NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP Technical Report on the Toxicology and Carcinogenesis Studies of Methyl Isobutyl Ketone (CAS No. 108-10-1) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies)

NTP TR 538

FEBRUARY 2007

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF METHYL ISOBUTYL KETONE

(CAS NO. 108-10-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

February 2007

NTP TR 538

NIH Publication No 07-4476

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

FOREWORD

The National Toxicology Program (NTP) is an interagency program within the Public Health Service (PHS) of the Department of Health and Human Services (HHS) and is headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH). Three agencies contribute resources to the program: NIEHS/NIH, the National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC), and the National Center for Toxicological Research of the Food and Drug Administration (NCTR/FDA). Established in 1978, the NTP is charged with coordinating toxicological testing activities, strengthening the science base in toxicology, developing and validating improved testing methods, and providing information about potentially toxic substances to health regulatory and research agencies, scientific and medical communities, and the public.

The Technical Report series began in 1976 with carcinogenesis studies conducted by the National Cancer Institute. In 1981, this bioassay program was transferred to the NTP. The studies described in the Technical Report series are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected substances in laboratory animals (usually two species, rats and mice). Substances selected for NTP toxicity and carcinogenicity studies are chosen primarily on the basis of human exposure, level of production, and chemical structure. The interpretive conclusions presented in NTP Technical Reports are based only on the results of these NTP studies. Extrapolation of these results to other species, including characterization of hazards and risks to humans, requires analyses beyond the intent of these reports. Selection *per se* is not an indicator of a substance's carcinogenic potential.

The NTP conducts its studies in compliance with its laboratory health and safety guidelines and FDA Good Laboratory Practice Regulations and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use are in accordance with the Public Health Service Policy on Humane Care and Use of Animals. Studies are subjected to retrospective quality assurance audits before being presented for public review.

NTP Technical Reports are indexed in the NIH/NLM PubMed database and are available free of charge electronically on the NTP website (*http://ntp.niehs.nih.gov*) or in hardcopy upon request from the NTP Central Data Management group at *cdm@niehs.nih.gov* or (919) 541-3419.

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF METHYL ISOBUTYL KETONE

(CAS NO. 108-10-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

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

February 2007

NTP TR 538

NIH Publication No 07-4476

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

CONTRIBUTORS

National Toxicology Program

Evaluated and interpreted results and reported findings

F.A. Suarez, M.D., M.S., Study Scientist
R.A. Herbert, D.V.M., Ph.D., Study Pathologist
R.S. Chhabra, Ph.D.
D.W. Bristol, Ph.D.
J.R. Bucher, Ph.D.
G.E. Kissling, Ph.D.
D.E. Malarkey, D.V.M, Ph.D.
R.R. Maronpot, D.V.M.
S.D. Peddada, Ph.D.
J.H. Roycroft, Ph.D.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
K.L. Witt, M.S.

Battelle Northwest Operations

Conducted studies and evaluated pathology findings

J.A. Dill, Ph.D., Principal Investigator
S.L. Grumbein, D.V.M., Ph.D.
B.K. Hayden
R.A. Renne, D.V.M.

Experimental Pathology Laboratories, Inc.

Provided pathology review

M.H. Hamlin, II, D.V.M., Principal Investigator
A.E. Brix, D.V.M.
K.J. Cimon, D.V.M., M.S.
R.A. Miller, D.V.M., Ph.D.
J.C. Peckham, D.V.M., M.S., Ph.D.
J.C. Seely, D.V.M.

Dynamac Corporation

Prepared quality assurance audits

S. Brecher, Ph.D., Principal Investigator

NTP Pathology Working Group

Evaluated slides and prepared pathology report on rats (January 8, 2004)

M.A. Hanes, D.V.M., Chairperson
Integrated Laboratory Systems
K.J. Cimon, D.V.M., M.S.
Experimental Pathology Laboratories, Inc.
S.A. Elmore, D.V.M., Observer
National Toxicology Program
R.A. Herbert, D.V.M., Ph.D.
National Toxicology Program
G.D. Hill, D.V.M., Ph.D.
National Toxicology Program
Y.B. Kim, D.V.M., Ph.D., Observer
National Toxicology Program
J.F. Mann, D.V.M., M.S., Observer
Southern Research Institute
R.A. Miller, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
G. Pearse, B.V.M.&S.
National Toxicology Program
J.C. Peckham, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.
H. Satoh, D.V.M., Ph.D., Observer
National Toxicology Program
J.C. Seely, D.V.M.
Experimental Pathology Laboratories, Inc.

Evaluated slides and prepared pathology report on mice (November 6, 2003)

A.W. Suttie, B.V.Sc., Ph.D., Chairperson
Integrated Laboratory Systems
A.E. Brix, D.V.M., Ph.D.
Experimental Pathology Laboratories, Inc.
M.F. Cesta, D.V.M., Observer
National Toxicology Program
S.A Elmore, D.V.M., Observer
National Toxicology Program
R.A Herbert, D.V.M., Ph.D.
National Toxicology Program
G.D. Hill, D.V.M., Ph.D.
National Toxicology Program
K. Karli, D.V.M., Observer
National Toxicology Program
G. Pearse, B.V.M.&S.
National Toxicology Program
J.C Peckham, D.V.M., M.S., Ph.D.
Experimental Pathology Laboratories, Inc.

Constella Group, Inc.
Provided statistical analyses

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

Biotechnical Services, Inc.
Prepared Technical Report

S.R. Gunnels, M.A., Principal Investigator
L.M. Harper, B.S.
P.C. Rathman, B.S.E.
D.C. Serbus, Ph.D.

CONTENTS

SUMMARY

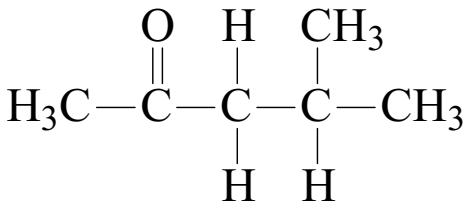
Background
Methyl isobutyl ketone has many industrial uses, including as a solvent for paints and lacquers and in dry cleaning. We studied methyl isobutyl ketone to determine if it caused cancer in rats or mice.

Methods
We exposed groups of 50 male and 50 female rats and mice to air containing concentrations of 450, 900, or 1,800 parts per million (ppm) of methyl isobutyl ketone 6 hours per day for 2 years. 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
Male rats and female mice exposed to 1,800 ppm methyl isobutyl ketone weighed less than controls, and the death rate of male rats exposed to 1,800 ppm was higher than in the controls. There were no differences in survival or body weights of any other groups exposed to methyl isobutyl ketone. Male rats exposed to methyl isobutyl ketone had tumors of the kidney, increased rates of hyperplasia of the kidney and adrenal gland, and mononuclear cell leukemia. Male and female mice exposed to methyl isobutyl ketone had increased rates of liver tumors.

Conclusions
We conclude that methyl isobutyl ketone caused cancer of the kidney in male rats and of the liver in male and female mice. Increases in mononuclear cell leukemia in male rats and mesenchymal tumors in the kidney of female rats may also have been related to exposure to methyl isobutyl ketone.

ABSTRACT



METHYL ISOBUTYL KETONE

CAS No. 108-10-1

Chemical Formula: $C_6H_{12}O$ Molecular Weight: 100.16

Synonyms: Hexanone, hexone, isobutylmethyl ketone, isopropyl-acetone, 4-methyl-2-oxopentane, 4-methyl pentan-2-one, 2-methyl-4-pentanone, 4-methyl-2-pentanone, 2-methyl propyl methyl ketone, MIBK, MIK

Methyl isobutyl ketone is used as a denaturant for rubbing alcohol; as a solvent for paints, varnishes, nitrocellulose, lacquers, and protective coatings; in industrial extraction processes; in dry-cleaning preparations; and in the synthesis of methyl isobutyl carbinol. Methyl isobutyl ketone was nominated for study by the National Cancer Institute and the United States Environmental Protection Agency because of its widespread use, the high potential for worker exposure due to its many industrial applications, and its high production volume. Male and female F344/N rats and B6C3F$_1$ mice were exposed to methyl isobutyl ketone (greater than 99% pure) by inhalation for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*.

2-Year Study in Rats

Groups of 50 males and 50 females were exposed to methyl isobutyl ketone at concentrations of 0, 450, 900, or 1,800 ppm by inhalation, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 104 weeks. Survival of males exposed to 1,800 ppm was significantly less than that of the chamber controls. The mean body weights of the 900 and 1,800 ppm males were less than those of the chamber controls after weeks 97 and 89, respectively.

In the standard evaluation of the kidney, there were slightly increased incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in males exposed to 900 or 1,800 ppm, and renal tubule carcinoma in males exposed to 1,800 ppm. The incidences of renal tubule hyperplasia were also significantly increased in the 450 and 1,800 ppm males, and the severities were greater than in the chamber controls. Chronic nephropathy occurred in all males exposed to 1,800 ppm and in 70% to 88% of exposed females, and the severity was increased in 1,800 ppm males. The incidences of transitional epithelial hyperplasia of the renal pelvis in males exposed to 900 or 1,800 ppm and mineralization of the renal papilla in all groups of exposed males were significantly increased. In addition, two female rats exposed to 1,800 ppm had renal mesenchymal tumors. In the extended evaluation of the kidney, renal tubule adenomas and renal tubule hyperplasia occurred in all groups of exposed male rats. In the combined single and step section analysis, the incidences of renal tubule adenoma and renal tubule adenoma or

carcinoma (combined) were significantly increased in males exposed to 1,800 ppm. The incidences of renal tubule hyperplasia were also significantly increased in all exposed groups of males.

There was a positive trend in the incidences of mononuclear cell leukemia in males, and the incidence in the 1,800 ppm group was significantly increased. The incidence of adrenal medulla hyperplasia in the 1,800 ppm males was significantly increased.

