A. (1986). A note on Shirley's nonparametric test for comparing several dose levels with a zero-dose control. *Biometrics* **42**, 183-186.

Witt, K.L., Knapton, A., Wehr, C.M., Hook, G.J., Mirsalis, J., Shelby, M.D., and MacGregor, J.T. (2000). Micronucleated erythrocyte frequency in peripheral blood of $B6C3F_1$ mice from short-term, prechronic, and chronic studies of the NTP Carcinogenesis Bioassay Program. *Environ. Mol. Mutagen.* **36,** 163-194.

World Health Organization (WHO) (1996). White Spirit (Stoddard Solvent). Environmental Health Criteria 187. WHO, Geneva, Switzerland.

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., and Tennant, R.W. (1990). Evaluation of four in vitro genetic toxicity tests for predicting rodent carcinogenicity: Confirmation of earlier results with 41 additional chemicals. *Environ. Mol. Mutagen.* **16** (Suppl. 18), 1-14.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., and Mortelmans, K. (1992). Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environ. Mol. Mutagen.* **19** (Suppl. 21), 2-141.

APPENDIX A
SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF STODDARD SOLVENT IIC

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	18	27	21	27
Natural deaths	3	4	8	7
Survivors				
Terminal sacrifice	29	19	21	16
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(49)	(49)	(48)	(48)
Intestine small, ileum	(49)	(48)	(46)	(46)
Liver	(50)	(50)	(50)	(50)
Cholangiocarcinoma			1 (2%)	
Hepatocellular adenoma		1 (2%)		1 (2%)
Mesentery	(7)	(11)	(11)	(13)
Oral mucosa				(1)
Squamous cell carcinoma				1 (100%)
Stomach, glandular	(50)	(50)	(49)	(50)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Atrium, carcinoma, metastatic, kidney			1 (2%)	
Endocrine System				
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)			2 (4%)
Pheochromocytoma benign	5 (10%)	8 (16%)	12 (24%)	13 (26%)
Bilateral, pheochromocytoma benign		1 (2%)	1 (2%)	4 (8%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma	3 (6%)	2 (4%)	1 (2%)	3 (6%)
Carcinoma	1 (2%)		3 (6%)	
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, adenoma	38 (76%)	36 (72%)	35 (70%)	31 (62%)
Pars distalis, carcinoma	1 (2%)			
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, C-cell, adenoma		1 (2%)	1 (2%)	
C-cell, adenoma	7 (14%)	5 (10%)	5 (10%)	4 (8%)
C-cell, carcinoma	2 (4%)	3 (6%)	2 (4%)	
Follicular cell, adenoma			1 (2%)	
Follicular cell, carcinoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
General Body System				
Peritoneum	(14)	(41)	(41)	(32)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Preputial gland	(50)	(50)	(50)	(50)
Adenoma		1 (2%)	2 (4%)	1 (2%)
Carcinoma		1 (2%)	3 (6%)	
Prostate	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	26 (52%)	22 (44%)	28 (56%)	30 (60%)
Interstitial cell, adenoma	15 (30%)	17 (34%)	10 (20%)	12 (24%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph node	(7)	(16)	(11)	(17)
Lymph node, bronchial	(15)	(12)	(16)	(13)
Carcinoma, metastatic, kidney			1 (6%)	
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Carcinoma, metastatic, thyroid gland			1 (2%)	
Lymph node, mediastinal	(42)	(44)	(43)	(40)
Carcinoma, metastatic, thyroid gland				1 (3%)
Spleen	(50)	(50)	(50)	(50)
Thymus	(49)	(49)	(47)	(50)
Thymoma malignant	1 (2%)			1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)	2 (4%)	
Fibroadenoma	3 (6%)	1 (2%)	2 (4%)	4 (8%)
Skin	(50)	(50)	(50)	(50)
Basal cell carcinoma		1 (2%)	1 (2%)	3 (6%)
Squamous cell papilloma	1 (2%)	2 (4%)		2 (4%)
Sebaceous gland, adenoma	3 (6%)	1 (2%)	1 (2%)	
Subcutaneous tissue, fibroma	2 (4%)	4 (8%)	2 (4%)	2 (4%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	1 (2%)		
Subcutaneous tissue, hemangioma				1 (2%)
Subcutaneous tissue, lipoma	2 (4%)			1 (2%)
Subcutaneous tissue, schwannoma benign		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, osteosarcoma	1 (2%)			
Femur, osteosarcoma	1 (2%)			
Skeletal muscle	(1)	(1)	(1)	(1)
Carcinoma, metastatic, thyroid gland				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant	1 (2%)			
Carcinoma, metastatic, pituitary gland	1 (2%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Respiratory System				
Lung	(50)	(50)	(50)	(49)
Alveolar/bronchiolar adenoma	1 (2%)		2 (4%)	
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)	
Carcinoma, metastatic, kidney			1 (2%)	
Osteosarcoma, metastatic, bone	1 (2%)			
Pheochromocytoma malignant, metastatic, adrenal medulla				1 (2%)
Thymoma malignant, metastatic, thymus				1 (2%)
Nose	(50)	(50)	(50)	(50)
Carcinoma, metastatic, oral mucosa				1 (2%)
Respiratory epithelium, adenoma	1 (2%)			
Special Senses System				
Zymbal's gland				(1)
Carcinoma				1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Lipoma		1 (2%)		
Liposarcoma				1 (2%)
Cortex, renal tubule, adenoma			1 (2%)	
Pelvis, transitional epithelium, carcinoma			1 (2%)	
Renal tubule, carcinoma	1 (2%)			1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Leukemia mononuclear	25 (50%)	29 (58%)	30 (60%)	30 (60%)
Lymphoma malignant		1 (2%)		
Mesothelioma malignant		1 (2%)		2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	50	50	50
Total primary neoplasms	145	143	149	153
Total animals with benign neoplasms	50	50	49	48
Total benign neoplasms	107	104	104	109
Total animals with malignant neoplasms	33	33	35	35
Total malignant neoplasms	38	39	45	44
Total animals with metastatic neoplasms	2		2	4
Total metastatic neoplasms	2		4	5

[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 Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	4 7 6	5 7 6	6 1 1	6 1 1	6 2 1	6 2 6	6 5 6	6 7 0	6 7 0	6 7 0	6 7 4	6 7 4	6 8 4	6 9 1	6 9 6	7 0 5	7 1 2	7 1 2	7 1 6	7 1 7	7 2 6	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 1 7	0 3 4	0 1 5	0 3 5	0 0 8	0 4 8	0 3 7	0 0 9	0 3 2	0 3 9	0 2 3	0 3 6	0 4 9	0 1 8	0 1 4	0 0 7	0 4 1	0 4 4	0 1 6	0 1 3	0 2 4	0 0 4	0 0 6	0 1 0	0 1 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery					+										+			+					+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant													X												
Pheochromocytoma benign						X				X															
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X								X		X			
Carcinoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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, carcinoma										X															
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma										X		X				X								X	
C-cell, carcinoma				X																		X			
Follicular cell, carcinoma																									
General Body System																									
Peritoneum			+			+	+					+	+		+		+	+		+	+			+	

+: 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 Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	01 12	01 29	02 00	02 21	02 25	02 26	02 27	02 28	02 29	03 30	03 33	03 38	04 43	04 46	05 00	00 01	00 12	00 23	00 25	02 22	03 31	04 40	04 42	04 45	04 47	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+	+				+																				7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																+										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																										1
Pheochromocytoma benign								X													X		X			5
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										3
Carcinoma													X													1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X		X			X		X	X	X	X		X	X		X	X	X		X	X	X	X	X	38
Pars distalis, carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma			X												X			X								7
C-cell, carcinoma																										2
Follicular cell, carcinoma																							X			1
General Body System																										
Peritoneum												+	+	+												14

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	4 7 6	5 7 6	6 1 1	6 1 1	6 2 1	6 2 6	6 5 6	6 7 0	6 7 0	6 7 0	6 7 4	6 7 4	6 8 4	6 9 1	6 9 6	7 0 5	7 1 2	7 1 2	7 1 6	7 1 7	7 2 6	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 1 7	0 3 4	0 1 5	0 3 5	0 0 8	0 4 8	0 3 7	0 0 9	0 3 2	0 3 9	0 2 3	0 3 6	0 4 9	0 1 8	0 1 4	0 0 7	0 4 1	0 4 4	0 1 6	0 1 3	0 2 4	0 0 4	0 0 6	0 1 0	0 1 1
Genital System																									
Coagulating gland	+																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma						X	X		X		X		X								X	X	X		X
Interstitial cell, adenoma	X		X					X								X	X	X	X	X					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+			+			+							+											
Lymph node, bronchial	M	M	M	M	M	+	M	+	M	+	+	+	M	M	+	M	+	M	M	M	+	M	M	+	M
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	M	+	+	+	+	+	+	M	+	M	+	M	+	M	+	+	+	M	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant																			X						
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Sebaceous gland, adenoma									X			X													
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, lipoma																							X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, osteosarcoma																							X		
Femur, osteosarcoma																									
Skeletal muscle																	+								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant																									
Carcinoma, metastatic, pituitary gland										X															

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 1 2	0 1 9	0 2 0	0 2 1	0 2 5	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 3	0 3 8	0 4 3	0 4 6	0 5 0	0 1	0 0 1	0 0 2	0 0 3	0 0 5	0 2 2	0 3 1	0 4 0	0 4 2	0 4 5	0 4 7	Total Tissues/ Tumors
Genital System																											
Coagulating gland																	+										2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X			X	X	X	X	X		X		X	X	X	X					X	X	X		X	X	26
Interstitial cell, adenoma			X	X						X		X					X	X	X								15
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node													+									+			+		7
Lymph node, bronchial	M	M	+	M	M	+	M	M	+	M	M	+	M	M	M	M	+	M	M	M	+	M	M	M	M		15
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M		2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	42
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymoma malignant																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma																X	X				X						3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma												X															1
Sebaceous gland, adenoma													X														3
Subcutaneous tissue, fibroma												X								X							2
Subcutaneous tissue, fibrosarcoma									X																		1
Subcutaneous tissue, lipoma																										X	2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, osteosarcoma																											1
Femur, osteosarcoma																				X							1
Skeletal muscle																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant							X																				1
Carcinoma, metastatic, pituitary gland																											1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	4 7 6	5 7 6	6 1 1	6 1 1	6 2 1	6 2 6	6 5 6	6 7 0	6 7 0	6 7 0	6 7 4	6 7 4	6 8 4	6 9 1	6 9 6	7 0 5	7 1 2	7 1 2	7 1 6	7 1 7	7 2 6	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 1 7	0 3 4	0 1 5	0 3 5	0 0 8	0 4 8	0 3 7	0 0 9	0 3 2	0 3 9	0 2 3	0 3 6	0 4 9	0 1 8	0 1 4	0 0 7	0 4 1	0 4 4	0 1 6	0 1 3	0 2 4	0 0 4	0 0 6	0 1 0	0 1 1
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, metastatic, bone																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory epithelium, adenoma																	X								
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																	X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X	X		X	X					X		X	X	X		X	X	X	X	X	X	X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	0 1 2	0 1 9	0 2 0	0 2 1	0 2 5	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 3	0 3 8	0 4 3	0 4 6	0 5 0	0 1	0 1 2	0 2 3	0 2 5	0 2 2	0 3 1	0 4 0	0 4 2	0 4 5	0 4 7	Total Tissues/ Tumors
Respiratory System																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma					X																						1
Alveolar/bronchiolar carcinoma															X												1
Osteosarcoma, metastatic, bone																			X								1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory epithelium, adenoma																											1
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X								X					X	X	X		X	X		X	X			25

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 138 mg/m³

Number of Days on Study	403	421	472	537	565	579	582	590	605	621	621	621	625	636	640	642	642	642	642	645	652	656	658	667
Carcass ID Number	20207	20225	20233	20243	20008	20099	20229	20244	21016	21022	21046	21047	21118	21119	21440	21161	21171	21227	21233	21341	21420	21426	21428	21435
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								
Mesentery					+			+	+		+						+							
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																								
Cardiovascular System																								
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign									X												X			
Bilateral, pheochromocytoma benign																								
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma	X		X			X	X		X	X		X	X	X	X	X		X	X		X	X	X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																								
C-cell, adenoma		X														X								
C-cell, carcinoma																								
Follicular cell, carcinoma																								
General Body System																								
Peritoneum										+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 138 mg/m³

Number of Days on Study	6 7 0	6 7 0	6 7 0	6 7 1	6 8 2	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 0 4	2 1 5	2 3 2	2 3 7	2 2 4	2 5 0	2 0 3	2 0 5	2 0 6	2 1 3	2 2 1	2 2 3	2 3 0	2 3 1	2 3 8	2 4 1	2 4 2	2 4 5	2 4 9	2 0 1	2 1 0	2 1 2	2 2 2	2 3 9	2 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X																			1
Mesentery		+					+						+							+	+	+				11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue												+														1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign			X							X		X	X		X									X		8
Bilateral, pheochromocytoma benign						X																				1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X											X														2
Parathyroid gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma			X	X	X	X	X	X	X			X		X	X	X	X	X	X	X		X	X	X		36
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																			X							1
C-cell, adenoma										X	X									X						5
C-cell, carcinoma								X							X		X									3
Follicular cell, carcinoma						X																				1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 138 mg/m³

Number of Days on Study	403	421	472	537	565	579	582	590	605	621	622	621	625	636	640	642	644	644	644	644	652	656	656	658	667
Carcass ID Number	20207	20225	20233	20243	20308	20009	20229	20244	20216	20202	20246	20247	20118	20119	20240	20111	20117	20227	20233	20236	20211	20220	20226	20228	20235
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X																			
Carcinoma											X														
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma											X		X						X	X		X	X	X	
Interstitial cell, adenoma				X	X	X		X	X			X			X		X				X				X
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+		+	+			+			+								+			+		+	+
Lymph node, bronchial	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	+	M	M	M	M	M	+	M	+	M
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	M	+	M	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Squamous cell papilloma														X											
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma						X													X						
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, schwannoma benign													X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																					+				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 138 mg/m³

Number of Days on Study	670	670	670	671	682	726	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	
Carcass ID Number	20414	21455	23232	23737	22454	25060	20303	20055	20066	21013	22123	22330	23091	23318	23381	24141	24212	24525	24649	20191	21102	21222	22299	23448	24498	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X			X			X	X		X	X			X	X		X	X	X		X	X	X		22
Interstitial cell, adenoma						X	X			X			X				X				X				X	17
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+	+							+		+	+					+			+					16
Lymph node, bronchial	+	+	M	M	M	+	+	M	+	+	M	M	M	M	+	M	M	M	M	+	M	M	M	M	M	12
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma									X																	1
Fibroadenoma																			X							1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																							X			1
Squamous cell papilloma											X															2
Sebaceous gland, adenoma																			X							1
Subcutaneous tissue, fibroma									X												X					4
Subcutaneous tissue, fibrosarcoma							X																			1
Subcutaneous tissue, schwannoma benign																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 138 mg/m³

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 138 mg/m³

Number of Days on Study	6 7 0	6 7 0	6 7 0	6 7 1	6 8 2	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 0 4	2 1 5	2 3 2	2 3 7	2 2 4	2 5 0	2 0 3	2 0 5	2 0 6	2 1 3	2 2 1	2 2 3	2 3 0	2 3 1	2 3 8	2 4 1	2 4 2	2 4 5	2 4 9	2 0 1	2 1 0	2 1 2	2 2 2	2 3 9	2 4 8	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma						X																				1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X	X	X	X			X	X	X			X	X		X			X			X	X	29
Lymphoma malignant											X															1
Mesothelioma malignant											X															1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	3 9 6	5 0 9	5 2 9	5 4 1	5 4 6	5 5 6	5 5 8	5 8 9	5 9 3	6 1 8	6 2 1	6 3 3	6 4 2	6 4 7	6 7 3	6 7 5	6 7 5	6 9 1	6 9 6	6 9 8	7 0 2	7 0 5	7 0 8	7 1 2	7 1 5
Carcass ID Number	4 2 8	4 2 2	4 4 0	4 1 7	4 3 7	4 3 6	4 3 3	4 2 5	4 4 5	4 4 4	4 4 3	4 1 9	4 0 8	4 1 3	4 2 4	4 0 4	4 0 5	4 1 5	4 2 3	4 4 2	4 0 2	4 4 7	4 0 3	4 3 0	4 0 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cholangiocarcinoma																									
Mesentery		+	+		+										+				+	+	+		+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Tongue																							+		
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Atrium, carcinoma, metastatic, kidney																						X			
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign				X				X	X									X	X	X					
Bilateral, pheochromocytoma benign																X									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																							X		
Carcinoma											X													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		X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma								X																	
C-cell, carcinoma																					X				
Follicular cell, adenoma																									
Follicular cell, carcinoma					X																				
General Body System																									
Peritoneum										+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	7 1 5	7 1 7	7 2 0	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	4 4 9	4 2 0	4 1 8	4 1 1	4 0 5	4 0 6	4 0 9	4 1 4	4 2 6	4 2 7	4 2 9	4 3 2	4 3 4	4 3 5	4 3 8	4 4 1	4 4 6	4 4 8	4 0 1	4 1 0	4 1 2	4 1 6	4 2 1	4 3 1	4 3 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cholangiocarcinoma																	X									1
Mesentery												+						+							+	11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue							+						+													3
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Atrium, carcinoma, metastatic, kidney																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign	X				X		X	X		X						X										12
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma								X																		3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X		X	X				X	X	X		X	X	X	X		X	X	X	X	X	X	35
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma															X											1
C-cell, adenoma			X	X		X																		X		5
C-cell, carcinoma										X																2
Follicular cell, adenoma																		X								1
Follicular cell, carcinoma																										1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	3 9 6	5 0 9	5 2 9	5 4 1	5 4 6	5 5 6	5 5 8	5 8 9	5 9 3	6 1 8	6 2 1	6 3 3	6 4 2	6 4 7	6 7 3	6 7 5	6 7 5	6 9 1	6 9 6	6 9 8	7 0 2	7 0 5	7 0 8	7 1 2	7 1 5
Carcass ID Number	4 2 8	4 2 2	4 4 0	4 1 7	4 3 7	4 3 6	4 3 3	4 2 5	4 4 5	4 4 4	4 4 3	4 1 9	4 0 8	4 1 3	4 2 4	4 0 4	4 5 0	4 1 5	4 2 3	4 4 2	4 0 2	4 4 7	4 0 3	4 3 0	4 0 7
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma	X																			X					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma		X					X		X					X		X		X	X	X	X	X		X	X
Interstitial cell, adenoma				X		X		X			X		X				X						X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+								+	+						+			+		+	+
Lymph node, bronchial	M	M	+	+	M	+	M	+	M	M	+	M	M	+	M	M	+	M	M	M	M	+	M	+	+
Carcinoma, metastatic, kidney																						X			
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																					X				
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	7 1 5	7 1 7	7 2 0	7 2 6	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	4 4 9	4 2 0	4 1 8	4 1 1	4 0 5	4 0 6	4 0 9	4 1 4	4 2 6	4 2 7	4 2 9	4 3 2	4 3 4	4 3 5	4 3 8	4 4 1	4 4 6	4 4 8	4 0 1	4 1 0	4 1 2	4 1 6	4 2 1	4 3 1	4 3 9	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																			X			X				2
Carcinoma																	X									3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X	X		X			X	X	X	X	X		X		X		X	X		X	X		X	X	28
Interstitial cell, adenoma	X						X								X											10
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+													+					+	+			11
Lymph node, bronchial	+	+	M	M	M	M	+	M	M	+	M	M	M	M	M	M	+	M	M	M	M	M	+	M	M	16
Carcinoma, metastatic, kidney																										1
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	M	M	+	M	+	+	43
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma												X			X											2
Fibroadenoma							X				X															2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma											X															1
Sebaceous gland, adenoma																									X	1
Subcutaneous tissue, fibroma										X														X		2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle													+													1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	3 9 6	5 0 9	5 2 9	5 4 1	5 4 6	5 5 6	5 5 8	5 8 9	5 9 3	6 1 8	6 2 1	6 3 3	6 4 2	6 4 7	6 7 3	6 7 5	6 7 5	6 9 1	6 9 6	6 9 8	7 0 2	7 0 5	7 0 8	7 1 2	7 1 5
Carcass ID Number	4 2 8	4 2 2	4 4 0	4 1 7	4 3 7	4 3 6	4 3 3	4 2 5	4 4 5	4 4 4	4 4 3	4 1 9	4 0 8	4 1 3	4 2 4	4 0 4	4 5 0	4 1 5	4 2 3	4 4 2	4 0 2	4 4 7	4 0 3	4 3 0	4 0 7
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, kidney																						X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortex, renal tubule, adenoma		X																							
Pelvis, transitional epithelium, carcinoma																						X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X	X	X	X	X			X	X	X	X	X	X		X	X	X		X	X	X	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	715	717	720	726	729	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	
Carcass ID Number	44249	44320	44418	44411	44005	44006	44009	44014	44026	44027	44029	44032	44034	44035	44038	44041	44416	44428	44701	44810	44811	44812	44821	44823	44839	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																	X			X						2
Alveolar/bronchiolar carcinoma																X										1
Carcinoma, metastatic, kidney																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortex, renal tubule, adenoma																										1
Pelvis, transitional epithelium, carcinoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X		X					X	X			X		X	X	X			X				30

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	43	46	52	52	54	56	56	57	58	59	60	61	63	64	64	64	64	65	67	67	68	68	68	68	69
	25	25	29	49	28	43	35	88	13	36	06	04	67	02	45	57	22	73	55	83	44	44	44	44	91
Carcass ID Number	60	63	63	61	61	64	62	61	61	63	60	60	63	65	64	62	62	62	62	63	64	61	62	63	64
	05	55	59	44	22	11	33	77	33	44	08	44	77	30	33	20	44	99	88	11	22	20	77	22	44
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	A	+	A	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	A	+	A	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma									X																
Mesentery		+		+		+			+	+	+									+					
Oral mucosa					+																				
Squamous cell carcinoma					X																				
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant							X																		
Pheochromocytoma benign																		X	X	X	X				
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X									X								
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X				X	X	X	X	X			X	X			X				X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																		X	X						
Follicular cell, carcinoma															X										
General Body System																									
Peritoneum						+	+					+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	6 9 1	6 9 1	6 9 8	7 0 5	7 0 5	7 1 2	7 1 2	7 1 7	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 4 6	6 4 7	6 0 3	6 1 1	6 2 5	6 0 1	6 1 5	6 4 9	6 0 6	6 0 2	6 0 7	6 1 6	6 1 2	6 2 2	6 2 6	6 3 0	6 3 3	6 3 6	6 3 8	6 4 0	6 4 5	6 0 9	6 1 8	6 1 9	6 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery					+					+		+					+	+						+		13
Oral mucosa																										1
Squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant			X																							2
Pheochromocytoma benign					X	X						X	X			X		X	X	X				X		13
Bilateral, pheochromocytoma benign		X		X				X	X																	4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X											3
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X			X	X	X	X	X	X	X	X	X			X	X	X	X	X	X		X	X	X		31
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																	X							X		4
Follicular cell, carcinoma																										1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+						+		+	+	+	+				+	+	32

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	43	46	52	52	54	56	56	57	58	59	60	61	63	64	64	64	65	67	67	68	68	68	68	69
Carcass ID Number	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
	05	03	03	01	01	04	02	01	01	03	04	00	04	03	05	03	02	02	02	03	04	01	02	03	04
		55	59	44	42	41	43	47	43	44	08	04	47	70	43	20	04	49	98	11	12	20	07	22	44
Genital System																								
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma					X	X	X					X		X	X	X	X	X	X	X	X	X	X	X
Interstitial cell, adenoma			X						X				X											
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+			+			+				+	+		+	+	+		+		+		+	+
Lymph node, bronchial	M	M	M	M	M	M	M	M	M	M	+	M	M	+	M	M	+	+	M	M	+	M	M	M	+
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	M	+	+	+	M	+	+	+	+	M	+	+	M	M	+	+	+	+	+	M	+
Carcinoma, metastatic, thyroid gland															X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymoma malignant							X																		
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																							X		
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, lipoma																									
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle															+										
Carcinoma, metastatic, thyroid gland															X										
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	6 9 1	6 9 1	6 9 8	7 0 5	7 0 5	7 1 2	7 1 2	7 1 7	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 4 4 6	6 4 4 7	6 4 0 3	6 4 1 1	6 4 2 5	6 4 0 1	6 4 1 5	6 4 4 9	6 4 0 6	6 4 0 2	6 4 0 7	6 4 1 6	6 4 2 1	6 4 2 2	6 4 2 6	6 4 3 0	6 4 3 3	6 4 3 6	6 4 3 8	6 4 4 0	6 4 4 5	6 4 0 9	6 4 1 8	6 4 1 9	6 4 1 4	6 4 6 8	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																					X					1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma									X																	1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma		X	X			X			X		X	X	X		X			X			X	X	X	X	X	30
Interstitial cell, adenoma				X	X		X	X		X				X			X		X	X						12
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+										+														17
Lymph node, bronchial	M	M	M	M	M	+	+	+	M	M	+	M	M	+	+	M	M	M	M	M	M	M	+	M	M	13
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	M	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	40
Carcinoma, metastatic, thyroid gland																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymoma malignant																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma			X											X							X					4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma						X														X						3
Squamous cell papilloma												X						X								2
Subcutaneous tissue, fibroma								X												X						2
Subcutaneous tissue, hemangioma																					X					1
Subcutaneous tissue, lipoma							X																			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Carcinoma, metastatic, thyroid gland																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	432	456	522	529	548	563	565	578	581	593	606	610	636	642	645	647	652	672	673	675	683	684	688	689	691
Carcass ID Number	60505	60355	60339	60614	60112	60641	60223	60117	60113	60334	60088	60044	60377	60550	60433	60220	60224	60429	60238	60341	60412	60420	60423	60442	60444
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Thymoma malignant, metastatic, thymus							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, oral mucosa					X																				
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland			+																						
Carcinoma			X																						
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liposarcoma																	X								
Renal tubule, carcinoma																									
Ureter																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X			X	X			X			X	X	X		X	X	X		X	X	X	X	X	X
Mesothelioma malignant						X																		X	

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	6 9 1	6 9 1	6 9 8	7 0 5	7 0 5	7 1 2	7 1 2	7 1 7	7 2 5	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 4 6	6 4 7	6 0 3	6 1 1	6 2 5	6 0 1	6 1 5	6 4 9	6 0 6	6 0 2	6 0 7	6 1 6	6 1 2	6 2 1	6 2 2	6 2 6	6 3 0	6 3 3	6 3 6	6 3 8	6 4 0	6 4 5	6 0 9	6 1 8	6 1 9	6 4 8	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma malignant, metastatic, adrenal medulla			X																							1
Thymoma malignant, metastatic, thymus																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, oral mucosa																										1
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liposarcoma																										1
Renal tubule, carcinoma							X																			1
Ureter																				+						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X			X	X		X	X	X								X		X	X	X	X	30
Mesothelioma malignant																										2

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	5/50 (10%)	9/50 (18%)	13/50 (26%)	17/50 (34%)
Adjusted rate[b]	11.0%	22.9%	29.9%	41.6%
Terminal rate[c]	3/29 (10%)	5/19 (26%)	5/21 (24%)	7/16 (44%)
First incidence (days)	626	605	541	652
Poly-3 test[d]	P<0.001	P=0.117	P=0.022	P<0.001
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	6/50 (12%)	9/50 (18%)	13/50 (26%)	19/50 (38%)
Adjusted rate	13.1%	22.9%	29.9%	45.8%
Terminal rate	3/29 (10%)	5/19 (26%)	5/21 (24%)	7/16 (44%)
First incidence (days)	626	605	541	565
Poly-3 test	P<0.001	P=0.185	P=0.044	P<0.001
Kidney (Renal Tubule): Adenoma (Step Sections)				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	7/50 (14%)
Adjusted rate	6.6%	5.1%	4.8%	17.5%
Terminal rate	1/29 (3%)	0/19 (0%)	1/21 (5%)	1/16 (6%)
First incidence (days)	621	636	673	667
Poly-3 test	P=0.041	P=0.569N	P=0.541N	P=0.110
Kidney (Renal Tubule): Adenoma (Single and Step Sections)				
Overall rate	3/50 (6%)	2/50 (4%)	3/50 (6%)	7/50 (14%)
Adjusted rate	6.6%	5.1%	7.1%	17.5%
Terminal rate	1/29 (3%)	0/19 (0%)	1/21 (5%)	1/16 (6%)
First incidence (days)	621	636	509	667
Poly-3 test	P=0.039	P=0.569N	P=0.628	P=0.110
Kidney (Renal Tubule): Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	4/50 (8%)	2/50 (4%)	3/50 (6%)	7/50 (14%)
Adjusted rate	8.8%	5.1%	7.1%	17.5%
Terminal rate	1/29 (3%)	0/19 (0%)	1/21 (5%)	1/16 (6%)
First incidence (days)	621	636	509	667
Poly-3 test	P=0.077	P=0.411N	P=0.541N	P=0.191
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/50 (4%)	0/50 (0%)	3/50 (6%)	0/49 (0%)
Adjusted rate	4.4%	0.0%	7.3%	0.0%
Terminal rate	2/29 (7%)	0/19 (0%)	3/21 (14%)	0/16 (0%)
First incidence (days)	729 (T)	—[e]	729 (T)	—
Poly-3 test	P=0.389N	P=0.274N	P=0.461	P=0.272N
Mammary Gland: Fibroadenoma				
Overall rate	3/50 (6%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted rate	6.7%	2.6%	4.8%	10.1%
Terminal rate	3/29 (10%)	1/19 (5%)	2/21 (10%)	2/16 (13%)
First incidence (days)	729 (T)	729 (T)	729 (T)	691
Poly-3 test	P=0.236	P=0.364N	P=0.539N	P=0.431
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	3/50 (6%)	2/50 (4%)	4/50 (8%)	4/50 (8%)
Adjusted rate	6.7%	5.2%	9.7%	10.1%
Terminal rate	3/29 (10%)	2/19 (11%)	4/21 (19%)	2/16 (13%)
First incidence (days)	729 (T)	729 (T)	729 (T)	691
Poly-3 test	P=0.265	P=0.572N	P=0.453	P=0.431

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted rate	6.6%	5.2%	2.4%	7.5%
Terminal rate	1/29 (3%)	1/19 (5%)	0/21 (0%)	1/16 (6%)
First incidence (days)	674	670	708	578
Poly-3 test	P=0.535	P=0.572N	P=0.338N	P=0.606
Pancreatic Islets: Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.2%	0.0%	7.2%	0.0%
Terminal rate	1/29 (3%)	0/19 (0%)	1/21 (5%)	0/16 (0%)
First incidence (days)	729 (T)	—	621	—
Poly-3 test	P=0.589N	P=0.531N	P=0.279	P=0.527N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	4/50 (8%)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted rate	8.8%	5.2%	9.6%	7.5%
Terminal rate	2/29 (7%)	1/19 (5%)	1/21 (5%)	1/16 (6%)
First incidence (days)	674	670	621	578
Poly-3 test	P=0.555	P=0.412N	P=0.600	P=0.565N
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	38/50 (76%)	36/50 (72%)	35/50 (70%)	31/50 (62%)
Adjusted rate	77.7%	78.1%	75.2%	69.4%
Terminal rate	21/29 (72%)	14/19 (74%)	15/21 (71%)	12/16 (75%)
First incidence (days)	476	403	529	522
Poly-3 test	P=0.162N	P=0.584	P=0.481N	P=0.239N
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	39/50 (78%)	36/50 (72%)	35/50 (70%)	31/50 (62%)
Adjusted rate	79.4%	78.1%	75.2%	69.4%
Terminal rate	21/29 (72%)	14/19 (74%)	15/21 (71%)	12/16 (75%)
First incidence (days)	476	403	529	522
Poly-3 test	P=0.125N	P=0.539N	P=0.401N	P=0.180N
Preputial Gland: Carcinoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	2.6%	7.1%	0.0%
Terminal rate	0/29 (0%)	0/19 (0%)	1/21 (5%)	0/16 (0%)
First incidence (days)	—	621	396	—[f]
Poly-3 test	P=0.562	P=0.470	P=0.108	—
Preputial Gland: Adenoma or Carcinoma				
Overall rate	0/50 (0%)	2/50 (4%)	5/50 (10%)	1/50 (2%)
Adjusted rate	0.0%	5.1%	11.8%	2.5%
Terminal rate	0/29 (0%)	0/19 (0%)	3/21 (14%)	1/16 (6%)
First incidence (days)	—	579	396	729 (T)
Poly-3 test	P=0.327	P=0.208	P=0.025	P=0.473
Skin: Basal Cell Carcinoma				
Overall rate	0/50 (0%)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted rate	0.0%	2.6%	2.4%	7.6%
Terminal rate	0/29 (0%)	1/19 (5%)	1/21 (5%)	1/16 (6%)
First incidence (days)	—	729 (T)	729 (T)	684
Poly-3 test	P=0.048	P=0.469	P=0.483	P=0.097

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Skin: Squamous Cell Papilloma or Basal Cell Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	5/50 (10%)
Adjusted rate	2.2%	7.7%	2.4%	12.6%
Terminal rate	1/29 (3%)	2/19 (11%)	1/21 (5%)	3/16 (19%)
First incidence (days)	729 (T)	636	729 (T)	684
Poly-3 test	P=0.075	P=0.253	P=0.741	P=0.074
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	2/50 (4%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate	4.4%	10.2%	4.8%	5.1%
Terminal rate	2/29 (7%)	2/19 (11%)	2/21 (10%)	1/16 (6%)
First incidence (days)	729 (T)	579	729 (T)	717
Poly-3 test	P=0.451N	P=0.276	P=0.663	P=0.646
Skin (Subcutaneous Tissue): Fibroma or Fibrosarcoma				
Overall rate	3/50 (6%)	5/50 (10%)	2/50 (4%)	2/50 (4%)
Adjusted rate	6.7%	12.7%	4.8%	5.1%
Terminal rate	3/29 (10%)	3/19 (16%)	2/21 (10%)	1/16 (6%)
First incidence (days)	729 (T)	579	729 (T)	717
Poly-3 test	P=0.266N	P=0.283	P=0.539N	P=0.560N
Skin (Sebaceous Gland): Adenoma				
Overall rate	3/50 (6%)	1/50 (2%)	1/50 (2%)	0/50 (0%)
Adjusted rate	6.6%	2.6%	2.4%	0.0%
Terminal rate	1/29 (3%)	1/19 (5%)	1/21 (5%)	0/16 (0%)
First incidence (days)	670	729 (T)	729 (T)	—
Poly-3 test	P=0.090N	P=0.368N	P=0.340N	P=0.146N
Testes: Adenoma				
Overall rate	41/50 (82%)	39/50 (78%)	38/50 (76%)	42/50 (84%)
Adjusted rate	85.4%	86.0%	80.9%	90.7%
Terminal rate	27/29 (93%)	18/19 (95%)	16/21 (76%)	15/16 (94%)
First incidence (days)	476	537	509	522
Poly-3 test	P=0.293	P=0.596	P=0.365N	P=0.300
Thyroid Gland (C-Cell): Adenoma				
Overall rate	7/50 (14%)	6/50 (12%)	6/50 (12%)	4/50 (8%)
Adjusted rate	15.4%	15.2%	14.3%	10.0%
Terminal rate	4/29 (14%)	4/19 (21%)	3/21 (14%)	2/16 (13%)
First incidence (days)	670	421	589	652
Poly-3 test	P=0.269N	P=0.609N	P=0.566N	P=0.341N
Thyroid Gland (C-Cell): Carcinoma				
Overall rate	2/50 (4%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	4.4%	7.8%	4.8%	0.0%
Terminal rate	1/29 (3%)	3/19 (16%)	1/21 (5%)	0/16 (0%)
First incidence (days)	611	729 (T)	702	—
Poly-3 test	P=0.140N	P=0.424	P=0.661	P=0.270N
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	9/50 (18%)	9/50 (18%)	8/50 (16%)	4/50 (8%)
Adjusted rate	19.6%	22.8%	19.1%	10.0%
Terminal rate	5/29 (17%)	7/19 (37%)	4/21 (19%)	2/16 (13%)
First incidence	611	421	589	652
Poly-3 test	P=0.108N	P=0.463	P=0.583N	P=0.176N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
All Organs: Mononuclear Cell Leukemia				
Overall rate	25/50 (50%)	29/50 (58%)	30/50 (60%)	30/50 (60%)
Adjusted rate	52.1%	64.8%	63.4%	65.3%
Terminal rate	12/29 (41%)	10/19 (53%)	8/21 (38%)	8/16 (50%)
First incidence	476	421	509	432
Poly-3 test	P=0.175	P=0.144	P=0.178	P=0.133
All Organs: Benign Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	49/50 (98%)	48/50 (96%)
Adjusted rate	100.0%	100.0%	99.7%	99.0%
Terminal rate	29/29 (100%)	19/19 (100%)	21/21 (100%)	16/16 (100%)
First incidence	476	403	509	522
Poly-3 test	P=0.366N	—	P=1.000N	P=0.942N
All Organs: Malignant Neoplasms				
Overall rate	33/50 (66%)	33/50 (66%)	35/50 (70%)	35/50 (70%)
Adjusted rate	68.1%	73.8%	72.5%	73.6%
Terminal rate	17/29 (59%)	14/19 (74%)	11/21 (52%)	8/16 (50%)
First incidence	476	421	396	432
Poly-3 test	P=0.364	P=0.348	P=0.399	P=0.352
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	50/50 (100%)	50/50 (100%)	50/50 (100%)
Adjusted rate	100.0%	100.0%	100.0%	100.0%
Terminal rate	29/29 (100%)	19/19 (100%)	21/21 (100%)	16/16 (100%)
First incidence	476	403	396	432
Poly-3 test	—	—	—	—

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal medulla, lung, pancreatic islets, pituitary gland, preputial gland, testes, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4
Historical Incidence of Adrenal Medulla Neoplasms in Control Male F344/N Rats[a]