2-Year Study in Mice

Groups of 50 males and 50 females were exposed to methyl isobutyl ketone at concentrations of 0, 450, 900, or 1,800 ppm by inhalation, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 105 weeks. Survival of males and females was similar to that of the chamber controls. The mean body weights of females exposed to 1,800 ppm were less than those of the chamber controls after week 17.

The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were significantly increased in males and females exposed to 1,800 ppm. The incidences of eosinophilic foci were significantly increased in 450 and 1,800 ppm females.

Genetic Toxicology

Methyl isobutyl ketone was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535 when tested with and without hamster or rat liver metabolic activation enzymes.

Conclusions

Under the conditions of these 2-year studies, there was *some evidence of carcinogenic activity** of methyl isobutyl ketone in male F344/N rats based on increased incidences of renal tubule neoplasms. Increased incidences of mononuclear cell leukemia in 1,800 ppm male F344/N rats may have been related to methyl isobutyl ketone exposure. There was *equivocal evidence of carcinogenic activity* of methyl isobutyl ketone in female F344/N rats based on the occurrence of renal mesenchymal tumors in the 1,800 ppm group. There was *some evidence of carcinogenic activity* of methyl isobutyl ketone in male and female $B6C3F_1$ mice based on increased incidences of liver neoplasms.

Exposure to methyl isobutyl ketone resulted in nonneoplastic lesions of the kidney characteristic of α2u-globulin accumulation in male rats and nephropathy in female rats.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Methyl Isobutyl Ketone

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations in air	Chamber control, 450, 900, or 1,800 ppm	Chamber control, 450, 900, or 1,800 ppm	Chamber control, 450, 900, or 1,800 ppm	Chamber control, 450, 900, or 1,800 ppm
Body weights	900 and 1,800 ppm groups less than the chamber controls	Exposed groups similar to the chamber controls	Exposed groups similar to the chamber controls	1,800 ppm group less than the chamber controls
Survival rates	32/50, 28/50, 25/50, 19/50	35/50, 34/50, 26/50, 32/50	40/50, 42/50, 35/50, 37/50	35/50, 37/50, 39/50, 38/50
Nonneoplastic effects	Kidney: renal tubule hyperplasia (standard evaluation - 1/50, 11/50, 3/50, 18/50; standard and extended evaluation combined - 1/50, 14/50, 7/50, 21/50); nephropathy (42/50, 45/50, 47/50, 50/50); severity (2.0, 2.6, 2.4, 3.1); pelvis transitional epithelium hyperplasia (1/50, 5/50, 6/50, 19/50); papilla mineralization (1/50, 6/50, 22/50, 29/50) Adrenal Gland: adrenal medulla hyperplasia (13/50, 18/48, 18/50, 24/50)	Kidney: nephropathy (19/50, 35/50, 38/50, 44/50)	None	None
Neoplastic effects	Kidney: renal tubule adenoma (standard evaluation - 0/50, 0/50, 2/50, 3/50; standard and extended evaluation combined - 2/50, 3/50, 3/50, 10/50); renal tubule carcinoma (standard evaluation - 0/50, 1/50, 0/50, 2/50); renal tubule adenoma or carcinoma (combined) (standard evaluation - 0/50, 1/50, 2/50, 4/50; standard and extended evaluation - 2/50, 4/50, 3/50, 11/50);	None	Liver: hepatocellular adenoma (17/50, 25/50, 23/50, 34/50); hepatocellular adenoma or carcinoma (27/50, 34/50, 28/50, 37/50)	Liver: hepatocellular adenoma (13/50, 15/50, 20/50, 23/50); hepatocellular adenoma or carcinoma (17/50, 17/50, 22/50, 27/50)
Equivocal findings	Mononuclear cell leukemia: (25/50, 26/50, 32/50, 35/50)	Kidney: mesenchymal tumor malignant (0/50, 0/50, 0/50, 2/50)	None	None
Level of evidence of carcinogenic activity	Some evidence	Equivocal evidence	Some evidence	Some evidence
Genetic toxicology *Salmonella typhimurium* gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535 with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

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

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

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

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 methyl isobutyl ketone on September 27, 2005, 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.

Charlene A. McQueen, Ph.D., Chairperson
College of Pharmacy
University of Arizona
Tucson, AZ

Diane F. Birt, Ph.D.
Department of Food Science & Human Nutrition
Iowa State University
Ames, IA

Michael R. Elwell, D.V.M., Ph.D., Principal Reviewer
Pathology, Drug Safety Evaluation
Pfizer Global Research and Development
Groton, CT

Thomas A. Gasiewicz, Ph.D.
Department of Environmental Medicine
Environmental Health Sciences Center
University of Rochester School of Medicine
Rochester, NY

John P. Giesy, Jr., Ph.D., Principal Reviewer
Department of Zoology
Michigan State University
East Lansing, MI

Shuk-Mei Ho, Ph.D.*
Department of Surgery, Division of Urology
University of Massachusetts Medical School
Worcester, MA

Stephen M. Roberts, Ph.D.
Center for Environmental & Human Toxicology
University of Florida
Gainesville, FL

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

Special Ad Hoc Reviewers

Kenny Crump, Ph.D.
Environ International
Ruston, LA

Prescott Deininger, Ph.D.*
Tulane University Medical Center
New Orleans, LA

Harish Sikka, Ph.D.
Environmental Toxicology and Chemistry Laboratory
State University of New York College at Buffalo
Buffalo, NY

Keith Soper, Ph.D.
Merck Research Laboratories
Westpoint, PA

Vernon Walker, Ph.D.*
Lovelace Respiratory Institute
Albuquerque, NM

---

* Did not attend

SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On September 27, 2005, the draft Technical Report on the toxicology and carcinogenicity studies of methyl isobutyl ketone 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. F.A. Suarez, NIEHS, introduced the toxicology and carcinogenesis studies of methyl isobutyl ketone by describing its uses, reviewing the literature that served as the basis for dose selection, and presenting the study design and results. The proposed conclusions were *some evidence of carcinogenic activity* of methyl isobutyl ketone in male F344/N rats, *equivocal evidence of carcinogenic activity* of methyl isobutyl ketone in female F344/N rats, and *some evidence of carcinogenic activity* of methyl isobutyl ketone in male and female $B6C3F_1$ mice.

Dr. Elwell, the first principal reviewer, had no scientific criticisms. He noted that this was the first study in which a conclusion was based on mesenchymal tumors.

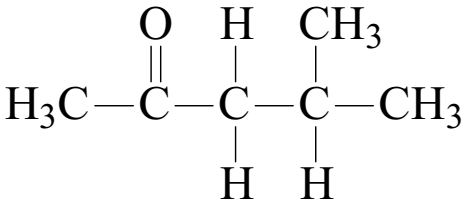
Dr. Giesy, the second principal reviewer, also agreed with the proposed conclusions and asked if the doses may have been too high.

Dr. Suarez noted that while the dose selection was based on literature values, other studies performed elsewhere had used similar doses, and the present doses seemed appropriate.

Dr. Ralph Gingell, speaking on behalf of the American Chemistry Council ketone panel, said their group felt the studies were well performed and the conclusions were appropriate. They suggested that qualifying statements about mode of action be added to the discussion.

Dr. Elwell moved that the conclusions be accepted as written. Dr. Giesy seconded the motion. The motion was passed unanimously with six votes.

INTRODUCTION



METHYL ISOBUTYL KETONE

CAS No. 108-10-1

Chemical Formula: $C_6H_{12}O$ Molecular Weight: 100.16

Synonyms: Hexanone, hexone, isobutylmethyl ketone, isopropyl-acetone, 4-methyl-2-oxopentane, 4-methyl pentan-2-one, 2-methyl-4-pentanone, 4-methyl-2-pentanone, 2-methyl propyl methyl ketone, MIBK, MIK

Chemical and Physical Properties

Methyl isobutyl ketone is a colorless, flammable liquid that is slightly soluble in water (17 g/L at 20° C) but readily soluble in acetone and ethanol. Methyl isobutyl ketone has a sweet camphor odor, with an odor threshold of 0.10 ppm and a vapor pressure of 15 mmHg at 20° C (Ruth, 1986). Technical grade methyl isobutyl ketone is about 99% pure (Johnson, 2004). Reported impurities include dimethyl heptane (<0.3%), water (<0.1%), and methyl isobutyl carbinol (<0.03%) (IPCS, 1990). Methyl isobutyl ketone is currently classified as a volatile organic compound and listed as a hazardous air pollutant.

Production, Use and Human Exposure

More than 60% of methyl isobutyl ketone production comes from aldol condensation of acetone and derivative intermediates diacetone alcohol and mesityl oxide (CMR, 2004). Acetone is treated with barium hydroxide to yield diacetone alcohol; this is dehydrated to mesityl oxide, which can be hydrogenated to saturate the double bond and produce methyl isobutyl ketone (ILO, 1971). Another method is by hydrogenation of mesityl oxide over nickel at 160° to 190° C (Furia and Bellanca, 1975). Furthermore, methyl isobutyl ketone is prepared by reacting sodium acetoacetic ester with isopropyl bromide and treating the resulting 2-isopropyl acetoacetic ester with dilute acid to saponify the ester and decarboxylate the resulting keto acid (Osol *et al*., 1980). In 1995 and 1996, the United States alone produced 80,000 metric tons of methyl isobutyl ketone (CMA, 1997), and the projected demand for the chemical in the year 2006 has been calculated at 147 million pounds (CMR, 2004).

The major uses of methyl isobutyl ketone are as a denaturant for rubbing alcohol; a solvent for paints, varnishes, nitrocellulose, and lacquers; and the manufacture of methyl amyl alcohol. Methyl isobutyl ketone is also used in industrial extraction processes, including extraction of uranium from fission products. In addition, methyl isobutyl ketone is used as a solvent for protective coatings and in rare metals extraction and in dewaxing of mineral oils. Methyl isobutyl ketone is also used in drycleaning preparations and in the synthesis of methyl isobutyl carbinol. Methyl isobutyl ketone is also frequently used in combination with other solvents, such as toluene (IPCS, 1990).

The most probable routes of exposure to methyl isobutyl ketone by the general population are ingestion of contaminated drinking water and dermal contact with consumer products that contain the chemical, which is used as a denaturant and solvent in nail products (Johnson, 2004). Additionally, methyl isobutyl ketone is a permitted flavoring agent with generally recognized as safe status in the United States and is used in food-contact packaging materials. It can be found in a wide range of fruit, baked potatoes, cheese, milk, some meats, and some alcoholic beverages. The intake via food flavorings based on a 1970 survey of usage in the United States was estimated to be 3.35 mg/person per day (NTIS, 1985). Methyl isobutyl ketone has also been detected in human breast milk (Pellizzari *et al.*, 1982).

The most likely exposures in the work place are by inhalation of the vapors and by skin and eye contact. Based on a National Institute for Occupational Safety and Health (1990) survey conducted from 1981 to 1983, the number of workers potentially exposed to methyl isobutyl ketone was estimated as 48,000. Exposure to methyl isobutyl ketone during spray painting was found to be 0.6 ppm time-weighted average (TWA) (Whitehead *et al*., 1984). In addition, methyl isobutyl ketone has been identified as a volatile degradation product of polypropylene at temperatures of 220° to 280° C (Frostling *et al*., 1984). Occupational exposure limits range from 100 to 410 mg/m^3 TWA and 5 to 300 mg/m^3 ceiling value in different countries (IPCS, 1990). The TWA and short-term exposure limit values recommended by the American Conference of Governmental Industrial Hygienists (2005) are 205 mg/m^3 (50 ppm) and 307 mg/m^3 (75 ppm), respectively.

Methyl isobutyl ketone may be released into the environment in effluent and emissions from its manufacture and use, in exhaust gas from vehicles (Hampton *et al.*, 1982), and from land disposal of waste that contains this compound (Verschueren, 1983). Methyl isobutyl ketone release into the atmosphere may occur during its production through fugitive emissions and incomplete removal of vapors from reaction gases before they are vented or disposed of in a scrubber. In addition, methyl isobutyl ketone has been identified frequently in leakages from landfills and could potentially contaminate groundwater (Francis *et al.*, 1980; Sawhney and Kozloski, 1984; Garman *et al.*, 1987; Brown and Donnelly, 1988). Another source of environmental contamination is the release of methyl isobutyl ketone during the discharge of spent scrubbing water from industrial production processes. Traces of methyl isobutyl ketone have also been detected in tap water in the United States (CEC, 1976).

Biodegradation, photolysis, and volatilization are possible mechanisms by which methyl isobutyl ketone may be removed from aqueous systems (Lande *et al.*, 1976). However, the overall rate of removal could not be located in the literature. Based on its relatively high water solubility and low soil absorption coefficient, methyl isobutyl ketone is predicted to be highly mobile in soil (Swann *et al.*, 1983).

Absorption, Distibution, Metabolism and Excretion

Experimental Animals

Methyl isobutyl ketone is readily absorbed into the bloodstream after inhalation exposure and is likely to be widely distributed in the body (Duguay and Plaa, 1995). Methyl isobutyl ketone may also be absorbed through the skin (Hjelm *et al.*, 1991), and in the gastrointestinal tract. A study of the relationship between blood and lung concentrations of methyl isobutyl ketone after oral or inhalation exposure indicated that exposure to atmospheric concentrations of 200, 400, or 600 ppm of methyl isobutyl ketone for 4 hours resulted in absorption of the same amount of methyl isobutyl ketone as from the oral administrations of 1.5, 3.0, or 6 mmol/kg, respectively, in male Sprague-Dawley rats (Duguay and Plaa, 1995).

Methyl isobutyl ketone is metabolized by reduction of the carbonyl group to a secondary alcohol, 4-methyl-2-pentanol and by oxidation at the ω-1 carbon atom to form a hydroxylated ketone, 4-hydroxymethyl isobutyl ketone, also known as diacetone alcohol (DiVincenzo *et al.*, 1976). The authors suggest that 4-methyl-2-pentanol may be conjugated further with sulfuric and glucuronic acid, or it may enter the intermediary metabolism to be eliminated as carbon dioxide or incorporated into tissues.

Male Sprague-Dawley rats exposed to methyl isobutyl ketone vapor at concentrations of 200, 400, or 600 ppm, 4 hours/day for 3 days exhibited plasma methyl isobutyl ketone concentrations of 5, 8.1, and 14.3 µg/mL, respectively (Duguay and Plaa, 1995). The major metabolite detected in plasma was 4-hydroxymethyl isobutyl ketone (diacetone alcohol) basically at the same concentration as methyl isobutyl ketone. 4-Methyl-2-pentanol was detected in plasma at about two thirds of the concentration of 4-hydroxymethyl isobutyl ketone. Both metabolites were detected in the liver at comparable concentrations as methyl isobutyl ketone. In the lung, 4-methyl-2-pentanol was the major metabolite (about twice as much as 4-hydroxymethyl isobutyl ketone) and

at similar concentrations as methyl isobutyl ketone. In another study, methyl isobutyl ketone was injected in the peritoneum of male CD-1 mice and the metabolites 4-methyl-2-pentanol and 4-hydroxymethyl isobutyl ketone were detected in blood and brain (Granvil *et al.*, 1994).

Humans

The inhalation kinetics of methyl isobutyl ketone have been studied in humans. Exposure of eight male volunteers by inhalation to concentrations of 10, 100, or 200 mg/m^3 methyl isobutyl ketone for 2 hours resulted in a pulmonary retention of about 60% (Hjelm *et al.*, 1990). The average apparent blood clearance was 1.6 L/hr per kilogram at all exposure concentrations. After exposure, two elimination phases were distinguished in blood. The calculated half time was about 12 minutes for the faster elimination phase (0 to 30 minutes postexposure) and 60 to 70 minutes for the slower elimination phase (60 to 180 minutes postexposure). About 0.04% of the total dose of methyl isobutyl ketone was excreted unchanged in the urine within 3 hours postexposure.

TOXICITY

Experimental Animals

The oral LD_{50} of methyl isobutyl ketone in rats has been reported to range from 2,080 to 4,600 mg/kg, whereas the LD_{50} in mice ranged from 1,900 to 2,850 mg/kg. The LD_{50} in mice after intraperitoneal administration was 590 mg/kg. The LD_{50} by inhalation was 8 to 16 g/m^3 in rats after 4 hours of exposure, 21 g/m^3 in mice after 2 hours of exposure, and 74 g/m^3 in mice after 45 minutes of exposure (IPCS, 1990).

Inhalation exposure of rats to methyl isobutyl ketone at a concentration of 100 ppm for 2 weeks increased kidney weight. An increase in both liver and kidney weights was also observed after exposing animals to 200 ppm methyl isobutyl ketone for 2 weeks or to 100 ppm for 90 days (MacEwen *et al.*, 1971; Vernot *et al.*, 1971). Exposure of male Swiss OF1 mice to methyl isobutyl ketone for 5 minutes resulted in a decreased respiratory rate. The concentration at which a 50% decrease in respiratory rate (RD_{50}) occurred was calculated to be 3,200 ppm methyl isobutyl ketone (De Ceaurriz *et al.*, 1981).

Twelve-week-old male and female F344 rats and B6C3F$_1$ mice were exposed by inhalation to 100, 500, and 2,000 ppm methyl isobutyl ketone, 6 hours/day for a total of 9 days (5 days with 2 days off followed by 4 more consecutive days) (Dodd *et al.*, 1982). Lacrimation was observed in the 2,000 ppm group, but no ophthalmological lesions or changes in body weight were found. The relative liver weight was increased in male and female rats and female mice exposed to 2,000 ppm. In addition, the liver weight of male rats exposed to 500 ppm was also increased. Male and female rats and female mice exposed to 2,000 ppm had increased absolute and relative kidney weights. Hyaline droplets were found in the kidney of male rats exposed to 500 or 2,000 ppm methyl isobutyl ketone. Epithelial regeneration of the proximal convoluted tubes was also seen in male rats exposed to 2,000 ppm (Dodd *et al.*, 1982). Phillips *et al.* (1987) conducted a 2-week inhalation study in groups of six male and female F344 rats and B6C3F$_1$ mice, in which exposure to 2,000 ppm methyl isobutyl ketone resulted in mitotic figures (qualitative assessment) in the liver of one female and two male rats. Furthermore, one female mouse exposed to 2,000 ppm developed increased hepatic mitosis and four female mice exhibited hepatic glycogen depletion.

Twelve-week-old male and female F344 rats and B6C3F$_1$ mice were exposed to 50, 250, or 1,000 ppm methyl isobutyl ketone by inhalation for 14 weeks (Phillips *et al.*, 1987). Male rats exposed to 50 or 1,000 ppm methyl isobutyl ketone had increased liver weights. Female rats exposed to 250 ppm had increased kidney weights. In male mice, increased absolute liver weights occurred in the 250 and 1,000 ppm groups. Serum cholesterol levels were increased in male rats exposed to 250 or 1,000 ppm methyl isobutyl ketone. Urinary glucose excretion was increased in male rats exposed to 250 ppm and in male and female rats exposed to 1,000 ppm. Total protein excretion was enhanced in male rats exposed to 1,000 ppm. Histopathological changes revealed an increase in the incidences and extent of hyaline droplets in the kidneys of male rats exposed to 250 or 1,000 ppm methyl isobutyl ketone. Results from a 14-week inhalation study performed by Bushy Run Research Center (1983) revealed that, in addition to the effects reported by Phillips *et al.* (1987), water consumption and urine volume were increased in male rats exposed to 1,000 ppm methyl isobutyl ketone.