Study	Incidence in Controls	
	Benign Pheochromocytoma	Benign or Malignant Pheochromocytoma
Historical Incidence: Inhalation Studies		
Decalin	7/49	8/49
Indium phosphide	10/50	10/50
Naphthalene	4/49	5/49
Propylene glycol mono-*t*-butyl ether	12/50	14/50
Stoddard solvent IIC	5/50	6/50
Vanadium pentoxide	4/50	5/50
Overall Historical Incidence: Inhalation Studies		
Total (%)	42/298 (14.1%)	48/298 (16.1%)
Mean ± standard deviation	14.1% ± 6.7%	16.1% ± 7.0%
Range	8%-24%	10%-28%
Overall Historical Incidence		
Total (%)	125/1,053 (11.9%)	145/1,053 (13.8%)
Mean ± standard deviation	11.8% ± 6.2%	13.8% ± 6.5%
Range	5%-24%	5%-28%

[a] Data as of March 3, 2003

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	18	27	21	27
Natural death	3	4	8	7
Survivors				
Terminal sacrifice	29	19	21	16
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Intestine large, cecum	(49)	(49)	(48)	(48)
Atrophy				1 (2%)
Necrosis		1 (2%)		
Epithelium, cyst		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	
Basophilic focus	1 (2%)			
Clear cell focus	6 (12%)	4 (8%)	3 (6%)	3 (6%)
Eosinophilic focus				1 (2%)
Hemorrhage	1 (2%)			
Hepatodiaphragmatic nodule	7 (14%)	3 (6%)	5 (10%)	3 (6%)
Inflammation, granulomatous	1 (2%)	1 (2%)		1 (2%)
Necrosis	1 (2%)			1 (2%)
Thrombosis				1 (2%)
Vacuolization cytoplasmic	3 (6%)	3 (6%)	1 (2%)	2 (4%)
Bile duct, hyperplasia			3 (6%)	2 (4%)
Hepatocyte, regeneration				1 (2%)
Periportal, pigmentation	1 (2%)		2 (4%)	
Mesentery	(7)	(11)	(11)	(13)
Necrosis	7 (100%)	11 (100%)	11 (100%)	12 (92%)
Pancreas	(50)	(50)	(50)	(50)
Acinus, atrophy	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Stomach, forestomach	(50)	(50)	(49)	(50)
Hyperplasia, squamous	1 (2%)		1 (2%)	
Ulcer	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Stomach, glandular	(50)	(50)	(49)	(50)
Erosion		1 (2%)	3 (6%)	
Hyperplasia			1 (2%)	
Mineralization		1 (2%)		
Ulcer		1 (2%)	1 (2%)	2 (4%)
Tongue	(1)	(1)	(3)	
Epithelium, hyperkeratosis			1 (33%)	
Epithelium, hyperplasia	1 (100%)	1 (100%)	1 (33%)	

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

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Cardiovascular System				
Blood vessel	(50)	(50)	(50)	(50)
Mineralization		1 (2%)		
Pulmonary artery, thrombosis				1 (2%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	13 (26%)	4 (8%)	5 (10%)	9 (18%)
Artery, mineralization		1 (2%)		
Atrium, thrombosis	1 (2%)		1 (2%)	5 (10%)
Myocardium, thrombosis				1 (2%)
Ventricle, thrombosis				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Mineralization			1 (2%)	
Necrosis	1 (2%)	1 (2%)	1 (2%)	
Vacuolization cytoplasmic	15 (30%)	5 (10%)	14 (28%)	10 (20%)
Adrenal medulla	(50)	(50)	(50)	(50)
Hyperplasia	12 (24%)	14 (28%)	23 (46%)	15 (30%)
Mineralization				1 (2%)
Necrosis				2 (4%)
Thrombosis			1 (2%)	
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Pituitary gland	(50)	(50)	(50)	(50)
Pars distalis, cyst	1 (2%)		1 (2%)	1 (2%)
Pars distalis, hemorrhage		1 (2%)	1 (2%)	3 (6%)
Pars distalis, hyperplasia	4 (8%)	5 (10%)	6 (12%)	5 (10%)
Thyroid gland	(50)	(50)	(50)	(50)
C-cell, hyperplasia	8 (16%)	4 (8%)	6 (12%)	11 (22%)
Follicular cell, hyperplasia		1 (2%)		
General Body System				
Peritoneum	(14)	(41)	(41)	(32)
Inflammation, granulomatous				1 (3%)
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm			1 (2%)	
Preputial gland	(50)	(50)	(50)	(50)
Cyst	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Hyperplasia	1 (2%)	1 (2%)		2 (4%)
Inflammation, suppurative			4 (8%)	
Prostate	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)		3 (6%)
Inflammation, suppurative	10 (20%)	10 (20%)	14 (28%)	12 (24%)
Seminal vesicle	(50)	(50)	(50)	(50)
Dilatation			1 (2%)	1 (2%)
Hyperplasia				1 (2%)
Testes	(50)	(50)	(50)	(50)
Artery, inflammation, chronic active	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Germinal epithelium, atrophy	11 (22%)	9 (18%)	15 (30%)	11 (22%)
Interstitial cell, hyperplasia	5 (10%)	4 (8%)	2 (4%)	2 (4%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Thrombosis				1 (2%)
Myeloid cell, hyperplasia			1 (2%)	
Lymph node	(7)	(16)	(11)	(17)
Hyperplasia, lymphoid				1 (6%)
Deep cervical, angiectasis				1 (6%)
Deep cervical, ectasia		1 (6%)		
Pancreatic, angiectasis	1 (14%)			
Pancreatic, ectasia	1 (14%)		1 (9%)	
Pancreatic, infiltration cellular, histiocyte		1 (6%)		
Pancreatic, pigmentation		1 (6%)		1 (6%)
Thoracic, ectasia				1 (6%)
Lymph node, bronchial	(15)	(12)	(16)	(13)
Fibrosis	1 (7%)			
Hematopoietic cell proliferation	1 (7%)			
Hyperplasia, lymphoid	1 (7%)			
Infiltration cellular, histiocyte	1 (7%)	1 (8%)		
Pigmentation	1 (7%)	1 (8%)		
Lymph node, mandibular	(2)			
Hematopoietic cell proliferation	1 (50%)			
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Hyperplasia, lymphoid		1 (2%)		
Necrosis			2 (4%)	
Lymph node, mediastinal	(42)	(44)	(43)	(40)
Angiectasis			2 (5%)	
Hyperplasia, lymphoid	1 (2%)	1 (2%)	1 (2%)	
Infiltration cellular			1 (2%)	
Infiltration cellular, histiocyte				1 (3%)
Pigmentation			1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Accessory spleen	1 (2%)		3 (6%)	1 (2%)
Fibrosis	2 (4%)	3 (6%)	4 (8%)	6 (12%)
Hematopoietic cell proliferation	1 (2%)		2 (4%)	
Hemorrhage	2 (4%)	2 (4%)	4 (8%)	1 (2%)
Necrosis	3 (6%)		3 (6%)	
Thrombosis			1 (2%)	
Thymus	(49)	(49)	(47)	(50)
Cyst				1 (2%)
Thrombosis			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocele	3 (6%)	2 (4%)	3 (6%)	2 (4%)
Hyperplasia		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	5 (10%)	2 (4%)	2 (4%)	3 (6%)
Hyperkeratosis	1 (2%)		1 (2%)	2 (4%)
Hyperplasia				1 (2%)
Inflammation, chronic			2 (4%)	
Inflammation, granulomatous			1 (2%)	
Ulcer				1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Rib, cartilage, degeneration	1 (2%)			
Turbinate, cartilage, hyperplasia				1 (2%)
Skeletal muscle	(1)	(1)	(1)	(1)
Hemorrhage	1 (100%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	13 (26%)	15 (30%)	10 (20%)	9 (18%)
Hemorrhage	4 (8%)	4 (8%)	5 (10%)	3 (6%)
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Foreign body	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Inflammation, chronic			2 (4%)	
Inflammation, suppurative		2 (4%)		2 (4%)
Epiglottis, metaplasia, squamous		1 (2%)		
Lung	(50)	(50)	(50)	(49)
Foreign body				1 (2%)
Hemorrhage	5 (10%)	5 (10%)	6 (12%)	4 (8%)
Inflammation, suppurative				2 (4%)
Alveolar epithelium, hyperplasia	10 (20%)	3 (6%)	6 (12%)	7 (14%)
Alveolar epithelium, metaplasia, squamous			2 (4%)	
Alveolus, foreign body				1 (2%)
Alveolus, infiltration cellular, histiocyte	13 (26%)	11 (22%)	7 (14%)	5 (10%)
Alveolus, mineralization		1 (2%)		
Alveolus, proteinosis		1 (2%)		
Interstitium, fibrosis	1 (2%)	5 (10%)	2 (4%)	1 (2%)
Nose	(50)	(50)	(50)	(50)
Foreign body	2 (4%)	3 (6%)	1 (2%)	2 (4%)
Inflammation, suppurative	4 (8%)	4 (8%)	2 (4%)	5 (10%)
Glands, hyperplasia	1 (2%)			
Goblet cell, hyperplasia	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Nasolacrimal duct, inflammation, suppurative	1 (2%)			
Olfactory epithelium, degeneration, hyaline	2 (4%)	8 (16%)	2 (4%)	3 (6%)
Respiratory epithelium, hyperplasia	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Turbinate, hyperplasia, atypical				1 (2%)
Turbinate, necrosis	1 (2%)			
Pleura	(50)	(50)	(50)	(50)
Fibrosis	2 (4%)	12 (24%)	5 (10%)	1 (2%)
Inflammation, chronic	11 (22%)	2 (4%)	1 (2%)	5 (10%)
Special Senses System				
Eye	(50)	(50)	(49)	(50)
Atrophy	1 (2%)			
Inflammation, suppurative		1 (2%)		
Lens, cataract	6 (12%)	1 (2%)	3 (6%)	2 (4%)

Table A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cyst				2 (4%)
Hemorrhage				1 (2%)
Nephropathy, chronic	50 (100%)	49 (98%)	50 (100%)	50 (100%)
Cortex, infarct	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Cortex, renal tubule, accumulation, hyaline droplet	2 (4%)	5 (10%)	3 (6%)	2 (4%)
Cortex, renal tubule, casts granular		1 (2%)	1 (2%)	3 (6%)
Cortex, renal tubule, hyperplasia		1 (2%)	8 (16%)	23 (46%)
Cortex, renal tubule, mineralization				1 (2%)
Medulla, casts granular		3 (6%)	1 (2%)	3 (6%)
Papilla, mineralization	1 (2%)	8 (16%)	30 (60%)	39 (78%)
Papilla, necrosis		1 (2%)		
Pelvis, dilatation		1 (2%)	1 (2%)	1 (2%)
Pelvis, transitional epithelium, hyperplasia		2 (4%)	8 (16%)	5 (10%)
Renal tubule, mineralization		1 (2%)		
Urinary bladder	(50)	(50)	(50)	(50)
Hemorrhage		1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)		
Muscularis, transitional epithelium, mineralization		1 (2%)		
Transitional epithelium, hyperplasia				1 (2%)

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF STODDARD SOLVENT IIC

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	12	19	15	23
Natural deaths	2	1	3	2
Survivors				
Terminal sacrifice	36	30	32	25
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, jejunum	(49)	(49)	(47)	(48)
Leiomyoma			1 (2%)	
Liver	(49)	(50)	(50)	(50)
Salivary glands	(49)	(50)	(50)	(50)
Carcinoma			1 (2%)	
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Adenoma			1 (2%)	
Carcinoma	1 (2%)			
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma complex		1 (2%)		
Pheochromocytoma benign	2 (4%)	4 (8%)	2 (4%)	2 (4%)
Islets, pancreatic	(49)	(50)	(50)	(50)
Adenoma	1 (2%)		1 (2%)	
Carcinoma			1 (2%)	
Pituitary gland	(49)	(50)	(50)	(50)
Pars distalis, adenoma	27 (55%)	34 (68%)	33 (66%)	28 (56%)
Pars distalis, carcinoma		1 (2%)		1 (2%)
Thyroid gland	(49)	(50)	(50)	(50)
C-cell, adenoma	3 (6%)	5 (10%)	2 (4%)	4 (8%)
C-cell, carcinoma	1 (2%)	2 (4%)		1 (2%)
Follicular cell, adenoma			1 (2%)	
General Body System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Genital System				
Clitoral gland	(49)	(50)	(50)	(50)
Adenoma		3 (6%)	5 (10%)	6 (12%)
Carcinoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Ovary	(50)	(50)	(50)	(50)
Granulosa cell tumor malignant			1 (2%)	
Uterus	(49)	(50)	(50)	(50)
Leiomyosarcoma			1 (2%)	
Polyp stromal	10 (20%)	9 (18%)	10 (20%)	9 (18%)
Sarcoma stromal		1 (2%)		1 (2%)
Cervix, sarcoma stromal	1 (2%)			
Vagina			(1)	
Sarcoma			1 (100%)	
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Lymph node	(5)	(5)	(5)	(4)
Lymph node, bronchial	(12)	(7)	(8)	(11)
Lymph node, mandibular	(3)		(2)	
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Lymph node, mediastinal	(45)	(39)	(42)	(45)
Carcinoma, metastatic, thyroid gland				1 (2%)
Spleen	(49)	(50)	(50)	(50)
Sarcoma, metastatic, skin			1 (2%)	
Thymus	(47)	(47)	(46)	(48)
Thymoma malignant				1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma	3 (6%)	2 (4%)	9 (18%)	7 (14%)
Carcinoma, multiple	1 (2%)		1 (2%)	1 (2%)
Fibroadenoma	14 (28%)	13 (26%)	10 (20%)	16 (32%)
Fibroadenoma, multiple	5 (10%)	13 (26%)	12 (24%)	8 (16%)
Fibroma			1 (2%)	
Skin	(50)	(50)	(50)	(50)
Basal cell adenoma				1 (2%)
Basal cell carcinoma			1 (2%)	
Keratoacanthoma	1 (2%)			
Sarcoma			1 (2%)	
Subcutaneous tissue, fibroma				2 (4%)
Subcutaneous tissue, fibrosarcoma			2 (4%)	
Subcutaneous tissue, sarcoma			1 (2%)	
Subcutaneous tissue, schwannoma benign	1 (2%)			1 (2%)
Musculoskeletal System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Nervous System				
Brain	(49)	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland		1 (2%)		
Glioma malignant				1 (2%)
Cerebellum, glioma malignant				1 (2%)
Respiratory System				
Lung	(49)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma				1 (2%)
Alveolar/bronchiolar carcinoma			1 (2%)	
Carcinoma, metastatic, mammary gland	1 (2%)		2 (4%)	1 (2%)
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)			
Pleura	(48)	(50)	(50)	(50)
Mesothelium, carcinoma, metastatic, lung			1 (2%)	
Special Senses System				
Zymbal's gland	(1)			
Carcinoma	1 (100%)			
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Urinary bladder	(49)	(50)	(50)	(50)
Leiomyosarcoma	1 (2%)			
Transitional epithelium, papilloma	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Leukemia mononuclear	26 (52%)	28 (56%)	26 (52%)	29 (58%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	44	50	50	48
Total primary neoplasms	102	118	127	123
Total animals with benign neoplasms	37	47	42	43
Total benign neoplasms	65	81	79	78
Total animals with malignant neoplasms	30	30	36	37
Total malignant neoplasms	37	37	48	45
Total animals with metastatic neoplasms	2	1	4	2
Total metastatic neoplasms	2	1	4	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 Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	4 8 1	4 9 5	5 0 9	5 3 7	5 4 0	5 8 2	6 0 6	6 3 4	6 5 6	6 5 6	6 9 8	7 1 2	7 1 2	7 2 2	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 4 7	1 3 2	1 4 0	1 2 5	1 4 6	1 1 2	1 2 4	1 0 4	1 0 3	1 2 7	1 3 1	1 0 8	1 1 8	1 0 1	1 1 1	1 1 5	1 2 1	1 2 6	1 3 0	1 3 4	1 3 7	1 3 6	1 0 9	1 1 0	1 1 6
Alimentary System																									
Esophagus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery		+					+			+						+			+					
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma					X																				
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																X									X
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X					X			X	X	X		X			X				X		X	X
Thyroid gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma											X														
C-cell, carcinoma																									
General Body System																									
Peritoneum								+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal						X		X												X					
Cervix, sarcoma stromal												X													

+: 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 Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 2 2	1 2 3	1 2 8	1 2 9	1 3 3	1 3 8	1 4 2	1 4 3	1 4 4	1 4 8	1 4 9	1 5 0	1 0 2	1 0 5	1 0 7	1 1 3	1 1 4	1 1 7	1 1 9	1 2 0	1 3 5	1 3 6	1 3 9	1 4 1	1 4 5	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Mesentery	+	+										+	+	+											+	11
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tongue																		+								1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant																			X							1
Pheochromocytoma benign																										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																				X						1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma	X	X	X			X		X	X		X	X	X	X	X				X	X	X	X	X		X	27
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma				X							X															3
C-cell, carcinoma			X																							1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Genital System																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma				X																						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal		X					X					X	X		X				X	X						10
Cervix, sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	4 8 1	4 9 5	5 0 9	5 3 7	5 4 0	5 8 2	6 0 6	6 3 4	6 5 6	6 5 6	6 9 8	7 1 2	7 1 2	7 2 2	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 4 7	1 3 2	1 4 0	1 2 5	1 4 6	1 1 2	1 2 4	1 0 4	1 0 3	1 2 7	1 3 1	1 0 8	1 1 8	1 0 1	1 1 1	1 1 5	1 2 1	1 2 6	1 3 0	1 3 4	1 3 7	1 0 6	1 0 9	1 1 0	1 1 6
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+									+	+											
Lymph node, bronchial	M	+	+	+	M	+	M	M	M	M	+	M	M	M	M	M	+	+	+	M	M	M	M	+	M
Lymph node, mandibular	M	M	M	+	M	+	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																		X							
Carcinoma, multiple																								X	
Fibroadenoma	X				X	X	X	X	X						X	X									
Fibroadenoma, multiple											X											X			X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue, schwannoma benign																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																									
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+		A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																									
Carcinoma																									

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 2 2	1 2 3	1 2 8	1 2 9	1 3 3	1 3 8	1 4 2	1 4 3	1 4 4	1 4 8	1 4 9	1 5 0	1 0 2	1 0 5	1 0 7	1 1 3	1 1 4	1 1 7	1 1 9	1 2 0	1 3 5	1 3 6	1 3 9	1 4 1	1 4 5	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node		+								+																5
Lymph node, bronchial	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	+	M	+	12
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma						X					X															3
Carcinoma, multiple																										1
Fibroadenoma	X	X													X			X	X	X						14
Fibroadenoma, multiple																							X		X	5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma						X																				1
Subcutaneous tissue, schwannoma benign												X														1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle													+													1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, mammary gland						X																				1
Pheochromocytoma malignant, metastatic, adrenal medulla																			X							1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Zymbal's gland																									+	1
Carcinoma																									X	1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	4 8 1	4 9 5	5 0 9	5 3 7	5 4 0	5 8 2	6 0 6	6 3 4	6 5 6	6 5 6	6 9 8	7 1 2	7 1 2	7 2 2	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 4 7	1 3 2	1 4 0	1 2 5	1 4 6	1 1 2	1 2 4	1 0 4	1 0 3	1 2 7	1 3 1	1 0 8	1 1 8	1 0 1	1 1 1	1 1 5	1 2 1	1 2 6	1 3 0	1 3 4	1 3 7	1 0 6	1 0 9	1 1 0	1 1 6
Urinary System																									
Kidney	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma									X																
Transitional epithelium, papilloma																									
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X		X		X	X			X		X	X	X			X	X							X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 2 2	1 2 3	1 2 8	1 2 9	1 3 3	1 3 8	1 4 2	1 4 3	1 4 4	1 4 8	1 4 9	1 5 0	1 0 2	1 0 5	1 0 7	1 1 3	1 1 4	1 1 7	1 1 9	1 2 0	1 3 5	1 3 6	1 3 9	1 4 1	1 4 5	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leiomyosarcoma																										1
Transitional epithelium, papilloma																						X				1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X	X	X		X			X	X	X	X	X		X	X		X			X	X			X	26

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	4 4 5 5 5 5 6 6 6 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7
	8 8 0 3 7 9 0 4 5 5 5 7 7 9 0 0 1 2 2 2 3 3 3 3 3
	1 1 6 7 5 3 6 6 2 6 6 0 5 1 3 3 9 6 6 9 0 0 0 0 0
Carcass ID Number	5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5
	1 2 1 1 0 0 4 2 2 0 4 4 0 1 3 4 0 2 3 3 0 0 1 2 3
	1 6 4 0 5 6 4 5 8 2 8 0 9 1 4 8 1 3 6 4 5 7 8 1 7
Alimentary System	
Esophagus	+ +
Intestine large, colon	+ +
Intestine large, rectum	+ +
Intestine large, cecum	+ +
Intestine small, duodenum	+ + + + + + + A + + + + + + + + + + + + + + + + +
Intestine small, jejunum	+ + + + + + + A + + + + + + + + + + + + + + + + +
Intestine small, ileum	+ + + + + + + A + + + + + + + + + + + + + + + + +
Liver	+ +
Mesentery	+ +
Pancreas	+ +
Salivary glands	+ +
Stomach, forestomach	+ +
Stomach, glandular	+ +
Tongue	+
Cardiovascular System	
Blood vessel	+ +
Heart	+ +
Endocrine System	
Adrenal cortex	+ +
Adrenal medulla	+ +
Pheochromocytoma complex	X
Pheochromocytoma benign	X X
Islets, pancreatic	+ +
Parathyroid gland	+ + + + + + + + + M + + + + + + + + + + + + + + +
Pituitary gland	+ +
Pars distalis, adenoma	X X X X X X X X X X X X X X X X X X X X X
Pars distalis, carcinoma	
Thyroid gland	+ +
C-cell, adenoma	X
C-cell, carcinoma	X X
General Body System	
Peritoneum	+ +
Genital System	
Clitoral gland	+ +
Adenoma	X
Carcinoma	X
Ovary	+ +
Uterus	+ +
Polyp stromal	X X X
Sarcoma stromal	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	5 0 2	5 0 9	5 1 2	5 1 3	5 1 7	5 1 9	5 2 0	5 2 3	5 2 9	5 3 1	5 3 9	5 4 2	5 4 6	5 4 7	5 4 8	5 5 0	5 1 1	5 1 5	5 2 7	5 3 0	5 3 2	5 3 3	5 3 5	5 4 3	5 4 4	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery				+	+					+					+					+	+					15
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue							+	+																		3
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma complex																										1
Pheochromocytoma benign					X					X																4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X	X	X	X		X	X	X	X		X		X						X	X	X	X			X		34
Pars distalis, carcinoma					X																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																	X	X		X			X			5
C-cell, carcinoma																										2
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma															X										X	3
Carcinoma													X													2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal			X		X				X				X									X	X			9
Sarcoma stromal																										1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	5 0 2	5 0 9	5 1 2	5 1 3	5 1 7	5 1 9	5 2 0	5 2 3	5 2 9	5 3 1	5 3 9	5 4 2	5 4 6	5 4 7	5 4 8	5 5 0	5 1 1	5 1 5	5 2 7	5 3 0	5 3 2	5 3 3	5 3 5	5 4 3	5 4 4	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node										+																5
Lymph node, bronchial	M	M	M	M	M	M	M	M	M	M	M	+	+	M	M	M	M	M	M	+	M	M	M	M	M	7
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	M	M	M	+	+	+	+	M	+	+	+	+	M	M	+	M	M	+	+	+	39
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																								X		2
Fibroadenoma		X							X	X		X			X			X		X	X					13
Fibroadenoma, multiple	X				X		X				X					X						X		X		13
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland					X																					1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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				X			28

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	4 0 1	4 3 3	5 6 3	5 6 5	5 8 1	6 1 0	6 1 0	6 8 2	6 8 3	6 8 9	6 9 5	6 9 8	7 0 3	7 0 5	7 1 0	7 1 8	7 2 2	7 2 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	7 0 1	7 2 2	7 4 7	7 0 5	7 0 4	7 1 4	7 3 9	7 0 9	7 3 5	7 1 2	7 2 3	7 1 3	7 0 2	7 3 0	7 2 9	7 4 9	7 4 8	7 3 3	7 0 3	7 0 0 7	7 0 8	7 1 6	7 1 7	7 2 0	7 2 6
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Intestine small, ileum	+	+	+	+	A	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery				+	+			+	+	+			+		+	+				+	+	+	+		
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																	X								
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Carcinoma																				X					
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma				X	X		X		X	X	X		X	X		X	X		X	X	X		X	X	X
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma												X												X	
Follicular cell, adenoma																		X							
General Body System																									
Peritoneum						+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	7 2 8	7 3 1	7 4 1	7 4 4	7 4 6	7 0 6	7 1 1	7 1 8	7 1 9	7 2 7	7 3 2	7 3 4	7 3 6	7 3 7	7 4 2	7 4 3	7 4 5	7 1 0	7 1 5	7 2 1	7 2 4	7 2 5	7 3 8	7 4 0	7 5 0	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyoma						X																				1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery	+	+	+	+	+					+	+	+							+				+		+	23
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign							X									X										2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X		X	X	X	X	X	X					X		X		X	X	X	X		X	X	X	X	33
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										2
Follicular cell, adenoma																										1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	4 0 1	4 3 3	5 6 3	5 6 5	5 8 1	6 1 0	6 1 0	6 8 2	6 8 3	6 8 9	6 9 5	6 9 8	7 0 3	7 0 5	7 1 0	7 1 8	7 2 2	7 2 6	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0
Carcass ID Number	7 0 1	7 2 2	7 4 7	7 0 5	7 0 4	7 1 4	7 3 9	7 0 9	7 3 5	7 1 2	7 2 3	7 1 3	7 0 2	7 3 0	7 2 9	7 4 9	7 4 8	7 3 3	7 0 3	7 0 7	7 0 8	7 1 6	7 1 7	7 2 0	7 2 6
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X														X		
Carcinoma																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																								
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																	X							
Polyp stromal										X						X				X		X		
Vagina							+																	
Sarcoma							X																	
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node		+							+							+		+				+		
Lymph node, bronchial	M	M	+	M	M	+	M	M	M	M	M	M	M	M	+	M	M	M	M	M	+	+	M	M	M
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	+	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	M	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin														X										
Thymus	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X		X			X												X						
Carcinoma, multiple																								
Fibroadenoma										X		X	X	X		X								
Fibroadenoma, multiple											X										X		X	X
Fibroma																		X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma													X											
Sarcoma														X										
Subcutaneous tissue, fibrosarcoma						X				X														
Subcutaneous tissue, sarcoma																						X		
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	7 2 8	7 3 1	7 4 1	7 4 4	7 4 6	7 0 6	7 1 1	7 1 8	7 1 9	7 2 7	7 3 2	7 3 4	7 3 6	7 3 7	7 4 2	7 4 3	7 4 5	7 1 0	7 1 5	7 2 1	7 2 4	7 2 5	7 3 8	7 4 0	7 5 0	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X										X											X				5
Carcinoma																				X						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant						X																				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Polyp stromal																	X		X				X	X	X	10
Vagina																										1
Sarcoma																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										5
Lymph node, bronchial	+	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	8
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	42
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin																										1
Thymus	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma								X		X					X			X							X	9
Carcinoma, multiple					X																					1
Fibroadenoma							X						X					X		X				X		10
Fibroadenoma, multiple		X			X			X			X	X			X						X	X				12
Fibroma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Sarcoma																										1
Subcutaneous tissue, fibrosarcoma																										2
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	401	433	563	565	581	610	611	620	638	668	699	695	698	703	705	710	718	722	726	730	733	740	740	740	740	740
Carcass ID Number	70121	70222	70447	70055	70044	70114	70139	70209	70335	70412	70523	70613	70702	70830	70929	70949	70848	70933	70963	70007	70008	70116	70117	70220	70226
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma								X																		
Carcinoma, metastatic, mammary gland	X		X																							
Nose	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelium, carcinoma, metastatic, lung								X																		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear		X	X	X		X	X		X	X			X	X	X	X		X	X	X		X		X		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	730	730	730	733	730	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	
Carcass ID Number	728	731	741	744	746	706	711	718	719	727	732	734	736	737	742	743	745	710	715	721	724	725	738	740	750	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, mammary gland																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelium, carcinoma, metastatic, lung																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X	X			X	X					X		X	X		X		X	X				26

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	2 8 5	4 5 1	5 0 6	5 0 9	5 2 2	5 2 2	5 3 7	5 4 9	5 8 9	6 0 6	6 1 1	6 2 1	6 2 5	6 4 7	6 5 6	6 7 4	6 8 2	6 8 2	6 9 3	6 9 4	6 9 6	7 1 2	7 1 4	7 1 8	7 2 2
Carcass ID Number	9 4 4 8	9 4 4 4	9 1 5 5	9 2 6 6	9 2 2 2	9 3 4 4	9 4 9 9	9 1 1 1	9 2 1 7	9 1 0 0	9 3 2 2	9 4 2 3	9 2 1 1	9 3 6 6	9 4 0 0	9 3 0 7	9 0 1 1	9 0 5 5	9 1 2 2	9 3 3 3	9 3 3 8	9 0 7 7	9 1 4 4	9 4 7 8	9 4 5 2
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine small, ileum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesentery			+											+		+							+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																									
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign										X									X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma			X	X		X	X			X			X		X	X		X				X	X		X
Pars distalis, carcinoma																								X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma				X					X																
C-cell, carcinoma																									
General Body System																									
Peritoneum				+							+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X													X		
Carcinoma													X												
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X											X					X		X		X
Sarcoma stromal															X										

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	
Carcass ID Number	90203	90220	90233	90309	90411	90446	90502	90606	90713	91116	91217	91318	91419	91524	91628	91729	91842	91905	92004	92208	92309	92420	92504	92605	92731	92939	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+			+	+				+					+					+		+		+		14
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										+	1
Cardiovascular System																											
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																											2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma		X	X		X	X	X	X	X				X	X	X				X	X		X	X	X	X		28
Pars distalis, carcinoma																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma								X					X														4
C-cell, carcinoma								X																			1
General Body System																											
Peritoneum	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma													X		X	X	X										6
Carcinoma																											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal								X			X											X		X		9
Sarcoma stromal																											1

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	2 8 5	4 5 1	5 0 6	5 0 9	5 2 2	5 2 2	5 3 7	5 4 9	5 8 9	6 0 6	6 1 1	6 2 1	6 2 5	6 4 7	6 5 6	6 7 4	6 8 2	6 8 2	6 9 3	6 9 4	6 9 6	7 1 2	7 1 4	7 1 8	7 2 2
Carcass ID Number	9 4 4 8	9 4 4 4	9 1 5 5	9 2 6 6	9 2 2 2	9 3 4 4	9 4 9 1	9 1 1 1	9 2 7 7	9 1 0 0	9 3 2 2	9 4 3 3	9 2 1 1	9 3 6 6	9 4 0 0	9 3 7 7	9 0 1 1	9 0 5 5	9 1 2 2	9 3 3 3	9 3 8 8	9 3 7 7	9 0 4 4	9 1 4 4	9 4 7 8	9 4 5 5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Lymph node				+	+		+											+							
Lymph node, bronchial	M	+	M	M	M	+	+	M	M	M	M	M	+	M	M	+	M	+	M	M	M	+	+	M	M
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mediastinal	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+
Carcinoma, metastatic, thyroid gland																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Thymoma malignant																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma							X		X													X	X		
Carcinoma, multiple																X									
Fibroadenoma					X				X					X				X		X		X			X
Fibroadenoma, multiple																			X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma					X																				
Subcutaneous tissue, fibroma												X													
Subcutaneous tissue, schwannoma benign																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma malignant																									
Cerebellum, glioma malignant																			X						
Spinal cord																			+						
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																		X							
Carcinoma, metastatic, mammary gland									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	9 0 3	9 2 0	9 2 3	9 3 0	9 4 1	9 4 6	9 0 2	9 0 6	9 1 3	9 1 6	9 1 7	9 1 8	9 1 9	9 2 4	9 2 8	9 2 9	9 4 2	9 5 0	9 0 4	9 0 8	9 0 9	9 2 5	9 3 1	9 3 5	9 3 9	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																X										1
Lymph node																										4
Lymph node, bronchial	+	M	M	M	M	M	+	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	11
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	45
Carcinoma, metastatic, thyroid gland								X																		1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Thymoma malignant	X																									1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma														X									X		X	7
Carcinoma, multiple																										1
Fibroadenoma	X			X	X	X				X			X		X					X	X					16
Fibroadenoma, multiple		X					X	X			X	X		X					X							8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																										1
Subcutaneous tissue, fibroma								X																		2
Subcutaneous tissue, schwannoma benign									X																	1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma malignant										X																1
Cerebellum, glioma malignant																										1
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Carcinoma, metastatic, mammary gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear																+										1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	2	4	5	5	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	6	7	7	7	7		
	8	5	0	0	2	2	3	4	8	0	1	2	2	4	5	7	8	8	9	9	9	1	1	2		
	5	1	6	9	2	2	7	9	9	6	1	1	5	7	6	4	2	2	3	4	6	2	4	8	2	
Carcass ID Number	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9	
	4	4	1	2	2	3	4	1	2	1	3	4	2	3	4	3	0	0	1	3	3	0	1	4	4	
	8	4	5	6	2	4	9	1	7	0	2	3	1	6	0	7	1	5	2	3	8	7	4	7	5	
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Histiocytic sarcoma																										
Leukemia mononuclear		X		X	X	X	X	X		X	X		X	X	X	X	X	X		X	X		X	X	X

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	
Carcass ID Number	90203	92200	92303	93000	94101	94406	90026	90061	91013	91116	91187	91188	91199	91244	92248	92299	94202	95010	90048	90089	90239	92355	93151	93595	93939	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																	X									1
Leukemia mononuclear		X		X			X	X			X	X	X	X						X			X			29

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	2/50 (4%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate[b]	4.5%	9.1%	4.5%	4.9%
Terminal rate[c]	2/36 (6%)	2/30 (7%)	2/32 (6%)	0/25 (0%)
First incidence (days)	730 (T)	726	730 (T)	606
Poly-3 test[d]	P=0.490N	P=0.329	P=0.693N	P=0.665
Adrenal Medulla: Benign, Complex, or Malignant Pheochromocytoma				
Overall rate	3/50 (6%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate	6.7%	9.1%	4.5%	4.9%
Terminal rate	3/36 (8%)	2/30 (7%)	2/32 (6%)	0/25 (0%)
First incidence (days)	730 (T)	726	730 (T)	606
Poly-3 test	P=0.348N	P=0.491	P=0.498N	P=0.536N
Clitoral Gland: Adenoma				
Overall rate	0/49 (0%)	3/50 (6%)	5/50 (10%)	6/50 (12%)
Adjusted rate	0.0%	6.8%	11.1%	14.6%
Terminal rate	0/35 (0%)	3/30 (10%)	4/32 (13%)	4/25 (16%)
First incidence (days)	—[e]	730 (T)	682	606
Poly-3 test	P=0.011	P=0.119	P=0.033	P=0.012
Clitoral Gland: Adenoma or Carcinoma				
Overall rate	1/49 (2%)	5/50 (10%)	6/50 (12%)	7/50 (14%)
Adjusted rate	2.3%	11.4%	13.3%	16.9%
Terminal rate	1/35 (3%)	5/30 (17%)	5/32 (16%)	4/25 (16%)
First incidence (days)	730 (T)	730 (T)	682	606
Poly-3 test	P=0.029	P=0.102	P=0.060	P=0.024
Mammary Gland: Fibroadenoma				
Overall rate	19/50 (38%)	26/50 (52%)	22/50 (44%)	24/50 (48%)
Adjusted rate	39.9%	57.1%	48.4%	56.3%
Terminal rate	12/36 (33%)	18/30 (60%)	16/32 (50%)	16/25 (64%)
First incidence (days)	481	481	689	522
Poly-3 test	P=0.126	P=0.069	P=0.269	P=0.085
Mammary Gland: Fibroma or Fibroadenoma				
Overall rate	19/50 (38%)	26/50 (52%)	23/50 (46%)	24/50 (48%)
Adjusted rate	39.9%	57.1%	50.6%	56.3%
Terminal rate	12/36 (33%)	18/30 (60%)	16/32 (50%)	16/25 (64%)
First incidence (days)	481	481	689	522
Poly-3 test	P=0.118	P=0.069	P=0.203	P=0.085
Mammary Gland: Carcinoma				
Overall rate	4/50 (8%)	2/50 (4%)	10/50 (20%)	8/50 (16%)
Adjusted rate	9.0%	4.5%	21.5%	19.0%
Terminal rate	4/36 (11%)	1/30 (3%)	6/32 (19%)	3/25 (12%)
First incidence (days)	730 (T)	675	401	537
Poly-3 test	P=0.037	P=0.343N	P=0.085	P=0.148
Mammary Gland: Fibroma, Fibroadenoma, or Carcinoma				
Overall rate	23/50 (46%)	27/50 (54%)	28/50 (56%)	29/50 (58%)
Adjusted rate	48.3%	59.1%	59.2%	66.6%
Terminal rate	16/36 (44%)	18/30 (60%)	18/32 (56%)	18/25 (72%)
First incidence (days)	481	481	401	522
Poly-3 test	P=0.054	P=0.200	P=0.193	P=0.054