The neurotoxic potential of methyl isobutyl ketone has been studied in several animal models (Johnson, 2004). In a prechronic inhalation study, David *et al.* (1999) studied the potential of methyl isobutyl ketone to alter

behavior as an indicator of neurotoxicity. Sprague-Dawley rats were exposed by inhalation to concentrations of 250, 750, or 1,500 ppm methyl isobutyl ketone for 13 weeks. Microscopic analysis was not performed on exposed animals, and macroscopic examination did not reveal treatment-related changes. The authors concluded that repetitive exposures to methyl isobutyl ketone did not have any effect on the operant behavior of the rat. More recently, Nemec *et al*. (2004) observed a transitory decreased response to a novel sound stimulus (single loud noise) in adult rats exposed to 1,000 or 2,000 ppm methyl isobutyl ketone, and clinical signs of central nervous system depression in their pups during a two-generation reproductive toxicity study.

A single application of methyl isobutyl ketone to the skin of rabbits produced transient erythema, but repeated applications of 10 mL for 7 days resulted in dying and flaking of the skin (Krasavage *et al.*, 1982). Exposure of rats to dermal applications of methyl isobutyl ketone at 300 to 600 mg/kg for 4 months resulted in morphological changes in the skin, brain, liver, adrenal gland, spleen, and testis (Malysheva, 1988).

Application of undiluted methyl isobutyl ketone in the rabbit eye produced some irritation within 10 minutes of instillation. Inflammation and conjunctival swelling occurred within 8 hours and were still present after 24 hours, but disappeared after 60 hours (Krasavage *et al.*, 1982). Methyl isobutyl ketone has been studied using the Draize procedure, and results indicate that the chemical is mildly irritating and recovery occurs in about 4 days (Topping *et al.*, 2001).

Methyl isobutyl ketone has been shown to synergize the effects of some hepatotoxicants and to potentiate chemically induced cholestasis in rats (Raymond and Plaa, 1995a). Methyl isobutyl ketone increases chloroform-induced hepatotoxicity in male Sprague-Dawley rats (Vezina *et al.*, 1990), an effect in which methyl isobutyl ketone-induced cytochrome P450 enzymes are suggested to play a role (Raymond and Plaa, 1995b). This effect is not only seen with methyl isobutyl ketone itself, but also with its metabolites 4-methyl-2-pentanol and 4-hydroxymethyl isobutyl ketone. In addition, chloroform-induced nephrotoxicity in male Sprague-Dawley rats is increased (Vezina *et al.*, 1990).

Methyl isobutyl ketone and its metabolites have been shown to potentiate the intrahepatic cholestasis induced by taurolithocholic acid, a combination of manganese and bilirubin, and manganese alone (Plaa and Ayote, 1985; Vezina and Plaa, 1988). Furthermore, methyl isobutyl ketone strongly synergizes the *n*-hexane-induced neurotoxicity in hens by inducing its activation to 2,5-hexanedione (Abou-Donia *et al.*, 1985). The mechanistic explanation for the synergistic effect can be found in the induction of specific cytochrome P450 isozymes by methyl isobutyl ketone, leading to the metabolic activation of *n*-hexane to the potent neurotoxicant 2,5-hexanedione (Lapadula *et al.*, 1991). In addition, methyl isobutyl ketone synergizes the hexachlorobenzene-induced porphyrinogenic response seen in female Sprague-Dawley rats when administered after hexachlorobenzene. However, the simultaneous administration of methyl isobutyl ketone and hexachlorobenzene reduced the hexachlorobenzene-induced hepatic porphyrin accumulation. Again, involvement of the cytochrome P450 system is postulated in this dual effect (Krishnan *et al.*, 1992).

Humans

Epidemiology data available to evaluate the toxicity of methyl isobutyl ketone are scarce. The most commonly reported effect of exposure to solvent vapor mixtures that include methyl isobutyl ketone is decreased performance in behavioral tests. However, concentration values for individual solvents in these studies are not available, making it difficult to determine the contribution of methyl isobutyl ketone to the toxic effect. On the other hand, no decreases in task performance were observed in three of four inhalation studies of methyl isobutyl ketone in human volunteers (Hjelm *et al*., 1990; Dick *et al*., 1992; Iregren *et al*., 1993). Exposure-related effects after short-term inhalation exposure to methyl isobutyl ketone included headache, nausea, and tearing (Dick *et al.*, 1992). Although the treatment affected the results of a psychomotor test (visual vigilance) in females exposed to 100 ppm for 4 hours, no other effects were found in other tests including a sensoriomotor test and a test of mood, both in males and females (Dick *et al*., 1992).

Olfactory adaptation was observed in two men and two women after inhalation exposure to 20 and 40 ppm methyl isobutyl ketone (Gagnon *et al.*, 1994). This finding could mean that people exposed to methyl isobutyl ketone may suffer temporary loss of smell, which hinders odor detection. In a study to determine the effect of methyl isobutyl ketone in central nervous system function, Iregren *et al.* (1993) reported that 2-hour inhalation exposure produced increased discomfort in the subjects

at exposure levels of 10 and 200 mg/m^3 (about 2.5 and 50 ppm), as measured by symptom ratings. However, no effects were reported on heart rate or on the performance of a reaction time task and an arithmetic test.

Reproductive and Developmental Toxicity

Experimental Animals

Pregnant F344 rats and CD-1 mice were exposed to methyl isobutyl ketone by inhalation on gestational days 6 through 15 at concentrations of 300, 1,000 and 3,000 ppm (Tyl *et al*., 1987). The highest exposure level resulted in maternal toxicity determined by clinical observations, decreases in body weight and body weight gain, increased relative kidney weight, and decreased food consumption. Fetal toxicity was documented by reduced fetal body weight per litter and reductions in skeletal ossification. Pregnant mice exposed to 3,000 ppm also developed maternal toxicity characterized by increases in absolute and relative liver weights. Fetal toxicity in mice was documented by increased fetal mortality, reduced fetal body weight per litter, and reductions in skeletal ossification. There was no evidence of treatment-related maternal, embryo, or fetal toxicity (including malformation) at 300 or 1,000 ppm in either species, and teratogenicity was not observed at any exposure level.

To characterize the effects of methyl isobutyl ketone in reproductive performance, male and female Sprague-Dawley rats were exposed via whole-body inhalation to concentrations of 0, 500, 1,000, or 2,000 ppm, 6 hours/day, 7 days per week for 70 days prior to mating (Nemec *et al*., 2004). Subsequently, F_0 and F_1 females were exposed from mating through gestation day 20 and from postnatal day 5. F_2 litters were maintained through postnatal day 21. Results from this study did not reveal any effects of methyl isobutyl ketone in reproductive parameters or sexual maturation of pups.

Humans

There are no reports in the literature on the reproductive and developmental effects of methyl isobutyl ketone in humans.

Carcinogenicity

Experimental Animals

There are no published reports that study the carcinogenic potential of methyl isobutyl ketone in animal models. Phillips *et al*. (1987) reported the presence of mitotic figures in the livers of two of six male and one of six female Fischer 344 rats and increased hepatic mitosis in one of six female B6C3F$_1$ mice after 2 weeks of inhalation exposure to 2,000 ppm methyl isobutyl ketone.

Humans

No epidemiology studies of methyl isobutyl ketone were found in a review of the literature.

Genetic Toxicity

Methyl isobutyl ketone was tested for genotoxicity in the *Salmonella* mutagenicity assay, L5178Y/TK$^{+/-}$ mouse lymphoma assay, BALB/3T3 cell transformation assay, unscheduled DNA synthesis assay, and *in vivo* mouse bone marrow micronucleus assay (O'Donoghue *et al*., 1988; Zeiger *et al*., 1992). Based on the observation of a marginal response only at the highest, cytotoxic concentration tested in the L5178Y/TK$^{+/-}$ mouse lymphoma assay, the lack of reproducibility of response in the BALB/3T3 cell transformation assay, and clearly negative results in the *Salmonella* mutagenicity assay, the unscheduled DNA synthesis assay, and the micronucleus assay, methyl isobutyl ketone is not considered to be genotoxic.

Study Rationale

The National Cancer Institute and the United States Environmental Protection Agency nominated methyl isobutyl ketone for study because of its widespread use, its high potential for worker exposure due to its many industrial applications, and its high production volume. Because contact with methyl isobutyl ketone most commonly occurs in occupational settings by inhalation, this route was chosen to mimic the principal means of human exposure. Exposure concentrations were selected based on results from prechronic studies in the literature (Bushy Run Research Center, 1983; Phillips *et al*., 1987).

MATERIALS AND METHODS

Procurement and Characterization of Methyl Isobutyl Ketone

Methyl isobutyl ketone was obtained from ChemCentral (Kent, WA) in one lot (81KL119800085). Identity and purity analyses were conducted by the analytical chemistry laboratory at Chemir/Polytech Laboratories, Inc. (Maryland Heights, MO). Purity analyses were also conducted by the study laboratory (Battelle Northwest Operations, Richland, WA). Elemental analyses were performed by Galbraith Laboratories, Inc. (Knoxville, TN).

The chemical, a colorless liquid, was identified as methyl isobutyl ketone by infrared and proton nuclear magnetic resonance spectroscopy. The purity of the lot was determined by elemental analysis and gas chromatography. Elemental analysis for carbon, hydrogen, and oxygen was in agreement with the theoretical values for methyl isobutyl ketone. Gas chromatography indicated one major peak and three impurities; the total area of the impurities did not exceed 0.44% of the total major peak area. The overall purity was determined to be greater than 99%.

The bulk chemical was stored at room temperature, in 55-gallon metal drums. Stability and purity was monitored using gas chromatography. No degradation of the bulk chemical was detected.

Vapor Generation and Exposure System

Methyl isobutyl ketone was pumped onto the heated surface of the generator where it was vaporized. For the 1,800 ppm chambers, glass fiber filter material was wrapped around the generator cylinder to disperse more of the chemical over a larger area of the generator's surface.

Precision metering pumps controlled flow to each chamber. Exposure valves in the chambers automatically opened and allowed the vapor to flow through individual temperature-controlled delivery lines to each exposure chamber. The vapor was then injected into the chamber inlet duct where it was mixed and 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 condensation particle counter (Model 3022A, TSI Incorporated, St. Paul, MN) was used with and without animals in the exposure chambers to ensure that methyl isobutyl ketone vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

Vapor Concentration Monitoring

The methyl isobutyl ketone concentrations in the exposure chambers were monitored by an on-line gas chromatograph. Samples were drawn from each exposure chamber approximately every 28 minutes using a 16-port stream-select valve. The on-line gas chromatograph was checked throughout the day for instrument drift against an on-line standard of methyl isobutyl ketone in nitrogen supplied by a standard generator. The on-line gas chromatograph was calibrated monthly by a comparison of chamber concentration data to data from grab samples, which were collected with charcoal sampling tubes, extracted with hexanes containing nonane as an internal standard, and analyzed by an off-line gas chromatograph. The off-line gas chromatograph was calibrated with gravimetrically prepared standards of methyl isobutyl ketone containing nonane as an internal standard in hexanes.

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 the studies.

Evaluations of chamber uniformity and persistence and monitoring for methyl isobutyl ketone degradation impurities were conducted periodically throughout the studies by gas chromatography. Chamber uniformity was maintained; no degradation was detected.

2-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats and mice were exposed to methyl isobutyl ketone at concentrations of 0, 450, 900, or 1,800 ppm, 6 hours plus T_{90} (12 minutes) per day, 5 days per week for 104 (rats) or 105 (mice) weeks. These exposure concentrations were selected based on findings from pre-chronic studies reported in the literature (Phillips *et al*., 1987).

Source and Specification of Animals

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Taconic Laboratory Animals and Services (Germantown, NY) for use in the 2-year studies. Rats were quarantined for 14 days and mice were quarantined for 11 days before the beginning of the studies. 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 H).

Animal Maintenance

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

Clinical Examinations and Pathology

All animals were observed twice daily. Body weights were recorded initially and clinical findings and body weights were recorded weekly for the first 13 weeks, monthly through week 89 for rats and week 93 for mice, every 2 weeks thereafter, and at the end of the studies.

Complete necropsies and microscopic examinations were performed on all 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. For extended evaluation of renal proliferative lesions, kidneys of male rats were step sectioned at 1 mm intervals, and 3 to 4 additional sections were obtained 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 kidney, liver, and spleen in male and female rats, the adrenal medulla in male rats, and the liver in male and female 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 2-Year Inhalation Studies of Methyl Isobutyl Ketone

Study Laboratory
Battelle Northwest Operations (Richland, WA)

Strain and Species
F344/N rats
$B6C3F_1$ mice

Animal Source
Taconic Laboratory Animals and Services (Germantown, NY)

Time Held Before Studies
Rats: 14 days
Mice: 11 days

Average Age When Studies Began
6 weeks

Date of First Exposure
Rats: May 25, 2000
Mice: June 5, 2000

Duration of Exposure
6 hours plus T_{90} (12 minutes) per day, 5 days per week, for 104 weeks (rats) or 105 weeks (mice)

Date of Last Exposure
Rats: May 22, 2002
Mice: June 6, 2002

Necropsy Dates
Rats: May 20-23, 2002
Mice: June 3-7, 2002

Average Age at Necropsy
110 weeks

Size of Study Groups
50 males and 50 females

Method of Distribution
Animals were distributed randomly into groups of approximately equal initial mean body weights.

Animals per Cage
1

Method of Animal Identification
Tail tattoo

Diet
NTP-2000 irradiated wafers (Zeigler Brothers, Inc., Gardners, PA), available *ad libitum*, except during exposure periods, changed weekly

Water
Tap water (Richland municipal supply), via automatic watering system (Edstrom Industries, Waterford, WI), available *ad libitum*

TABLE 1
Experimental Design and Materials and Methods in the 2-Year Inhalation Studies of Methyl Isobutyl Ketone

Cages
Stainless steel wire-bottom (Lab Products, Inc., Seaford, DE), changed and rotated weekly

Chamber Air Supply Filters
Single HEPA, changed annually; charcoal (RSE, Inc., New Baltimore, MI); and Purafil (Environmental Systems, Lynnwood, WA) not changed

Chambers
Stainless steel (Lab Products, Inc., Harford Systems Division, Aberdeen, MD), changed weekly

Chamber Environment
Temperature: 75° ± 3° F
Relative humidity: 55% ± 15%
Room fluorescent light: 12 hours/day
Chamber air changes: 15 ± 2/hour

Exposure Concentrations
0, 450, 900, or 1,800 ppm

Type and Frequency of Observation
Observed twice daily; animals were weighed initially, weekly for the first 13 weeks, monthly through week 89 (rats) or week 93 (mice), every 2 weeks thereafter, and at the end of the studies; clinical findings were recorded weekly for the first 13 weeks, monthly through week 89 (rats) or week 93 (mice), every 2 weeks thereafter, and at the end of the studies

Method of Sacrifice
70% carbon dioxide

Necropsy
Necropsies were performed on all animals.

Histopathology
Complete histopathology was performed on all 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, gallbladder (mice), harderian gland, heart and aorta, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung and bronchi, lymph nodes (mandibular, mesenteric, bronchial, mediastinal), mammary gland, nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary glands, skin, spleen, stomach (forestomach and glandular), testis with epididymis and seminal vesicle, thymus, thyroid gland, trachea, urinary bladder, and uterus.

STATISTICAL METHODS

Survival Analyses

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

Calculation of Incidence

The incidences of neoplasms or nonneoplastic lesions are presented in Tables A1, A5, B1, B5, 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, only to site-specific, lesion-free 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

Body weight data, which historically have approximately normal distributions, were analyzed with the parametric multiple comparison procedures of Dunnett (1955) and Williams (1971, 1972). Average severity values were analyzed for significance with the Mann-Whitney U test (Hollander and Wolfe, 1973).

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 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, including the present study.

Quality Assurance Methods

The 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 methyl isobutyl ketone was assessed by testing the ability of the chemical to induce mutations in various strains of *Salmonella typhimurium*. 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.

RESULTS

RATS

Survival

Estimates of 2-year survival probabilities for male and female rats are shown in Table 2 and in the Kaplan-Meier survival curves (Figure 1). Survival of the 1,800 ppm males was significantly less than that of the chamber controls. Survival of 450 and 900 ppm males and all exposed groups of females was similar to that of the chamber controls.

TABLE 2
Survival of Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Male				
Animals initially in study	50	50	50	50
Accidental death[a]	0	1	0	0
Moribund	14	16	21	29
Natural deaths	4	5	4	2
Animals surviving to study termination	32	28	25	19
Percent probability of survival at end of study[b]	64	57	50	38
Mean survival (days)[c]	693	673	668	677
Survival analysis[d]	P=0.010	P=0.512	P=0.221	P=0.015
Female				
Animals initially in study	50	50	50	50
Moribund	14	14	20	15
Natural deaths	1	2	4	3
Animals surviving to study termination	35	34[e]	26	32
Percent probability of survival at end of study	70	68	52	64
Mean survival (days)	694	691	679	681
Survival analysis	P=0.439	P=0.993	P=0.093	P=0.621

[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.
[e] Includes one animal that died during the last week of the study

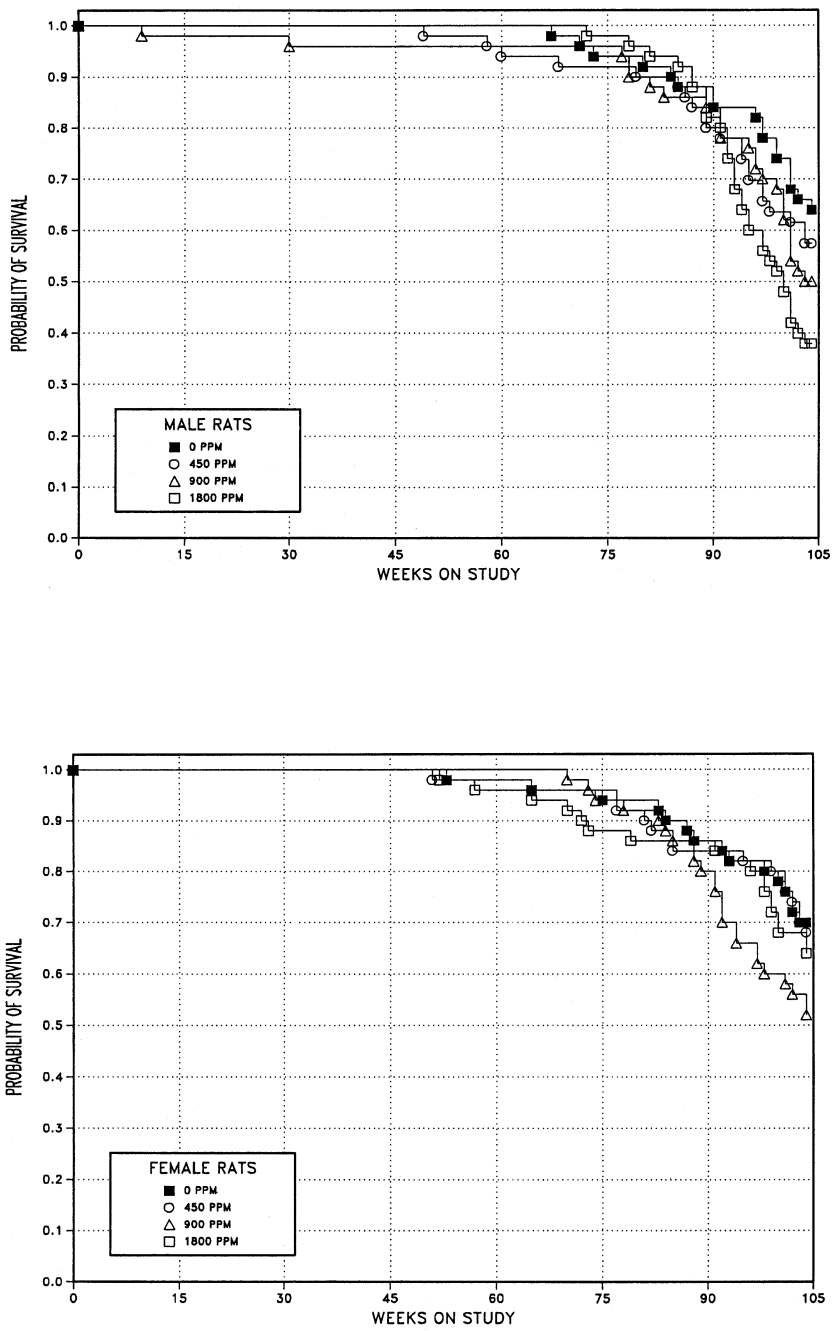


FIGURE 1
Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Methyl Isobutyl Ketone by Inhalation for 2 Years