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	27/49 (55%)	34/50 (68%)	33/50 (66%)	28/50 (56%)
Adjusted rate	59.4%	71.2%	70.2%	62.4%
Terminal rate	22/36 (61%)	19/30 (63%)	23/32 (72%)	16/25 (64%)
First incidence (days)	509	481	565	506
Poly-3 test	P=0.525	P=0.157	P=0.185	P=0.466
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	27/49 (55%)	35/50 (70%)	33/50 (66%)	29/50 (58%)
Adjusted rate	59.4%	73.2%	70.2%	64.6%
Terminal rate	22/36 (61%)	20/30 (67%)	23/32 (72%)	16/25 (64%)
First incidence (days)	509	481	565	506
Poly-3 test	P=0.463	P=0.108	P=0.185	P=0.381
Skin: Fibrosarcoma or Sarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	0/50 (0%)
Adjusted rate	0.0%	0.0%	8.8%	0.0%
Terminal rate	0/36 (0%)	0/30 (0%)	1/32 (3%)	0/25 (0%)
First incidence (days)	—	—[f]	610	—
Poly-3 test	P=0.427	—	P=0.063	—
Skin: Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	0/50 (0%)	0/50 (0%)	4/50 (8%)	2/50 (4%)
Adjusted rate	0.0%	0.0%	8.8%	4.9%
Terminal rate	0/36 (0%)	0/30 (0%)	1/32 (3%)	1/25 (4%)
First incidence (days)	—	—	610	621
Poly-3 test	P=0.079	—	P=0.063	P=0.219
Thyroid Gland (C-Cell): Adenoma				
Overall rate	3/49 (6%)	5/50 (10%)	2/50 (4%)	4/50 (8%)
Adjusted rate	6.8%	11.4%	4.5%	9.6%
Terminal rate	2/36 (6%)	5/30 (17%)	1/32 (3%)	2/25 (8%)
First incidence (days)	698	730 (T)	698	509
Poly-3 test	P=0.506	P=0.350	P=0.494N	P=0.468
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	4/49 (8%)	7/50 (14%)	2/50 (4%)	4/50 (8%)
Adjusted rate	9.0%	15.9%	4.5%	9.6%
Terminal rate	3/36 (8%)	5/30 (17%)	1/32 (3%)	2/25 (8%)
First incidence (days)	698	691	698	509
Poly-3 test	P=0.410N	P=0.257	P=0.331N	P=0.611
Uterus: Stromal Polyp				
Overall rate	10/50 (20%)	9/50 (18%)	10/50 (20%)	9/50 (18%)
Adjusted rate	22.0%	20.0%	22.2%	21.6%
Terminal rate	8/36 (22%)	6/30 (20%)	8/32 (25%)	4/25 (16%)
First incidence (days)	582	593	689	522
Poly-3 test	P=0.535	P=0.510N	P=0.590	P=0.583N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	11/50 (22%)	10/50 (20%)	10/50 (20%)	10/50 (20%)
Adjusted rate	24.2%	22.2%	22.2%	23.8%
Terminal rate	8/36 (22%)	6/30 (20%)	8/32 (25%)	4/25 (16%)
First incidence (days)	582	593	689	522
Poly-3 test	P=0.544N	P=0.512N	P=0.512N	P=0.584N

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
All Organs: Mononuclear Cell Leukemia				
Overall rate	26/50 (52%)	28/50 (56%)	26/50 (52%)	29/50 (58%)
Adjusted rate	55.0%	58.1%	54.0%	61.3%
Terminal rate	18/36 (50%)	14/30 (47%)	14/32 (44%)	10/25 (40%)
First incidence (days)	495	506	433	451
Poly-3 test	P=0.329	P=0.460	P=0.542N	P=0.339
All Organs: Benign Neoplasms				
Overall rate	37/50 (74%)	47/50 (94%)	42/50 (84%)	43/50 (86%)
Adjusted rate	76.4%	95.5%	88.7%	91.4%
Terminal rate	27/36 (75%)	29/30 (97%)	29/32 (91%)	24/25 (96%)
First incidence (days)	481	481	565	506
Poly-3 test	P=0.058	P=0.005	P=0.085	P=0.036
All Organs: Malignant Neoplasms				
Overall rate	30/50 (60%)	30/50 (60%)	36/50 (72%)	37/50 (74%)
Adjusted rate	62.3%	62.0%	73.1%	77.1%
Terminal rate	20/36 (56%)	15/30 (50%)	21/32 (66%)	15/25 (60%)
First incidence (days)	495	506	401	451
Poly-3 test	P=0.041	P=0.570N	P=0.175	P=0.084
All Organs: Benign or Malignant Neoplasms				
Overall rate	44/50 (88%)	50/50 (100%)	50/50 (100%)	48/50 (96%)
Adjusted rate	88.0%	100.0%	100.0%	97.8%
Terminal rate	30/36 (83%)	30/30 (100%)	32/32 (100%)	24/25 (96%)
First incidence (days)	481	481	401	451
Poly-3 test	P=0.029	P=0.016	P=0.016	P=0.063

(T)Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal medulla, clitoral gland, pituitary gland, and thyroid gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparison between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	12	19	15	23
Natural death	2	1	3	2
Survivors				
Terminal sacrifice	36	30	32	25
Animals examined microscopically	50	50	50	50
Alimentary System				
Esophagus	(49)	(50)	(50)	(50)
Periesophageal tissue, necrosis, fatty	1 (2%)			
Intestine small, jejunum	(49)	(49)	(47)	(48)
Ulcer			1 (2%)	
Liver	(49)	(50)	(50)	(50)
Angiectasis	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Basophilic focus	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Clear cell focus	7 (14%)	7 (14%)	6 (12%)	2 (4%)
Clear cell focus, multiple	2 (4%)		1 (2%)	1 (2%)
Degeneration, cystic			1 (2%)	
Hematopoietic cell proliferation			1 (2%)	
Hemorrhage	1 (2%)			
Hepatodiaphragmatic nodule	5 (10%)	9 (18%)	5 (10%)	6 (12%)
Necrosis			2 (4%)	
Thrombosis	1 (2%)			
Vacuolization cytoplasmic	2 (4%)	5 (10%)	6 (12%)	1 (2%)
Bile duct, cyst	1 (2%)			
Hepatocyte, regeneration				3 (6%)
Serosa, fibrosis	1 (2%)			1 (2%)
Mesentery	(11)	(15)	(23)	(14)
Necrosis	11 (100%)	15 (100%)	23 (100%)	13 (93%)
Pancreas	(49)	(50)	(50)	(50)
Acinus, atrophy	2 (4%)	1 (2%)	1 (2%)	
Artery, thrombosis				1 (2%)
Stomach, forestomach	(49)	(50)	(50)	(50)
Hyperplasia, squamous	1 (2%)			
Ulcer		2 (4%)		2 (4%)
Stomach, glandular	(49)	(50)	(50)	(50)
Necrosis	1 (2%)			
Tongue	(1)	(3)		(1)
Epithelium, hyperkeratosis	1 (100%)			
Epithelium, hyperplasia		3 (100%)		1 (100%)
Cardiovascular System				
Heart	(49)	(50)	(50)	(50)
Cardiomyopathy	1 (2%)		1 (2%)	2 (4%)
Atrium, thrombosis	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Myocardium, degeneration				1 (2%)
Ventricle, hypertrophy			1 (2%)	

[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 Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)			
Necrosis	1 (2%)	1 (2%)		2 (4%)
Vacuolization cytoplasmic	9 (18%)	4 (8%)	15 (30%)	12 (24%)
Adrenal medulla	(50)	(50)	(50)	(50)
Atrophy	1 (2%)			
Degeneration, cystic				1 (2%)
Hyperplasia	4 (8%)	2 (4%)	7 (14%)	4 (8%)
Parathyroid gland	(49)	(49)	(49)	(50)
Hyperplasia		1 (2%)		
Pituitary gland	(49)	(50)	(50)	(50)
Mineralization			1 (2%)	
Pars distalis, angiectasis	2 (4%)		2 (4%)	2 (4%)
Pars distalis, cyst	5 (10%)	3 (6%)	3 (6%)	3 (6%)
Pars distalis, hemorrhage				1 (2%)
Pars distalis, hyperplasia	9 (18%)	9 (18%)	8 (16%)	8 (16%)
Thyroid gland	(49)	(50)	(50)	(50)
C-cell, hyperplasia	11 (22%)	6 (12%)	4 (8%)	5 (10%)
General Body System				
None				
Genital System				
Clitoral gland	(49)	(50)	(50)	(50)
Cyst	1 (2%)			
Hyperplasia	2 (4%)	3 (6%)	3 (6%)	1 (2%)
Inflammation, chronic		1 (2%)	1 (2%)	1 (2%)
Metaplasia, squamous		1 (2%)		
Ovary	(50)	(50)	(50)	(50)
Cyst	8 (16%)	9 (18%)	8 (16%)	5 (10%)
Uterus	(49)	(50)	(50)	(50)
Atrophy		1 (2%)		
Decidual reaction				1 (2%)
Degeneration				1 (2%)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Necrosis				2 (4%)
Prolapse				1 (2%)
Capillary, myometrium, hyperplasia				1 (2%)
Endometrium, hyperplasia	1 (2%)		1 (2%)	1 (2%)
Endometrium, hyperplasia, cystic	1 (2%)	5 (10%)	2 (4%)	
Endometrium, inflammation, suppurative				1 (2%)
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Hyperplasia, reticulum cell		1 (2%)		
Lymph node	(5)	(5)	(5)	(4)
Pancreatic, infiltration cellular, histiocyte		1 (20%)		
Lymph node, bronchial	(12)	(7)	(8)	(11)
Infiltration cellular, histiocyte				1 (9%)
Pigmentation			2 (25%)	

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Hematopoietic System (continued)				
Lymph node, mesenteric	(50)	(50)	(50)	(49)
Necrosis				1 (2%)
Lymph node, mediastinal	(45)	(39)	(42)	(45)
Angiectasis		1 (3%)		
Hemorrhage				1 (2%)
Hyperplasia, lymphoid			1 (2%)	
Spleen	(49)	(50)	(50)	(50)
Accessory spleen	1 (2%)		2 (4%)	
Fibrosis		1 (2%)	1 (2%)	1 (2%)
Hematopoietic cell proliferation	2 (4%)	1 (2%)	2 (4%)	
Hemorrhage	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Necrosis	2 (4%)	1 (2%)		3 (6%)
Thrombosis				1 (2%)
Thymus	(47)	(47)	(46)	(48)
Cyst		1 (2%)		
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocele	1 (2%)		2 (4%)	2 (4%)
Inflammation, chronic	1 (2%)			
Epithelium, hyperplasia				1 (2%)
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion		1 (2%)	1 (2%)	1 (2%)
Hyperkeratosis	1 (2%)		1 (2%)	
Inflammation, chronic				1 (2%)
Inflammation, granulomatous			1 (2%)	
Ulcer			1 (2%)	1 (2%)
Musculoskeletal System				
None				
Nervous System				
Brain	(49)	(50)	(50)	(50)
Compression	9 (18%)	8 (16%)	3 (6%)	6 (12%)
Gliosis			1 (2%)	
Hemorrhage	4 (8%)	3 (6%)	6 (12%)	1 (2%)
Necrosis			1 (2%)	
Cerebellum, developmental malformation			1 (2%)	
Cerebellum, gliosis			1 (2%)	
Respiratory System				
Larynx	(49)	(50)	(50)	(49)
Foreign body	2 (4%)	1 (2%)	2 (4%)	1 (2%)
Inflammation, chronic	3 (6%)	1 (2%)		
Epiglottis, metaplasia, squamous	1 (2%)			1 (2%)
Respiratory epithelium, hyperplasia		1 (2%)		

TABLE B4
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Respiratory System (continued)				
Lung	(49)	(50)	(50)	(50)
Hemorrhage	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Necrosis				1 (2%)
Alveolar epithelium, hyperplasia	3 (6%)	1 (2%)	1 (2%)	3 (6%)
Alveolar epithelium, metaplasia, squamous		1 (2%)		
Alveolus, infiltration cellular, histiocyte	22 (45%)	14 (28%)	13 (26%)	15 (30%)
Alveolus, proteinosis				1 (2%)
Bronchiole, hyperplasia, focal				1 (2%)
Interstitium, fibrosis	2 (4%)	2 (4%)	2 (4%)	2 (4%)
Vein, fibrosis		1 (2%)		
Nose	(49)	(50)	(49)	(50)
Foreign body	2 (4%)	2 (4%)		
Inflammation, suppurative	1 (2%)	5 (10%)	3 (6%)	
Goblet cell, hyperplasia	1 (2%)	3 (6%)	3 (6%)	1 (2%)
Nasolacrimal duct, inflammation, suppurative	2 (4%)		1 (2%)	1 (2%)
Olfactory epithelium, degeneration, hyaline	12 (24%)	18 (36%)	15 (31%)	28 (56%)
Olfactory epithelium, hyperplasia		1 (2%)		
Respiratory epithelium, metaplasia, squamous		2 (4%)		
Pleura	(48)	(50)	(50)	(50)
Fibrosis	18 (38%)	6 (12%)	9 (18%)	12 (24%)
Inflammation, chronic	21 (44%)	20 (40%)	13 (26%)	5 (10%)
Mesothelium, hyperplasia		1 (2%)		
Special Senses System				
Eye	(49)	(50)	(50)	(49)
Atrophy		1 (2%)		
Anterior chamber, inflammation, suppurative		1 (2%)		
Cornea, hyperplasia	1 (2%)			
Lens, cataract	3 (6%)	2 (4%)	1 (2%)	4 (8%)
Urinary System				
Kidney	(49)	(50)	(50)	(50)
Cyst		2 (4%)		1 (2%)
Fibrosis		1 (2%)		
Infarct		1 (2%)	1 (2%)	
Nephropathy, chronic	42 (86%)	44 (88%)	46 (92%)	44 (88%)
Cortex, infarct	1 (2%)			
Cortex, inflammation, suppurative				1 (2%)
Cortex, renal tubule, accumulation, hyaline droplet				1 (2%)
Cortex, renal tubule, hyperplasia			1 (2%)	
Cortex, renal tubule, inflammation	1 (2%)			
Papilla, mineralization	3 (6%)	1 (2%)	1 (2%)	
Pelvis, transitional epithelium, hyperplasia	4 (8%)	3 (6%)	7 (14%)	3 (6%)
Pelvis, transitional epithelium, mineralization	25 (51%)	23 (46%)	27 (54%)	27 (54%)
Urinary bladder	(49)	(50)	(50)	(50)
Hemorrhage		1 (2%)		
Muscularis, hyperplasia				1 (2%)
Muscularis, infiltration cellular, histiocyte		1 (2%)		
Transitional epithelium, hyperplasia	1 (2%)		2 (4%)	
Transitional epithelium, ulcer	1 (2%)			

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF STODDARD SOLVENT IIC

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death			1	
Moribund	7	9	16	13
Natural deaths	9	9	6	5
Survivors				
Terminal sacrifice	34	32	27	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, duodenum	(46)	(41)	(46)	(47)
Sarcoma, metastatic, skin	1 (2%)			
Intestine small, jejunum	(46)	(41)	(46)	(47)
Carcinoma		3 (7%)		
Sarcoma, metastatic, skin	1 (2%)			
Intestine small, ileum	(45)	(41)	(46)	(47)
Adenoma		1 (2%)		
Carcinoma				2 (4%)
Liver	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma		1 (2%)	3 (6%)	
Hepatoblastoma				1 (2%)
Hepatocellular carcinoma	10 (20%)	11 (22%)	12 (24%)	9 (18%)
Hepatocellular carcinoma, multiple	6 (12%)	4 (8%)	5 (10%)	1 (2%)
Hepatocellular adenoma	13 (26%)	16 (32%)	14 (28%)	11 (22%)
Hepatocellular adenoma, multiple	10 (20%)	12 (24%)	7 (14%)	18 (36%)
Histiocytic sarcoma		1 (2%)	1 (2%)	
Ito cell tumor benign		1 (2%)		
Sarcoma		1 (2%)		
Sarcoma, metastatic, skin	1 (2%)			
Mesentery	(6)	(6)	(7)	(5)
Sarcoma, metastatic, skin	1 (17%)			
Pancreas	(49)	(49)	(49)	(50)
Sarcoma		1 (2%)		
Sarcoma, metastatic, skin	1 (2%)			
Stomach, forestomach	(49)	(48)	(49)	(49)
Sarcoma, metastatic, skin	1 (2%)			
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma			2 (4%)	1 (2%)
Stomach, glandular	(48)	(44)	(49)	(48)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Endocrine System				
Adrenal cortex	(49)	(50)	(49)	(50)
Adenoma	1 (2%)			
Carcinoma, metastatic, parathyroid gland				1 (2%)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Histiocytic sarcoma		1 (2%)		
Bilateral, subcapsular, adenoma		1 (2%)		
Subcapsular, adenoma	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Subcapsular, carcinoma			1 (2%)	
Adrenal medulla	(48)	(49)	(49)	(50)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Islets, pancreatic	(48)	(49)	(49)	(50)
Adenoma			1 (2%)	1 (2%)
Pituitary gland	(49)	(49)	(48)	(46)
Thyroid gland	(49)	(48)	(47)	(50)
C-cell, carcinoma				1 (2%)
Follicular cell, adenoma	1 (2%)			
General Body System				
Peritoneum	(1)	(1)	(1)	
Histiocytic sarcoma			1 (100%)	
Sarcoma		1 (100%)		
Genital System				
Coagulating gland			(2)	
Adenoma			1 (50%)	
Epididymis	(50)	(50)	(50)	(50)
Histiocytic sarcoma			1 (2%)	
Preputial gland	(49)	(49)	(50)	(48)
Histiocytic sarcoma			1 (2%)	
Prostate	(46)	(50)	(50)	(50)
Seminal vesicle	(48)	(46)	(50)	(48)
Histiocytic sarcoma			1 (2%)	
Sarcoma, metastatic, skin	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma	1 (2%)	2 (4%)		2 (4%)
Hematopoietic System				
Bone marrow	(49)	(50)	(49)	(50)
Hemangiosarcoma			1 (2%)	
Lymph node	(1)		(1)	(3)
Pancreatic, hepatocellular carcinoma, metastatic, liver			1 (100%)	
Lymph node, bronchial	(38)	(32)	(28)	(28)
Hemangiosarcoma	1 (3%)			
Hepatocellular carcinoma, metastatic, liver				1 (4%)
Histiocytic sarcoma		1 (3%)		
Lymph node, mandibular	(29)	(26)	(26)	(36)
Lymph node, mesenteric	(48)	(46)	(48)	(48)
Alveolar/bronchiolar carcinoma, metastatic, lung				1 (2%)
Sarcoma		1 (2%)		

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Hematopoietic System (continued)				
Lymph node, mediastinal	(39)	(40)	(36)	(43)
Hemangiosarcoma	1 (3%)			
Hepatocellular carcinoma, metastatic, liver	1 (3%)			1 (2%)
Histiocytic sarcoma		1 (3%)		
Sarcoma, metastatic, skin	1 (3%)			
Spleen	(49)	(49)	(49)	(50)
Hemangiosarcoma				1 (2%)
Sarcoma, metastatic, skin	1 (2%)			
Thymus	(41)	(39)	(40)	(42)
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Melanoma malignant	1 (2%)			1 (2%)
Squamous cell papilloma		1 (2%)		
Subcutaneous tissue, fibrous histiocytoma				1 (2%)
Subcutaneous tissue, hemangiosarcoma			2 (4%)	1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)			
Musculoskeletal System				
None				
Nervous System				
None				
Respiratory System				
Lung	(50)	(49)	(50)	(50)
Alveolar/bronchiolar adenoma	5 (10%)	2 (4%)	3 (6%)	1 (2%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma	5 (10%)	2 (4%)	4 (8%)	5 (10%)
Alveolar/bronchiolar carcinoma, multiple	2 (4%)			
Carcinoma, metastatic, harderian gland		1 (2%)	1 (2%)	
Carcinoma, metastatic, parathyroid gland				1 (2%)
Hepatocellular carcinoma, metastatic, liver	6 (12%)	6 (12%)	9 (18%)	3 (6%)
Histiocytic sarcoma			1 (2%)	
Special Senses System				
Harderian gland	(50)	(50)	(50)	(49)
Adenoma	6 (12%)	6 (12%)	5 (10%)	4 (8%)
Carcinoma		4 (8%)	3 (6%)	3 (6%)
Bilateral, adenoma	1 (2%)			
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		1 (2%)	3 (6%)	
Lymphoma malignant	3 (6%)	1 (2%)		2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	42	43	41	41
Total primary neoplasms	73	75	68	68
Total animals with benign neoplasms	32	31	30	33
Total benign neoplasms	43	44	34	39
Total animals with malignant neoplasms	23	23	25	23
Total malignant neoplasms	30	31	34	29
Total animals with metastatic neoplasms	6	7	10	5
Total metastatic neoplasms	16	7	14	8

[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 Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	458	499	525	534	540	600	603	617	628	632	644	651	681	687	694	710	729	729	729	729	729	729	729	729	729
Carcass ID Number	00015	00013	00022	00018	00046	00017	00111	00101	00021	00241	00323	00331	00212	00326	00299	00207	00033	00044	00066	00088	00099	00101	00115	00116	00120
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	A	M	A	A	+	+	+	A	I	M	+	I	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	A	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	M	A	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	A	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin			X																						
Intestine small, jejunum	+	A	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin			X																						
Intestine small, ileum	+	A	A	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									X
Hepatocellular carcinoma	X	X	X		X			X				X													
Hepatocellular carcinoma, multiple				X		X			X		X						X								
Hepatocellular adenoma	X									X								X		X	X				
Hepatocellular adenoma, multiple																			X			X	X	X	
Sarcoma, metastatic, skin			X																						
Mesentery			+				+																	+	
Sarcoma, metastatic, skin			X																						
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin			X																						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin			X																						
Stomach, glandular	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth						+				+					+	+					+		+	+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Subcapsular, adenoma																					X				
Adrenal medulla	+	+	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	M	+	A	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	M	+	+	M
Pituitary gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma													X												
General Body System																									
Peritoneum																+									
Tissue, nonspecified site												+													

+: 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 Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	02424	02427	03030	03434	03535	03838	04242	04444	04545	04949	01202	01404	01909	02303	02505	02606	02808	03303	03707	03909	04040	04343	04747	04848	04950	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	39
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Sarcoma, metastatic, skin																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Sarcoma, metastatic, skin																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hepatocellular carcinoma						X				X			X			X										10
Hepatocellular carcinoma, multiple											X															6
Hepatocellular adenoma	X			X					X	X				X		X			X			X				13
Hepatocellular adenoma, multiple			X								X	X	X							X				X		10
Sarcoma, metastatic, skin																										1
Mesentery			+					+													+					6
Sarcoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, skin																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, skin																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tooth			+	+		+	+	+						+	+	+				+	+	+	+			19
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X																			1
Subcapsular, adenoma												X								X						3
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	M	M	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	M	M	M	+	32
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma																										1
General Body System																										
Peritoneum																										1
Tissue, nonspecified site																					+					2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	4 5 8	4 9 9	5 2 5	5 3 4	5 4 0	6 0 0	6 0 3	6 1 7	6 2 8	6 3 2	6 4 4	6 5 1	6 8 1	6 8 7	6 9 4	7 1 0	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	0 0 1 5	0 1 3	0 0 2	0 1 8	0 4 6	0 1 7	0 1 1	0 1 1	0 2 1	0 4 1	0 3 2	0 3 1	0 2 2	0 3 6	0 2 9	0 0 7	0 0 3	0 0 4	0 0 6	0 0 8	0 0 9	0 1 0	0 1 5	0 1 6	0 2 0
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	A	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin			X																						
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									X
Hematopoietic System																									
Bone marrow	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, bronchial	+	+	+	+	A	M	+	+	+	+	M	+	+	+	I	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma								X																	
Lymph node, mandibular	M	+	+	+	+	M	+	+	M	+	M	+	M	+	+	M	M	M	+	+	M	M	M	+	+
Lymph node, mesenteric	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	A	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+
Hemangiosarcoma								X																	
Hepatocellular carcinoma, metastatic, liver				X																					
Sarcoma, metastatic, skin			X																						
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin			X																						
Thymus	+	+	M	M	A	+	+	+	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Melanoma malignant																									
Subcutaneous tissue, sarcoma			X																						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma									X											X					
Alveolar/bronchiolar carcinoma, multiple													X												
Hepatocellular carcinoma, metastatic, liver		X	X	X		X			X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	02424	02427	02430	02434	02435	02438	03942	03944	03945	03949	04012	04014	04019	04023	04025	04026	04028	04033	04037	04039	04044	04043	04047	04048	04050	Total Tissues/ Tumors
Genital System																												
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	I		46
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Sarcoma, metastatic, skin																												1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Interstitial cell, adenoma																												1
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Lymph node														+														1
Lymph node, bronchial	+	+	+	+	M	+	+	M	+	+	+	+	M	+	M	M	+	M	M	+	M	+	+	+	+			38
Hemangiosarcoma																												1
Lymph node, mandibular	+	+	+	M	+	M	+	+	+	+	+	+	+	M	M	+	+	+	M	M	M	+	M	M	M			29
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			48
Lymph node, mediastinal	+	+	+	+	+	+	M	M	+	+	+	+	M	+	+	+	M	+	M	+	+	M	M	+	+			39
Hemangiosarcoma																												1
Hepatocellular carcinoma, metastatic, liver																												1
Sarcoma, metastatic, skin																												1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			49
Sarcoma, metastatic, skin																												1
Thymus	M	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+			41
Integumentary System																												
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M			
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Melanoma malignant														X														1
Subcutaneous tissue, sarcoma																												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Respiratory System																												
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Alveolar/bronchiolar adenoma					X	X		X	X																			5
Alveolar/bronchiolar adenoma, multiple																							X					1
Alveolar/bronchiolar carcinoma		X					X							X														5
Alveolar/bronchiolar carcinoma, multiple										X																		2
Hepatocellular carcinoma, metastatic, liver											X																	6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	02424	02427	03030	03434	03535	03838	04242	04444	04445	04449	04612	04614	04619	04623	04625	04626	04628	04633	04637	04639	04640	04643	04647	04648	04650	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				6
Bilateral, adenoma																			X							1
Zymbal's gland										+																1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant														X								X				3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	3 9 8	4 0 3	5 1 7	5 3 4	5 6 6	5 7 6	5 8 2	6 1 8	6 4 6	6 5 9	6 7 3	6 7 3	6 7 5	6 7 6	6 8 3	6 9 5	6 9 5	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 0 9	2 5 0	2 3 2	2 1 5	2 2 3	2 1 9	2 2 6	2 2 9	2 0 4	2 0 3	2 3 8	2 4 1	2 3 1	2 1 3	2 0 7	2 1 6	2 4 8	2 4 5	2 0 5	2 0 6	2 1 8	2 2 2	2 2 5	2 2 8	2 3 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	A	A	+	A	+	A	+	+	A	+	+	A	A	M	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	A	A	+	A	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	A	A	+	A	+	A	+	+	A	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	A	+	A	+	A	+	+	A	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	A	A	+	A	+	A	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	A	+	A	+	A	+	+	A	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+
Carcinoma																					X				
Intestine small, ileum	A	A	A	+	A	+	A	+	+	A	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma															X										
Hepatocellular carcinoma	X	X	X	X		X		X			X	X													
Hepatocellular carcinoma, multiple					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																	
Ito cell tumor benign																									
Sarcoma								X																	
Mesentery	+				+																				
Pancreas	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma								X																	
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	A	+	A	+	+	A	+	+	A	A	A	+	+	+	+	+	+	+	+	+	+
Tooth							+				+									+	+		+	+	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Bilateral, subcapsular, adenoma								X																	
Subcapsular, adenoma																			X						
Adrenal medulla	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	M	M	M	+	+	M	+	+	+	+	M	M	M	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
Peritoneum								+																	
Sarcoma								X																	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	23343	23355	23359	24400	24433	24436	24467	20011	20012	20028	21210	21211	21212	21214	21217	22200	22201	22214	22227	23344	23366	23377	24422	24449	24459		Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder	+	+	+	+	+	+	I	I	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	I	+		36
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		41
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		41
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+		41
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		41
Carcinoma																				X				X			3
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		41
Adenoma															X												1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hemangiosarcoma																											1
Hepatocellular carcinoma		X					X								X												11
Hepatocellular carcinoma, multiple																											4
Hepatocellular adenoma					X										X		X					X	X	X	X		16
Hepatocellular adenoma, multiple	X		X			X	X	X								X											12
Histiocytic sarcoma																											1
Ito cell tumor benign				X																							1
Sarcoma																											1
Mesentery				+						+	+							+									6
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Sarcoma																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Tooth	+		+	+						+			+	+				+		+	+				+		16
Cardiovascular System																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Endocrine System																											
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																											1
Bilateral, subcapsular, adenoma																											1
Subcapsular, adenoma																	X										2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Parathyroid gland	M	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+		35
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+		48
General Body System																											
Peritoneum																											1
Sarcoma																											1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	3 9 8	4 0 3	5 1 7	5 3 4	5 6 6	5 7 6	5 8 2	6 1 8	6 4 6	6 5 9	6 7 3	6 7 3	6 7 5	6 7 6	6 8 3	6 9 5	6 9 5	7 2 3	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	2 0 9	2 5 0	2 3 2	2 1 5	2 2 3	2 1 9	2 2 6	2 2 9	2 0 4	2 0 3	2 3 8	2 4 1	2 3 1	2 1 3	2 0 7	2 1 6	2 4 8	2 4 5	2 0 5	2 0 6	2 1 8	2 2 2	2 2 5	2 2 8	2 3 0
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis									+								+								
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	A	+	+	+	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																							X		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	+	+	+	+	+	M	+	M	M	M	M	+	M	M	+	+	M	+	+	+	+	+	+	M
Histiocytic sarcoma								X																	
Lymph node, mandibular	M	M	M	+	M	+	M	M	M	M	M	+	+	+	M	+	+	M	M	M	+	M	M	+	M
Lymph node, mesenteric	+	+	M	+	A	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma								X																	
Lymph node, mediastinal	+	+	+	+	+	M	+	+	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Histiocytic sarcoma								X																	
Spleen	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	A	+	M	A	+	M	+	+	M	M	+	M	+	+	M	+	+	+	M
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																				X					
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma													X												
Carcinoma, metastatic, harderian gland													X												
Hepatocellular carcinoma, metastatic, liver						X		X				X			X	X					X				
Nose	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	A	+	+	+	A	+	A	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	A	+	A	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma								X																	X
Carcinoma													X					X							

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	23303	23305	23309	24400	24403	24406	24407	20001	20002	20008	21010	21011	21012	21014	21017	22020	22021	22024	22027	23034	23036	23037	24422	24424	24429	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis					+																					3
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																					X					2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	M	+	M	M	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	M	+	+	M	32
Histiocytic sarcoma																										1
Lymph node, mandibular	+	M	+	M	+	+	+	+	+	M	M	+	M	+	+	+	M	+	+	M	+	I	+	+	+	26
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Sarcoma																										1
Lymph node, mediastinal	+	M	+	M	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	40
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma					X						X															2
Alveolar/bronchiolar carcinoma													X													2
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										6
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X											X					X					X			6
Carcinoma																					X			X		4

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	3	4	5	5	5	5	5	6	6	6	6	6	6	6	6	6	6	7	7	7	7	7	7	7	7
	9	0	1	3	6	7	8	1	4	5	7	7	7	7	8	9	9	2	2	2	2	2	2	2	2
	8	3	7	4	6	6	2	8	6	9	3	3	5	6	3	5	5	3	9	9	9	9	9	9	9
Carcass ID Number	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
	0	5	3	1	2	1	2	2	0	0	3	4	3	1	0	1	4	4	0	0	1	2	2	2	3
	9	0	2	5	3	9	6	9	4	3	8	1	1	3	7	6	8	5	5	6	8	2	5	8	0
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	A	+	A	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymphoma malignant																						X			

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	2 3 3	2 3 5	2 3 9	2 4 0	2 4 3	2 4 6	2 4 7	2 0 1	2 0 2	2 0 8	2 1 0	2 1 1	2 1 2	2 1 4	2 1 7	2 2 0	2 2 1	2 2 4	2 2 7	2 3 4	2 3 6	2 3 7	2 4 2	2 4 4	2 4 9	Total Tissues/ Tumors	
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46	
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50	
Histiocytic sarcoma																										1	
Lymphoma malignant																										1	

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	0 7 5	4 0 0	4 7 0	4 7 8	4 8 4	5 0 9	5 2 7	5 2 7	6 1 7	6 2 8	6 4 4	6 5 0	6 5 3	6 6 7	6 8 1	6 9 8	7 0 2	7 0 2	7 0 3	7 0 7	7 0 9	7 0 9	7 2 3	7 2 9	7 2 9
Carcass ID Number	4 2 0	4 2 2	4 4 1	4 0 8	4 1 6	4 2 7	4 2 1	4 2 9	4 3 3	4 4 5	4 4 4	4 4 9	4 0 6	4 3 7	4 3 9	4 1 4	4 0 7	4 4 3	4 3 8	4 0 5	4 1 1	4 2 5	4 0 4	4 0 2	4 0 9
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	A	M	+	+	A	+	+	M	+	I	I	A	+	+	+	A	+	+	+	+	+
Intestine large, colon	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+
Intestine small, duodenum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+
Intestine small, ileum	+	+	+	+	A	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X									X			X			
Hepatocellular carcinoma					X			X	X			X		X			X	X	X		X		X	X	
Hepatocellular carcinoma, multiple				X		X	X								X										
Hepatocellular adenoma						X						X		X	X							X			X
Hepatocellular adenoma, multiple								X													X		X		
Histiocytic sarcoma																									
Mesentery		+							+					+											
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																X									
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth			+												+				+		+		+	+	+
Cardiovascular System																									
Blood vessel																						+			
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																									
Subcapsular, adenoma																									
Subcapsular, carcinoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																									
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X																				
Parathyroid gland	+	+	+	+	+	+	M	+	M	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
General Body System																									
Peritoneum														+											
Histiocytic sarcoma														X											

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	41 10	41 17	42 23	42 26	42 28	43 30	43 31	43 32	43 34	44 40	44 46	44 48	45 01	40 01	40 13	41 02	41 23	41 15	41 18	41 19	42 24	43 35	43 36	44 02	44 07	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	41
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										3
Hepatocellular carcinoma		X																								12
Hepatocellular carcinoma, multiple					X																					5
Hepatocellular adenoma	X			X	X		X				X	X						X						X		14
Hepatocellular adenoma, multiple																X					X	X			X	7
Histiocytic sarcoma												X														1
Mesentery				+					+			+			+											7
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma					X																					2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth			+	+				+	+	+	+				+		+	+	+	+		+		+	+	21
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver					X																					1
Subcapsular, adenoma																						X				1
Subcapsular, carcinoma						X																				1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																										1
Parathyroid gland	+	+	+	+	+	M	M	+	+	M	M	+	+	M	+	+	+	+	+	+	M	+	+	+	M	38
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	47
General Body System																										
Peritoneum																										1
Histiocytic sarcoma																										1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	0 7 5	4 0 0	4 7 0	4 7 8	4 8 4	5 0 9	5 2 7	5 2 7	6 1 7	6 2 8	6 4 4	6 5 0	6 5 3	6 6 7	6 8 1	6 9 8	7 0 2	7 0 2	7 0 3	7 0 7	7 0 9	7 0 9	7 2 3	7 2 9	7 2 9
Carcass ID Number	4 2 0	4 2 2	4 4 1	4 0 8	4 1 6	4 2 7	4 2 1	4 2 9	4 3 3	4 4 5	4 4 4	4 4 9	4 0 6	4 3 7	4 3 9	4 1 4	4 0 7	4 4 3	4 3 8	4 0 5	4 1 1	4 2 5	4 0 4	4 0 2	4 0 9
Genital System																									
Coagulating gland																									
Adenoma																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																	X								
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X											
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																					X				
Lymph node															+										
Pancreatic, hepatocellular carcinoma, metastatic, liver															X										
Lymph node, bronchial	+	M	M	M	+	+	M	M	A	+	+	M	M	M	M	M	M	+	+	+	+	M	M	M	M
Lymph node, mandibular	+	+	+	M	+	+	+	+	A	M	M	+	+	M	+	+	M	+	+	M	+	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymph node, mediastinal	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	M	+	+
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	M	+	+	+	M	M	+	+	+	M	+	M	M	+	+	+	+	+	+	+	M	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma																					X				
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X								
Alveolar/bronchiolar carcinoma																	X				X			X	
Carcinoma, metastatic, harderian gland																									
Hepatocellular carcinoma, metastatic, liver				X			X		X			X		X	X			X					X		
Histiocytic sarcoma																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	4 1 0	4 1 7	4 2 3	4 2 6	4 2 8	4 3 0	4 3 1	4 3 2	4 3 4	4 4 0	4 4 6	4 4 8	4 5 0	4 0 1	4 0 3	4 1 2	4 1 3	4 1 5	4 1 8	4 1 9	4 2 4	4 2 5	4 3 6	4 4 2	4 4 7	Total Tissues/ Tumors
Genital System																										
Coagulating gland				+					+																	2
Adenoma				X																						1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Lymph node																										1
Pancreatic, hepatocellular carcinoma, metastatic, liver																										1
Lymph node, bronchial	+	+	+	+	M	M	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	28
Lymph node, mandibular	+	M	M	+	+	M	+	+	+	M	M	M	M	M	+	M	+	+	+	+	M	+	M	M	M	26
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	+	+	M	M	+	M	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	M	36
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	40
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, hemangiosarcoma				X																						2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma								X	X																	3
Alveolar/bronchiolar carcinoma																							X			4
Carcinoma, metastatic, harderian gland														X												1
Hepatocellular carcinoma, metastatic, liver					X																					9
Histiocytic sarcoma												X														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	0 7 5	4 0 0	4 7 0	4 7 8	4 8 4	5 0 9	5 2 7	5 2 7	6 1 7	6 2 8	6 4 4	6 5 0	6 5 3	6 6 7	6 8 1	6 9 8	7 0 2	7 0 2	7 0 3	7 0 7	7 0 9	7 0 9	7 2 3	7 2 9	7 2 9
Carcass ID Number	4 2 0	4 2 2	4 4 1	4 0 8	4 1 6	4 2 7	4 2 1	4 2 9	4 3 3	4 4 5	4 4 4	4 4 9	4 0 6	4 3 7	4 3 9	4 1 4	4 0 7	4 4 3	4 3 8	4 0 5	4 1 1	4 2 5	4 0 4	4 0 2	4 0 9
Special Senses System																									
Eye	+	+	+	+	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X														
Carcinoma							X																		
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver							X																		
Urinary bladder	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma														X			X								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	41 0	41 7	42 3	42 6	42 8	43 0	43 1	43 2	43 4	44 0	44 6	44 8	45 0	40 1	40 3	41 2	41 3	41 5	41 8	41 9	42 4	42 5	43 6	44 2	44 7	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma			X							X		X		X												5
Carcinoma											X		X													3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma												X														3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	365	506	521	550	557	563	575	593	593	593	626	645	653	655	669	681	710	728	729	729	729	729	729	729	729
Carcass ID Number	642	634	640	606	644	604	611	625	631	645	650	637	647	618	621	633	643	615	600	617	609	610	644	617	619
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	A	A	+	+	+	I	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+
Intestine large, colon	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma									X		X														
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatoblastoma																									
Hepatocellular carcinoma						X		X				X		X		X									
Hepatocellular carcinoma, multiple										X															
Hepatocellular adenoma		X	X							X									X						
Hepatocellular adenoma, multiple						X	X	X				X						X		X	X		X	X	
Mesentery										+								+							+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma													X												
Squamous cell papilloma																									
Stomach, glandular	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Tongue					+																				
Tooth			+						+		+				+				+		+		+	+	
Cardiovascular System																									
Blood vessel									+																
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, parathyroid gland																									
Subcapsular, adenoma																								X	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Parathyroid gland	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Pituitary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	I	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, carcinoma																									
General Body System																									
Tissue, nonspecified site																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	62424	62426	62427	62428	62429	63030	63035	63036	64046	64049	60202	60023	60025	60058	61212	61313	61616	62040	62202	62323	63232	63838	63939	64141	64448	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										2
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatoblastoma				X																						1
Hepatocellular carcinoma											X										X	X	X			9
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X	X			X		X										X				X			X		11
Hepatocellular adenoma, multiple			X	X		X		X			X	X								X			X		X	18
Mesentery											+								+							5
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																										1
Squamous cell papilloma												X														1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																										1
Tooth									+			+	+	+		+		+		+				+	+	17
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, parathyroid gland										X																1
Subcapsular, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, carcinoma										X																1
General Body System																										
Tissue, nonspecified site																+				M						1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	365	506	521	550	557	563	575	593	593	593	626	645	653	655	669	681	710	728	729	729	729	729	729	729	729
Carcass ID Number	64 2	63 4	64 0	60 6	64 4	60 4	61 1	62 5	63 1	64 5	65 0	63 7	64 7	61 8	62 1	63 3	64 3	61 5	61 0	60 0	60 9	61 0	61 4	61 7	61 9
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis											+														
Preputial gland	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																	X								
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node				+													+								
Lymph node, bronchial	M	+	+	+	+	M	+	M	M	+	+	M	+	+	M	+	M	+	+	M	+	M	M	M	M
Hepatocellular carcinoma, metastatic, liver																X									
Lymph node, mandibular	M	+	+	+	M	+	M	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																									
Lymph node, mediastinal	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																X									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Thymus	+	M	+	A	+	M	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Melanoma malignant																					X				
Subcutaneous tissue, fibrous histiocytoma																					X				
Subcutaneous tissue, hemangiosarcoma																		X							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+																					
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord															+										
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma		X																X							
Carcinoma, metastatic, parathyroid gland																									
Hepatocellular carcinoma, metastatic, liver																X									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	7 3 0	
Carcass ID Number	6 2 4	6 2 6	6 2 7	6 2 8	6 2 9	6 3 0	6 3 5	6 3 6	6 4 6	6 4 9	6 0 2	6 0 3	6 0 5	6 0 8	6 1 2	6 1 3	6 1 6	6 2 0	6 2 2	6 2 3	6 3 2	6 3 8	6 3 9	6 4 1	6 4 8	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma							X																			2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node											+															3
Lymph node, bronchial	+	M	+	M	M	+	M	+	+	M	+	+	+	M	+	+	M	M	+	+	+	M	+	M	+	28
Hepatocellular carcinoma, metastatic, liver																										1
Lymph node, mandibular	M	+	+	+	+	M	+	M	+	+	+	M	I	+	+	+	+	+	+	+	M	+	M	+	M	36
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar carcinoma, metastatic, lung					X																					1
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	43
Hepatocellular carcinoma, metastatic, liver																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	42
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Melanoma malignant																										1
Subcutaneous tissue, fibrous histiocytoma																										1
Subcutaneous tissue, hemangiosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma										X																1
Alveolar/bronchiolar carcinoma	X				X																			X		5
Carcinoma, metastatic, parathyroid gland										X																1
Hepatocellular carcinoma, metastatic, liver											X										X					3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	3 6 5	5 0 6	5 2 1	5 5 0	5 5 7	5 6 3	5 7 5	5 9 3	5 9 3	5 9 3	6 2 6	6 4 5	6 5 3	6 5 5	6 6 9	6 8 1	7 1 0	7 2 8	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9	7 2 9
Carcass ID Number	6 4 2	6 3 4	6 4 0	6 0 6	6 4 4	6 0 4	6 1 1	6 2 5	6 3 1	6 4 5	6 5 0	6 3 7	6 4 7	6 1 8	6 2 1	6 3 3	6 4 3	6 1 5	6 0 1	6 0 7	6 0 9	6 1 0	6 1 4	6 1 7	6 1 9
Special Senses System																									
Ear																									
Eye	A	+	A	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Carcinoma											X														
Lacrimal gland																									
Zymbal's gland									+																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	729	729	729	729	729	729	729	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	
Carcass ID Number	62404	62206	62207	62208	62209	63000	63305	63306	64006	64409	60002	60003	60005	60008	61012	61013	61016	62000	62202	62303	63202	63308	63309	64001	64008		Total Tissues/ Tumors
Special Senses System																											
Ear	+																										1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		46
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenoma		X																						X	X		4
Carcinoma									X									X									3
Lacrimal gland									+																		1
Zymbal's gland																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant	X										X																2