Body Weights and Clinical Findings

Mean body weights of 900 and 1,800 ppm males were less than those of the chamber control group after weeks 97 and 89, respectively; mean body weights of exposed female rats were generally similar to those of the chamber controls throughout the study (Tables 3 and 4; Figure 2). On average, more male rats in the 900 ppm and 1,800 ppm exposure groups appeared thin and lethargic.

Primarily during the second year of the study, seizures were observed sporadically in a few male and female rats from each exposure group, including chamber controls. More female rats were affected than males (males: chamber control, 2/50; 450 ppm, 3/50; 900 ppm, 4/50; 1,800 ppm, 5/50; females: 12/50, 4/50, 6/50, 14/50), and the first onset was earlier in females (week 40) than in males (week 57). Most seizures were mild, characterized by an abnormal hunched posture and chewing movements sometimes accompanied by clonic spasms of alternate muscle contraction and relaxation, and lasted approximately 30 seconds with a rapid recovery. Uncommon seizures of greater severity produced more pronounced jerking motions lasting up to 60 seconds with a recovery time of two minutes. Most seizure-prone animals had multiple episodes, and neither the incidences nor the number of episodes per rat was related to dose.

Similar, sporadic lesions have been observed in F344/N rats in six other NTP inhalation or dermal exposure studies at three different laboratories. In all these studies, the single common factor is that the animals were housed individually. No such episodes have been observed in concurrent dosed feed, gavage, or drinking water studies in which rats were group housed. In the individually housed animals, most seizures were observed early in the day, when technical and maintenance activities were commencing following the animals' dark cycle period. No deaths were associated with seizures, and there were no correlations with body weight, feed consumption, or histopathological lesions. Thus these transient events were not considered to have affected the toxicologic or carcinogenicity evaluations of this study.

TABLE 3
Mean Body Weights and Survival of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

Weeks on Study	Chamber Control		450 ppm			900 ppm			1,800 ppm		
	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	117	50	115	99	50	115	99	50	113	97	50
2	159	50	157	99	50	158	100	50	157	99	50
3	187	50	187	100	50	190	102	50	191	102	50
4	209	50	210	101	50	214	102	50	217	104	50
5	232	50	234	101	50	238	103	50	241	104	50
6	248	50	250	101	50	254	102	50	257	104	50
7	263	50	266	101	50	269	102	50	273	104	50
8	277	50	281	101	50	282	102	50	287	104	50
9	290	50	292	101	50	297	102	49	300	104	50
10	301	50	304	101	50	307	102	49	312	104	50
11	311	50	312	101	50	316	102	49	321	103	50
12	320	50	323	101	50	327	102	49	333	104	50
13	331	50	333	100	50	336	101	49	343	104	50
17	365	50	365	100	50	367	101	49	374	102	50
21	387	50	388	100	50	389	100	49	396	102	50
25	409	50	408	100	50	407	100	49	416	102	50
29	427	50	427	100	50	427	100	49	433	101	50
33	438	50	441	101	50	440	100	48	446	102	50
37	450	50	451	100	50	449	100	48	454	101	50
42	460	50	461	100	50	454	99	48	465	101	50
45	472	50	472	100	50	468	99	48	475	101	50
49	479	50	482	101	49	475	99	48	481	101	50
53	488	50	490	101	49	481	99	48	488	100	50
57	493	50	496	101	49	486	99	48	492	100	50
61	498	50	502	101	47	490	99	48	496	100	50
65	504	50	504	100	47	492	98	48	499	99	50
69	507	49	508	100	46	495	98	48	502	99	50
73	507	47	512	101	46	500	99	48	503	99	49
77	515	47	518	101	46	498	97	48	503	98	49
81	522	46	525	101	45	505	97	45	505	97	48
85	526	44	523	99	45	503	96	43	506	96	47
89	525	44	526	100	39	505	96	42	505	96	42
91	527	42	524	99	39	503	95	41	497	94	40
93	527	42	524	99	38	509	97	39	503	95	34
95	523	42	529	101	34	501	96	38	497	95	31
97	521	41	532	102	32	500	96	35	495	95	28
99	529	37	525	99	31	490	93	34	485	92	27
101	529	34	521	99	30	487	92	29	488	92	21
103	521	33	508	97	29	489	94	26	490	94	19
Mean for weeks											
1-13	250		251	101		254	102		257	103	
14-52	432		433	100		431	100		438	101	
53-103	515		516	100		496	97		497	97	

TABLE 4
Mean Body Weights and Survival of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

Weeks on Study	Chamber Control		450 ppm			900 ppm			1,800 ppm		
	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	100	50	99	99	50	99	98	50	100	100	50
2	122	50	121	99	50	120	99	50	123	101	50
3	134	50	133	99	50	134	100	50	136	102	50
4	142	50	144	101	50	145	102	50	147	104	50
5	153	50	153	100	50	155	101	50	157	102	50
6	160	50	162	101	50	163	102	50	165	103	50
7	166	50	168	101	50	169	102	50	172	104	50
8	170	50	173	101	50	173	102	50	175	103	50
9	175	50	177	101	50	178	102	50	181	104	50
10	180	50	183	101	50	184	102	50	186	103	50
11	183	50	187	102	50	188	103	50	190	104	50
12	187	50	190	102	50	193	103	50	194	104	50
13	190	50	193	102	50	196	103	50	197	104	50
17	206	50	208	101	50	210	102	50	212	103	50
21	213	50	214	101	50	217	102	50	218	102	50
25	225	50	225	100	50	228	101	50	228	101	50
29	234	50	234	100	50	237	101	50	236	101	50
33	241	50	239	99	50	245	102	50	241	100	50
37	250	50	248	100	50	253	101	50	248	99	50
42	258	50	256	99	50	259	100	50	256	99	50
45	268	50	265	99	50	269	100	50	266	99	50
49	279	50	278	100	50	282	101	50	277	99	50
53	292	49	291	100	49	295	101	50	290	100	49
57	300	49	299	100	49	304	101	50	296	99	48
61	311	49	309	99	49	316	102	50	307	99	48
65	319	48	314	98	49	323	101	50	312	98	47
69	326	48	322	99	48	329	101	50	317	97	47
73	336	48	330	98	48	337	100	48	328	98	44
77	344	47	337	98	47	345	100	47	335	97	44
81	350	47	343	98	45	351	100	46	340	97	43
85	355	45	346	98	43	353	100	43	345	97	43
89	363	43	357	98	42	357	98	40	348	96	43
91	365	43	359	98	42	358	98	39	351	96	42
93	365	41	360	99	42	370	101	35	350	96	42
95	365	41	358	98	42	369	101	33	353	97	41
97	366	41	360	98	41	373	102	31	355	97	40
99	362	40	354	98	41	366	101	30	357	99	36
101	359	39	350	98	40	371	103	29	360	100	34
103	363	35	358	99	36	375	103	28	358	99	34
Mean for weeks											
1-13	159		160	101		161	101		163	103	
14-52	242		241	100		244	101		242	100	
53-103	344		338	98		347	101		335	98	

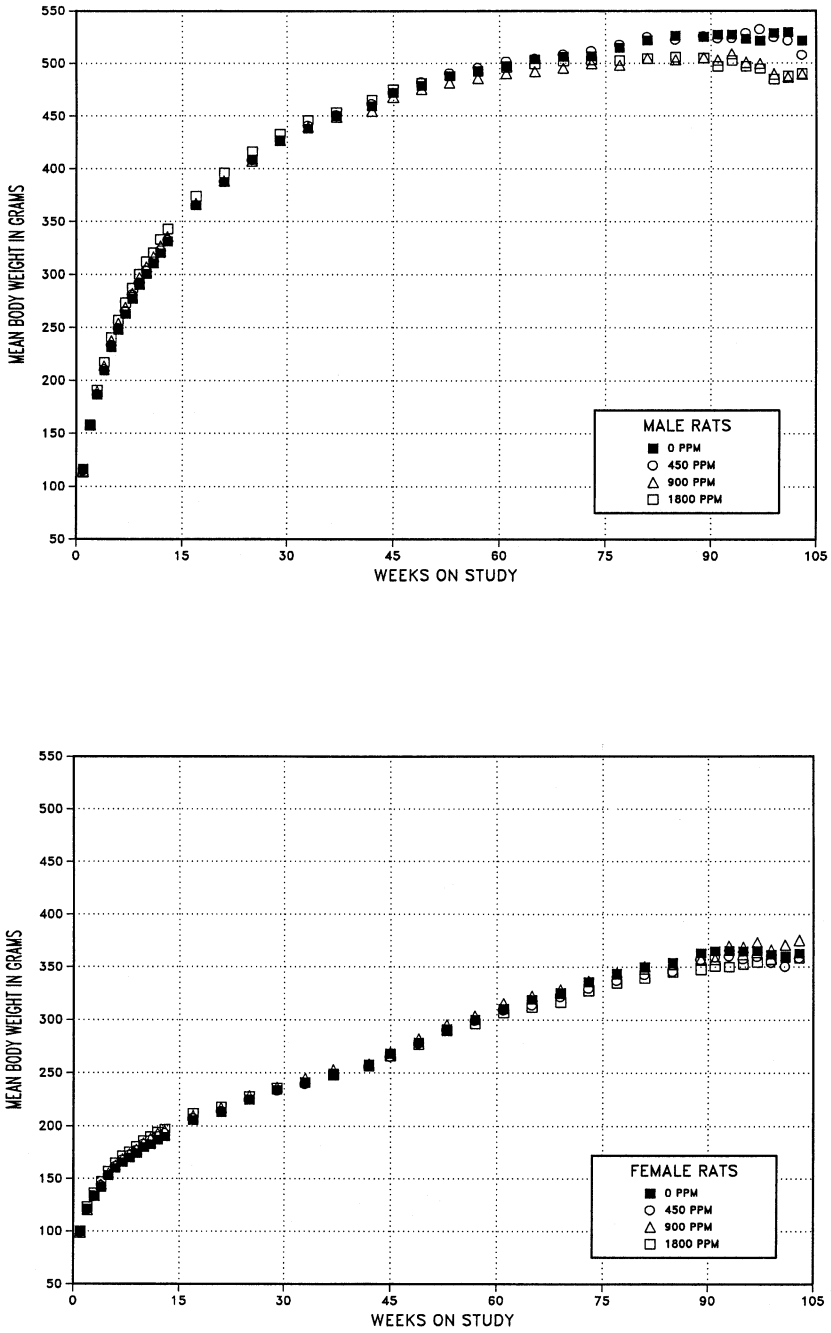


FIGURE 2
Growth Curves for Male and Female Rats Exposed to Methyl Isobutyl Ketone by Inhalation for 2 Years

Pathology and Statistical Analyses

This section describes the statistically significant or biologically noteworthy changes in the incidences of mononuclear cell leukemia and neoplasms and/or nonneoplastic lesions of the kidney, adrenal gland, 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 A for male rats and Appendix B for female rats.

Kidney: The kidney was the primary site of methyl isobutyl ketone-related toxicity. In male rats, chronic nephropathy of the kidney similar to that which occurs in aged rats was observed in most male rats including chamber controls. The incidences and severities of chronic nephropathy and mineralization in the renal papilla increased with increasing exposure concentration (Tables 5 and A5). While generally exacerbated in exposed rats, the severity of nephropathy was increased only in the 1,800 ppm group; increased incidences of papillary mineralization were significant in all exposed groups of males.

In female rats, the incidences of chronic nephropathy were significantly increased in all exposed groups (Tables 5 and B5). The average severity of nephropathy ranged from minimal to mild but was slightly increased in exposed females.

Nephropathy is an age-related disease process. In both sexes, changes consistent with nephropathy consisted of a spectrum of lesions that included varying degrees of renal tubule dilation with and without hyaline (proteinaceous) casts, multifocal degeneration, regeneration, and hypertrophy of the tubular epithelium; thickening of the tubular and glomerular basement membranes; glomerulosclerosis; interstitial fibrosis; and varying numbers and aggregates of mononuclear inflammatory cells within the interstitium (Plates 1 and 2). Minimal nephropathy consisted of focal to multifocal regenerative renal tubules surrounded by a thickened basement membrane, affecting less than 10% of the renal parenchyma. These regenerative tubules had increased numbers of more intensely stained basophilic cells. Mild nephropathy consisted of multifocal regenerative renal tubules, thickening of the glomerular basement membrane, tubular protein casts, and scattered focal chronic inflammatory cell infiltrates affecting approximately 10% to 39% of the renal parenchyma. Moderate nephropathy had similar but more severe and widespread changes including glomerular atrophy and variable interstitial fibrosis. Marked nephropathy was diffuse and of greater severity.

Mineralization was generally of minimal to mild severity and appeared as lamellated intraluminal or intracellular concretions within the collecting tubules of the renal papilla usually forming linear deposits (Plates 3 and 4). Papillary mineralization of the renal papilla oriented in a linear fashion is characteristic of α2u-globulin inducers in 2-years studies, as is exacerbated nephropathy.

The incidences of transitional epithelial hyperplasia in the renal pelvis of male rats were increased in all exposed groups of male rats; the increased incidences were significant in the 900 and 1,800 ppm groups (Tables 5 and A5). Transitional epithelial hyperplasia was characterized by focal increased thickness of the transitional epithelium lining the renal pelvis often forming papillary projections into the urinary space (Plates 5 and 6). It was generally of minimal to mild severity and occurred mostly in rats with moderate to severe nephropathy. Hyperplasia of the transitional epithelium lining the renal pelvis frequently accompanies severe nephropathy (Montgomery and Seely, 1990), and the increased incidences of epithelial hyperplasia in the current study may reflect the enhanced nephropathy.

In the standard evaluation of the kidney, the incidences of renal tubule hyperplasia were significantly increased in male rats exposed to 450 or 1,800 ppm, and the severities in these groups were greater than that of the chamber controls (Tables 5 and A5). In addition, there were slightly increased incidences of renal tubule adenoma, carcinoma, and adenoma or carcinoma (combined) in male rats (Tables 5, A1, and A3). Although not statistically significant, the incidences of renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in the 900 and 1,800 ppm groups and renal tubule carcinoma in the 1,800 ppm group exceeded the historical ranges for chamber controls from inhalation studies (Tables 5 and A4a).

Renal tubule hyperplasia is considered a preneoplastic lesion distinguished from regenerative epithelial changes that commonly occur as a component of age-related nephropathy. Hyperplasia was single or multiple expanded cortical tubules composed of increased numbers of tubular epithelial cells arranged in multiple layers that partially or completely filled the tubule (Plates 7 and 8).

TABLE 5
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Male				
Single Sections (Standard Evaluation)				
Number Examined Microscopically	50	50	50	50
Nephropathy[a]	42 (2.0)[b]	45 (2.6)	47 (2.4)	50* (3.1)
Papilla Mineralization	1 (1.0)	6* (1.2)	22** (1.6)	29** (1.5)
Pelvis Transitional Epithelium Hyperplasia	1 (1.0)	5 (1.8)	6* (1.2)	19** (1.4)
Renal Tubule Hyperplasia	1 (2.0)	11** (3.2)	3 (2.0)	18** (2.7)
Renal Tubule Adenoma[c]	0	0	2	3
Renal Tubule Carcinoma[d]	0	1	0	2
Renal Tubule Adenoma or Carcinoma[e]	0	1	2	4
Step Sections (Extended Evaluation)				
Number Examined Microscopically	50	50	50	50
Renal Tubule Hyperplasia	0	3 (2.0)	4 (2.0)	6* (2.3)
Renal Tubule Adenoma				
Overall rate[f]	2/50 (4%)	3/50 (6%)	1/50 (2%)	7/50 (14%)
Adjusted rate[g]	4.5%	7.2%	2.4%	16.8%
Terminal rate[h]	1/32 (3%)	2/28 (7%)	0/25 (0%)	5/19 (26%)
First incidence (days)	713	677	695	677
Poly-3 test[i]	P=0.029	P=0.473	P=0.519N	P=0.062
Renal Tubule Adenoma or Carcinoma	2	3	1	7
Single Sections and Step Sections (Combined)				
Number Examined Microscopically	50	50	50	50
Renal Tubule Hyperplasia	1 (2.0)	14* (2.9)	7* (2.0)	21** (2.5)
Renal Tubule Adenoma				
Overall rate	2/50 (4%)	3/50 (6%)	3/50 (6%)	10/50 (20%)
Adjusted rate	4.5%	7.2%	7.1%	24.0%
Terminal rate	1/32 (3%)	2/28 (7%)	1/25 (4%)	7/19 (37%)
First incidence (days)	713	677	695	677
Poly-3 test	P=0.002	P=0.473	P=0.477	P=0.009
Renal Tubule Carcinoma				
Overall rate	0/50 (%)	1/50 (2%)	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	2.4%	0.0%	4.8%
Terminal rate	0/32 (0%)	1/28 (4%)	0/25 (0%)	2/19 (11%)
First incidence (days)	—[j]	726 (T)	—[k]	726 (T)
Poly-3 test	P=0.129	P=0.487	—	P=0.221
Renal Tubule Adenoma or Carcinoma				
Overall rate	2/50 (4%)	4/50 (8%)	3/50 (6%)	11/50 (22%)
Adjusted rate	4.5%	9.5%	7.1%	26.4%
Terminal rate	1/32 (3%)	3/28 (11%)	1/25 (4%)	8/19 (42%)
First incidence (days)	713	677	695	677
Poly-3 test	P<0.001	P=0.309	P=0.477	P=0.004

TABLE 5
Incidences of Neoplasms and Nonneoplastic Lesions of the Kidney in Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Female				
Number Examined Microscopically	50	50	50	50
Nephropathy	19 (1.4)	35** (1.5)	38** (1.5)	44** (1.9)
Mesenchymal Tumor Malignant[l]				
Overall rate	0/50 (0%)	0/50 (0%)	0/50 (0%)	2/50 (4%)
Adjusted rate	0.0%	0.0%	0.0%	4.6%
Terminal rate	0/35 (0%)	0/34 (0%)	0/26 (0%)	2/32 (6%)
First indicence (days)	—	—	—	727 (T)
Poly-3 test	P=0.043	—	—	P=0.229

(T) Terminal sacrifice
* Significantly different (P≤0.05) from the chamber control group by the Poly-3 test
** P≤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] Historical incidence for 2-year inhalation studies with chamber controls given NTP-2000 diet (mean ± standard deviation): 3/399 (0.8% ± 1.0%); range, 0%-2%
[d] Historical incidence: 1/399 (0.3% ± 0.7%); range, 0%-2%
[e] Historical incidence: 4/399 (1.0% ± 1.1%); range, 0%-2%
[f] Number of animals with neoplasm per number of animals with kidney examined microscopically
[g] Poly-3 estimated neoplasm incidence after adjustment for intercurrent mortality
[h] Observed incidence at terminal kill
[i] Beneath the chamber control incidence is the P value associated with the trend test. Beneath the exposed group incidences 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 lower incidence in an exposure group is indicated by **N**.
[j] Not applicable; no neoplasms in animal group
[k] Value of statistic cannot be computed.
[l] Historical incidence: 0/396

Renal tubule adenomas were discrete, highly cellular, proliferative lesions that were larger than focal hyperplasias (generally greater than the combined diameter of five normal-sized renal tubules) (Plates 9 and 10). Adenomas tended to have a more complex structure than hyperplasias and were characterized by closely packed tubules and solid nests composed of a mixture of cells with large vesicular nuclei and abundant pale eosinophilic cytoplasm and vacuolated cells.