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Adrenal Cortex: Adenoma				
Overall rate[a]	4/49 (8%)	3/50 (6%)	1/49 (2%)	1/50 (2%)
Adjusted rate[b]	9.3%	6.9%	2.5%	2.4%
Terminal rate[c]	4/34 (12%)	2/32 (6%)	1/27 (4%)	1/32 (3%)
First incidence (days)	729 (T)	618	729 (T)	729 (T)
Poly-3 test[d]	P=0.096N	P=0.494N	P=0.196N	P=0.183N
Harderian Gland: Adenoma				
Overall rate	7/50 (14%)	6/50 (12%)	5/50 (10%)	4/50 (8%)
Adjusted rate	15.9%	13.7%	12.0%	9.4%
Terminal rate	5/34 (15%)	5/32 (16%)	4/27 (15%)	4/32 (13%)
First incidence (days)	651	618	644	729 (T)
Poly-3 test	P=0.219N	P=0.507N	P=0.419N	P=0.280N
Harderian Gland: Carcinoma				
Overall rate	0/50 (0%)	4/50 (8%)	3/50 (6%)	3/50 (6%)
Adjusted rate	0.0%	9.2%	7.2%	7.0%
Terminal rate	0/34 (0%)	2/32 (6%)	2/27 (7%)	2/32 (6%)
First incidence (days)	—[e]	675	527	626
Poly-3 test	P=0.211	P=0.060	P=0.112	P=0.115
Harderian Gland: Adenoma or Carcinoma				
Overall rate	7/50 (14%)	10/50 (20%)	8/50 (16%)	7/50 (14%)
Adjusted rate	15.9%	22.8%	18.9%	16.3%
Terminal rate	5/34 (15%)	7/32 (22%)	6/27 (22%)	6/32 (19%)
First incidence (days)	651	618	527	626
Poly-3 test	P=0.477N	P=0.292	P=0.465	P=0.594
Intestine Small (Jejunum): Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted rate	0.0%	6.9%	0.0%	0.0%
Terminal rate	0/34 (0%)	3/32 (9%)	0/27 (0%)	0/32 (0%)
First incidence (days)	—	729 (T)	—[f]	—
Poly-3 test	P=0.319N	P=0.117	—	—
Intestine Small (Unspecified Site): Carcinoma				
Overall rate	0/50 (0%)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	6.9%	0.0%	4.6%
Terminal rate	0/34 (0%)	3/32 (9%)	0/27 (0%)	0/32 (0%)
First incidence (days)	—	729 (T)	—	593
Poly-3 test	P=0.345	P=0.117	—	P=0.236
Intestine Small (Unspecified Site): Adenoma or Carcinoma				
Overall rate	0/50 (0%)	4/50 (8%)	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	9.2%	0.0%	4.6%
Terminal rate	0/34 (0%)	4/32 (13%)	0/27 (0%)	0/32 (0%)
First incidence (days)	—	729 (T)	—	593
Poly-3 test	P=0.437	P=0.059	—	P=0.236
Liver: Hemangiosarcoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	2.3%	7.2%	0.0%
Terminal rate	0/34 (0%)	0/32 (0%)	0/27 (0%)	0/32 (0%)
First incidence (days)	—	683	628	—
Poly-3 test	P=0.621	P=0.499	P=0.111	—

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Liver: Hepatocellular Adenoma				
Overall rate	23/50 (46%)	28/50 (56%)	21/50 (42%)	29/50 (58%)
Adjusted rate	51.5%	60.7%	48.3%	62.9%
Terminal rate	21/34 (62%)	20/32 (63%)	14/27 (52%)	21/32 (66%)
First incidence (days)	458	398	509	506
Poly-3 test	P=0.225	P=0.244	P=0.466N	P=0.180
Liver: Hepatocellular Carcinoma				
Overall rate	16/50 (32%)	15/50 (30%)	17/50 (34%)	10/50 (20%)
Adjusted rate	32.9%	31.0%	36.8%	22.3%
Terminal rate	6/34 (18%)	4/32 (13%)	3/27 (11%)	4/32 (13%)
First incidence (days)	458	398	478	563
Poly-3 test	P=0.181N	P=0.508N	P=0.427	P=0.182N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	34/50 (68%)	37/50 (74%)	30/50 (60%)	32/50 (64%)[g]
Adjusted rate	69.4%	74.8%	64.8%	68.7%
Terminal rate	23/34 (68%)	21/32 (66%)	15/27 (56%)	22/32 (69%)
First incidence (days)	458	398	478	506
Poly-3 test	P=0.402N	P=0.355	P=0.399N	P=0.560N
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	16/50 (32%)	15/50 (30%)	17/50 (34%)	11/50 (22%)
Adjusted rate	32.9%	31.0%	36.8%	24.6%
Terminal rate	6/34 (18%)	4/32 (13%)	3/27 (11%)	5/32 (16%)
First incidence (days)	458	398	478	563
Poly-3 test	P=0.253N	P=0.508N	P=0.427	P=0.256N
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	6/50 (12%)	2/49 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	13.8%	4.7%	7.2%	2.4%
Terminal rate	6/34 (18%)	2/32 (6%)	2/27 (7%)	1/32 (3%)
First incidence (days)	729 (T)	729 (T)	702	729 (T)
Poly-3 test	P=0.055N	P=0.140N	P=0.266N	P=0.059N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	7/50 (14%)	2/49 (4%)	4/50 (8%)	5/50 (10%)
Adjusted rate	15.9%	4.7%	9.6%	11.6%
Terminal rate	5/34 (15%)	1/32 (3%)	2/27 (7%)	3/32 (9%)
First incidence (days)	628	675	702	506
Poly-3 test	P=0.475N	P=0.085N	P=0.296N	P=0.394N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	13/50 (26%)	4/49 (8%)	6/50 (12%)	6/50 (12%)
Adjusted rate	29.5%	9.4%	14.5%	13.9%
Terminal rate	11/34 (32%)	3/32 (9%)	4/27 (15%)	4/32 (13%)
First incidence (days)	628	675	702	506
Poly-3 test	P=0.091N	P=0.016N	P=0.076N	P=0.063N
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	1/50 (2%)	5/50 (10%)	2/50 (4%)
Adjusted rate	2.3%	2.3%	11.9%	4.7%
Terminal rate	0/34 (0%)	0/32 (0%)	1/27 (4%)	0/32 (0%)
First incidence (days)	617	683	628	681
Poly-3 test	P=0.285	P=0.758	P=0.090	P=0.490

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	1/50 (2%)	5/50 (10%)	2/50 (4%)
Adjusted rate	4.6%	2.3%	11.9%	4.7%
Terminal rate	1/34 (3%)	0/32 (0%)	1/27 (4%)	0/32 (0%)
First incidence (days)	617	683	628	681
Poly-3 test	P=0.439	P=0.504N	P=0.196	P=0.684
All Organs: Histiocytic Sarcoma				
Overall rate	0/50 (0%)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted rate	0.0%	2.3%	7.2%	0.0%
Terminal rate	0/34 (0%)	0/32 (0%)	1/27 (4%)	0/32 (0%)
First incidence (days)	—	618	667	—
Poly-3 test	P=0.621	P=0.500	P=0.110	—
All Organs: Malignant Lymphoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Adjusted rate	6.9%	2.3%	0.0%	4.7%
Terminal rate	2/34 (6%)	1/32 (3%)	0/27 (0%)	2/32 (6%)
First incidence (days)	694	729 (T)	—	729 (T)
Poly-3 test	P=0.451N	P=0.309N	P=0.129N	P=513N
All Organs: Benign Neoplasms				
Overall rate	32/50 (64%)	31/50 (62%)	30/50 (60%)	33/50 (66%)
Adjusted rate	70.6%	67.2%	67.1%	71.1%
Terminal rate	27/34 (79%)	23/32 (72%)	19/27 (70%)	23/32 (72%)
First incidence (days)	458	398	484	506
Poly-3 test	P=0.484	P=0.448N	P=0.445N	P=0.574
All Organs: Malignant Neoplasms				
Overall rate	23/50 (46%)	23/50 (46%)	25/50 (50%)	23/50 (46%)
Adjusted rate	47.0%	47.3%	53.6%	49.4%
Terminal rate	11/34 (32%)	10/32 (31%)	9/27 (33%)	12/32 (38%)
First incidence (days)	458	398	478	506
Poly-3 test	P=0.406	P=0.566	P=0.328	P=0.486
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/50 (84%)	43/50 (86%)	41/50 (82%)	41/50 (82%)
Adjusted rate	84.9%	86.5%	87.1%	85.4%
Terminal rate	28/34 (82%)	26/32 (81%)	23/27 (85%)	26/32 (81%)
First incidence (days)	458	398	478	506
Poly-3 test	P=0.539	P=0.520	P=0.490	P=0.584

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal cortex, liver, and lung; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.
[g] A single incidence of hepatoblastoma occurred in an animal that also had an adenoma.

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: Inhalation Studies			
Decalin	22/50	10/50	28/50
Indium phosphide	17/50	11/50	26/50
Propylene glycol mono-*t*-butyl ether	18/50	9/50	25/50
Stoddard solvent IIC	23/50	16/50	34/50
Vanadium pentoxide	15/50	14/50	26/50
Overall Historical Incidence: Inhalation Studies			
Total (%)	95/250 (38%)	60/250 (24%)	139/250 (56%)
Mean ± standard deviation	38.0% ± 6.8%	24.0% ± 5.8%	55.6% ± 7.3%
Range	30%-46%	18%-32%	50%-68%
Overall Historical Incidence			
Total (%)	357/1,159 (31%)	247/1,159 (21%)	543/1,159 (47%)
Mean ± standard deviation	32.2% ± 10.5%	22.3% ± 8.7%	48.9% ± 14.5%
Range	12%-46%	8%-34%	26%-72%

[a] Data as of March 3, 2003

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death			1	
Moribund	7	9	16	13
Natural deaths	9	9	6	5
Survivors				
Terminal sacrifice	34	32	27	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(39)	(36)	(41)	(43)
Degeneration, hyaline		1 (3%)		
Hyperplasia	1 (3%)			
Infiltration cellular, mixed cell	1 (3%)			
Inflammation, chronic active		1 (3%)		
Intestine large, cecum	(45)	(41)	(46)	(47)
Hemorrhage	1 (2%)			1 (2%)
Intestine small, duodenum	(46)	(41)	(46)	(47)
Inflammation, chronic active			1 (2%)	
Intestine small, jejunum	(46)	(41)	(46)	(47)
Serosa, inflammation, granulomatous	1 (2%)			
Intestine small, ileum	(45)	(41)	(46)	(47)
Infiltration cellular, plasma cell			1 (2%)	
Inflammation		1 (2%)		
Liver	(50)	(50)	(50)	(50)
Amyloid deposition	1 (2%)			
Basophilic focus	9 (18%)	13 (26%)	17 (34%)	11 (22%)
Clear cell focus	13 (26%)	11 (22%)	15 (30%)	10 (20%)
Eosinophilic focus	5 (10%)	7 (14%)	14 (28%)	9 (18%)
Fatty change	1 (2%)		1 (2%)	
Infarct	1 (2%)			1 (2%)
Inflammation, chronic				1 (2%)
Mitotic alteration		1 (2%)		
Mixed cell focus	2 (4%)	1 (2%)		1 (2%)
Necrosis	4 (8%)	4 (8%)	2 (4%)	4 (8%)
Tension lipidosis	2 (4%)	3 (6%)	1 (2%)	2 (4%)
Bile duct, cyst				1 (2%)
Centrilobular, necrosis	1 (2%)			1 (2%)
Mesentery	(6)	(6)	(7)	(5)
Artery, inflammation	1 (17%)		1 (14%)	
Fat, hemorrhage		1 (17%)		
Fat, necrosis	4 (67%)	5 (83%)	5 (71%)	5 (100%)
Pancreas	(49)	(49)	(49)	(50)
Atrophy	1 (2%)	1 (2%)		
Salivary glands	(50)	(50)	(49)	(50)
Atrophy			1 (2%)	
Stomach, forestomach	(49)	(48)	(49)	(49)
Hyperplasia, squamous	5 (10%)	3 (6%)		4 (8%)
Inflammation, chronic active	5 (10%)	1 (2%)		2 (4%)
Ulcer	2 (4%)	1 (2%)		2 (4%)

[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 Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Alimentary System (continued)				
Stomach, glandular	(48)	(44)	(49)	(48)
Degeneration, hyaline				1 (2%)
Hyperplasia		1 (2%)		
Mineralization	2 (4%)	1 (2%)		
Necrosis	2 (4%)		1 (2%)	1 (2%)
Vacuolization cytoplasmic			1 (2%)	
Tongue				(1)
Mineralization				1 (100%)
Tooth	(19)	(16)	(21)	(17)
Malformation				1 (6%)
Cardiovascular System				
Blood vessel			(1)	(1)
Aorta, mineralization			1 (100%)	
Heart	(50)	(50)	(50)	(50)
Amyloid deposition	1 (2%)			
Angiectasis		1 (2%)		
Cardiomyopathy	15 (30%)	12 (24%)	21 (42%)	19 (38%)
Infiltration cellular, polymorphonuclear			1 (2%)	
Mineralization	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Thrombosis		1 (2%)	1 (2%)	1 (2%)
Artery, inflammation			1 (2%)	
Capillary, endothelium, hyperplasia		1 (2%)		
Endocrine System				
Adrenal cortex	(49)	(50)	(49)	(50)
Atrophy			1 (2%)	
Hyperplasia	13 (27%)	10 (20%)	7 (14%)	15 (30%)
Hypertrophy	30 (61%)	29 (58%)	20 (41%)	20 (40%)
Adrenal medulla	(48)	(49)	(49)	(50)
Hyperplasia	3 (6%)	4 (8%)	3 (6%)	1 (2%)
Islets, pancreatic	(48)	(49)	(49)	(50)
Hyperplasia		1 (2%)	1 (2%)	
Pituitary gland	(49)	(49)	(48)	(46)
Pars distalis, hyperplasia	2 (4%)		2 (4%)	2 (4%)
Pars intermedia, hyperplasia				1 (2%)
Thyroid gland	(49)	(48)	(47)	(50)
Follicular cell, hyperplasia	3 (6%)	2 (4%)	3 (6%)	2 (4%)
General Body System				
Peritoneum	(1)	(1)	(1)	
Inflammation, suppurative	1 (100%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Genital System				
Coagulating gland			(2)	
Hyperplasia			1 (50%)	
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	3 (6%)		3 (6%)	2 (4%)
Infiltration cellular, mononuclear cell				1 (2%)
Penis		(3)		(1)
Inflammation, acute		2 (67%)		1 (100%)
Preputial gland	(49)	(49)	(50)	(48)
Ectasia	1 (2%)			
Inflammation, chronic active	2 (4%)	3 (6%)	2 (4%)	1 (2%)
Prostate	(46)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)		1 (2%)
Artery, inflammation			1 (2%)	
Seminal vesicle	(48)	(46)	(50)	(48)
Amyloid deposition				1 (2%)
Infiltration cellular, mononuclear cell		1 (2%)		
Inflammation, chronic		1 (2%)		
Inflammation, suppurative		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Atrophy	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Mineralization		1 (2%)		
Germinal epithelium, degeneration	1 (2%)			
Interstitial cell, hyperplasia	2 (4%)			
Hematopoietic System				
Lymph node	(1)		(1)	(3)
Deep cervical, hyperplasia, lymphoid				1 (33%)
Lumbar, infiltration cellular, plasma cell				2 (67%)
Lymph node, mesenteric	(48)	(46)	(48)	(48)
Angiectasis			1 (2%)	
Hyperplasia, lymphoid				1 (2%)
Infiltration cellular, plasma cell			1 (2%)	
Lymph node, mediastinal	(39)	(40)	(36)	(43)
Infiltration cellular, plasma cell				1 (2%)
Spleen	(49)	(49)	(49)	(50)
Amyloid deposition	1 (2%)			
Angiectasis			1 (2%)	
Hematopoietic cell proliferation		3 (6%)	3 (6%)	2 (4%)
Thymus	(41)	(39)	(40)	(42)
Cyst	1 (2%)			
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)			
Infiltration cellular, mixed cell	1 (2%)			
Inflammation, chronic active	6 (12%)	7 (14%)	11 (22%)	18 (36%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Intervertebral disc, necrosis			1 (2%)	
Skeletal muscle				(1)
Inflammation, suppurative				1 (100%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Inflammation, granulomatous			1 (2%)	
Meninges, infiltration cellular, mononuclear cell			1 (2%)	
Spinal cord				(1)
Degeneration				1 (100%)
Respiratory System				
Lung	(50)	(49)	(50)	(50)
Fibrosis			1 (2%)	
Hemorrhage	1 (2%)	1 (2%)	2 (4%)	
Inflammation, chronic active				1 (2%)
Thrombosis	1 (2%)		1 (2%)	
Alveolar epithelium, hyperplasia		4 (8%)		2 (4%)
Alveolus, infiltration cellular, histiocyte	2 (4%)	1 (2%)	3 (6%)	1 (2%)
Bronchiole, hyperplasia	2 (4%)			
Mediastinum, thrombosis		1 (2%)		
Nose	(50)	(48)	(50)	(50)
Inflammation, suppurative	3 (6%)	2 (4%)	1 (2%)	2 (4%)
Polyp, inflammatory	1 (2%)		1 (2%)	
Olfactory epithelium, atrophy	3 (6%)	1 (2%)	2 (4%)	
Olfactory epithelium, inflammation, granulomatous			1 (2%)	
Special Senses System				
Eye	(46)	(46)	(47)	(46)
Cornea, inflammation, chronic active		3 (7%)	1 (2%)	1 (2%)
Harderian gland	(50)	(50)	(50)	(49)
Hyperplasia	3 (6%)	4 (8%)	1 (2%)	1 (2%)
Zymbal's gland	(1)			(1)
Cyst	1 (100%)			

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Amyloid deposition	1 (2%)			
Cyst	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Inflammation, granulomatous			1 (2%)	
Inflammation, suppurative	1 (2%)		2 (4%)	2 (4%)
Metaplasia, osseous	3 (6%)	4 (8%)		2 (4%)
Nephropathy	44 (88%)	43 (86%)	42 (86%)	44 (88%)
Capsule, fibrosis	1 (2%)			1 (2%)
Papilla, necrosis		1 (2%)	1 (2%)	
Pelvis, dilatation		1 (2%)		2 (4%)
Renal tubule, hyperplasia	2 (4%)	1 (2%)		
Renal tubule, necrosis		2 (4%)		
Transitional epithelium, hyperplasia			1 (2%)	2 (4%)
Urinary bladder	(49)	(46)	(49)	(50)
Infiltration cellular, mixed cell		1 (2%)	1 (2%)	
Inflammation, acute			1 (2%)	
Inflammation, chronic active	1 (2%)		1 (2%)	2 (4%)
Transitional epithelium, hyperplasia	1 (2%)		1 (2%)	1 (2%)

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF STODDARD SOLVENT IIC

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	6	11	11	10
Natural deaths	8	5	12	6
Survivors				
Terminal sacrifice	36	34	27	34
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(40)	(43)	(32)	(45)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Intestine large, rectum	(44)	(48)	(44)	(47)
Intestine large, cecum	(43)	(47)	(44)	(46)
Leiomyosarcoma	1 (2%)			
Intestine small, duodenum	(43)	(45)	(44)	(47)
Carcinoma				1 (2%)
Intestine small, jejunum	(43)	(47)	(43)	(47)
Carcinoma		1 (2%)		
Intestine small, ileum	(43)	(47)	(44)	(46)
Carcinoma			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)		1 (2%)
Hepatocellular carcinoma	4 (8%)	7 (14%)	4 (8%)	6 (12%)
Hepatocellular carcinoma, multiple	2 (4%)		1 (2%)	
Hepatocellular adenoma	9 (18%)	9 (18%)	11 (22%)	11 (22%)
Hepatocellular adenoma, multiple		3 (6%)	4 (8%)	7 (14%)
Hepatocholangiocarcinoma		2 (4%)		
Hepatocholangiocarcinoma, multiple				1 (2%)
Histiocytic sarcoma	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Sarcoma, metastatic, skin			1 (2%)	
Mesentery	(4)	(15)	(21)	(11)
Carcinoma, metastatic, intestine small, ileum			1 (5%)	
Hepatocholangiocarcinoma, metastatic, liver				1 (9%)
Histiocytic sarcoma				1 (9%)
Sarcoma		1 (7%)		
Sarcoma, metastatic, skin			2 (10%)	
Oral mucosa	(1)			
Pharyngeal, squamous cell carcinoma	1 (100%)			
Pancreas	(49)	(50)	(48)	(49)
Carcinoma, metastatic, intestine small, ileum			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Sarcoma, metastatic, skin			1 (2%)	
Salivary glands	(50)	(49)	(49)	(50)
Stomach, forestomach	(49)	(50)	(49)	(50)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Squamous cell papilloma			1 (2%)	1 (2%)
Stomach, glandular	(47)	(49)	(47)	(47)
Adenoma	1 (2%)			1 (2%)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Sarcoma, metastatic, skin			1 (2%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Carcinoma, metastatic, intestine small, ileum			1 (2%)	
Histiocytic sarcoma				1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Carcinoma, metastatic, intestine small, ileum			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Subcapsular, adenoma	1 (2%)	1 (2%)		
Adrenal medulla	(49)	(50)	(48)	(49)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Pheochromocytoma malignant	1 (2%)			
Pheochromocytoma benign	1 (2%)			1 (2%)
Islets, pancreatic	(49)	(50)	(48)	(48)
Adenoma	1 (2%)	1 (2%)		
Pituitary gland	(47)	(49)	(49)	(48)
Pars distalis, adenoma	10 (21%)	8 (16%)	10 (20%)	10 (21%)
Pars distalis, carcinoma		1 (2%)		
Pars intermedia, adenoma		1 (2%)		
Thyroid gland	(50)	(49)	(47)	(48)
Follicular cell, adenoma	2 (4%)			
Follicular cell, carcinoma		1 (2%)		
General Body System				
None				
Genital System				
Clitoral gland	(40)	(42)	(47)	(41)
Carcinoma				1 (2%)
Ovary	(49)	(50)	(48)	(49)
Carcinoma		1 (2%)		
Cystadenoma	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Granulosa cell tumor benign		1 (2%)		
Granulosa-theca tumor benign			1 (2%)	
Hemangioma	1 (2%)		1 (2%)	
Histiocytic sarcoma	2 (4%)	2 (4%)		1 (2%)
Sarcoma, metastatic, skin			2 (4%)	
Teratoma benign	1 (2%)			
Uterus	(49)	(50)	(49)	(49)
Adenoma		1 (2%)		
Carcinoma		1 (2%)		
Hemangiosarcoma		1 (2%)		
Histiocytic sarcoma		2 (4%)		1 (2%)
Polyp stromal	2 (4%)			1 (2%)
Sarcoma stromal	1 (2%)			
Sarcoma stromal, multiple		1 (2%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Hematopoietic System				
Bone marrow	(49)	(49)	(48)	(50)
Hemangiosarcoma		1 (2%)		1 (2%)
Histiocytic sarcoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Lymph node	(5)	(7)	(9)	(10)
Lumbar, hemangiosarcoma, metastatic, spleen				1 (10%)
Lumbar, histiocytic sarcoma	1 (20%)			
Lumbar, sarcoma stromal, metastatic, uterus		1 (14%)		
Renal, histiocytic sarcoma	1 (20%)	1 (14%)		
Lymph node, bronchial	(41)	(37)	(40)	(42)
Carcinoma, metastatic, intestine small, ileum			1 (3%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (3%)		1 (2%)
Histiocytic sarcoma		1 (3%)	1 (3%)	1 (2%)
Lymph node, mandibular	(42)	(32)	(40)	(40)
Histiocytic sarcoma	2 (5%)	1 (3%)		1 (3%)
Lymph node, mesenteric	(47)	(49)	(47)	(50)
Carcinoma, metastatic, uterus		1 (2%)		
Carcinoma, metastatic, intestine small, ileum			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Sarcoma, metastatic, skin			1 (2%)	
Lymph node, mediastinal	(40)	(42)	(43)	(43)
Carcinoma, metastatic, intestine small, ileum			1 (2%)	
Hemangioma		1 (2%)		
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	2 (5%)	1 (2%)		2 (5%)
Spleen	(49)	(50)	(48)	(47)
Hemangiosarcoma	1 (2%)			1 (2%)
Histiocytic sarcoma	2 (4%)		1 (2%)	1 (2%)
Thymus	(43)	(45)	(47)	(46)
Carcinoma, metastatic, intestine small, ileum			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)		1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		1 (2%)
Skin	(50)	(50)	(50)	(50)
Basosquamous tumor malignant				1 (2%)
Squamous cell papilloma	1 (2%)			
Sebaceous gland, adenoma	1 (2%)			
Subcutaneous tissue, hemangioma				1 (2%)
Subcutaneous tissue, hemangiosarcoma		1 (2%)		
Subcutaneous tissue, histiocytic sarcoma	1 (2%)			1 (2%)
Subcutaneous tissue, sarcoma	1 (2%)		3 (6%)	2 (4%)
Subcutaneous tissue, sarcoma, multiple			2 (4%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Osteosarcoma	1 (2%)			
Skeletal muscle	(1)	(1)	(1)	(2)
Hepatocholangiocarcinoma, metastatic, liver				1 (50%)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Nervous System				
Brain	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	3 (6%)	1 (2%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma				2 (4%)
Basosquamous tumor malignant, metastatic, skin				1 (2%)
Carcinoma, metastatic, harderian gland	1 (2%)			
Carcinoma, metastatic, islets, pancreatic		1 (2%)		
Carcinoma, metastatic, intestine small, ileum			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	2 (4%)	4 (8%)	1 (2%)	3 (6%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		1 (2%)
Histiocytic sarcoma	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Pheochromocytoma malignant, metastatic, adrenal medulla	1 (2%)			
Sarcoma, metastatic, skin			1 (2%)	
Nose	(49)	(50)	(50)	(49)
Carcinoma, metastatic, harderian gland	1 (2%)			
Histiocytic sarcoma				1 (2%)
Sarcoma	1 (2%)			
Pleura		(1)	(1)	
Carcinoma, metastatic, intestine small, ileum			1 (100%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (100%)		
Special Senses System				
Eye	(46)	(49)	(45)	(46)
Carcinoma, metastatic, harderian gland	1 (2%)			
Histiocytic sarcoma		1 (2%)		1 (2%)
Sarcoma	1 (2%)			
Harderian gland	(49)	(49)	(49)	(49)
Adenoma	4 (8%)	2 (4%)	4 (8%)	3 (6%)
Carcinoma	1 (2%)	1 (2%)	1 (2%)	
Histiocytic sarcoma		1 (2%)		
Bilateral, adenoma			2 (4%)	
Urinary System				
Kidney	(50)	(50)	(49)	(49)
Carcinoma, metastatic, intestine small, ileum			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Urinary bladder	(48)	(50)	(49)	(48)
Hepatocholangiocarcinoma, metastatic, liver				1 (2%)
Histiocytic sarcoma		2 (4%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)	2 (4%)	1 (2%)	2 (4%)
Lymphoma malignant	5 (10%)	9 (18%)	11 (22%)	8 (16%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	39	41	41	39
Total primary neoplasms	61	65	62	66
Total animals with benign neoplasms	27	24	30	27
Total benign neoplasms	38	32	38	38
Total animals with malignant neoplasms	19	26	23	23
Total malignant neoplasms	23	33	24	28
Total animals with metastatic neoplasms	4	8	4	6
Total metastatic neoplasms	6	11	21	19

[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 Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	4 2 4	4 9 2	5 3 0	5 9 0	5 9 4	6 1 8	6 4 9	6 6 8	6 8 1	6 8 3	6 9 4	7 0 2	7 0 8	7 2 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 1 4	1 4 6	1 1 8	1 3 7	1 1 7	1 3 2	1 4 7	1 3 3	1 3 0	1 4 1	1 2 2	1 0 3	1 3 6	1 4 2	1 0 2	1 0 4	1 0 5	1 0 7	1 0 8	1 0 9	1 1 2	1 1 6	1 2 0	1 2 1	1 2 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	A	+	A	+	A	A	I	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	A	+	A	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	A	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	A	+	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma															X										
Intestine small, duodenum	A	A	A	+	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	A	A	A	+	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	A	A	+	A	+	A	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma								X														X			
Hepatocellular carcinoma, multiple												X													
Hepatocellular adenoma				X						X		X	X				X								X
Histiocytic sarcoma	X																								
Mesentery														+	+						+				
Oral mucosa						+																			
Pharyngeal, squamous cell carcinoma						X																			
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Tooth																								+	
Cardiovascular System																									
Blood vessel							+																		
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Subcapsular, adenoma			X																						
Adrenal medulla	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Pheochromocytoma malignant					X																				
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	M	+	+
Pituitary gland	A	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																X						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 D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 2 4	1 2 5	1 3 4	1 3 8	1 4 5	1 4 8	1 5 0	1 0 1	1 0 6	1 1 0	1 1 1	1 1 3	1 1 5	1 1 9	1 2 6	1 2 7	1 2 8	1 2 9	1 3 1	1 3 5	1 3 9	1 4 0	1 4 3	1 4 4	1 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Leiomyosarcoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																X						X				4
Hepatocellular carcinoma, multiple						X																				2
Hepatocellular adenoma						X									X		X									9
Histiocytic sarcoma																										1
Mesentery																					+					4
Oral mucosa																										1
Pharyngeal, squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma						X																				1
Tooth					+																					2
Cardiovascular System																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Subcapsular, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Pheochromocytoma malignant																										1
Pheochromocytoma benign																							X			1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma														X												1
Parathyroid gland	M	+	M	+	+	M	+	+	+	M	+	M	+	M	+	+	+	+	+	+	+	+	+	M	+	39
Pituitary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Pars distalis, adenoma				X					X			X			X	X			X	X	X					10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma			X																							2
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	4 2 4	4 9 2	5 3 0	5 9 0	5 9 4	6 1 8	6 4 9	6 6 8	6 8 1	6 8 3	6 9 4	7 0 2	7 0 8	7 2 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 1 4	1 4 6	1 1 8	1 3 7	1 1 7	1 3 2	1 4 7	1 3 3	1 3 0	1 4 1	1 2 2	1 0 3	1 3 6	1 4 2	1 0 2	1 0 4	1 0 5	1 0 7	1 0 8	1 0 9	1 1 2	1 1 6	1 2 0	1 2 1	1 2 3
Genital System																									
Clitoral gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	I	+	+	+	+	+	+	I	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+
Cystadenoma																									
Hemangioma						X																			
Histiocytic sarcoma	X																						X		
Teratoma benign					X																				
Uterus	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal																								X	
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																						X		
Lymph node		+												+									+		
Lumbar, histiocytic sarcoma																							X		
Renal, histiocytic sarcoma																							X		
Lymph node, bronchial	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	M	+	+
Lymph node, mandibular	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																						X		
Lymph node, mesenteric	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																						X		
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+
Histiocytic sarcoma	X																						X		
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma					X																				
Histiocytic sarcoma	X																						X		
Thymus	A	+	+	+	+	+	A	+	M	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																							X		
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Sebaceous gland, adenoma																								X	
Subcutaneous tissue, histiocytic sarcoma																							X		
Subcutaneous tissue, sarcoma													X												
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma															X										
Skeletal muscle																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Spinal cord																			M						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 2 4	1 2 5	1 3 4	1 3 8	1 4 5	1 4 8	1 5 0	1 0 1	1 0 6	1 1 0	1 1 1	1 1 3	1 1 5	1 1 9	1 2 6	1 2 7	1 2 8	1 2 9	1 3 1	1 3 5	1 3 9	1 4 0	1 4 3	1 4 4	1 4 9	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	M	+	+	M	+	+	I	+	+	+	+	+	+	+	+	I	+	I	40
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma								X																		1
Hemangioma																										1
Histiocytic sarcoma																										2
Teratoma benign																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp stromal																				X						2
Sarcoma stromal											X															1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										2
Lymph node		+								+																5
Lumbar, histiocytic sarcoma																										1
Renal, histiocytic sarcoma																										1
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	M	+	+	M	+	41
Lymph node, mandibular	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	M	+	+	+	+	M	+	42
Histiocytic sarcoma																										2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										2
Lymph node, mediastinal	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	M	+	40
Histiocytic sarcoma																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																										1
Histiocytic sarcoma																										2
Thymus	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	43
Histiocytic sarcoma																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																							X			1
Sebaceous gland, adenoma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Subcutaneous tissue, sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma																										1
Skeletal muscle													+													1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Spinal cord																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	4 2 4	4 9 2	5 3 0	5 9 0	5 9 4	6 1 8	6 4 9	6 6 8	6 8 1	6 8 3	6 9 4	7 0 2	7 0 8	7 2 7	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	1 1 4	1 4 6	1 1 8	1 3 7	1 1 7	1 3 2	1 4 7	1 3 3	1 3 0	1 4 1	1 2 2	1 0 3	1 3 6	1 4 2	1 0 2	1 0 4	1 0 5	1 0 7	1 0 8	1 0 9	1 1 2	1 1 6	1 2 0	2 2 1	2 2 3
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar adenoma, multiple																									
Carcinoma, metastatic, harderian gland									X																
Hepatocellular carcinoma, metastatic, liver								X				X													
Histiocytic sarcoma	X																								
Pheochromocytoma malignant, metastatic, adrenal medulla					X																				
Nose	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland									X																
Sarcoma									X																
Trachea	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	A	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, harderian gland									X																
Sarcoma									X																
Harderian gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X						X				X									
Carcinoma									X																
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma	X																								
Urinary bladder	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Inhalation Study of Stoddard Solvent IIC: Chamber Control

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	1 2 4	1 2 5	1 3 4	1 3 8	1 4 5	1 4 8	1 5 0	1 0 1	1 0 6	1 1 0	1 1 1	1 1 3	1 1 5	1 1 9	1 2 6	1 2 7	1 2 8	1 2 9	1 3 1	1 3 5	1 3 9	1 4 0	1 4 3	1 4 4	1 4 9	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar adenoma, multiple													X													1
Carcinoma, metastatic, harderian gland																										1
Hepatocellular carcinoma, metastatic, liver																										2
Histiocytic sarcoma																										1
Pheochromocytoma malignant, metastatic, adrenal medulla																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, harderian gland																										1
Sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, metastatic, harderian gland																										1
Sarcoma																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																		X								4
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant		X					X																			5

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 2 3	3 2 4	3 3 1	3 3 3	3 4 4	3 4 7	3 5 0	3 0 1	3 0 2	3 0 4	3 0 6	3 0 8	3 0 9	3 1 0	3 1 2	3 1 9	3 2 0	3 2 7	3 2 8	3 2 9	3 3 4	3 3 5	3 3 8	3 4 0	3 4 3	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	I	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	45
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																												1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma												X																1
Hepatocellular carcinoma		X												X					X	X								7
Hepatocellular adenoma		X						X								X				X							X	9
Hepatocellular adenoma, multiple	X											X																3
Hepatocholangiocarcinoma																												2
Histiocytic sarcoma																												2
Mesentery		+			+					+	+		+	+											+		15
Sarcoma														X														1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth				+																								2
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																												1
Subcapsular, adenoma																			X									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																												1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	+	+	+	+	+	M	+	+			41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			49
Pars distalis, adenoma						X					X						X						X					8
Pars distalis, carcinoma																												1
Pars intermedia, adenoma																												1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			49
Follicular cell, carcinoma																					X							1
General Body System																												
Peritoneum																												1
Tissue, nonspecified site																												1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	3 6 6	4 5 5	4 7 0	5 5 7	5 7 8	5 8 6	5 9 7	6 2 0	6 3 7	6 5 3	6 5 3	6 6 6	6 7 5	6 7 7	6 8 8	6 9 5	7 3 0	7 3 0	7 3 0	7 3 0	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	3 1 3	3 2 5	3 4 1	3 1 5	3 2 6	3 4 6	3 3 6	3 1 6	3 4 9	3 0 5	3 3 9	3 4 8	3 3 2	3 1 1	3 3 0	3 1 7	3 1 8	3 3 7	3 4 2	3 4 5	3 0 3	3 0 7	3 1 4	3 2 1	3 2 2
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																					X				
Cystadenoma														X											
Granulosa cell tumor benign																						X			
Histiocytic sarcoma		X					X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Carcinoma																									
Hemangiosarcoma					X																				
Histiocytic sarcoma		X					X																		
Sarcoma stromal, multiple						X																			
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma							X																		
Lymph node						+	+											+	+			+			
Lumbar, sarcoma stromal, metastatic, uterus						X																			
Renal, histiocytic sarcoma							X																		
Lymph node, bronchial	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	M	+	+	+	M	+	+	I	+
Hepatocholangiocarcinoma, metastatic, liver													X												
Histiocytic sarcoma							X																		
Lymph node, mandibular	M	+	+	+	+	+	+	M	+	+	M	+	+	M	M	M	M	+	+	+	+	+	M	+	M
Histiocytic sarcoma							X																		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, uterus																									
Histiocytic sarcoma							X																		
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Hemangioma																									
Histiocytic sarcoma							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	M	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver													X												
Histiocytic sarcoma							X																		
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, hemangiosarcoma															X										
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 2 2 3	3 2 3 4	3 3 3 1	3 3 3 3	3 4 4 4	3 4 4 7	3 5 5 0	3 0 1 1	3 0 0 2	3 0 0 4	3 0 0 6	3 0 0 8	3 0 0 9	3 0 1 0	3 1 1 2	3 1 1 9	3 2 2 0	3 2 2 7	3 2 2 8	3 2 3 9	3 3 3 4	3 3 3 5	3 3 3 8	3 4 4 0	3 4 4 3	Total Tissues/ Tumors
Genital System																												
Clitoral gland	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	I	+	M	+	+	+	+	+			42
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Carcinoma																												1
Cystadenoma																									X			2
Granulosa cell tumor benign																												1
Histiocytic sarcoma																												2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Adenoma																												1
Carcinoma										X																		1
Hemangiosarcoma																												1
Histiocytic sarcoma																												2
Sarcoma stromal, multiple																												1
Hematopoietic System																												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			49
Hemangiosarcoma																								X				1
Histiocytic sarcoma																												1
Lymph node	+								+																			7
Lumbar, sarcoma stromal, metastatic, uterus																												1
Renal, histiocytic sarcoma																												1
Lymph node, bronchial	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	M	M	+	M	+	+	M	+	+	+			37
Hepatocholangiocarcinoma, metastatic, liver																												1
Histiocytic sarcoma																												1
Lymph node, mandibular	M	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	M	M	+	M	+	+	M	+	M			32
Histiocytic sarcoma																												1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+			49
Carcinoma, metastatic, uterus										X																		1
Histiocytic sarcoma																												1
Lymph node, mediastinal	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	M	+			42
Hemangioma													X															1
Histiocytic sarcoma																												1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+			45
Hepatocholangiocarcinoma, metastatic, liver																												1
Histiocytic sarcoma																												1
Integumentary System																												
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Carcinoma																												1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Subcutaneous tissue, hemangiosarcoma																												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+			50
Skeletal muscle																		+										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 550 mg/m³

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	3 2 3	3 2 4	3 3 1	3 3 3	3 4 4	3 4 7	3 5 0	3 0 1	3 0 2	3 0 4	3 0 6	3 0 8	3 0 9	3 1 0	3 1 2	3 1 9	3 2 0	3 2 7	3 2 8	3 2 9	3 3 4	3 3 5	3 3 8	3 4 0	3 4 3	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																		X								2
Carcinoma, metastatic, islets, pancreatic																										1
Hepatocellular carcinoma, metastatic, liver		X												X												4
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma				X															X							2
Carcinoma														X												1
Histiocytic sarcoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant									X	X			X	X								X				9

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	0151	5061	5355	5557	5563	5690	6000	6034	6039	6052	6055	6059	6064	6073	6075	6095	7053	7003	7034	7055	7058	7141	7234	7301	7331
Carcass ID Number	54505	52505	54404	54422	51505	52808	50404	53505	52403	54808	54407	53700	54303	51101	53707	54909	50505	50606	53303	53304	52404	51404	52200	51202	50202
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	A	+	I	+	+	A	M	+	A	A	A	I	A	+	A	+	A	A	+	I	+	I	+
Intestine large, colon	+	+	+	+	+	+	+	A	+	+	+	A	A	+	+	+	A	+	+	A	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	A	+	+	A	A	A	+	+	+	A	+	+	A	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	+	+	+	A	A	+	+	+	A	+	A	A	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	A	A	A	+	+	+	A	+	A	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	+	A	A	A	+	+	+	A	+	A	A	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	A	+	+	A	A	A	+	+	+	A	+	+	A	+	+	+	+	+
Carcinoma				X																					
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma									X			X	X												
Hepatocellular carcinoma, multiple																									
Hepatocellular adenoma									X				X				X	X			X		X		
Hepatocellular adenoma, multiple							X			X															
Histiocytic sarcoma								X																	
Sarcoma, metastatic, skin		X																							
Mesentery		+	+	+	+		+			+		+		+	+	+	+				+				
Carcinoma, metastatic, intestine small, ileum					X																				
Sarcoma, metastatic, skin		X													X										
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+
Carcinoma, metastatic, intestine small, ileum					X																				
Sarcoma, metastatic, skin		X																							
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	A	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin		X																							
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small, ileum					X																				
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small, ileum				X																					
Histiocytic sarcoma								X																	
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	M	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma						X	X				X														
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	M	+	+	+
General Body System																									
None																									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	50808	51103	51136	51167	51181	52202	52291	53101	54101	54601	50107	50209	50901	51901	52101	52206	52307	53201	53401	53606	53808	53909	54002	55002		Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder	+	+	I	+	+	+	I	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	M	+	32
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		45
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		43
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Carcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular carcinoma																	X									4
Hepatocellular carcinoma, multiple																								X		1
Hepatocellular adenoma	X		X													X		X			X					11
Hepatocellular adenoma, multiple							X												X							4
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin																										1
Mesentery	+			+					+							+	+	+	+			+			+		21
Carcinoma, metastatic, intestine small, ileum																										1
Sarcoma, metastatic, skin																										2
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Carcinoma, metastatic, intestine small, ileum																										1
Sarcoma, metastatic, skin																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Squamous cell papilloma										X																1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Sarcoma, metastatic, skin																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, metastatic, intestine small, ileum																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Carcinoma, metastatic, intestine small, ileum																										1
Histiocytic sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Histiocytic sarcoma																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Parathyroid gland	+	M	+	+	+	+	+	+	I	+	+	+	+	M	+	M	+	+	M	+	+	+	+	+		42
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Pars distalis, adenoma		X			X							X		X		X					X	X				10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
General Body System																										
None																										

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	0 1 5	5 0 6	5 3 5	5 5 7	5 6 3	5 9 0	6 0 0	6 3 4	6 3 9	6 5 2	6 5 5	6 5 9	6 6 4	6 7 3	6 7 5	6 9 5	7 0 3	7 0 3	7 0 4	7 0 5	7 0 8	7 1 4	7 2 3	7 3 0	7 3 1
Carcass ID Number	5 4 5	5 2 5	5 4 4	5 4 2	5 1 5	5 2 8	5 0 4	5 3 5	5 2 3	5 4 8	5 4 7	5 3 0	5 4 3	5 1 1	5 3 7	5 4 9	5 0 5	5 0 6	5 0 3	5 3 3	5 2 4	5 1 4	5 2 0	5 1 2	5 0 2
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	I	+	+	+	+
Cystadenoma																									
Granulosa-theca tumor benign																									
Hemangioma																									
Sarcoma, metastatic, skin		X													X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymph node					+					+				+						+	+				
Lymph node, bronchial	M	M	+	+	+	M	+	+	M	+	+	A	+	+	+	+	M	+	+	+	M	+	+	+	M
Carcinoma, metastatic, intestine small, ileum				X																					
Histiocytic sarcoma								X																	
Lymph node, mandibular	+	M	+	+	+	+	+	M	M	+	+	A	M	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	M	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small, ileum				X																					
Histiocytic sarcoma								X																	
Sarcoma, metastatic, skin															X										
Lymph node, mediastinal	+	+	+	+	M	M	+	M	+	+	+	A	M	+	+	+	M	M	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small, ileum				X																					
Spleen	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Thymus	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	M	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine small, ileum				X																					
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, sarcoma					X										X										
Subcutaneous tissue, sarcoma, multiple		X																					X		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle										+															
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Peripheral nerve																+									

Table D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	508	510	513	516	517	518	522	529	531	541	546	501	507	509	519	521	526	527	532	534	536	538	539	540	550	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	47
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma																X										1
Granulosa-theca tumor benign																					X					1
Hemangioma															X											1
Sarcoma, metastatic, skin																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Lymph node								+						+								+			+	9
Lymph node, bronchial	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Carcinoma, metastatic, intestine small, ileum																										1
Histiocytic sarcoma																										1
Lymph node, mandibular	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	40
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, intestine small, ileum																										1
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Carcinoma, metastatic, intestine small, ileum																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, metastatic, intestine small, ileum																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, sarcoma																					X					3
Subcutaneous tissue, sarcoma, multiple																										2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Peripheral nerve																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 1,100 mg/m³

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	50808	51100	51133	51166	51177	51188	52202	52229	53231	54241	54246	50161	50167	50209	51921	52216	52266	52327	53234	53346	53366	53389	53399	54400	55050	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X															X		3
Carcinoma, metastatic, intestine small, ileum																										1
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura																										1
Carcinoma, metastatic, intestine small, ileum																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X					X				X																4
Carcinoma																										1
Bilateral, adenoma																			X							2
Lacrimal gland																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, intestine small, ileum																										1
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant					X									X								X			X	11

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	7 2 2 2	7 2 2 5	7 2 2 7	7 2 2 8	7 3 3 0	7 3 3 6	7 3 3 7	7 3 3 9	7 4 4 3	7 4 4 4	7 4 4 8	7 5 0 0	7 0 1	7 0 0 4	7 0 0 7	7 0 0 9	7 1 4	7 2 2 0	7 2 2 6	7 3 3 4	7 3 3 8	7 4 4 2	7 4 4 5	7 4 4 6	7 4 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Hepatocholangiocarcinoma, metastatic, liver																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma										X												X				6
Hepatocellular adenoma	X		X			X	X	X					X								X					11
Hepatocellular adenoma, multiple				X										X									X			7
Hepatocholangiocarcinoma, multiple																										1
Histiocytic sarcoma																										2
Mesentery		+																	+				+			11
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma						X																				1
Hepatocholangiocarcinoma, metastatic, liver																										1
Cardiovascular System																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	41
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma			X		X								X				X				X					10
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	2 8 2	4 0 8	4 6 5	5 0 3	5 5 4	6 3 4	6 3 9	6 7 2	6 9 4	6 9 5	7 0 5	7 0 7	7 0 8	7 0 9	7 2 4	7 2 5	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1
Carcass ID Number	7 3 1	7 0 3	7 3 2	7 3 3	7 2 4	7 4 1	7 3 5	7 2 3	7 1 3	7 2 9	7 4 7	7 1 7	7 1 2	7 4 0	7 0 6	7 2 1	7 0 2	7 0 5	7 0 8	7 1 0	7 1 1	7 1 5	7 1 6	7 1 8	7 1 9
General Body System																									
None																									
Genital System																									
Clitoral gland	+	M	M	+	+	M	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M
Carcinoma							X																		
Ovary	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma				X																					
Histiocytic sarcoma		X																							
Uterus	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Polyp stromal							X																		
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma										X															
Lymph node								+				+				+					+				+
Lumbar, hemangiosarcoma, metastatic, spleen																									
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Histiocytic sarcoma		X																							
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Histiocytic sarcoma		X								X															
Lymph node, mediastinal	+	+	A	M	+	+	M	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Histiocytic sarcoma		X								X															
Spleen	+	+	A	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Histiocytic sarcoma										X															
Thymus	+	+	+	+	M	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Histiocytic sarcoma		X																							
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant	X																								
Subcutaneous tissue, hemangioma			X																						
Subcutaneous tissue, histiocytic sarcoma		X																							
Subcutaneous tissue, sarcoma																X									

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	
Carcass ID Number	7 2 2 2	7 2 2 5	7 2 2 7	7 2 2 8	7 3 3 0	7 3 3 6	7 3 3 7	7 3 3 9	7 4 4 3	7 4 4 4	7 4 4 8	7 5 0 0	7 0 0 1	7 0 0 4	7 0 0 7	7 0 0 9	7 1 4 4	7 2 2 0	7 2 2 6	7 3 3 4	7 3 3 8	7 4 4 2	7 4 4 5	7 4 4 6	7 4 4 9	Total Tissues/ Tumors
General Body System																											
None																											
Genital System																											
Clitoral gland	+	+	+	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Carcinoma																											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenoma																											1
Histiocytic sarcoma																											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Polyp stromal																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																			X								1
Histiocytic sarcoma																											1
Lymph node							+										+		+	+			+				10
Lumbar, hemangiosarcoma, metastatic, spleen																							X				1
Lymph node, bronchial	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+		42
Hepatocholangiocarcinoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Lymph node, mandibular	+	+	M	M	M	+	M	+	+	+	+	+	M	M	M	+	+	+	+	+	+	+	M	+	+		40
Histiocytic sarcoma																											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																											1
Histiocytic sarcoma																											2
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	43
Hepatocholangiocarcinoma, metastatic, liver																											1
Histiocytic sarcoma																											2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																							X				1
Histiocytic sarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hepatocholangiocarcinoma, metastatic, liver																											1
Histiocytic sarcoma																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																							X				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor malignant																											1
Subcutaneous tissue, hemangioma																											1
Subcutaneous tissue, histiocytic sarcoma																											1
Subcutaneous tissue, sarcoma				X																							2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	282	408	465	503	554	634	639	672	694	695	705	707	708	709	724	725	731	733	733	733	733	733	733	733	733
Carcass ID Number	731	703	732	733	724	741	735	723	713	729	744	711	712	740	706	721	725	700	701	715	716	718	719		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+			+																
Hepatocholangiocarcinoma, metastatic, liver									X																
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Peripheral nerve						+																			
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					
Alveolar/bronchiolar carcinoma			X																						
Basosquamous tumor malignant, metastatic, skin		X																							
Hepatocellular carcinoma, metastatic, liver														X							X				
Hepatocholangiocarcinoma, metastatic, liver									X																
Histiocytic sarcoma		X								X															
Nose	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Trachea	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	A	A	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																							
Harderian gland	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																								X	
Lacrimal gland																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Histiocytic sarcoma		X								X															
Urinary bladder	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver									X																
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X								X															
Lymphoma malignant								X				X				X					X			X	X

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC: 2,200 mg/m³

Number of Days on Study	731	731	731	731	731	731	731	731	731	731	731	731	732	732	732	732	732	732	732	732	732	732	732	732	732	
Carcass ID Number	72202	72205	72207	72208	73030	73036	73037	73039	74043	74044	74048	75001	00104	00407	00909	01414	02006	02206	02334	03338	04202	04245	04246	04249	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Hepatocholangiocarcinoma, metastatic, liver																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Peripheral nerve																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																									X	2
Basosquamous tumor malignant, metastatic, skin																										1
Hepatocellular carcinoma, metastatic, liver																					X					3
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Histiocytic sarcoma																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma		X	X																							3
Lacrimal gland		+																								1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocholangiocarcinoma, metastatic, liver																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										2
Lymphoma malignant					X						X															8

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Harderian Gland: Adenoma				
Overall rate[a]	4/50 (8%)	2/50 (4%)	6/50 (12%)	3/50 (6%)
Adjusted rate[b]	8.7%	4.6%	13.9%	6.7%
Terminal rate[c]	2/36 (6%)	2/34 (6%)	4/27 (15%)	3/34 (9%)
First incidence (days)	618	730 (T)	673	730 (T)
Poly-3 test[d]	P=0.558N	P=0.362N	P=0.332	P=0.514N
Harderian Gland: Adenoma or Carcinoma				
Overall rate	5/50 (10%)	3/50 (6%)	7/50 (14%)	3/50 (6%)
Adjusted rate	10.9%	6.9%	16.1%	6.7%
Terminal rate	2/36 (6%)	3/34 (9%)	4/27 (15%)	3/34 (9%)
First incidence (days)	618	730 (T)	664	730 (T)
Poly-3 test	P=0.408N	P=0.389N	P=0.338	P=0.373N
Liver: Hepatocellular Adenoma				
Overall rate	9/50 (18%)	12/50 (24%)	15/50 (30%)	18/50 (36%)
Adjusted rate	19.5%	27.3%	33.8%	38.8%
Terminal rate	5/36 (14%)	11/34 (32%)	7/27 (26%)	13/34 (38%)
First incidence (days)	590	578	600	465
Poly-3 test	P=0.023	P=0.264	P=0.095	P=0.032
Liver: Hepatocellular Carcinoma				
Overall rate	6/50 (12%)	7/50 (14%)	5/50 (10%)	6/50 (12%)
Adjusted rate	13.1%	15.8%	11.5%	13.4%
Terminal rate	4/36 (11%)	4/34 (12%)	2/27 (7%)	4/34 (12%)
First incidence (days)	668	620	639	705
Poly-3 test	P=0.512N	P=0.479	P=0.532N	P=0.609
Liver: Hepatocellular Adenoma or Carcinoma				
Overall rate	13/50 (26%)	17/50 (34%)	18/50 (36%)	21/50 (42%)
Adjusted rate	28.0%	37.9%	40.3%	45.2%
Terminal rate	8/36 (22%)	13/34 (38%)	9/27 (33%)	15/34 (44%)
First incidence (days)	590	578	600	465
Poly-3 test	P=0.059	P=0.217	P=0.154	P=0.063
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted rate	4.4%	4.6%	7.0%	2.2%
Terminal rate	2/36 (6%)	1/34 (3%)	3/27 (11%)	1/34 (3%)
First incidence (days)	730 (T)	578	730 (T)	730 (T)
Poly-3 test	P=0.408N	P=0.683	P=0.474	P=0.505N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	2/50 (4%)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted rate	4.4%	4.6%	7.0%	6.6%
Terminal rate	2/36 (6%)	1/34 (3%)	3/27 (11%)	2/34 (6%)
First incidence (days)	730 (T)	578	730 (T)	465
Poly-3 test	P=0.377	P=0.683	P=0.474	P=0.501
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	10/47 (21%)	8/49 (16%)	10/49 (20%)	10/48 (21%)
Adjusted rate	23.0%	18.9%	23.1%	23.0%
Terminal rate	10/35 (29%)	8/33 (24%)	7/27 (26%)	8/34 (24%)
First incidence (days)	730 (T)	730 (T)	590	554
Poly-3 test	P=0.490	P=0.417N	P=0.597	P=0.597N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Pituitary Gland (Pars Distalis): Adenoma or Carcinoma				
Overall rate	10/47 (21%)	9/49 (18%)	10/49 (20%)	10/48 (21%)
Adjusted rate	23.0%	21.2%	23.1%	23.0%
Terminal rate	10/35 (29%)	8/33 (24%)	7/27 (26%)	8/34 (24%)
First incidence (days)	730 (T)	695	590	554
Poly-3 test	P=0.525	P=0.520N	P=0.597	P=0.597N
Skin: Sarcoma				
Overall rate	1/50 (2%)	0/50 (0%)	5/50 (10%)	2/50 (4%)
Adjusted rate	2.2%	0.0%	11.3%	4.5%
Terminal rate	0/36 (0%)	0/34 (0%)	1/27 (4%)	1/34 (3%)
First incidence (days)	708	—[e]	506	725
Poly-3 test	P=0.231	P=0.509N	P=0.095	P=0.495
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adjusted rate	6.6%	2.3%	0.0%	2.2%
Terminal rate	3/36 (8%)	0/34 (0%)	0/27 (0%)	0/34 (0%)
First incidence (days)	730 (T)	586	—	639
Poly-3 test	P=0.200N	P=0.317N	P=0.129N	P=0.308N
All Organs: Hemangiosarcoma				
Overall rate	1/50 (2%)	4/50 (8%)	0/50 (0%)	3/50 (6%)
Adjusted rate	2.2%	9.1%	0.0%	6.7%
Terminal rate	0/36 (0%)	2/34 (6%)	0/27 (0%)	2/34 (6%)
First incidence (days)	594	578	—	725
Poly-3 test	P=0.388	P=0.167	P=0.513N	P=0.297
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	2/50 (4%)	5/50 (10%)	1/50 (2%)	4/50 (8%)
Adjusted rate	4.3%	11.4%	2.3%	8.8%
Terminal rate	0/36 (0%)	3/34 (9%)	1/27 (4%)	2/34 (6%)
First incidence (days)	594	578	730 (T)	465
Poly-3 test	P=0.408	P=0.197	P=0.526N	P=0.330
All Organs: Malignant Lymphoma				
Overall rate	5/50 (10%)	9/50 (18%)	11/50 (22%)	8/50 (16%)
Adjusted rate	10.9%	20.6%	25.1%	17.8%
Terminal rate	3/36 (8%)	8/34 (24%)	5/27 (19%)	5/34 (15%)
First incidence (days)	492	666	652	672
Poly-3 test	P=0.276	P=0.163	P=0.066	P=0.261
All Organs: Benign Neoplasms				
Overall rate	27/50 (54%)	24/50 (48%)	30/50 (60%)	27/50 (54%)
Adjusted rate	56.7%	54.4%	65.9%	56.9%
Terminal rate	20/36 (56%)	22/34 (65%)	18/27 (67%)	18/34 (53%)
First incidence (days)	530	578	590	465
Poly-3 test	P=0.462	P=0.497N	P=0.239	P=0.572
All Organs: Malignant Neoplasms				
Overall rate	19/50 (38%)	26/50 (52%)	23/50 (46%)	23/50 (46%)
Adjusted rate	39.3%	54.9%	48.9%	47.6%
Terminal rate	10/36 (28%)	15/34 (44%)	8/27 (30%)	12/34 (35%)
First incidence (days)	424	455	506	282
Poly-3 test	P=0.362	P=0.091	P=0.231	P=0.269

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
All Organs: Benign or Malignant Neoplasms				
Overall rate	39/50 (78%)	41/50 (82%)	41/50 (82%)	39/50 (78%)
Adjusted rate	78.7%	86.2%	84.9%	78.5%
Terminal rate	27/36 (75%)	29/34 (85%)	21/27 (78%)	24/34 (71%)
First incidence (days)	424	455	506	282
Poly-3 test	P=0.444N	P=0.235	P=0.295	P=0.590N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and pituitary gland; for other tissues, denominator is number of animals necropsied.
[b] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[c] Observed incidence at terminal kill
[d] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidence are the P values corresponding to pairwise comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposed group is indicated by **N**.
[e] 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: Inhalation Studies			
Decalin	7/49	4/49	11/49
Indium phosphide	12/50	6/50	18/50
Propylene glycol mono-*t*-butyl ether	14/49	4/49	18/49
Stoddard solvent IIC	9/50	6/50	13/50
Vanadium pentoxide	6/50	6/50	12/50
Overall Historical Incidence: Inhalation Studies			
Total (%)	48/248 (19%)	26/248 (10%)	72/248 (29%)
Mean ± standard deviation	19.4% ± 6.9%	10.5% ± 2.1%	29.0% ± 6.8%
Range	12%-29%	8%-12%	22%-37%
Overall Historical Incidence			
Total (%)	179/1,152 (16%)	87/1,152 (8%)	250/1,152 (22%)
Mean ± standard deviation	16.3% ± 6.6%	8.1% ± 4.2%	22.8% ± 9.4%
Range	6%-29%	3%-14%	8%-40%

[a] Data as of March 3, 2003

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	6	11	11	10
Natural deaths	8	5	12	6
Survivors				
Terminal sacrifice	36	34	27	34
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine small, duodenum	(43)	(45)	(44)	(47)
Infiltration cellular, plasma cell			1 (2%)	
Intestine small, jejunum	(43)	(47)	(43)	(47)
Necrosis			1 (2%)	
Intestine small, ileum	(43)	(47)	(44)	(46)
Inflammation				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)	1 (2%)		
Basophilic focus	4 (8%)	5 (10%)	8 (16%)	4 (8%)
Clear cell focus	4 (8%)		2 (4%)	2 (4%)
Eosinophilic focus	4 (8%)	9 (18%)	6 (12%)	11 (22%)
Fatty change		2 (4%)	2 (4%)	
Hematopoietic cell proliferation		1 (2%)		
Infarct	1 (2%)			
Inflammation, granulomatous		1 (2%)		
Inflammation, suppurative				1 (2%)
Mixed cell focus			1 (2%)	1 (2%)
Necrosis	3 (6%)	3 (6%)	1 (2%)	
Parasite metazoan		1 (2%)		
Tension lipidosis	2 (4%)		1 (2%)	2 (4%)
Centrilobular, necrosis	1 (2%)	2 (4%)		
Mesentery	(4)	(15)	(21)	(11)
Artery, mineralization		1 (7%)		
Fat, hemorrhage		1 (7%)	1 (5%)	1 (9%)
Fat, necrosis	3 (75%)	10 (67%)	15 (71%)	9 (82%)
Pancreas	(49)	(50)	(48)	(49)
Atrophy		2 (4%)		
Atypia cellular	1 (2%)			
Inflammation, suppurative				1 (2%)
Lipomatosis			1 (2%)	1 (2%)
Acinus, hypertrophy				1 (2%)
Duct, cyst		2 (4%)		1 (2%)
Salivary glands	(50)	(49)	(49)	(50)
Atrophy		1 (2%)	1 (2%)	
Stomach, forestomach	(49)	(50)	(49)	(50)
Hyperplasia, squamous	2 (4%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic active		2 (4%)	1 (2%)	
Ulcer	1 (2%)		1 (2%)	
Stomach, glandular	(47)	(49)	(47)	(47)
Amyloid deposition			1 (2%)	
Mineralization		1 (2%)	1 (2%)	1 (2%)
Necrosis		1 (2%)	1 (2%)	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 Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Cardiovascular System				
Blood vessel	(1)			(2)
Aorta, mineralization	1 (100%)			2 (100%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	6 (12%)	6 (12%)	6 (12%)	9 (18%)
Mineralization	3 (6%)	4 (8%)		4 (8%)
Thrombosis	2 (4%)			
Artery, inflammation	1 (2%)		1 (2%)	
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Hematopoietic cell proliferation		1 (2%)		
Hyperplasia	4 (8%)	3 (6%)	3 (6%)	6 (12%)
Hypertrophy	2 (4%)	3 (6%)	2 (4%)	3 (6%)
Necrosis			1 (2%)	
Vacuolization cytoplasmic	1 (2%)			
Adrenal medulla	(49)	(50)	(48)	(49)
Hyperplasia	2 (4%)	3 (6%)	4 (8%)	2 (4%)
Islets, pancreatic	(49)	(50)	(48)	(48)
Hyperplasia	1 (2%)	1 (2%)		
Pituitary gland	(47)	(49)	(49)	(48)
Angiectasis	1 (2%)			
Pars distalis, hyperplasia	10 (21%)	12 (24%)	16 (33%)	16 (33%)
Pars intermedia, hypertrophy			1 (2%)	
Thyroid gland	(50)	(49)	(47)	(48)
Inflammation, chronic	1 (2%)			
Follicular cell, hyperplasia		2 (4%)	1 (2%)	3 (6%)
General Body System				
Peritoneum		(1)		
Inflammation, acute		1 (100%)		
Genital System				
Clitoral gland	(40)	(42)	(47)	(41)
Fibrosis		1 (2%)		
Ovary	(49)	(50)	(48)	(49)
Angiectasis	2 (4%)			
Cyst	12 (24%)	12 (24%)	9 (19%)	6 (12%)
Uterus	(49)	(50)	(49)	(49)
Angiectasis	1 (2%)			
Inflammation, suppurative				1 (2%)
Endometrium, hyperplasia, cystic	5 (10%)	3 (6%)	9 (18%)	8 (16%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Hematopoietic System				
Bone marrow	(49)	(49)	(48)	(50)
Atrophy		1 (2%)	1 (2%)	
Cytoplasmic alteration, focal		1 (2%)		
Hyperplasia				1 (2%)
Lymph node	(5)	(7)	(9)	(10)
Angiectasis				1 (10%)
Iliac, angiectasis				2 (20%)
Renal, angiectasis	1 (20%)	2 (29%)	1 (11%)	1 (10%)
Renal, ectasia			1 (11%)	
Lymph node, mandibular	(42)	(32)	(40)	(40)
Infiltration cellular, plasma cell				1 (3%)
Lymph node, mesenteric	(47)	(49)	(47)	(50)
Angiectasis		1 (2%)		1 (2%)
Lymph node, mediastinal	(40)	(42)	(43)	(43)
Infiltration cellular, polymorphonuclear		1 (2%)		
Spleen	(49)	(50)	(48)	(47)
Angiectasis			1 (2%)	1 (2%)
Congestion		1 (2%)		
Hematopoietic cell proliferation	2 (4%)	8 (16%)	5 (10%)	3 (6%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)		1 (2%)
Necrosis	1 (2%)			
Thymus	(43)	(45)	(47)	(46)
Atrophy			2 (4%)	
Integumentary System				
Skin	(50)	(50)	(50)	(50)
Infiltration cellular, mixed cell	1 (2%)		1 (2%)	
Inflammation, chronic active	1 (2%)		1 (2%)	1 (2%)
Subcutaneous tissue, cyst epithelial inclusion	1 (2%)			
Subcutaneous tissue, edema		1 (2%)		1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fracture		1 (2%)	1 (2%)	
Skeletal muscle	(1)	(1)	(1)	(2)
Hemorrhage		1 (100%)		
Inflammation, suppurative				1 (50%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression		1 (2%)		
Necrosis		1 (2%)	1 (2%)	
Artery, inflammation	1 (2%)			
Meninges, infiltration cellular, mononuclear cell	6 (12%)	2 (4%)	2 (4%)	3 (6%)
Peripheral nerve			(1)	(1)
Inflammation, suppurative				1 (100%)

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Stoddard Solvent IIC

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Artery, inflammation			1 (2%)	
Lung	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)			
Alveolar epithelium, hyperplasia	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Alveolus, infiltration cellular, histiocyte			1 (2%)	1 (2%)
Nose	(49)	(50)	(50)	(49)
Inflammation, suppurative		1 (2%)	1 (2%)	1 (2%)
Respiratory epithelium, degeneration		1 (2%)		
Trachea	(49)	(50)	(49)	(47)
Artery, inflammation	1 (2%)			
Special Senses System				
Eye	(46)	(49)	(45)	(46)
Cataract	1 (2%)	2 (4%)	2 (4%)	
Inflammation, chronic	1 (2%)			
Cornea, inflammation, chronic active		1 (2%)	1 (2%)	2 (4%)
Harderian gland	(49)	(49)	(49)	(49)
Hyperplasia	4 (8%)	3 (6%)	4 (8%)	7 (14%)
Infiltration cellular			1 (2%)	
Inflammation, granulomatous	1 (2%)			
Urinary System				
Kidney	(50)	(50)	(49)	(49)
Amyloid deposition		1 (2%)		
Cyst	1 (2%)			
Infarct	1 (2%)			
Inflammation, suppurative				1 (2%)
Metaplasia, osseous		2 (4%)	1 (2%)	2 (4%)
Mineralization	1 (2%)	1 (2%)		2 (4%)
Nephropathy	39 (78%)	32 (64%)	33 (67%)	40 (82%)
Capsule, fibrosis	1 (2%)			
Papilla, necrosis				1 (2%)
Pelvis, dilatation		1 (2%)		
Renal tubule, karyomegaly		1 (2%)		
Renal tubule, necrosis				1 (2%)
Urinary bladder	(48)	(50)	(49)	(48)
Inflammation, suppurative				1 (2%)

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

Salmonella typhimurium Mutagenicity Test Protocol

Testing was performed as reported by Zeiger *et al.* (1992). Stoddard solvent IIC was sent to the laboratory as a coded aliquot from Radian Corporation (Austin, TX). It was incubated with the *Salmonella typhimurium* tester strains TA97, TA98, TA100, and TA1535 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 Stoddard solvent IIC. All trials were repeated at the same or a higher S9 fraction.

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 that is not dose related, is not reproducible, or is not of sufficient 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 Peripheral Blood Micronucleus Test Protocol

A detailed discussion of this assay is presented by MacGregor *et al.* (1990). At the end of the 3-month toxicity study, peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with acridine orange and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 normochromatic erythrocytes (NCEs) in up to 10 animals per exposure group. In addition, the percentage of polychromatic erythrocytes (PCEs) among 1,000 total erythrocytes was scored for each exposure group as a measure of toxicity.

The results were tabulated as the mean of the pooled results from all animals within a treatment group plus or minus the standard error of the mean. The frequency of micronucleated cells among NCEs was analyzed by a statistical software package that tested for increasing trend over exposure groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each exposure group and the control group (ILS, 1990). In the presence of excess binomial variation, as detected by a binomial dispersion test, the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. In the micronucleus test, an individual trial is considered positive if the trend test P value is less than or equal to 0.025 or if the P value for any single exposed group is less than or equal to 0.025 divided by the number of exposed groups. A final call of positive for micronucleus induction is preferably based on reproducibly positive trials (as noted above). Results of the 3-month studies were accepted without repeat tests, because additional test data could not be obtained. Ultimately, the final call is determined by the scientific staff after considering the results of statistical analyses, the reproducibility of any effects observed, and the magnitudes of those effects.

Evaluation Protocol

These are the basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program. Statistical as well as biological factors are considered. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and different results were obtained among

aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the *in vitro* assays have another variable that must be considered in arriving at an overall test result. *In vitro* assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately. The summary table in the Abstract of this Technical Report presents a result that represents a scientific judgement of the overall evidence for activity of the chemical in an assay.

RESULTS

Stoddard solvent IIC, tested over a concentration range of 33 to 10,000 ug/plate, was not mutagenic in *S. typhimurium* tester strains TA97, TA98, TA100, or TA1535 with or without S9 metabolic activation enzymes (Table E1). *In vivo*, the frequency of micronucleated erythrocytes was assessed in peripheral blood samples obtained from male and female B6C3F_1 mice after 3 months of inhalation exposure to Stoddard solvent IIC over a concentration range of 138 to 2,200 mg/m^3; results of this test showed no indication of induced chromosomal damage in the form of micronuclei in either male or female mice (Table E2). Furthermore, there was no significant alteration in the percentages of PCEs in either male or female mice over the concentration range tested, indicating an absence of notable toxicity to the bone marrow.

TABLE E1
Mutagenicity of Stoddard Solvent IIC in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b] –S9 Trial 1	–S9 Trial 2	+hamster S9 5%	+hamster S9 10%	+hamster S9 10%	+hamster S9 30%
TA100	0	112 ± 5.9	122 ± 6.5	103 ± 7.8	118 ± 14.4	129 ± 4.7	121 ± 5.9
	33			111 ± 6.3		123 ± 4.2	
	100	117 ± 1.7	115 ± 0.6	100 ± 2.2	135 ± 1.3	101 ± 4.2	111 ± 4.6
	166			107 ± 3.5		111 ± 2.8	
	333	114 ± 3.2	122 ± 2.0	103 ± 6.0	178 ± 7.0	121 ± 4.9	110 ± 10.4
	666			85 ± 6.7		117 ± 6.7	
	1,000	113 ± 5.0	118 ± 2.0		141 ± 19.7		117 ± 5.6
	3,333	113 ± 7.6	113 ± 2.9		157 ± 3.3		106 ± 9.2
	10,000	112 ± 2.2	117 ± 5.2		128 ± 7.0		104 ± 6.8
Trial summary		Negative	Negative	Negative	Equivocal	Negative	Negative
Positive control[c]		890 ± 8.2	1,012 ± 18.4	1,240 ± 89.3	1,022 ± 26.6	889 ± 18.5	519 ± 9.5

		+rat S9 10%	+rat S9 30%
TA100	0	123 ± 3.5	123 ± 4.2
(continued)	100	116 ± 3.8	124 ± 2.6
	333	115 ± 5.5	123 ± 4.9
	1,000	118 ± 5.0	122 ± 4.6
	3,333	116 ± 0.7	119 ± 3.2
	10,000	113 ± 5.2	109 ± 4.7
Trial summary		Negative	Negative
Positive control		605 ± 11.8	475 ± 11.6

		–S9 Trial 1	–S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA1535	0	10 ± 1.2	10 ± 1.2	10 ± 1.2	10 ± 1.5	10 ± 1.5	11 ± 1.2
	100	10 ± 1.2	8 ± 0.9	8 ± 1.2	10 ± 1.0	8 ± 0.0	8 ± 0.7
	333	8 ± 0.6	10 ± 1.2	11 ± 0.7	6 ± 0.3	10 ± 0.3	8 ± 0.9
	1,000	8 ± 0.9	10 ± 2.2	11 ± 1.5	11 ± 0.6	11 ± 0.7	9 ± 1.3
	3,333	7 ± 1.2	10 ± 0.9	11 ± 1.0	11 ± 0.9	10 ± 1.0	10 ± 1.2
	10,000	7 ± 0.3	7 ± 0.6	8 ± 0.3	9 ± 0.7	9 ± 2.5	9 ± 1.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		955 ± 8.3	845 ± 31.0	146 ± 16.8	333 ± 15.3	145 ± 7.0	231 ± 32.4
TA97	0	154 ± 16.6	164 ± 11.4	162 ± 9.7	171 ± 8.3	166 ± 10.8	166 ± 10.6
	100	158 ± 21.1	176 ± 9.1	169 ± 8.8	197 ± 11.3	146 ± 12.1	180 ± 9.2
	333	147 ± 5.5	178 ± 0.9	175 ± 11.1	170 ± 12.9	171 ± 15.4	198 ± 5.9
	1,000	171 ± 8.7	175 ± 5.8	182 ± 8.1	181 ± 3.2	177 ± 9.7	192 ± 9.3
	3,333	170 ± 6.8	169 ± 6.0	168 ± 11.8	172 ± 20.0	157 ± 10.2	181 ± 6.3
	10,000	178 ± 10.0	175 ± 5.5	186 ± 14.0	175 ± 11.7	160 ± 14.2	179 ± 11.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		623 ± 23.5	506 ± 4.6	1,001 ± 42.4	626 ± 24.9	783 ± 25.0	586 ± 38.7

TABLE E1
Mutagenicity of Stoddard Solvent IIC in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate –S9 Trial 1	–S9 Trial 2	+hamster S9 10%	+hamster S9 30%	+rat S9 10%	+rat S9 30%
TA98	0	17 ± 2.0	14 ± 0.9	19 ± 1.2	19 ± 3.4	19 ± 3.2	16 ± 0.6
	100	17 ± 3.0	13 ± 2.6	17 ± 1.2	17 ± 0.9	19 ± 0.3	15 ± 2.0
	333	18 ± 0.3	15 ± 2.2	18 ± 1.9	17 ± 1.2	19 ± 1.5	24 ± 2.5
	1,000	20 ± 2.9	14 ± 0.9	22 ± 2.8	20 ± 4.3	18 ± 3.2	25 ± 1.3
	3,333	18 ± 1.3	16 ± 0.9	15 ± 1.8	21 ± 0.3	13 ± 3.3	22 ± 3.0
	10,000	15 ± 2.0	14 ± 2.7	14 ± 1.0	17 ± 1.8	16 ± 0.6	15 ± 2.5
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		303 ± 12.5	327 ± 3.8	1,281 ± 23.5	426 ± 15.5	745 ± 16.5	349 ± 16.5

[a] Study performed at SRI International. The detailed protocol is presented by Zeiger *et al*. (1992). 0 µg/plate was the solvent control.
[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 (TA97), and 4-nitro-*o*-phenylenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

TABLE E2
Frequency of Micronuclei in Mouse Peripheral Blood Erythrocytes Following Treatment with Stoddard Solvent IIC by Inhalation for 3 Months[a]

	Dose (mg/m^3)	Number of Mice with Erythrocytes Scored	Micronucleated NCEs/ 1,000 NCEs[b]	P Value[c]	PCEs (%)
Male					
Chamber Control	0	10	1.30 ± 0.13		1.79
Stoddard Solvent IIC	138	9	1.17 ± 0.26	0.6440	1.43
	275	10	1.15 ± 0.13	0.6660	1.86
	550	10	0.95 ± 0.24	0.8518	1.76
	1,100	10	1.00 ± 0.17	0.8120	2.07
	2,200	10	0.85 ± 0.22	0.9152	1.79
			P=0.915[d]		
Female					
Chamber Control	0	10	0.65 ± 0.24		1.86
Stoddard Solvent IIC	138	10	0.65 ± 0.17	0.5000	2.04
	275	10	0.80 ± 0.17	0.2887	1.88
	550	10	0.50 ± 0.11	0.7343	1.89
	1,100	10	0.85 ± 0.15	0.2325	2.02
	2,200	10	0.65 ± 0.18	0.5000	1.93
			P=0.457		

[a] Study was performed at SITEK Research Laboratories. The detailed protocol is presented by MacGregor *et al*. (1990).
[b] NCE=normochromatic erythrocyte; PCE=polychromatic erythrocyte
[c] Mean ± standard error
[d] Pairwise comparison with the chamber control; significant at $P \leq 0.05$ (ILS, 1990).
Significance of micronucleated NCEs/1,000 NCEs tested by the one-tailed trend test; significant at $P \leq 0.025$ (ILS, 1990).

APPENDIX F
CLINICAL PATHOLOGY RESULTS

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Male						
Hematology						
n						
Day 3	10	10	10	10	10	10
Day 23	10	10	10	10	10	10
Week 14	10	10	10	10	9	10
Hematocrit (%)						
Day 3	42.3 ± 0.6	42.2 ± 0.5	41.2 ± 0.4	42.0 ± 0.8	41.5 ± 0.6	43.3 ± 0.4
Day 23	47.0 ± 0.5	47.2 ± 0.5	46.0 ± 0.4	46.8 ± 0.5	46.7 ± 0.6	46.2 ± 0.4
Week 14	47.4 ± 0.4	46.6 ± 0.3	46.3 ± 0.2*	46.3 ± 0.4	46.5 ± 0.3	45.6 ± 0.4**
Packed cell volume (%)						
Day 3	40.9 ± 0.7	40.5 ± 0.6	39.6 ± 0.5	40.3 ± 0.8	40.4 ± 0.6	41.6 ± 0.6
Day 23	45.1 ± 0.6	46.1 ± 0.4	44.9 ± 0.6	45.5 ± 0.7	46.1 ± 0.8	45.2 ± 0.3
Week 14	47.1 ± 0.4	45.7 ± 0.3	46.2 ± 0.4	45.9 ± 0.5	45.8 ± 0.4	45.6 ± 0.2*
Hemoglobin (g/dL)						
Day 3	13.5 ± 0.2	13.5 ± 0.2	13.2 ± 0.1	13.4 ± 0.3	13.3 ± 0.2	13.7 ± 0.2
Day 23	15.0 ± 0.2	15.3 ± 0.2	14.9 ± 0.2	15.0 ± 0.2	15.2 ± 0.2	15.0 ± 0.1
Week 14	15.2 ± 0.1	14.8 ± 0.1	14.7 ± 0.1	14.8 ± 0.1	14.8 ± 0.1	14.7 ± 0.1*
Erythrocytes (10^6/µL)						
Day 3	6.38 ± 0.11	6.39 ± 0.11	6.25 ± 0.11	6.36 ± 0.12	6.42 ± 0.11 .	6.56 ± 0.12
Day 23	7.11 ± 0.12	7.27 ± 0.08	7.03 ± 0.12	7.12 ± 0.11	7.20 ± 0.14	7.09 ± 0.09
Week 14	8.46 ± 0.06	8.25 ± 0.06*	8.31 ± 0.05	8.27 ± 0.09	8.21 ± 0.08*	8.17 ± 0.04**
Reticulocytes (10^3/µL)						
Day 3	371.6 ± 13.3	363.9 ± 13.7	398.1 ± 20.6	393.4 ± 13.0	386.5 ± 12.2	397.4 ± 26.5
Day 23	261.2 ± 20.1	283.4 ± 12.1	302.4 ± 12.1	246.2 ± 15.9	281.7 ± 12.6	291.1 ± 17.0
Week 14	191.1 ± 9.1	175.9 ± 10.4	211.3 ± 7.6	189.5 ± 11.4	223.9 ± 10.3	221.6 ± 11.4
Mean cell volume (fL)						
Day 3	64.1 ± 0.3	63.4 ± 0.4	63.4 ± 0.3	63.3 ± 0.4	62.9 ± 0.4	63.6 ± 0.6
Day 23	63.4 ± 0.4	63.4 ± 0.4	64.0 ± 0.6	64.0 ± 0.6	64.1 ± 0.4	63.9 ± 0.5
Week 14	55.6 ± 0.2	55.3 ± 0.2	55.6 ± 0.2	55.5 ± 0.2	55.8 ± 0.1	55.9 ± 0.1
Mean cell hemoglobin (pg)						
Day 3	21.2 ± 0.1	21.1 ± 0.1	21.1 ± 0.2	21.0 ± 0.1	20.7 ± 0.2	21.0 ± 0.2
Day 23	21.1 ± 0.3	21.1 ± 0.2	21.2 ± 0.2	21.1 ± 0.2	21.1 ± 0.2	21.2 ± 0.2
Week 14	17.9 ± 0.1	17.9 ± 0.2	17.7 ± 0.1	17.9 ± 0.1	18.0 ± 0.1	18.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 3	33.0 ± 0.2	33.3 ± 0.1	33.3 ± 0.2	33.2 ± 0.2	32.9 ± 0.1	33.0 ± 0.2
Day 23	33.3 ± 0.3	33.3 ± 0.3	33.2 ± 0.4	32.9 ± 0.2	32.9 ± 0.3	33.2 ± 0.2
Week 14	32.2 ± 0.2	32.3 ± 0.2	31.9 ± 0.3	32.2 ± 0.2	32.2 ± 0.2	32.2 ± 0.3
Platelets (10^3/µL)						
Day 3	763.0 ± 9.3	775.9 ± 12.8	764.4 ± 13.8	769.4 ± 22.2	806.4 ± 21.7	788.2 ± 12.0
Day 23	769.1 ± 18.9	770.4 ± 21.7	787.9 ± 17.4	814.6 ± 14.0	818.2 ± 15.1	784.6 ± 10.2
Week 14	660.7 ± 18.3	643.3 ± 16.0	648.0 ± 11.7	665.6 ± 9.6	692.6 ± 14.0	626.9 ± 11.6
Leukocytes (10^3/µL)						
Day 3	9.69 ± 0.81	10.22 ± 0.44	9.51 ± 0.59	9.73 ± 0.28	9.75 ± 0.84	8.510 ± 0.44
Day 23	11.69 ± 0.59	12.67 ± 0.36	13.58 ± 0.33**	13.27 ± 0.51*	13.69 ± 0.36**	13.50 ± 0.40*
Week 14	6.39 ± 0.42	6.87 ± 0.53	6.57 ± 0.36	7.74 ± 0.39	7.47 ± 0.49	7.19 ± 0.41

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Male (continued)						
Hematology (continued)						
n						
Day 3	10	10	10	10	10	10
Day 19	10	10	10	10	10	10
Week 14	10	10	10	10	9	10
Segmented neutrophils (10^3/µL)						
Day 3	1.09 ± 0.15	1.35 ± 0.14	1.14 ± 0.16	1.20 ± 0.15	1.22 ± 0.22	1.31 ± 0.11
Day 23	1.28 ± 0.19	1.14 ± 0.16	1.28 ± 0.17	1.20 ± 0.11	1.34 ± 0.12	1.70 ± 0.15
Week 14	1.57 ± 0.09	1.70 ± 0.10	1.57 ± 0.07	1.69 ± 0.06	1.68 ± 0.07	1.77 ± 0.10
Lymphocytes (10^3/µL)						
Day 3	8.24 ± 0.74	8.45 ± 0.28	7.79 ± 0.49	8.15 ± 0.24	8.33 ± 0.70	6.86 ± 0.42
Day 23	10.03 ± 0.51	11.24 ± 0.38	11.92 ± 0.30*	11.58 ± 0.49	11.78 ± 0.29	11.52 ± 0.37
Week 14	4.52 ± 0.34	4.87 ± 0.44	4.73 ± 0.31	5.74 ± 0.34	5.49 ± 0.44	5.07 ± 0.35
Monocytes (10^3/µL)						
Day 3	0.31 ± 0.05	0.39 ± 0.07	0.55 ± 0.09	0.38 ± 0.09	0.17 ± 0.05	0.29 ± 0.05
Day 23	0.29 ± 0.10	0.25 ± 0.06	0.31 ± 0.11	0.43 ± 0.08	0.45 ± 0.06	0.24 ± 0.04
Week 14	0.24 ± 0.03	0.24 ± 0.02	0.22 ± 0.01	0.24 ± 0.02	0.24 ± 0.02	0.28 ± 0.03
Basophils (10^3/µL)						
Day 3	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 23	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.016 ± 0.002	0.016 ± 0.003	0.014 ± 0.002	0.017 ± 0.002	0.018 ± 0.003	0.014 ± 0.003
Eosinophils (10^3/µL)						
Day 3	0.05 ± 0.02	0.04 ± 0.02	0.03 ± 0.02	0.01 ± 0.01	0.03 ± 0.02	0.05 ± 0.01
Day 23	0.09 ± 0.02	0.05 ± 0.03	0.07 ± 0.02	0.06 ± 0.03	0.12 ± 0.04	0.04 ± 0.02
Week 14	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.06 ± 0.01
Clinical Chemistry						
n						
Day 3	10	10	9	10	10	10
Day 23	10	10	10	10	10	10
Week 14	10	10	10	10	10	10
Urea nitrogen (mg/dL)						
Day 3	5.3 ± 0.4	5.3 ± 0.4	5.1 ± 0.4	5.6 ± 0.5	5.7 ± 0.4	6.6 ± 0.5
Day 23	8.0 ± 0.4	7.7 ± 0.5	6.9 ± 0.4	8.0 ± 0.7	6.0 ± 0.2**	7.2 ± 0.2
Week 14	11.7 ± 0.3	11.8 ± 0.4	11.6 ± 0.3	12.4 ± 0.3	11.8 ± 0.4	11.8 ± 0.2
Creatinine (mg/dL)						
Day 3	0.67 ± 0.02	0.67 ± 0.02	0.70 ± 0.02	0.74 ± 0.02**	0.76 ± 0.02**	0.76 ± 0.02**
Day 23	0.68 ± 0.01	0.73 ± 0.02	0.74 ± 0.03	0.71 ± 0.02	0.73 ± 0.02	0.70 ± 0.02
Week 14	0.88 ± 0.02	0.84 ± 0.02	0.89 ± 0.02	0.93 ± 0.03	0.93 ± 0.02	0.92 ± 0.03
Total protein (g/dL)						
Day 3	5.2 ± 0.1	5.3 ± 0.1	5.3 ± 0.1	5.5 ± 0.1	5.7 ± 0.1**	5.6 ± 0.1**
Day 23	6.2 ± 0.1	6.1 ± 0.1	6.2 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.1 ± 0.1
Week 14	7.1 ± 0.1	6.8 ± 0.1**	6.8 ± 0.0**	6.9 ± 0.1	6.8 ± 0.0*	6.8 ± 0.1*
Albumin (g/dL)						
Day 3	3.7 ± 0.1	3.6 ± 0.1	3.7 ± 0.1	3.9 ± 0.1	3.9 ± 0.1	3.9 ± 0.1*
Day 23	3.8 ± 0.1	3.8 ± 0.1	3.9 ± 0.0	3.7 ± 0.1	3.8 ± 0.1	3.8 ± 0.1
Week 14	4.1 ± 0.1	4.0 ± 0.0	4.0 ± 0.1	4.2 ± 0.1	3.9 ± 0.1	3.9 ± 0.1

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Male (continued)						
Clinical Chemistry (continued)						
n						
Day 3	10	10	9	10	10	10
Day 23	10	10	10	10	10	10
Week 14	10	10	10	10	10	10
Globulin (g/dL)						
Day 3	1.6 ± 0.1	1.7 ± 0.0	1.6 ± 0.1	1.6 ± 0.1	1.8 ± 0.1*	1.7 ± 0.1
Day 23	2.3 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	2.4 ± 0.1	2.2 ± 0.1	2.3 ± 0.0
Week 14	3.0 ± 0.1	2.8 ± 0.1	2.8 ± 0.1	2.6 ± 0.1*	2.9 ± 0.0	2.9 ± 0.1
Albumin/globulin ratio						
Day 3	2.4 ± 0.1	2.2 ± 0.1	2.4 ± 0.1	2.4 ± 0.1	2.2 ± 0.1	2.4 ± 0.1
Day 23	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	1.8 ± 0.1	1.6 ± 0.0
Week 14	1.4 ± 0.1	1.4 ± 0.1	1.4 ± 0.1	1.7 ± 0.1	1.3 ± 0.0	1.4 ± 0.1
Alanine aminotransferase (IU/L)						
Day 3	49 ± 1	50 ± 1	50 ± 1	51 ± 1	51 ± 1	49 ± 1
Day 23	37 ± 1	36 ± 1	35 ± 1	34 ± 1**	33 ± 1**	31 ± 1**
Week 14	80 ± 5	73 ± 6	71 ± 4	62 ± 6**	46 ± 1**	42 ± 2**
Alkaline phosphatase (IU/L)						
Day 3	825 ± 15	808 ± 19	898 ± 26	880 ± 27	836 ± 20	802 ± 24
Day 23	572 ± 15	573 ± 20	590 ± 16	571 ± 12	564 ± 13	569 ± 13
Week 14	322 ± 10	310 ± 11	294 ± 8	305 ± 7	305 ± 8	299 ± 6
Creatine kinase (IU/L)						
Day 3	403 ± 37	542 ± 71	540 ± 71	569 ± 91	540 ± 51	437 ± 48
Day 23	397 ± 75	782 ± 252	432 ± 84	433 ± 30	416 ± 41	322 ± 31
Week 14	247 ± 41[b]	312 ± 106	276 ± 33	237 ± 38	262 ± 80	278 ± 46
Sorbitol dehydrogenase (IU/L)						
Day 3	12 ± 1	11 ± 1	13 ± 1	10 ± 0	12 ± 1	12 ± 1
Day 23	14 ± 1	13 ± 1	13 ± 1	12 ± 1	13 ± 1	13 ± 1
Week 14	24 ± 1	23 ± 1	26 ± 2	21 ± 2	19 ± 1**	18 ± 1**
Bile acids (µmol/L)						
Day 3	24.9 ± 2.2	26.9 ± 0.5	28.7 ± 2.1	29.7 ± 1.5	32.7 ± 3.0	30.0 ± 2.4
Day 23	30.2 ± 3.2	24.6 ± 1.1	32.6 ± 3.5	26.3 ± 1.7	33.5 ± 1.6	28.5 ± 1.2
Week 14	28.0 ± 2.9	28.1 ± 2.8	31.9 ± 4.2	27.9 ± 2.3	31.3 ± 3.7	30.3 ± 3.2

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Female						
n	10	10	10	10	10	10
Hematology						
Hematocrit (%)						
Day 3	43.8 ± 0.8	43.9 ± 0.5	43.8 ± 0.7	43.8 ± 0.5	44.1 ± 0.8	44.6 ± 0.9
Day 23	48.4 ± 0.5	49.1 ± 0.4	49.0 ± 0.6	48.7 ± 0.3	48.8 ± 0.4	48.0 ± 0.3
Week 14	46.2 ± 0.4	45.3 ± 0.2	46.0 ± 0.3	45.9 ± 0.3	45.4 ± 0.4	46.3 ± 0.2
Packed cell volume (%)						
Day 3	42.3 ± 0.7	42.7 ± 0.5	42.6 ± 0.6	42.1 ± 0.6	42.5 ± 0.7	42.8 ± 1.0
Day 23	47.9 ± 0.5	48.5 ± 0.5	48.5 ± 0.5	47.9 ± 0.4	47.9 ± 0.5	47.8 ± 0.4
Week 14	46.1 ± 0.3	44.9 ± 0.2*	45.8 ± 0.4	45.8 ± 0.3	45.5 ± 0.4	46.4 ± 0.3
Hemoglobin (g/dL)						
Day 3	14.2 ± 0.3	14.1 ± 0.2	14.1 ± 0.2	14.0 ± 0.2	14.1 ± 0.3	14.2 ± 0.4
Day 23	15.6 ± 0.2	15.7 ± 0.1	15.9 ± 0.2	15.5 ± 0.1	15.4 ± 0.1	15.4 ± 0.2
Week 14	14.9 ± 0.1	14.7 ± 0.1	14.8 ± 0.2	14.9 ± 0.1	14.6 ± 0.2	15.1 ± 0.1
Erythrocytes (10^6/µL)						
Day 3	6.70 ± 0.12	6.72 ± 0.12	6.73 ± 0.12	6.68 ± 0.11	6.72 ± 0.15	6.77 ± 0.18
Day 23	7.58 ± 0.10	7.58 ± 0.07	7.57 ± 0.08	7.47 ± 0.09	7.50 ± 0.11	7.49 ± 0.09
Week 14	7.76 ± 0.05	7.58 ± 0.04*	7.70 ± 0.07	7.69 ± 0.05	7.68 ± 0.05	7.80 ± 0.06
Reticulocytes (10^3/µL)						
Day 3	257.0 ± 18.7	283.0 ± 21.8	309.7 ± 11.7*	348.9 ± 15.7**	350.5 ± 14.0**	377.7 ± 19.6**
Day 23	174.8 ± 11.5	188.3 ± 12.3	188.0 ± 10.4	196.6 ± 8.3	195.4 ± 13.3	205.5 ± 11.0
Week 14	183.6 ± 9.7	199.5 ± 11.3	195.1 ± 11.8	184.0 ± 9.8	188.6 ± 11.6	181.5 ± 5.1
Mean cell volume (fL)						
Day 3	63.1 ± 0.3	63.5 ± 0.5	63.4 ± 0.3	63.0 ± 0.4	63.2 ± 0.4	63.5 ± 0.4
Day 23	63.1 ± 0.4	63.9 ± 0.5	63.9 ± 0.4	64.3 ± 0.4	63.9 ± 0.5	63.9 ± 0.7
Week 14	59.6 ± 0.2	59.2 ± 0.1	59.5 ± 0.2	59.5 ± 0.3	59.3 ± 0.2	59.6 ± 0.2
Mean cell hemoglobin (pg)						
Day 3	21.2 ± 0.2	21.0 ± 0.2	21.0 ± 0.1	21.0 ± 0.2	21.0 ± 0.2	21.1 ± 0.1
Day 23	20.6 ± 0.1	20.8 ± 0.2	21.0 ± 0.2	20.8 ± 0.2	20.6 ± 0.2	20.7 ± 0.3
Week 14	19.2 ± 0.2	19.4 ± 0.1	19.3 ± 0.2	19.3 ± 0.1	19.1 ± 0.1	19.3 ± 0.1
Mean cell hemoglobin concentration (g/dL)						
Day 3	33.6 ± 0.2	33.0 ± 0.2	33.2 ± 0.2	33.3 ± 0.2	33.2 ± 0.2	33.2 ± 0.2
Day 23	32.6 ± 0.2	32.5 ± 0.1	32.8 ± 0.2	32.4 ± 0.2	32.2 ± 0.1	32.3 ± 0.3
Week 14	32.3 ± 0.2	32.6 ± 0.1	32.4 ± 0.3	32.4 ± 0.2	32.2 ± 0.2	32.4 ± 0.2
Platelets (10^3/µL)						
Day 3	735.7 ± 12.0	760.7 ± 17.5	770.8 ± 14.7	762.8 ± 15.6	763.8 ± 14.5	740.4 ± 19.7
Day 23	757.1 ± 13.9	772.9 ± 13.5	791.7 ± 15.3	836.3 ± 14.1**	794.6 ± 15.1	793.6 ± 10.5
Week 14	653.4 ± 9.4	631.2 ± 15.9	659.3 ± 12.3	675.1 ± 16.3	656.2 ± 14.0	654.8 ± 9.7
Leukocytes (10^3/µL)						
Day 3	10.34 ± 0.63	9.83 ± 0.58	10.91 ± 0.65	10.24 ± 0.51	9.39 ± 0.48	9.40 ± 0.43
Day 23	13.49 ± 0.39	13.56 ± 0.61	12.87 ± 0.41	12.90 ± 0.55	12.59 ± 0.54	12.48 ± 0.45
Week 14	7.04 ± 0.48	7.12 ± 0.45	7.74 ± 0.88	8.21 ± 0.40	6.61 ± 0.38	7.77 ± 0.65
Segmented neutrophils (10^3/µL)						
Day 3	1.15 ± 0.13	1.12 ± 0.11	1.10 ± 0.10	1.07 ± 0.16	1.02 ± 0.13	1.13 ± 0.16
Day 23	0.92 ± 0.09	0.86 ± 0.13	1.10 ± 0.16	0.96 ± 0.14	1.09 ± 0.19	0.93 ± 0.08
Week 14	1.92 ± 0.15	1.65 ± 0.11	1.87 ± 0.20	1.85 ± 0.10	1.74 ± 0.14	1.90 ± 0.11

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Female (continued)						
n	10	10	10	10	10	10
Hematology (continued)						
Lymphocytes (10^3/μL)						
Day 3	8.77 ± 0.59	8.30 ± 0.58	9.43 ± 0.59	8.94 ± 0.51	8.26 ± 0.48	8.03 ± 0.45
Day 23	12.28 ± 0.35	12.32 ± 0.55	11.56 ± 0.46	11.50 ± 0.62	10.86 ± 0.46*	10.93 ± 0.39*
Week 14	4.75 ± 0.37	5.18 ± 0.39	5.44 ± 0.69	5.97 ± 0.34	4.54 ± 0.31	5.45 ± 0.57
Monocytes (10^3/μL)						
Day 3	0.37 ± 0.06	0.33 ± 0.08	0.28 ± 0.09	0.18 ± 0.04*	0.12 ± 0.03**	0.19 ± 0.04**
Day 23	0.21 ± 0.05	0.25 ± 0.07	0.15 ± 0.04	0.38 ± 0.09	0.53 ± 0.09*	0.46 ± 0.06*
Week 14	0.31 ± 0.04	0.25 ± 0.02	0.37 ± 0.07	0.33 ± 0.04	0.27 ± 0.04	0.35 ± 0.03
Basophils (10^3/μL)						
Day 3	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Day 23	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Week 14	0.015 ± 0.003	0.011 ± 0.002	0.009 ± 0.002	0.013 ± 0.002	0.013 ± 0.002	0.013 ± 0.002
Eosinophils (10^3/μL)						
Day 3	0.06 ± 0.03	0.08 ± 0.02	0.10 ± 0.05	0.05 ± 0.02	0.06 ± 0.02	0.05 ± 0.01
Day 23	0.07 ± 0.03	0.14 ± 0.03	0.06 ± 0.02	0.06 ± 0.03	0.11 ± 0.04	0.17 ± 0.06
Week 14	0.05 ± 0.00	0.04 ± 0.00	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.00	0.05 ± 0.01
Clinical Chemistry						
Urea nitrogen (mg/dL)						
Day 3	8.1 ± 0.5	8.1 ± 0.4	8.0 ± 0.3	8.3 ± 0.5	8.4 ± 0.3	8.7 ± 0.6
Day 23	10.1 ± 0.3	10.7 ± 0.4	10.0 ± 0.3	10.2 ± 0.5	9.8 ± 0.4	9.5 ± 0.5
Week 14	14.2 ± 0.5	13.4 ± 0.3	12.4 ± 0.4*	12.8 ± 0.4	13.7 ± 0.5	13.2 ± 0.5
Creatinine (mg/dL)						
Day 3	0.65 ± 0.02	0.64 ± 0.02	0.67 ± 0.02	0.69 ± 0.01	0.72 ± 0.02*	0.72 ± 0.01**
Day 23	0.69 ± 0.02	0.71 ± 0.02	0.74 ± 0.02	0.67 ± 0.02	0.72 ± 0.01	0.71 ± 0.01
Week 14	0.81 ± 0.03	0.78 ± 0.04	0.78 ± 0.01	0.76 ± 0.02	0.79 ± 0.02	0.80 ± 0.02
Total protein (g/dL)						
Day 3	5.4 ± 0.1	5.4 ± 0.1	5.3 ± 0.1	5.4 ± 0.1	5.5 ± 0.1	5.5 ± 0.1
Day 23	5.9 ± 0.1	6.0 ± 0.1	5.9 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	5.9 ± 0.1
Week 14	6.9 ± 0.1	6.7 ± 0.1	6.9 ± 0.1	6.7 ± 0.1	6.9 ± 0.1	6.9 ± 0.1
Albumin (g/dl)						
Day 3	3.7 ± 0.1	3.7 ± 0.1	3.6 ± 0.0	3.7 ± 0.0	3.8 ± 0.0	3.8 ± 0.1
Day 23	3.9 ± 0.0	4.0 ± 0.1	3.9 ± 0.0	3.8 ± 0.0	3.9 ± 0.1	3.9 ± 0.1
Week 14	4.4 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.4 ± 0.1	4.4 ± 0.1	4.3 ± 0.1
Globulin (g/dL)						
Day 3	1.7 ± 0.1	1.7 ± 0.0	1.7 ± 0.1	1.7 ± 0.0	1.7 ± 0.1	1.7 ± 0.0
Day 23	2.0 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	2.2 ± 0.1	2.1 ± 0.1	2.1 ± 0.1
Week 14	2.6 ± 0.1	2.4 ± 0.1	2.7 ± 0.1	2.4 ± 0.1	2.5 ± 0.1	2.6 ± 0.1
Albumin/globulin ratio						
Day 3	2.1 ± 0.1	2.1 ± 0.1	2.1 ± 0.1	2.1 ± 0.1	2.3 ± 0.1	2.2 ± 0.1
Day 23	2.0 ± 0.1	2.0 ± 0.1	2.0 ± 0.1	1.8 ± 0.1	1.9 ± 0.1	1.9 ± 0.1
Week 14	1.7 ± 0.1	1.8 ± 0.0	1.6 ± 0.0	1.9 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
Alanine aminotransferase (IU/L)						
Day 3	45 ± 1	42 ± 1*	42 ± 1*	40 ± 1**	40 ± 1**	40 ± 2**
Day 23	33 ± 1	32 ± 1	29 ± 1	29 ± 1*	28 ± 1**	26 ± 1**
Week 14	52 ± 3	55 ± 3	56 ± 4	42 ± 2*	46 ± 3	39 ± 2**

TABLE F1
Hematology and Clinical Chemistry Data for Rats in the 3-Month Inhalation Study of Stoddard Solvent IIC

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Female (continued)						
n	10	10	10	10	10	10
Clinical Chemistry (continued)						
Alkaline phosphatase (IU/L)						
Day 3	652 ± 18	669 ± 24	649 ± 16	647 ± 16	634 ± 19	627 ± 21
Day 23	432 ± 14	423 ± 14	401 ± 13	409 ± 12	391 ± 14	374 ± 12**
Week 14	282 ± 12	255 ± 10	246 ± 10	258 ± 8	254 ± 8	246 ± 10
Creatine kinase (IU/L)						
Day 3	528 ± 92	481 ± 68	451 ± 47	463 ± 72	420 ± 64	373 ± 42[b]
Day 23	415 ± 49	373 ± 71	341 ± 26	237 ± 19**	295 ± 36**	254 ± 17**
Week 14	195 ± 29	178 ± 21	165 ± 19	176 ± 28	202 ± 24	196 ± 28
Sorbitol dehydrogenase (IU/L)						
Day 3	14 ± 1	13 ± 1	13 ± 1	13 ± 1	13 ± 1	14 ± 1
Day 23	12 ± 1	15 ± 1	15 ± 1	15 ± 0*	15 ± 1	15 ± 1*
Week 14	18 ± 1	19 ± 1	20 ± 1	16 ± 0	17 ± 1	15 ± 1*
Bile acids (μmol/L)						
Day 3	19.6 ± 1.4	24.8 ± 1.3*	25.5 ± 1.4*	31.2 ± 2.5**	28.7 ± 2.7**	30.6 ± 2.6**
Day 23	23.3 ± 3.5	18.1 ± 0.7	24.5 ± 2.1	22.7 ± 1.0	19.5 ± 1.1	20.2 ± 0.9
Week 14	17.1 ± 0.8	28.8 ± 6.2	22.2 ± 1.3	18.8 ± 1.1	25.7 ± 3.8	22.0 ± 2.4

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Mean ± standard error. Statistical tests were performed on unrounded data.
[b] n=9

TABLE F2
Hematology Data for Mice in the 3-Month Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Male						
n	10	9	10	10	9	10
Hematocrit (%)	44.4 ± 0.4	44.6 ± 0.2	44.7 ± 0.3	45.0 ± 0.6	44.5 ± 0.3	45.1 ± 0.4
Packed cell volume (%)	44.8 ± 0.4	45.5 ± 0.5	45.0 ± 0.3	45.4 ± 0.8	44.7 ± 0.4	44.8 ± 0.4
Hemoglobin (g/dL)	14.9 ± 0.1	15.0 ± 0.1	15.0 ± 0.1	15.2 ± 0.2	14.8 ± 0.2	15.0 ± 0.1
Erythrocytes (10^6/µL)	9.47 ± 0.08	9.60 ± 0.09	9.49 ± 0.05	9.50 ± 0.17	9.35 ± 0.13	9.39 ± 0.09
Reticulocytes (10^3/µL)	198.8 ± 14.7	185.1 ± 11.7	183.2 ± 10.4	187.8 ± 13.5	207.8 ± 9.5	203.5 ± 18.3
Mean cell volume (fL)	47.3 ± 0.2	47.3 ± 0.2	47.4 ± 0.2	47.7 ± 0.2	48.0 ± 0.4*	47.8 ± 0.2
Mean cell hemoglobin (pg)	15.8 ± 0.2	15.6 ± 0.1	15.9 ± 0.1	16.0 ± 0.1	15.8 ± 0.2	16.0 ± 0.1
Mean cell hemoglobin concentration (g/dL)	33.4 ± 0.3	33.0 ± 0.1	33.5 ± 0.3	33.5 ± 0.3	33.1 ± 0.3	33.6 ± 0.3
Platelets (10^3/µL)	790.6 ± 24.4	810.7 ± 27.6	795.6 ± 18.3	765.9 ± 26.0	744.4 ± 47.7	771.7 ± 25.1
Leukocytes (10^3/µL)	2.93 ± 0.19	3.29 ± 0.27	3.49 ± 0.33	2.96 ± 0.28	2.97 ± 0.18	3.09 ± 0.32
Segmented neutrophils (10^3/µL)	0.28 ± 0.02	0.32 ± 0.05	0.42 ± 0.05	0.33 ± 0.04	0.24 ± 0.03	0.26 ± 0.04
Lymphocytes (10^3/µL)	2.64 ± 0.19	2.95 ± 0.23	3.06 ± 0.30	2.62 ± 0.25	2.70 ± 0.17	2.81 ± 0.29
Monocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Basophils (10^3/µL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/µL)	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.01 ± 0.00	0.02 ± 0.01	0.03 ± 0.01
Female						
n	9	10	10	10	10	10
Hematocrit (%)	50.5 ± 0.4	50.2 ± 0.5	49.0 ± 0.4	50.3 ± 0.5	48.2 ± 0.8*	49.8 ± 0.5
Packed cell volume (%)	49.5 ± 0.4	49.0 ± 0.5	48.0 ± 0.5	49.1 ± 0.5	47.1 ± 0.9	48.5 ± 0.6
Hemoglobin (g/dL)	16.3 ± 0.1	16.3 ± 0.2	16.0 ± 0.2	16.3 ± 0.2	15.5 ± 0.3	16.2 ± 0.2
Erythrocytes (10^6/µL)	10.15 ± 0.10	10.06 ± 0.11	9.86 ± 0.08	10.08 ± 0.10	9.64 ± 0.21	9.93 ± 0.12
Reticulocytes (10^3/µL)	220.89 ± 14.68	221.50 ± 16.16	210.00 ± 9.42	231.50 ± 10.55	253.90 ± 29.27	230.50 ± 10.66
Mean cell volume (fL)	48.9 ± 0.1	48.7 ± 0.3	48.7 ± 0.3	48.8 ± 0.1	48.9 ± 0.2	48.7 ± 0.2
Mean cell hemoglobin (pg)	16.0 ± 0.2	16.2 ± 0.1	16.2 ± 0.1	16.2 ± 0.1	16.1 ± 0.1	16.3 ± 0.2
Mean cell hemoglobin concentration (g/dL)	32.9 ± 0.3	33.3 ± 0.2	33.3 ± 0.1	33.2 ± 0.3	33.0 ± 0.2	33.4 ± 0.4
Platelets (10^3/µL)	833.2 ± 30.0	800.5 ± 25.6	798.6 ± 30.1	823.3 ± 21.8	807.0 ± 37.3	845.3 ± 9.2
Leukocytes (10^3/µL)	3.26 ± 0.24	3.26 ± 0.37	3.49 ± 0.43	3.70 ± 0.45	3.09 ± 0.39	3.19 ± 0.28
Segmented neutrophils (10^3/µL)	0.40 ± 0.05	0.37 ± 0.06	0.35 ± 0.04	0.41 ± 0.05	0.53 ± 0.16	0.37 ± 0.06
Lymphocytes (10^3/µL)	2.85 ± 0.21	2.87 ± 0.34	3.11 ± 0.40	3.28 ± 0.41	2.55 ± 0.27	2.81 ± 0.24
Monocytes (10^3/µL)	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Basophils (10^3/µL)	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.000
Eosinophils (10^3/µL)	0.01 ± 0.01	0.03 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01

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

APPENDIX G
RENAL TOXICITY RESULTS

TABLE G1
Renal Toxicity Data for Rats at 3 Months in the 2-Year Inhalation Study of Stoddard Solvent IIC[a]

Male	Chamber Control	138 mg/m^3	550 mg/m^3	1,100 mg/m^3
n	10	10	10	10
Cells labeled	70.8 ± 5.8	78.4 ± 7.0	108.2 ± 6.5**	166.6 ± 16.1**
Cells counted	2,214.0 ± 28.3	2,191.7 ± 47.9	2,152.6 ± 28.4	2,224.3 ± 46.6
Labeling index (%)	3.212 ± 0.285	3.580 ± 0.323	5.034 ± 0.310**	7.549 ± 0.764**
Soluble protein (g/dL)	2.891 ± 0.044	3.070 ± 0.045*	2.997 ± 0.038	3.000 ± 0.060
∝2u-Globulin (ng/µg soluble protein)	198.076 ± 46.917	300.344 ± 34.248	352.942 ± 29.848*	487.976 ± 72.177**
∝2u-Globulin (nmol/g kidney)	621.182 ± 151.420	983.746 ± 112.122	1,134.900 ± 102.009**	1,548.327 ± 216.396**

Female	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
n	10	10	10	10
Cells labeled	41.5 ± 4.0	37.0 ± 4.0	35.2 ± 3.8	35.8 ± 3.2
Cells counted	2,176.0 ± 32.8	2,121.0 ± 38.6	2,152.7 ± 40.3	2,178.1 ± 31.1
Labeling index (%)	1.906 ± 0.185	1.739 ± 0.183	1.624 ± 0.164	1.643 ± 0.143
Soluble protein (g/dL)	2.727 ± 0.073	2.830 ± 0.035	2.741 ± 0.071	2.908 ± 0.037*
∝2u-Globulin (ng/µg soluble protein)	0.035 ± 0.008	0.060 ± 0.012	0.045 ± 0.007	0.065 ± 0.011
∝2u-Globulin (nmol/g kidney)	0.106 ± 0.030	0.182 ± 0.038	0.133 ± 0.023	0.198 ± 0.031*

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's or Shirley's test
** $P \leq 0.01$
[a] Data are presented as mean ± standard error.

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

TABLE H1
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 2-Week Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
n	5	5	5	5	5	5
Male						
Necropsy body wt	144 ± 3	141 ± 4	144 ± 2	147 ± 2	146 ± 3	145 ± 2
Heart						
Absolute	0.554 ± 0.015	0.524 ± 0.014	0.524 ± 0.018	0.534 ± 0.007	0.540 ± 0.017	0.548 ± 0.005
Relative	3.853 ± 0.070	3.706 ± 0.028	3.645 ± 0.086*	3.643 ± 0.036*	3.689 ± 0.033	3.785 ± 0.010
R. Kidney						
Absolute	0.574 ± 0.015	0.632 ± 0.018	0.628 ± 0.015	0.614 ± 0.045	0.628 ± 0.014	0.634 ± 0.014
Relative	3.993 ± 0.070	4.469 ± 0.043	4.370 ± 0.047	4.205 ± 0.345	4.296 ± 0.058	4.378 ± 0.078
Liver						
Absolute	6.772 ± 0.159	7.150 ± 0.385	7.208 ± 0.260	7.854 ± 0.129**	7.526 ± 0.145	7.594 ± 0.116
Relative	47.1 ± 0.7	50.4 ± 1.6	50.2 ± 1.5	53.6 ± 1.1**	51.5 ± 0.7**	52.4 ± 0.4**
Lung						
Absolute	1.040 ± 0.050	1.214 ± 0.103	1.344 ± 0.074	1.266 ± 0.089	1.324 ± 0.129	1.156 ± 0.066
Relative	7.268 ± 0.483	8.542 ± 0.551	9.347 ± 0.457	8.639 ± 0.605	9.003 ± 0.703	7.999 ± 0.509
R. Testis						
Absolute	0.865 ± 0.024	0.866 ± 0.022	0.886 ± 0.016	0.881 ± 0.025	0.918 ± 0.017	0.909 ± 0.014
Relative	6.015 ± 0.134	6.131 ± 0.145	6.173 ± 0.115	6.021 ± 0.223	6.282 ± 0.093	6.283 ± 0.142
Thymus						
Absolute	0.417 ± 0.006	0.401 ± 0.025	0.433 ± 0.016	0.437 ± 0.009	0.412 ± 0.029	0.434 ± 0.020
Relative	2.905 ± 0.048	2.830 ± 0.119	3.014 ± 0.079	2.982 ± 0.089	2.810 ± 0.163	2.999 ± 0.126
Female						
Necropsy body wt	116 ± 1	116 ± 4	116 ± 2	117 ± 2	115 ± 2	115 ± 3
Heart						
Absolute	0.472 ± 0.020	0.460 ± 0.017	0.446 ± 0.010	0.460 ± 0.014	0.448 ± 0.007	0.452 ± 0.007
Relative	4.052 ± 0.151	3.951 ± 0.070	3.850 ± 0.082	3.916 ± 0.094	3.896 ± 0.028	3.937 ± 0.029
R. Kidney						
Absolute	0.502 ± 0.012	0.544 ± 0.016	0.546 ± 0.011	0.554 ± 0.007*	0.548 ± 0.018	0.538 ± 0.013
Relative	4.310 ± 0.083	4.681 ± 0.109*	4.717 ± 0.125*	4.720 ± 0.069*	4.761 ± 0.096**	4.684 ± 0.047*
Liver						
Absolute	5.144 ± 0.093	5.636 ± 0.256	5.750 ± 0.215*	5.652 ± 0.115*	5.772 ± 0.059*	6.124 ± 0.214**
Relative	44.2 ± 0.7	48.4 ± 1.1**	49.6 ± 1.3**	48.1 ± 0.7**	50.2 ± 0.7**	53.3 ± 1.1**
Lung						
Absolute	0.860 ± 0.058	1.124 ± 0.083*	0.910 ± 0.047	1.112 ± 0.092*	1.016 ± 0.023	0.966 ± 0.033
Relative	7.377 ± 0.451	9.640 ± 0.566**	7.849 ± 0.369	9.446 ± 0.694*	8.833 ± 0.118	8.438 ± 0.409
Thymus						
Absolute	0.364 ± 0.019	0.366 ± 0.017	0.385 ± 0.017	0.382 ± 0.013	0.369 ± 0.014	0.372 ± 0.013
Relative	3.130 ± 0.184	3.136 ± 0.072	3.319 ± 0.116	3.257 ± 0.110	3.206 ± 0.118	3.239 ± 0.085

* Significantly different ($P \leq 0.05$) from the chamber 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 H2
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Rats in the 3-Month Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
n	10	10	10	10	10	10
Male						
Necropsy body wt	334 ± 7	331 ± 6	332 ± 5	331 ± 6	333 ± 6	315 ± 6
Heart						
Absolute	0.932 ± 0.015	0.933 ± 0.012	0.904 ± 0.007	0.907 ± 0.018	0.897 ± 0.015	0.868 ± 0.019**
Relative	2.793 ± 0.024	2.825 ± 0.029	2.728 ± 0.036	2.742 ± 0.031	2.700 ± 0.034	2.755 ± 0.051
R. Kidney						
Absolute	0.917 ± 0.021	0.958 ± 0.016	0.967 ± 0.025	0.984 ± 0.026*	1.022 ± 0.022**	1.020 ± 0.024**
Relative	2.747 ± 0.045	2.901 ± 0.042*	2.911 ± 0.040**	2.972 ± 0.041**	3.073 ± 0.029**	3.235 ± 0.050**
Liver						
Absolute	9.575 ± 0.282	9.945 ± 0.222	10.026 ± 0.222	10.081 ± 0.289	10.277 ± 0.334	10.210 ± 0.247
Relative	28.6 ± 0.4	30.1 ± 0.5*	30.2 ± 0.4*	30.4 ± 0.4**	30.8 ± 0.5**	32.4 ± 0.4**
Lung						
Absolute	1.489 ± 0.058	1.495 ± 0.036	1.509 ± 0.040	1.489 ± 0.023	1.545 ± 0.055	1.463 ± 0.039
Relative	4.457 ± 0.144	4.528 ± 0.111	4.543 ± 0.069	4.503 ± 0.039	4.646 ± 0.132	4.641 ± 0.099
R. Testis						
Absolute	1.360 ± 0.035	1.405 ± 0.016	1.423 ± 0.012	1.432 ± 0.020	1.424 ± 0.029	1.405 ± 0.021
Relative	4.076 ± 0.081	4.258 ± 0.059*	4.294 ± 0.053*	4.332 ± 0.047**	4.285 ± 0.068**	4.459 ± 0.040**
Thymus						
Absolute	0.316 ± 0.013	0.339 ± 0.022	0.343 ± 0.014	0.319 ± 0.014	0.321 ± 0.013	0.331 ± 0.012
Relative	0.944 ± 0.031	1.025 ± 0.066	1.033 ± 0.042	0.965 ± 0.041	0.964 ± 0.028	1.049 ± 0.034
Female						
Necropsy body wt	173 ± 4	188 ± 2*	192 ± 5**	181 ± 5	188 ± 4*	182 ± 3
Heart						
Absolute	0.570 ± 0.019	0.608 ± 0.009	0.607 ± 0.011	0.599 ± 0.018	0.606 ± 0.012	0.590 ± 0.013
Relative	3.290 ± 0.088	3.233 ± 0.040	3.163 ± 0.035	3.315 ± 0.058	3.232 ± 0.032	3.251 ± 0.060
R. Kidney						
Absolute	0.571 ± 0.016	0.611 ± 0.011	0.608 ± 0.017	0.603 ± 0.022	0.628 ± 0.015*	0.592 ± 0.008
Relative	3.297 ± 0.063	3.249 ± 0.044	3.164 ± 0.054	3.331 ± 0.051	3.349 ± 0.053	3.263 ± 0.039
Liver						
Absolute	5.290 ± 0.146	5.445 ± 0.110	5.397 ± 0.164	5.314 ± 0.157	5.862 ± 0.200*	5.711 ± 0.131
Relative	30.6 ± 0.7	28.9 ± 0.3	28.1 ± 0.5	29.4 ± 0.3	31.2 ± 0.6	31.4 ± 0.4
Lung						
Absolute	1.018 ± 0.045	1.109 ± 0.015	1.108 ± 0.014	1.051 ± 0.038	1.119 ± 0.022	1.042 ± 0.025
Relative	5.861 ± 0.172	5.903 ± 0.106	5.784 ± 0.114	5.808 ± 0.091	5.982 ± 0.151	5.741 ± 0.123
Thymus						
Absolute	0.241 ± 0.010	0.262 ± 0.015	0.283 ± 0.015	0.244 ± 0.010	0.258 ± 0.011	0.253 ± 0.010
Relative	1.386 ± 0.036	1.390 ± 0.070	1.463 ± 0.052	1.351 ± 0.049	1.369 ± 0.041	1.392 ± 0.043

* Significantly different ($P \leq 0.05$) from the chamber 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 H3
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 2-Week Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
n	5	5	5	5	5	5
Male						
Necropsy body wt	27.9 ± 0.3	27.2 ± 0.3	26.9 ± 0.5	26.9 ± 0.6	27.9 ± 0.4	27.1 ± 0.5
Heart						
Absolute	0.122 ± 0.002	0.122 ± 0.002	0.124 ± 0.002	0.122 ± 0.004	0.118 ± 0.005	0.118 ± 0.004
Relative	4.373 ± 0.057	4.480 ± 0.079	4.620 ± 0.160	4.529 ± 0.105	4.228 ± 0.155	4.348 ± 0.075
R. Kidney						
Absolute	0.226 ± 0.006	0.242 ± 0.004	0.242 ± 0.008	0.236 ± 0.007	0.248 ± 0.009	0.240 ± 0.007
Relative	8.104 ± 0.228	8.887 ± 0.159	8.995 ± 0.230*	8.760 ± 0.201	8.889 ± 0.290	8.855 ± 0.260
Liver						
Absolute	1.346 ± 0.022	1.398 ± 0.018	1.462 ± 0.037*	1.462 ± 0.040*	1.538 ± 0.045**	1.698 ± 0.029**
Relative	48.2 ± 0.6	51.3 ± 0.7	54.3 ± 1.0**	54.3 ± 1.2**	55.2 ± 2.2**	62.6 ± 0.6**
Lung						
Absolute	0.180 ± 0.003	0.176 ± 0.004	0.170 ± 0.007	0.176 ± 0.011	0.168 ± 0.007	0.178 ± 0.006
Relative	6.452 ± 0.090	6.468 ± 0.203	6.324 ± 0.270	6.523 ± 0.330	6.026 ± 0.250	6.580 ± 0.295
R. Testis						
Absolute	0.103 ± 0.002	0.101 ± 0.002	0.100 ± 0.002	0.100 ± 0.002	0.101 ± 0.003	0.096 ± 0.004
Relative	3.699 ± 0.039	3.696 ± 0.089	3.719 ± 0.060	3.713 ± 0.129	3.636 ± 0.099	3.551 ± 0.161
Thymus						
Absolute	0.056 ± 0.003	0.047 ± 0.006	0.055 ± 0.003	0.049 ± 0.002	0.052 ± 0.007	0.052 ± 0.004
Relative	2.006 ± 0.113	1.724 ± 0.214	2.025 ± 0.079	1.821 ± 0.075	1.863 ± 0.230	1.924 ± 0.139
Female						
Necropsy body wt	23.0 ± 0.4	22.6 ± 0.5	23.7 ± 0.6	22.4 ± 0.5	22.7 ± 0.5	23.2 ± 0.3
Heart						
Absolute	0.110 ± 0.000	0.114 ± 0.002	0.116 ± 0.004	0.110 ± 0.008	0.112 ± 0.002	0.110 ± 0.000
Relative	4.780 ± 0.080	5.043 ± 0.132	4.900 ± 0.135	4.900 ± 0.304	4.949 ± 0.155	4.737 ± 0.069
R. Kidney						
Absolute	0.154 ± 0.004	0.172 ± 0.004	0.176 ± 0.002*	0.166 ± 0.006	0.172 ± 0.006	0.172 ± 0.006
Relative	6.687 ± 0.167	7.613 ± 0.230**	7.440 ± 0.107*	7.398 ± 0.160	7.582 ± 0.187*	7.403 ± 0.242*
Liver						
Absolute	1.158 ± 0.027	1.216 ± 0.083	1.378 ± 0.041*	1.248 ± 0.056*	1.358 ± 0.041*	1.494 ± 0.035**
Relative	50.2 ± 0.6	53.5 ± 2.4	58.2 ± 0.7**	55.6 ± 1.7**	59.9 ± 1.1**	64.3 ± 1.0**
Lung						
Absolute	0.166 ± 0.002	0.172 ± 0.004	0.176 ± 0.004	0.176 ± 0.015	0.170 ± 0.005	0.172 ± 0.004
Relative	7.214 ± 0.173	7.615 ± 0.244	7.450 ± 0.258	7.825 ± 0.585	7.515 ± 0.315	7.399 ± 0.092
Thymus						
Absolute	0.078 ± 0.004	0.076 ± 0.002	0.069 ± 0.003	0.072 ± 0.004	0.078 ± 0.004	0.073 ± 0.006
Relative	3.397 ± 0.130	3.338 ± 0.065	2.905 ± 0.154	3.228 ± 0.185	3.437 ± 0.235	3.148 ± 0.243

* Significantly different (P≤0.05) from the chamber control group by Williams' or Dunnett's test
** P≤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 H4
Organ Weights and Organ-Weight-to-Body-Weight Ratios for Mice in the 3-Month Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	138 mg/m^3	275 mg/m^3	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
Male						
n	10	9	10	10	10	10
Necropsy body wt	39.5 ± 0.6	38.5 ± 0.5	39.6 ± 0.7	39.2 ± 0.6	39.0 ± 0.9	38.7 ± 0.9
Heart						
Absolute	0.160 ± 0.003	0.162 ± 0.003	0.155 ± 0.003	0.164 ± 0.003	0.163 ± 0.007	0.159 ± 0.006
Relative	4.058 ± 0.074	4.222 ± 0.106	3.916 ± 0.041	4.195 ± 0.097	4.191 ± 0.167	4.097 ± 0.071
R. Kidney						
Absolute	0.308 ± 0.005	0.314 ± 0.008	0.309 ± 0.009	0.318 ± 0.007	0.294 ± 0.007	0.306 ± 0.007
Relative	7.810 ± 0.124	8.193 ± 0.275	7.801 ± 0.162	8.129 ± 0.173	7.565 ± 0.207	7.913 ± 0.135
Liver						
Absolute	1.597 ± 0.042	1.560 ± 0.038	1.536 ± 0.047	1.638 ± 0.037	1.695 ± 0.051	1.774 ± 0.042**
Relative	40.4 ± 0.8	40.6 ± 1.2	38.7 ± 0.8	41.8 ± 0.7	43.5 ± 0.8*	45.9 ± 0.8**
Lung						
Absolute	0.220 ± 0.006	0.224 ± 0.007	0.218 ± 0.006	0.239 ± 0.012	0.226 ± 0.006	0.218 ± 0.006
Relative	5.580 ± 0.168	5.852 ± 0.232	5.505 ± 0.130	6.099 ± 0.274	5.815 ± 0.157	5.645 ± 0.186
R. Testis						
Absolute	0.117 ± 0.002	0.111 ± 0.004	0.111 ± 0.006	0.111 ± 0.004	0.114 ± 0.004	0.119 ± 0.003
Relative	2.967 ± 0.075	2.877 ± 0.099	2.786 ± 0.133	2.833 ± 0.110	2.929 ± 0.112	3.065 ± 0.049
Thymus						
Absolute	0.041 ± 0.002	0.042 ± 0.002	0.043 ± 0.002	0.041 ± 0.003	0.046 ± 0.005	0.046 ± 0.002
Relative	1.049 ± 0.062	1.084 ± 0.056	1.098 ± 0.052	1.036 ± 0.070	1.159 ± 0.117	1.189 ± 0.052
Female						
n	10	10	10	10	10	10
Necropsy body wt	33.9 ± 1.0	31.8 ± 0.7	33.4 ± 1.4	33.3 ± 0.5	33.6 ± 1.2	35.0 ± 1.0
Heart						
Absolute	0.132 ± 0.004	0.135 ± 0.003	0.138 ± 0.005	0.140 ± 0.004	0.133 ± 0.004	0.136 ± 0.003
Relative	3.912 ± 0.128	4.253 ± 0.091	4.154 ± 0.105	4.214 ± 0.129	3.984 ± 0.125	3.909 ± 0.104
R. Kidney						
Absolute	0.187 ± 0.003	0.191 ± 0.005	0.189 ± 0.004	0.194 ± 0.007	0.199 ± 0.007	0.194 ± 0.005
Relative	5.542 ± 0.140	6.023 ± 0.155	5.713 ± 0.181	5.834 ± 0.176	5.976 ± 0.270	5.571 ± 0.161
Liver						
Absolute	1.443 ± 0.036	1.416 ± 0.029	1.394 ± 0.059	1.471 ± 0.049	1.491 ± 0.062	1.573 ± 0.067
Relative	42.7 ± 0.8	44.6 ± 0.9	41.8 ± 0.9	44.2 ± 1.1	44.3 ± 1.0	45.0 ± 1.2
Lung						
Absolute	0.222 ± 0.008	0.225 ± 0.005	0.228 ± 0.006	0.225 ± 0.006	0.213 ± 0.004	0.229 ± 0.005
Relative	6.556 ± 0.185	7.095 ± 0.169	6.888 ± 0.242	6.772 ± 0.170	6.419 ± 0.298	6.566 ± 0.120
Thymus						
Absolute	0.045 ± 0.002	0.047 ± 0.003	0.052 ± 0.004	0.044 ± 0.004	0.047 ± 0.003	0.044 ± 0.002
Relative	1.334 ± 0.073	1.495 ± 0.095	1.559 ± 0.103	1.321 ± 0.108	1.422 ± 0.113	1.276 ± 0.064

* Significantly different ($P \le 0.05$) from the chamber control group by Williams' 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 I
REPRODUCTIVE TISSUE EVALUATIONS AND ESTROUS CYCLE CHARACTERIZATION

TABLE I1
Summary of Reproductive Tissue Evaluations for Male Rats in the 3-Month Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
n	10	10	10	10
Weights (g)				
Necropsy body wt	334 ± 7	331 ± 6	333 ± 6	315 ± 6
L. Cauda epididymis	0.1799 ± 0.0043	0.1835 ± 0.0042	0.1753 ± 0.0057	0.1789 ± 0.0054
L. Epididymis	0.4575 ± 0.0117	0.4620 ± 0.0073	0.4561 ± 0.0048	0.4470 ± 0.0100
L. Testis	1.4652 ± 0.0235	1.5092 ± 0.0157	1.4938 ± 0.0153	1.4647 ± 0.0181
Spermatid measurements				
Spermatid heads (10^7/g testis)	145.34 ± 6.41	160.60 ± 8.19	153.60 ± 5.71	156.31 ± 6.90
Spermatid heads (10^7/testis)	196.88 ± 7.70	221.50 ± 10.73	210.63 ± 7.93	208.75 ± 8.29
Spermatid heads (10^7/g cauda epididymis)	797.30 ± 59.10	753.90 ± 22.71	780.60 ± 31.90	842.60 ± 69.15
Spermatid heads (10^7/cauda epididymis)	142.66 ± 9.68	138.15 ± 4.15	135.65 ± 3.59	149.39 ± 10.64
Epididymal sperm motility (%)	90.28 ± 1.40	77.27 ± 3.99*	80.38 ± 2.62*	79.44 ± 1.59*

* Significantly different ($P \leq 0.05$) from the chamber control group by Shirley's test
[a] Data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (body and tissue weights) or by Dunn's test (spermatid measurements).

TABLE I2
Estrous Cycle Characterization for Female Rats in the 3-Month Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
n	10	10	10	10
Necropsy body wt (g)	173 ± 4	181 ± 5	188 ± 4	182 ± 3
Estrous cycle length (days)	4.85 ± 0.11	4.88 ± 0.13[b]	4.80 ± 0.13	4.55 ± 0.14
Estrous stages (% of cycle)				
Diestrus	54.2	65.8	57.5	58.3
Proestrus	18.3	10.8	9.2	5.8
Estrus	20.8	18.3	20.8	20.8
Metestrus	6.7	5.0	12.5	15.0

[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (body weight) or Dunn's test (estrous cycle length). By multivariate analysis of variance, exposed females do not differ significantly from the chamber control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle longer than 12 days or unclear in two of 10 animals

TABLE I3
Summary of Reproductive Tissue Evaluations for Male Mice in the 3-Month Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
n	10	10	10	10
Weights (g)				
Necropsy body wt	39.5 ± 0.6	39.2 ± 0.6	39.0 ± 0.9	38.7 ± 0.9
L. Cauda epididymis	0.0176 ± 0.0008	0.0190 ± 0.0013	0.0179 ± 0.0008	0.0202 ± 0.0009
L. Epididymis	0.0537 ± 0.0020	0.0551 ± 0.0022	0.0523 ± 0.0025	0.0551 ± 0.0016
L. Testis	0.1186 ± 0.0020	0.1094 ± 0.0046	0.1123 ± 0.0043	0.1192 ± 0.0030
Spermatid measurements				
Spermatid heads (10^7/g testis)	244.95 ± 8.59	226.60 ± 11.66	239.83 ± 17.88	227.83 ± 14.34
Spermatid heads (10^7/testis)	24.35 ± 1.27	21.30 ± 0.93	23.48 ± 1.75	23.57 ± 1.62
Spermatid heads (10^7/g cauda epididymis)	1,173.50 ± 72.76	1,100.56 ± 45.75[b]	1,059.89 ± 87.36[b]	1,024.60 ± 77.09
Spermatid heads (10^7/cauda epididymis)	20.36 ± 0.99	20.02 ± 0.96[b]	18.56 ± 0.77[b]	20.22 ± 1.05
Epididymal sperm motility (%)	61.20 ± 1.81	58.45 ± 1.80	63.39 ± 2.88[b]	54.82 ± 1.50*

* Significantly different ($P \leq 0.05$) from the chamber control group by Dunn's test
[a] Data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (body and tissue weights) or by Dunn's test (spermatid measurements).
[b] n=9

TABLE I4
Estrous Cycle Characterization for Female Mice in the 3-Month Inhalation Study of Stoddard Solvent IIC[a]

	Chamber Control	550 mg/m^3	1,100 mg/m^3	2,200 mg/m^3
n	10	10	10	10
Necropsy body wt (g)	33.9 ± 1.0	33.3 ± 0.5	33.6 ± 1.2	35.0 ± 1.0
Estrous cycle length (days)	4.12 ± 0.12	4.06 ± 0.06[b]	3.94 ± 0.04	4.15 ± 0.12
Estrous stages (% of cycle)				
Diestrus	28.3	35.0	26.7	29.2
Proestrus	19.2	19.2	20.8	19.2
Estrus	30.8	24.2	28.3	29.2
Metestrus	21.7	21.7	24.2	22.5

[a] Necropsy body weight and estrous cycle length data are presented as mean ± standard error. Differences from the chamber control group are not significant by Dunnett's test (body weight) or Dunn's test (estrous cycle length). By multivariate analysis of variance, exposed females do not differ significantly from the chamber control females in the relative length of time spent in the estrous stages.
[b] Estrous cycle longer than 12 days or unclear in one of 10 animals

APPENDIX J
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

Procurement and Characterization of Stoddard Solvent IIC

Stoddard solvent IIC was obtained from Shell Chemical Company (Houston, TX) in one lot (00106808). Lot 00106808 was used in the 2-week, 3-month, and 2-year studies. Identity and purity analyses were conducted by the analytical chemistry laboratory, Midwest Research Institute (Kansas City, MO), and the study laboratory. Stability analyses were conducted by the study laboratory. Reports on analyses performed in support of the Stoddard solvent IIC studies are on file at the National Institute of Environmental Health Sciences.

Lot 00106808 of the chemical, a clear liquid, was identified as Stoddard solvent IIC by the analytical chemistry laboratory using infrared and nuclear magnetic resonance proton and carbon-13 spectroscopy, gas chromatography with mass spectrometry (GC/MS), aromatic content, boiling range, and flash point. Identity was confirmed by the study laboratory using GC/MS and aromatic content. Infrared and nuclear magnetic resonance spectra were consistent with a mixture of saturated hydrocarbons (Figures J1 to J3). Spectra (at the analytical chemistry laboratory) by GC/MS system A (Table J1) were consistent with National Bureau of Standards Library spectra for hydrocarbons with 10 to 14 carbons; spectra by GC/MS system B were consistent with the NIST/EPA/NIH MS Database (NIST, 1994) for a mixture of *n*-paraffins, isoparaffins, or cycloparaffins with 10 to 13 carbons. Aromatic content was determined by GC using system C at the analytical chemistry laboratory and system D at the study laboratory. The observed aromatic contents of 0.93% and 0.58% by volume by systems C and D, respectively, were consistent with the designation of the chemical as a Class C material (ASTM, 1995). The determined boiling range of 184.7° to 206.1° C was consistent with designation of the chemical as a Type II material. The observed flash point of 60.2° C was slightly lower than the 61° C minimal ASTM specification for a Type II material. The difference was attributed to the use of a different instrument from that specified in the ASTM standard.

The purity of lot 00106808 was determined by the study laboratory using GC by system E. Gas chromatography indicated approximately 80 peaks with areas greater than 0.1% of the total peak area and approximately 30 peaks with areas greater than 1% of the total peak area. In these assays, concentrations of decane, undecane, and dodecane were determined by comparison to bracketing standards and yielded estimates of 1.70%, 19.3%, and 5.73% by weight for the three chemicals, respectively. Decalin contamination in lot 00106808 was determined by the analytical chemistry laboratory using GC by system F; approximately 0.56% decalin was detected.

To ensure stability, the bulk chemical was stored in its original shipping containers (55-gallon metal drums) under a nitrogen headspace at controlled room temperature (15° to 30° C). Stability of the bulk chemical was monitored by the study laboratory relative to frozen reference (–20° C, amber vials with a nitrogen headspace) standards during the 2-week, 3-month, and 2-year studies using GC by a system similar to system E. Weight percents of decane, undecane, and dodecane were determined using GC by system E. No degradation of the bulk chemical was detected.

Vapor Generation and Exposure System

A diagram of the vapor generation and delivery system used in the studies is shown in Figure J4. Stoddard solvent IIC was pumped through a preheater and then into the top of a heated glass column filled with glass beads to increase the surface area for evaporation. Heated nitrogen entering the column from below vaporized the chemical as it conveyed it out of the generator. Generator output was controlled by the delivery rate of the chemical metering pump.

Because the vapor leaving the generator was above room temperature, the transport line to the exposure room was heated to prevent condensation. In the exposure room, the vapor was mixed with additional heated air before it entered a short vapor distribution manifold. Concentration in the manifold was determined by the chemical pump rate, nitrogen flow rate, and dilution air flow rate. All three components were monitored by the exposure operator. The pressure in the distribution manifold was kept fixed to ensure constant flows through the manifold and into the chambers.

Electronically actuated metering valves controlled flow to each chamber. In the 2-year studies, a compressed air vacuum pump was attached to the delivery line and was used for fine control of vapor delivery to the 138 mg/m^3 chamber. An exposure shutoff valve, mounted in series with each chamber metering valve, stopped vapor delivery to each chamber. Vapor was diverted to the exposure chamber exhaust until the generation system was stable and exposures were initiated. To begin the exposures, the exposure valves were opened to allow the flow of vapor through chamber metering valves and into individual temperature-controlled delivery lines to the exposure chamber. The vapor was then injected into the chamber inlet duct where it was further diluted with conditioned chamber air to achieve the desired exposure concentration.

The study laboratory designed the inhalation exposure chamber (Harford Systems Division of Lab Products, Inc., Aberdeen, MD) so that uniform vapor concentrations could be maintained throughout the chamber with the catch pans in place. The total active mixing volume of each chamber was 1.7 m^3. A small particle detector (Type CN, Gardner Associates, Schenectady, NY) was used during the 2-week and 3-month studies and a condensation particle counter (Model 3022A, TSI Inc., St. Paul, MN) was used during the 2-year studies with and without animals in the exposure chambers to ensure that Stoddard solvent IIC vapor, and not aerosol, was produced. There were no appreciable or consistent differences between particle measurements before or during the exposure period.

Vapor Concentration Monitoring

Summaries of the chamber vapor concentrations are given in Tables J2 through J4. The Stoddard solvent IIC concentrations in the exposure chambers were monitored by an on-line gas chromatograph (system G). Samples were drawn from each exposure chamber approximately every 24 minutes using a 12-port stream select valve (VALCO Instruments Company, Houston, TX). The on-line gas chromatograph was checked throughout the day for instrument drift against an on-line standard of an approximately 400 mg/m^3 mixture of the *n*-paraffins decane, undecane, and dodecane in nitrogen supplied by a diffusion tube standard generator (Model 491, Kin-Tek, La Marque, TX). The on-line gas chromatograph was calibrated monthly or when excessive calibration drift was detected by a comparison of chamber concentration data to data from grab samples, which were collected with charcoal sampling tubes (ORBO-101, Supelco, Bellefonte, PA). Grab samples were extracted with hexanes containing nonane as an internal standard and analyzed by an off-line gas chromatograph (system H). Known volumes of chamber atmosphere from each chamber were sampled at a constant flow rate ensured by a calibrated critical orifice. The off-line gas chromatograph was calibrated with gravimetrically prepared standards of Stoddard solvent IIC and an internal standard (nonane) in hexanes.

The composition of Stoddard solvent IIC in the 2,200 mg/m^3 exposure chamber was monitored by a second on-line gas chromatograph (system I) in the 3-month and 2-year studies. Samples were drawn from the exposure chamber five or six times during each 6-hour exposure period using a 12-port stream select valve. The on-line gas chromatograph was checked against the on-line standard after exposure termination. The composition monitor provided enhanced chromatographic separation of the components and allowed reporting of the relative amounts of the major *n*-paraffins of Stoddard solvent IIC. Mean results for decane, undecane, and dodecane of 100.1%, 100.0%, and 99.9%, respectively, during the 2-year studies indicated that the composition of Stoddard solvent IIC did not change significantly during exposure.

Chamber Atmosphere Characterization

Buildup and decay rates for chamber vapor concentrations were determined with animals present in the chambers. At a chamber airflow rate of 15 air changes per hour, the theoretical value for the time to achieve 90% of the target concentration after the beginning of vapor generation (T_{90}) and the time for the chamber concentration to decay to 10% of the target concentration after vapor generation was terminated (T_{10}) was approximately 12.5 minutes. For rats and mice in the 2-week studies, T_{90} values ranged from 8 to 11 minutes; T_{10} values ranged from 9 to 12 minutes. For rats and mice in the 3-month studies, T_{90} values ranged from 9 to 12 minutes; T_{10} values ranged from 11 to 14 minutes. For rats and mice in the 2-year studies, T_{90} values ranged from 10 to 14 minutes; T_{10} values ranged from 14 to 18 minutes. A T_{90} value of 12 minutes was selected for all studies.

The uniformity of Stoddard solvent IIC vapor concentrations in the inhalation exposure chambers without animals was evaluated before the 2-year study; concentration uniformity with animals present in the chambers was also measured once during the 2-week studies, once during the 3-month studies, and every 3 months during the 2-year studies. The vapor concentration was measured using the on-line gas chromatograph with the automatic 12-port sample valve disabled to allow continuous monitoring from a single input line. Samples were collected from 12 chamber positions representing the front and back of each of the six possible animal cage unit positions within the exposure chamber. Chamber concentration uniformity was maintained throughout the studies.

The persistence of Stoddard solvent IIC in the chamber after vapor delivery ended was determined by monitoring the concentration in the 2,200 mg/m^3 chamber in the 2-week and 3-month studies and the 2-year mouse study with animals present in the chambers; in the 2-year rat studies, concentrations in the 1,100 mg/m^3 male and 2,200 mg/m^3 female chambers were monitored with animals present in the chambers. The concentration decreased to 1% of the target concentration within 32 minutes in the 2-week studies; 84 minutes in the 3-month studies; and 88 minutes in the 1,100 mg/m^3 male rat chamber and 68 minutes in the 2,200 mg/m^3 mouse and female rat chambers in the 2-year studies.

All exposure chambers were monitored for stability during the 2-week studies. Stability was monitored in the generator reservoir during the 3-month studies and in the distribution manifold and the 138, 550, 1,100, and 2,200 mg/m^3 exposure chambers during the 2-year studies. Exposure chamber samples were collected once and distribution manifold samples were collected twice before the studies began; a sample was collected from the generator reservoir 24 (2-week studies) or 105 (3-month studies) days or 39 weeks (2-year studies) after the reservoir was filled. All samples were analyzed by GC system J. No evidence of degradation was found, and no extraneous peaks were seen. The results indicated that Stoddard solvent IIC was stable in the generation and exposure system and for 273 days in the generator reservoir.

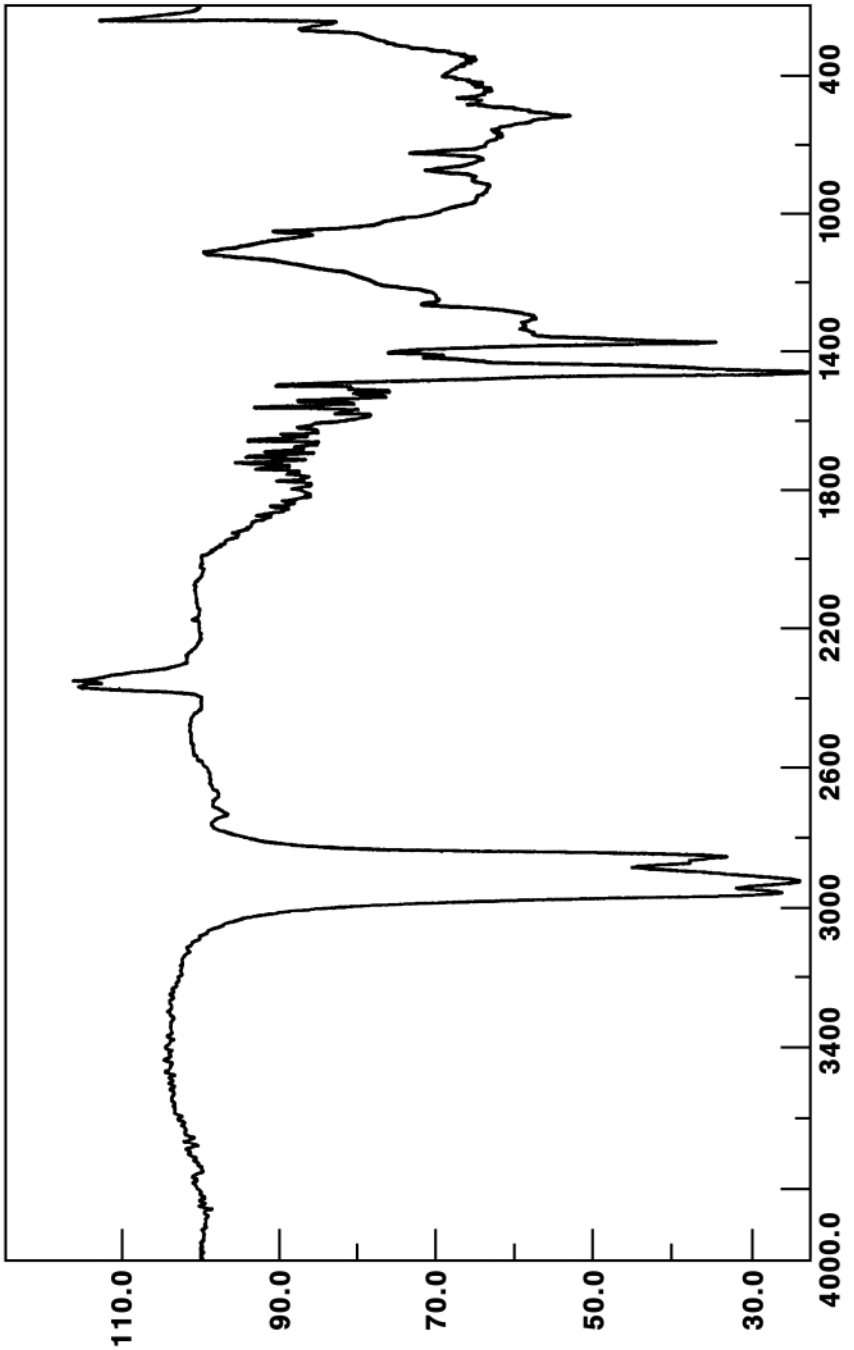

Figure J1
Infrared Absorption Spectrum of Stoddard Solvent IIC

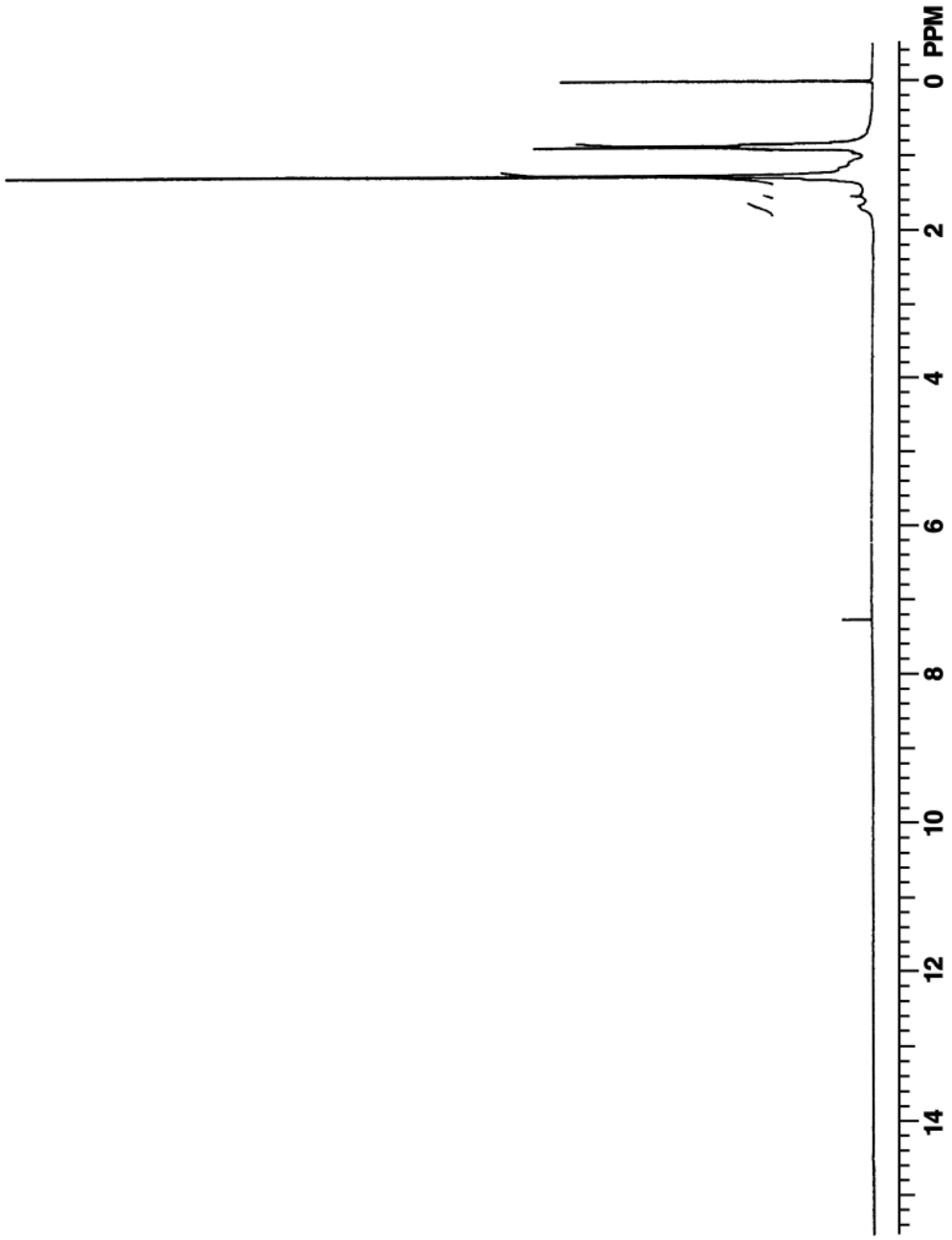

Figure J2
Proton Nuclear Magnetic Resonance Spectrum of Stoddard Solvent IIC

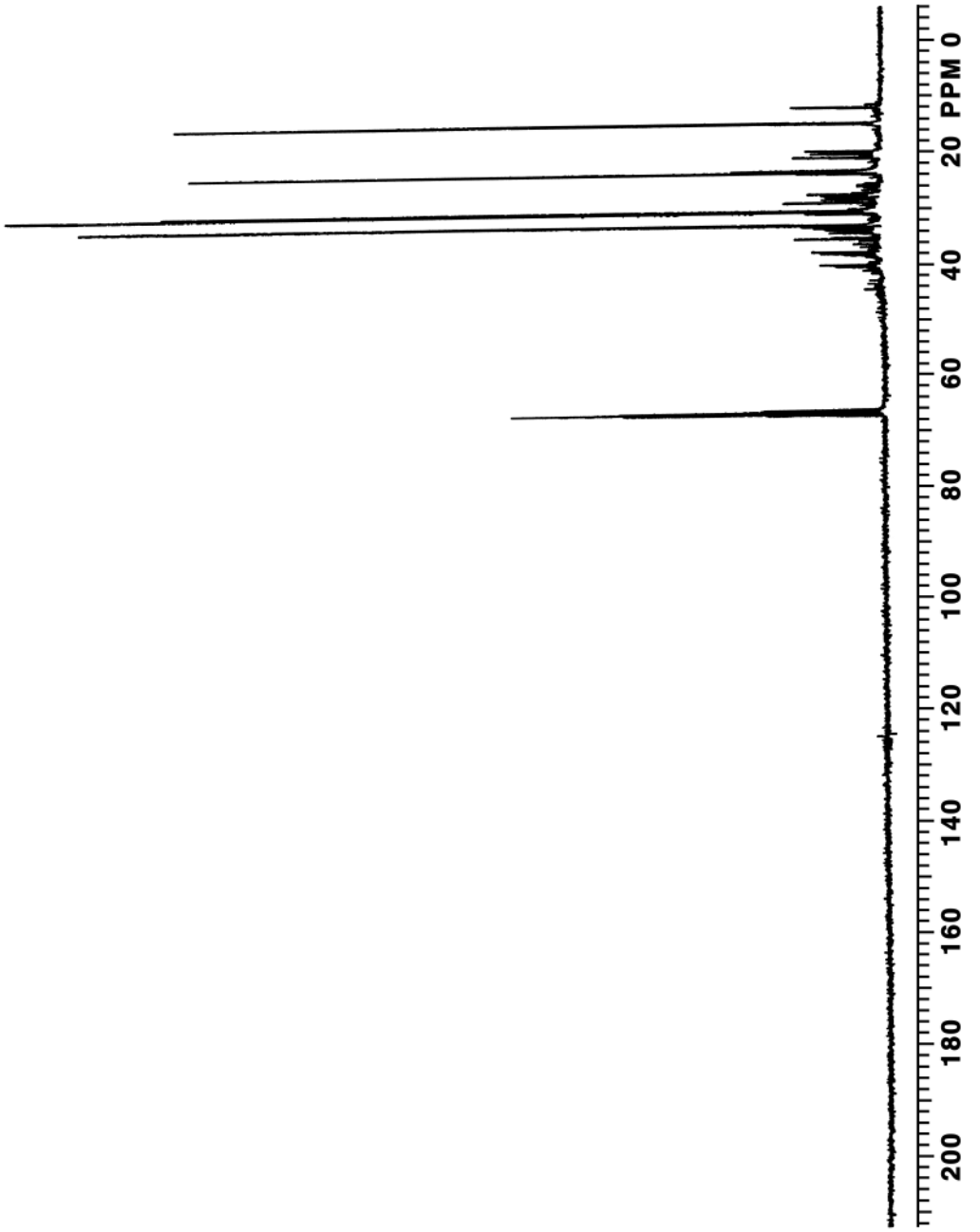

FIGURE J3
Carbon-13 Nuclear Magnetic Resonance Spectrum of Stoddard Solvent IIC

TABLE J1
Gas Chromatography Systems Used in the Inhalation Studies of Stoddard Solvent IIC[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Mass spectrometry	DB-5, 30 m × 0.25 mm, 0.25-µm film (J&W Scientific, Folsom, CA)	Helium at 1 mL/minute	40° C for 4 minutes, then 10° C/minute to 250° C, held for 5 minutes
System B			
Mass spectrometry	Petrocol DH, 100 m × 0.25 mm, 0.5-µm film (Supelco, Bellefonte, PA)	Helium at 15 psi	35° C for 15 minutes, then 2° C/minute to 200° C
System C			
Flame ionization	25% *N,N*-bis (2-cyanoethyl) formamide on 80-100 mesh Chromosorb-P, 10 ft × 2 mm	Helium at 34.1 mL/minute	108° C for 1 minute, then 15° C/minute to 115° C, held for 16 minutes
System D			
Flame ionization	TCEP, 60 m × 0.25 mm, 0.44-µm film (Supelco)	Helium at 25 psi	110° C for 20 minutes, then 10° C/minute to 140° C, held for 5 minutes
System E			
Flame ionization	Petrocol DH, 100 m × 0.25 mm, 0.5-µm film (Supelco)	Helium at 32 psi	35° C for 15 minutes, then 2° C/minute to 200° C
System F			
Flame ionization	Rtx-1, 30 m × 0.53 mm, 1.5-µm film (Restek, Bellefonte, PA)	Helium at 10 mL/minute	70° C for 5 minutes, then 2° C/minute to 150° C, then 25° C/minute to 200° C, held for 2 minutes
System G			
Flame ionization	DB-5, 15 m × 0.53 mm, 0.5-µm film (J&W Scientific)	Nitrogen at 13 psi	90° C
System H			
Flame ionization	5% phenyl, 95% methylpolysiloxane, 30 m × 0.53 mm, 1.5-µm film	Helium at 6 psi	55° C for 1 minute, then 10° C/minute to 200° C, held for 2 minutes
System I			
Flame ionization	Petrocol DH, 100 m × 0.25 mm, 0.5-µm film (Supelco)	Nitrogen at 32 psi	70° C for 0.5 minute, then 2° C/minute to 175° C
System J			
Flame ionization	Petrocol DH, 100 m × 0.25 mm, 0.5-µm film (Supelco)	Helium at 32 psi	35° C for 15 minutes, then 2° C/minute to 200° C, then 30° C/minute to 250° C, held for 5 minutes

[a] Gas chromatographs were manufactured by Hewlett-Packard (Palo Alto, CA), except system C, which was manufactured by Varian (Palo Alto, CA) and system F, which was manufactured by Agilent (Palo Alto, CA).

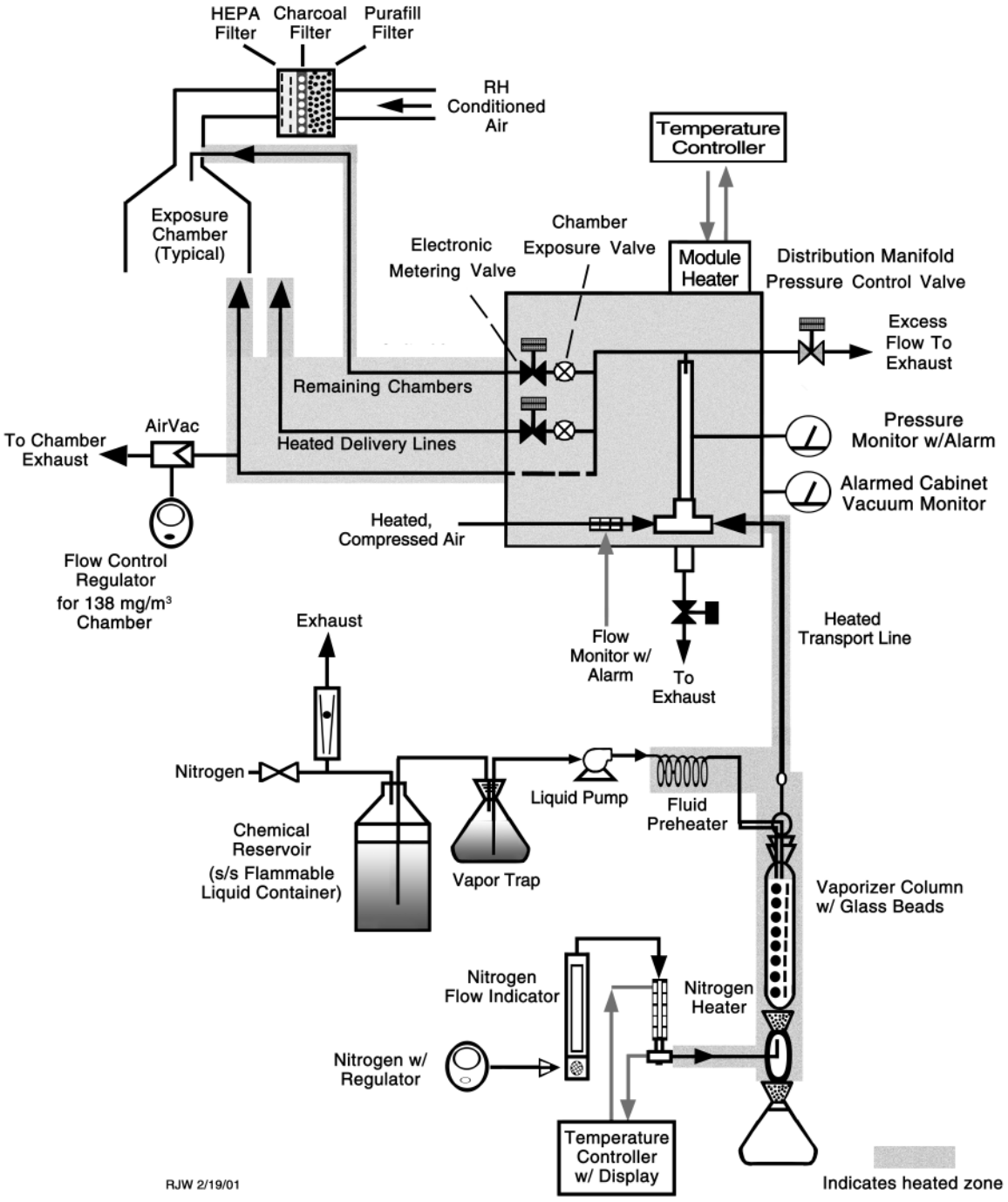

FIGURE J4
Schematic of the Vapor Generation and Delivery System in the Inhalation Studies of Stoddard Solvent IIC

TABLE J2
Summary of Chamber Concentrations in the 2-Week Inhalation Studies of Stoddard Solvent IIC

Target Concentration (mg/m^3)	Total Number of Readings	Average Concentration[a] (mg/m^3)
Rat Chambers		
138	174	136 ± 13
275	169	279 ± 18
550	171	560 ± 35
1,100	165	1,120 ± 104
2,200	180	2,200 ± 201
Mouse Chambers		
138	203	137 ± 12
275	184	279 ± 17
550	187	562 ± 34
1,100	181	1,120 ± 100
2,200	196	2,200 ± 193

[a] Mean ± standard deviation

TABLE J3
Summary of Chamber Concentrations in the 3-Month Inhalation Studies of Stoddard Solvent IIC

Target Concentration (mg/m^3)	Total Number of Readings	Average Concentration[a] (mg/m^3)
Rat Chambers		
138	1,053	137 ± 7.1
275	1,032	270 ± 13
550	1,028	549 ± 23
1,100	1,033	1,110 ± 33
2,200	1,026	2,220 ± 75
Mouse Chambers		
138	1,087	137 ± 7.0
275	1,066	270 ± 13
550	1,062	550 ± 23
1,100	1,067	1,110 ± 33
2,200	1,061	2,220 ± 74

[a] Mean ± standard deviation

TABLE J4
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Stoddard Solvent IIC

Target Concentration (mg/m^3)	Total Number of Readings	Average Concentration[a] (mg/m^3)
Rat Chambers		
Male		
138	7,598	139 ± 7
550	7,302	553 ± 16
1,100	7,365	1,107 ± 38
Female		
550	7,324	551 ± 15
1,100	7,349	1,109 ± 36
2,200	7,411	2,209 ± 76
Mouse Chambers		
550	7,328	551 ± 16
1,100	7,351	1,109 ± 36
2,200	7,414	2,210 ± 77

[a] Mean ± standard deviation

APPENDIX K
INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NTP-2000 RAT AND MOUSE RATION

TABLE K1
Ingredients of NTP-2000 Rat and Mouse Ration

Ingredients	Percent by Weight
Ground hard winter wheat	22.26
Ground #2 yellow shelled corn	22.18
Wheat middlings	15.0
Oat hulls	8.5
Alfalfa meal (dehydrated, 17% protein)	7.5
Purified cellulose	5.5
Soybean meal (49% protein)	5.0
Fish meal (60% protein)	4.0
Corn oil (without preservatives)	3.0
Soy oil (without preservatives)	3.0
Dried brewer's yeast	1.0
Calcium carbonate (USP)	0.9
Vitamin premix[a]	0.5
Mineral premix[b]	0.5
Calcium phosphate, dibasic (USP)	0.4
Sodium chloride	0.3
Choline chloride (70% choline)	0.26
Methionine	0.2

[a] Wheat middlings as carrier
[b] Calcium carbonate as carrier

TABLE K2
Vitamins and Minerals in NTP-2000 Rat and Mouse Ration[a]

	Amount	Source
Vitamins		
A	4,000 IU	Stabilized vitamin A palmitate or acetate
D	1,000 IU	D-activated animal sterol
K	1.0 mg	Menadione sodium bisulfite complex
α-Tocopheryl acetate	100 IU	
Niacin	23 mg	
Folic acid	1.1 mg	
d-Pantothenic acid	10 mg	*d*-Calcium pantothenate
Riboflavin	3.3 mg	
Thiamine	4 mg	Thiamine mononitrate
B_{12}	52 µg	
Pyridoxine	6.3 mg	Pyridoxine hydrochloride
Biotin	0.2 mg	*d*-Biotin
Minerals		
Magnesium	514 mg	Magnesium oxide
Iron	35 mg	Iron sulfate
Zinc	12 mg	Zinc oxide
Manganese	10 mg	Manganese oxide
Copper	2.0 mg	Copper sulfate
Iodine	0.2 mg	Calcium iodate
Chromium	0.2 mg	Chromium acetate

[a] Per kg of finished product

TABLE K3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	13.7 ± 0.45	12.8 – 14.5	24
Crude fat (% by weight)	8.1 ± 0.26	7.6 – 8.6	24
Crude fiber (% by weight)	9.2 ± 0.60	7.9 – 10.5	24
Ash (% by weight)	5.0 ± 0.20	4.7 – 5.4	24
Amino Acids (% of total diet)			
Arginine	0.731 ± 0.050	0.670 – 0.800	8
Cystine	0.224 ± 0.012	0.210 – 0.240	8
Glycine	0.684 ± 0.041	0.620 – 0.740	8
Histidine	0.333 ± 0.018	0.310 – 0.350	8
Isoleucine	0.524 ± 0.046	0.430 – 0.590	8
Leucine	1.061 ± 0.061	0.960 – 1.130	8
Lysine	0.708 ± 0.056	0.620 – 0.790	8
Methionine	0.401 ± 0.035	0.350 – 0.460	8
Phenylalanine	0.598 ± 0.036	0.540 – 0.640	8
Threonine	0.501 ± 0.051	0.430 – 0.590	8
Tryptophan	0.126 ± 0.014	0.110 – 0.150	8
Tyrosine	0.390 ± 0.056	0.280 – 0.460	8
Valine	0.640 ± 0.049	0.550 – 0.690	8
Essential Fatty Acids (% of total diet)			
Linoleic	3.97 ± 0.284	3.59 – 4.54	8
Linolenic	0.30 ± 0.042	0.21 – 0.35	8
Vitamins			
Vitamin A (IU/kg)	5,349 ± 1,087	3,460 – 7,790	24
Vitamin D (IU/kg)	1,000[a]		
α-Tocopherol (ppm)	82.2 ± 14.08	62.2 – 107.0	8
Thiamine (ppm)[b]	7.8 ± 0.79	6.3 – 9.2	24
Riboflavin (ppm)	5.6 ± 1.12	4.20 – 7.70	8
Niacin (ppm)	74.3 ± 5.94	66.4 – 85.8	8
Pantothenic acid (ppm)	22.5 ± 3.96	17.4 – 29.1	8
Pyridoxine (ppm)[b]	9.04 ± 2.37	6.4 – 12.4	8
Folic acid (ppm)	1.64 ± 0.38	1.26 – 2.32	8
Biotin (ppm)	0.333 ± 0.15	0.225 – 0.704	8
Vitamin B_{12} (ppb)	68.7 ± 63.0	18.3 – 174.0	8
Choline (ppm)[b]	3,155 ± 325	2,700 – 3,790	8
Minerals			
Calcium (%)	1.01 ± 0.042	0.903 – 1.090	24
Phosphorus (%)	0.574 ± 0.025	0.517 – 0.618	24
Potassium (%)	0.659 ± 0.022	0.627 – 0.691	8
Chloride (%)	0.357 ± 0.027	0.300 – 0.392	8
Sodium (%)	0.189 ± 0.019	0.160 – 0.212	8
Magnesium (%)	0.199 ± 0.009	0.185 – 0.213	8
Sulfur (%)	0.178 ± 0.021	0.153 – 0.209	8
Iron (ppm)	160 ± 14.7	135 – 177	8
Manganese (ppm)	50.3 ± 4.82	42.1 – 56.0	8
Zinc (ppm)	50.7 ± 6.59	43.3 – 61.1	8
Copper (ppm)	6.29 ± 0.828	5.08 – 7.59	8
Iodine (ppm)	0.461 ± 0.187	0.233 – 0.843	8
Chromium (ppm)	0.542 ± 0.128	0.330 – 0.707	7
Cobalt (ppm)	0.23 ± 0.049	0.20 – 0.30	7

[a] From formulation
[b] As hydrochloride (thiamine and pyridoxine) or chloride (choline)

TABLE K4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.18 ± 0.073	0.10 – 0.37	24
Cadmium (ppm)	0.04 ± 0.008	0.04 – 0.07	24
Lead (ppm)	0.11 ± 0.106	0.05 – 0.54	24
Mercury (ppm)	<0.02		24
Selenium (ppm)	0.19 ± 0.035	0.14 – 0.28	24
Aflatoxins (ppb)	<5.00		24
Nitrate nitrogen (ppm)[c]	11.2 ± 3.39	9.04 – 21.1	24
Nitrite nitrogen (ppm)[c]	<0.61		24
BHA (ppm)[d]	<1.0		24
BHT (ppm)[d]	<1.0		24
Aerobic plate count (CFU/g)	12 ± 6	10.0 – 40.0	24
Coliform (MPN/g)	0.90 ± 1.6	0.0 – 3.6	24
Escherichia coli (MPN/g)	<10		24
Salmonella (MPN/g)	Negative		24
Total nitrosoamines (ppb)[e]	4.6 ± 1.36	2.1 – 7.5	24
N-Nitrosodimethylamine (ppb)[e]	1.8 ± 0.52	1.0 – 3.0	24
N-Nitrosopyrrolidine (ppb)[e]	2.8 ± 1.1	1.0 – 5.1	24
Pesticides (ppm)			
α-BHC	<0.01		24
β-BHC	<0.02		24
γ-BHC	<0.01		24
δ-BHC	<0.01		24
Heptachlor	<0.01		24
Aldrin	<0.01		24
Heptachlor epoxide	<0.01		24
DDE	<0.01		24
DDD	<0.01		24
DDT	<0.01		24
HCB	<0.01		24
Mirex	<0.01		24
Methoxychlor	<0.05		24
Dieldrin	<0.01		24
Endrin	<0.01		24
Telodrin	<0.01		24
Chlordane	<0.05		24
Toxaphene	<0.10		24
Estimated PCBs	<0.20		24
Ronnel	<0.01		24
Ethion	<0.02		24
Trithion	<0.05		24
Diazinon	<0.10		24
Methyl chlorpyrifos	0.149 ± 0.119	0.023 – 0.449	24
Methyl parathion	<0.02		24
Ethyl parathion	<0.02		24
Malathion	0.204 ± 0.183	0.020 – 0.826	24
Endosulfan I	<0.01		24
Endosulfan II	<0.01		24
Endosulfan sulfate	<0.03		24

[a] All samples were irradiated. CFU=colony-forming units; MPN=most probable number; BHC=hexachlorocyclohexane or benzene 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 L
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 the rodents is monitored via serology on sera from extra (sentinel) animals in the study rooms. These animals and the study animals are 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 2-week, 3-month, 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./BioReliance Corp. (Rockville, 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 blood was collected during the studies are also listed.

Method and Test	Time of Analysis
RATS	
2-Week Study	
ELISA	
KRV/H1 (Kilham rat virus/Toolan's H-1 virus)	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	Study termination
RCV/SDA	
(rat coronavirus/sialodacryoadenitis virus)	Study termination
Sendai	Study termination
3-Month Study	
ELISA	
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	Study termination
RCV/SDA	Study termination
Sendai	Study termination
Immunofluorescence Assay	
Parvovirus	Study termination
2-Year Study	
ELISA	
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
RCV/SDA	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination
Immunofluorescence Assay	
Parvovirus	6, 12, and 18 months, study termination
Sendai	6 months

Method and Test	Time of Analysis
MICE	
2-Week Study	
ELISA	
GDVII (mouse encephalomyelitis virus)	Study termination
MVM (minute virus of mice)	Study termination
MHV (mouse hepatitis virus)	Study termination
M. pulmonis	Study termination
PVM	Study termination
Sendai	Study termination
3-Month Study	
ELISA	
Ectromelia virus	Study termination
EDIM (epizootic diarrhea of infant mice)	Study termination
GDVII	Study termination
LCM (lymphocytic choriomeningitis virus)	Study termination
Mouse adenoma virus-FL	Study termination
MHV	Study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	Study termination
Reovirus 3	Study termination
Sendai	Study termination
Immunofluorescence Assay	
Ectromelia virus	Study termination
EDIM	Study termination
LCM	Study termination
Mouse adenoma virus-FL	Study termination
MCMV (mouse cytomegalovirus)	Study termination
MHV	Study termination
Parvovirus	Study termination
PVM	Study termination
2-Year Study	
ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM	6, 12, and 18 months, study termination
GDVII	6, 12, and 18 months, study termination
LCM	6, 12, and 18 months, study termination
Mouse adenoma virus	6, 12, and 18 months, study termination
MHV	6, 12, and 18 months, study termination
M. arthritidis	Study termination
M. pulmonis	Study termination
PVM	6, 12, and 18 months, study termination
Reovirus 3	6, 12, and 18 months, study termination
Sendai	6, 12, and 18 months, study termination

Immunofluorescence Assay	
EDIM	18 months
GDVII	12 and 18 months
LCM	18 months, study termination
Mouse adenoma virus-FL	6 and 18 months
MCMV	Study termination
M. arthritidis	Study termination
Parvovirus	6, 12, and 18 months, study termination

RESULTS

All serology tests were negative.

National Toxicology Program Technical Reports

Printed as of September 2004

Environmental Health Persepctives (EHP) maintains the library of NTP Technical Reports in electronic and print format. To gain access to these reports, contact EHP online at http://ehp.niehs.nih.gov or call 866-541-3841 or 919-653-2590.

Chemical	TR No.
Acetaminophen	394
Acetonitrile	447
Acrylonitrile	506
Agar	230
Allyl Glycidyl Ether	376
Allyl Isothiocyanate	234
Allyl Isovalerate	253
1-Amino-2,4-Dibromoanthraquinone	383
2-Amino-4-Nitrophenol	339
2-Amino-5-Nitrophenol	334
11-Aminoundecanoic Acid	216
dl-Amphetamine Sulfate	387
Ampicillin Trihydrate	318
Asbestos, Amosite (Hamsters)	249
Asbestos, Amosite (Rats)	279
Asbestos, Chrysotile (Hamsters)	246
Asbestos, Chrysotile (Rats)	295
Asbestos, Crocidolite	280
Asbestos, Tremolite	277
L-Ascorbic Acid	247
AZT and AZT/α-Interferon A/D	469
Barium Chloride Dihydrate	432
Benzaldehyde	378
Benzene	289
Benzethonium Chloride	438
Benzofuran	370
Benzyl Acetate (Gavage)	250
Benzyl Acetate (Feed)	431
Benzyl Alcohol	343
o-Benzyl-*p*-Chlorophenol (Gavage)	424
o-Benzyl-*p*-Chlorophenol (Mouse Skin)	444
2-Biphenylamine Hydrochloride	233
2,2-Bis(Bromomethyl)-1,3-Propanediol	452
Bis(2-Chloro-1-Methylethyl) Ether	239
Bisphenol A	215
Boric Acid	324
Bromodichloromethane	321
Bromoethane	363
1,3-Butadiene	288
1,3-Butadiene	434
t-Butyl Alcohol	436
Butyl Benzyl Phthalate	213
Butyl Benzyl Phthalate	458
n-Butyl Chloride	312
t-Butylhydroquinone	459
γ-Butyrolactone	406
Caprolactam	214
d-Carvone	381
Chloral Hydrate	502
Chloral Hydrate	503
Chlorinated and Chloraminated Water	392
Chlorendic Acid	304
Chlorinated Paraffins: C_{23}, 43% Chlorine	305
Chlorinated Paraffins: C_{12}, 60% Chlorine	308
Chlorinated Trisodium Phosphate	294
2-Chloroacetophenone	379
p-Chloroaniline Hydrochloride	351
Chlorobenzene	261
Chlorodibromomethane	282
Chloroethane	346
2-Chloroethanol	275
3-Chloro-2-Methylpropene	300
Chloroprene	467
1-Chloro-2-Propanol	477
Chlorpheniramine Maleate	317
C.I. Acid Orange 3	335
C.I. Acid Orange 10	211
C.I. Acid Red 14	220
C.I. Acid Red 114	405
C.I. Basic Red 9 Monohydrochloride	285
C.I. Direct Blue 15	397
C.I. Direct Blue 218	430
C.I. Disperse Blue 1	299
C.I. Disperse Yellow 3	222
C.I. Pigment Red 3	407
C.I. Pigment Red 23	411
C.I. Solvent Yellow 14	226
trans-Cinnamaldehyde	514
Citral	505
Cobalt Sulfate Heptahydrate	471
Coconut Oil Acid Diethanolamine Condensate	479
Codeine	455
Comparative Initiation/Promotion Studies (Mouse Skin)	441
Corn Oil, Safflower Oil, and Tricaprylin	426
Coumarin	422
CS2	377
Cytembena	207
D&C Red No. 9	225
D&C Yellow No. 11	463
Decabromodiphenyl Oxide	309
Diallyl Phthalate (Mice)	242
Diallyl Phthalate (Rats)	284
4,4′-Diamino-2,2′-Stilbenedisulfonic Acid, Disodium Salt	412
2,4-Diaminophenol Dihydrochloride	401
1,2-Dibromo-3-Chloropropane	206
1,2-Dibromoethane	210
2,3-Dibromo-1-Propanol	400
1,2-Dichlorobenzene (*o*-Dichlorobenzene)	255
1,4-Dichlorobenzene (*p*-Dichlorobenzene)	319
p,p′-Dichlorodiphenyl sulfone	501
2,4-Dichlorophenol	353
2,6-Dichloro-*p*-Phenylenediamine	219
1,2-Dichloropropane	263
1,3-Dichloropropene (Telone II)	269
Dichlorvos	342
Dietary Restriction	460
Diethanolamine	478
Di(2-Ethylhexyl) Adipate	212
Di(2-Ethylhexyl) Phthalate	217
Diethyl Phthalate	429
Diglycidyl Resorcinol Ether	257
3,4-Dihydrocoumarin	423
1,2-Dihydro-2,2,4-Trimethylquinoline (Monomer)	456
Dimethoxane	354
3,3′-Dimethoxybenzidine Dihydrochloride	372
N,N-Dimethylaniline	360
3,3′-Dimethylbenzidine Dihydrochloride	390
Dimethyl Hydrogen Phosphite	287
Dimethyl Methylphosphonate	323
Dimethyl Morpholinophosphoramidate	298
Dimethylvinyl Chloride	316
Diphenhydramine Hydrochloride	355
5,5-Diphenylhydantoin	404
Dipropylene Glycol	511
Elmiron®	512
Emodin	493
Ephedrine Sulfate	307
Epinephrine Hydrochloride	380

Chemical	TR No.
1,2-Epoxybutane	329
Erythromycin Stearate	338
Ethyl Acrylate	259
Ethylbenzene	466
Ethylene Glycol	413
Ethylene Glycol Monobutyl Ether	484
Ethylene Oxide	326
Ethylene Thiourea	388
Eugenol	223
FD&C Yellow No. 6	208
Fumonisin B_1	496
Furan	402
Furfural	382
Furfuryl Alcohol	482
Furosemide	356
Gallium Arsenide	492
Geranyl Acetate	252
Glutaraldehyde	490
Glycidol	374
Guar Gum	229
Gum Arabic	227
HC Blue 1	271
HC Blue 2	293
HC Red 3	281
HC Yellow 4	419
Hexachlorocyclopentadiene	437
Hexachloroethane	361
2,4-Hexadienal	509
4-Hexylresorcinol	330
Hydrochlorothiazide	357
Hydroquinone	366
8-Hydroxyquinoline	276
Indium Phosphide	499
Iodinated Glycerol	340
Isobutene	487
Isobutyl Nitrite	448
Isobutyraldehyde	472
Isophorone	291
Isoprene	486
Lauric Acid Diethanolamine Condensate	480
d-Limonene	347
Locust Bean Gum	221
60-Hz Magnetic Fields	488
Magnetic Field Promotion	489
Malonaldehyde, Sodium Salt	331
Manganese Sulfate Monohydrate	428
D-Mannitol	236
Marine Diesel Fuel and JP-5 Navy Fuel	310
Melamine	245
2-Mercaptobenzothiazole	332
Mercuric Chloride	408
Methacrylonitrile	497
8-Methoxypsoralen	359
α-Methylbenzyl Alcohol	369
Methyl Bromide	385
Methyl Carbamate	328
Methyldopa Sesquihydrate	348
Methylene Chloride	306
4,4′-Methylenedianiline Dihydrochloride	248
Methyleugenol	491
Methyl Methacrylate	314
N-Methylolacrylamide	352
Methylphenidate Hydrochloride	439
Mirex	313
Molybdenum Trioxide	462
Monochloroacetic Acid	396
Monuron	266
Nalidixic Acid	368
Naphthalene (Mice)	410
Naphthalene (Rats)	500
Nickel (II) Oxide	451
Nickel Sulfate Hexahydrate	454
Nickel Subsulfide	453
p-Nitroaniline	418
o-Nitroanisole	416
p-Nitrobenzoic Acid	442
Nitrofurantoin	341
Nitrofurazone	337
Nitromethane	461
p-Nitrophenol	417
o-Nitrotoluene	504
p-Nitrotoluene	498
Ochratoxin A	358
Oleic Acid Diethanolamine Condensate	481
Oxazepam (Mice)	443
Oxazepam (Rats)	468
Oxymetholone	485
Oxytetracycline Hydrochloride	315
Ozone and Ozone/NNK	440
Penicillin VK	336
Pentachloroanisole	414
Pentachloroethane	232
Pentachloronitrobenzene	325
Pentachlorophenol, Purified	483
Pentachlorophenol, Technical Grade	349
Pentaerythritol Tetranitrate	365
Phenolphthalein	465
Phenylbutazone	367
Phenylephrine Hydrochloride	322
N-Phenyl-2-Naphthylamine	333
o-Phenylphenol	301
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Gavage)	244
Polybrominated Biphenyl Mixture (Firemaster FF-1) (Feed)	398
Polysorbate 80 (Glycol)	415
Polyvinyl Alcohol	474
Primidone	476
Probenecid	395
Promethazine Hydrochloride	425
Propylene	272
Propylene Glycol Mono-*t*-butyl Ether	515
1,2-Propylene Oxide	267
Propyl Gallate	240
Pyridine	470
Quercetin	409
Riddelliine	508
Resorcinol	403
Rhodamine 6G	364
Rotenone	320
Roxarsone	345
Salicylazosulfapyridine	457
Scopolamine Hydrobromide Trihydrate	445
Sodium Azide	389
Sodium Fluoride	393
Sodium Nitrite	495
Sodium Xylenesulfonate	464
Stannous Chloride	231
Stoddard Solvent IIC	519
Succinic Anhydride	373
Talc	421
Tara Gum	224
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Dermal)	201
2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (Gavage)	209
1,1,1,2-Tetrachloroethane	237
Tetrachloroethylene	311
Tetracycline Hydrochloride	344
Tetrafluoroethylene	450
1-Trans-Delta^9-Tetrahydrocannabinol	446
Tetrahydrofuran	475
Tetrakis(Hydroxymethyl)Phosphonium Sulfate	296
Tetrakis(Hydroxymethyl)Phosphonium Chloride	296
Tetranitromethane	386
Theophylline	473

Chemical	TR No.	Chemical	TR No.
4,4-Thiobis(6-*t*-Butyl-*m*-Cresol)	435	Tris(2-Ethylhexyl) Phosphate	274
Titanocene Dichloride	399	Turmeric Oleoresin (Curcumin)	427
Toluene	371	Urethane, Ethanol, and Urethane/Ethanol	510
2,4- & 2,6-Toluene Diisocyanate	251	Vanadium Pentoxide	507
Triamterene	420	4-Vinylcyclohexene	303
Tribromomethane	350	4-Vinyl-1-Cyclohexene Diepoxide	362
Trichloroethylene	243	Vinylidene Chloride	228
Trichloroethylene	273	Vinyl Toluene	375
1,2,3-Trichloropropane	384	Xylenes (Mixed)	327
Tricresyl Phosphate	433	2,6-Xylidine	278
Triethanolamine	449	Zearalenone	235
Triethanolamine	518	Ziram	238
Tris(2-Chloroethyl) Phosphate	391		