Renal tubule carcinomas were highly cellular, expansive, and invasive masses composed of large basophilic to amphophilic cells that formed large multilayered tubular structures, solid nests, and sheets (Plates 11 and 12).

Renal tubule hyperplasia, adenoma, and carcinoma are thought to represent a continuum in the progression of proliferative lesions in renal tubule epithelium. In the standard evaluation, a single section of each kidney was examined microscopically. Because the increased incidences of benign and malignant renal tubule neoplasms and hyperplasia indicated the possibility of a treatment-related carcinogenic effect, an extended evaluation of the kidney was performed in male rats.

In the extended evaluation, renal tubule adenomas were identified in all groups of male rats including the chamber controls (Tables 5 and A3). No additional renal tubule carcinomas were identified. Additional incidences of renal tubule hyperplasia were also observed in the extended evaluation, and the incidences in all exposed groups were significantly greater than that in the chamber controls in the combined single and step section analysis.

Two female rats in the 1,800 ppm group had renal mesenchymal tumors. These neoplasms are rare and in NTP

studies have not been found in male or female controls (all routes) fed NTP 2000 diet (Tables 5 and B4). In treated F344/N rats fed NTP 2000 diet, mesenchymal tumors were found in only one male and three female rats in three 2-year studies including the current study. Both neoplasms observed in this study were single, small to medium-sized masses with poorly defined margins and were composed of sheets of mature mesenchymal (spindle) cells that infiltrated the inner cortex, medulla, and renal pelvis encircling and sequestering glomeruli, tubules, and collecting ducts. In commonly used strains of rats, mesenchymal tumors are rare. They are malignant connective tissue neoplasms considered to arise from a stem cell of the primitive mesenchyme. They are usually single, variably sized, infiltrative masses with poorly defined margins and appear to originate in the cortex near the corticomedullary junction, and extend into the medulla and renal pelvis with time (Montgomery and Seely, 1990; Hard *et al.*, 1995). Mesenchymal tumors can be composed of a variety of connective tissue cell types, however, most are composed of fibroblastic spindle cells that are arranged in solid sheets. Collagen deposition is frequently present and mitotic cells are frequent.

Mononuclear cell leukemia: There was a positive trend in the incidences of mononuclear cell leukemia in male rats (chamber control, 25/50; 450 ppm, 26/50; 900 ppm, 32/50; 1,800 ppm, 35/50; Table A3). The increased incidence in the 1,800 ppm group was significant and exceeded the historical range for chamber controls in inhalation studies [188/399 (47% ± 10%), range 32%-66%; Table A4b].

Adrenal gland: There were increased incidences of adrenal medulla hyperplasia in male rats (13/50, 18/48, 18/50, 24/50; Table A5), and the increased incidence in the 1,800 ppm group was significant. Exposure-related increased incidences of benign or malignant pheochromocytoma (combined) occurred in male rats (8/50, 9/48, 11/50, 14/50; Tables A1 and A3). These increased incidences were not statistically significant and were within the historical control range for chamber controls in inhalation studies [69/398 (17% ± 7%), range 10%-28%], although the incidence in the 1,800 ppm group was at the upper limit of the historical range.

Lung: The incidence of alveolar/bronchiolar carcinoma was slightly increased in male rats exposed to 1,800 ppm methyl isobutyl ketone (0/50, 0/49, 0/50, 2/50; Table A1). Carcinoma occurred in the chamber controls in five out of eight contemporary inhalation studies [5/399 (1% ± 1%), range, 0%-2%]. Although the two carcinomas seen in the 1,800 ppm group in this study exceeded the historical control rate, they were not statistically significant compared to the concurrent control group and were considered not related to methyl isobutyl ketone exposure.

MICE

Survival

Estimates of 2-year survival probabilities for male and female mice are shown in Table 6 and in the Kaplan-Meier survival curves (Figure 3). Survival of male and female mice was similar to that of the chamber controls.

Body Weights and Clinical Findings

Mean body weights of male mice were generally similar to those of the chamber controls throughout the study (Figure 4 and Table 7). After week 17, body weights of 1,800 ppm females were less than those of the chamber controls (Figure 4 and Table 8). No clinical findings related to exposure to methyl isobutyl ketone were observed.

TABLE 6
Survival of Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Male				
Animals initially in study	50	50	50	50
Moribund	9	6	12	9
Natural deaths	1	2	3	4
Animals surviving to study termination	40	42	35[a]	37
Percent probability of survival at end of study[b]	80	84	70	74
Mean survival (days)[c]	709	714	671	700
Survival analysis[d]	P=0.322	P=0.759N	P=0.286	P=0.609
Female				
Animals initially in study	50	50	50	50
Accidental death[e]	0	1	0	0
Moribund	10	9	6	9
Natural deaths	5	3	5	3
Animals surviving to study termination	35	37	39	38
Percent probability of survival at end of study	70	76	78	76
Mean survival (days)	695	699	700	707
Survival analysis	P=0.567N	P=0.659N	P=0.527N	P=0.590N

[a] Includes one animal that died during the last week of the study
[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. A negative trend or lower mortality in an exposure group is indicated by **N**.
[e] Censored from survival analyses

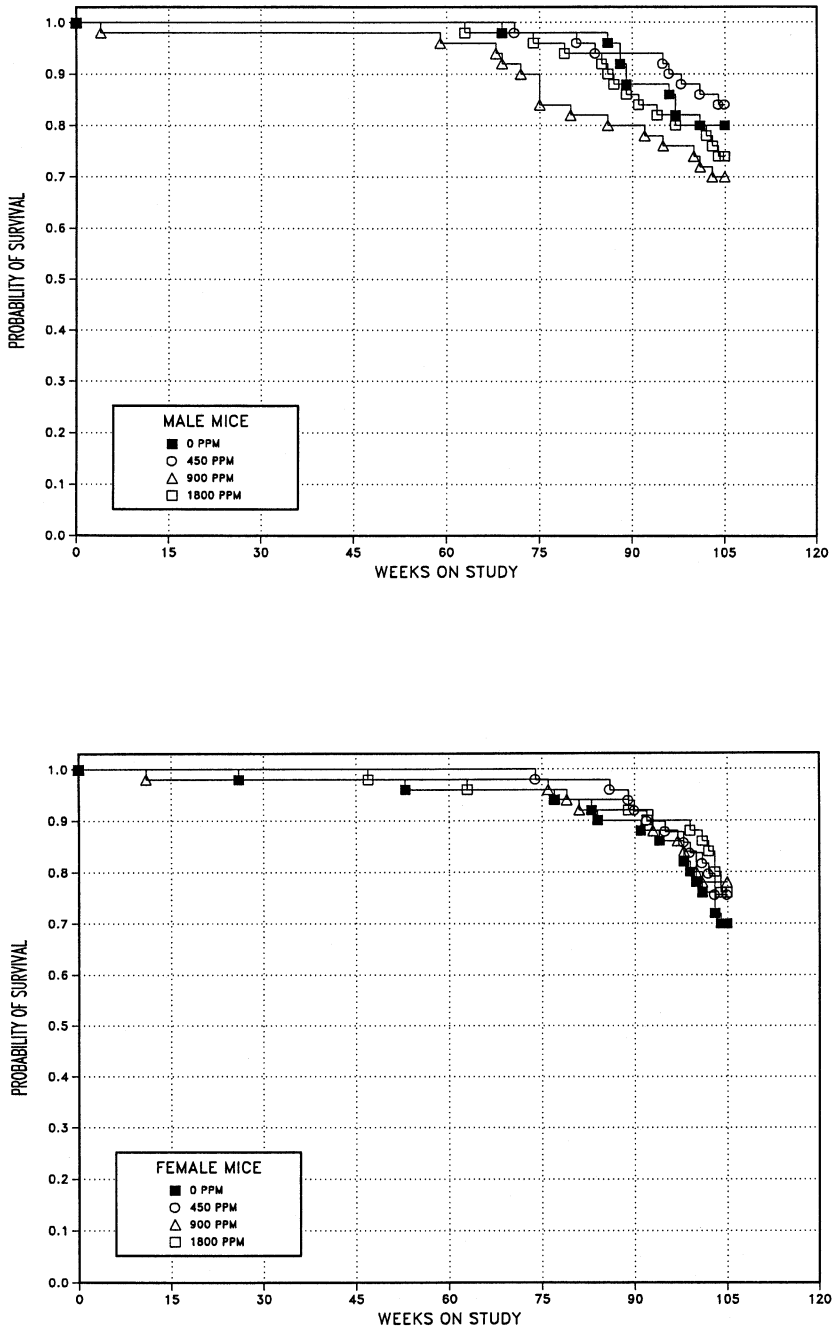


FIGURE 3
Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Methyl Isobutyl Ketone by Inhalation for 2 Years

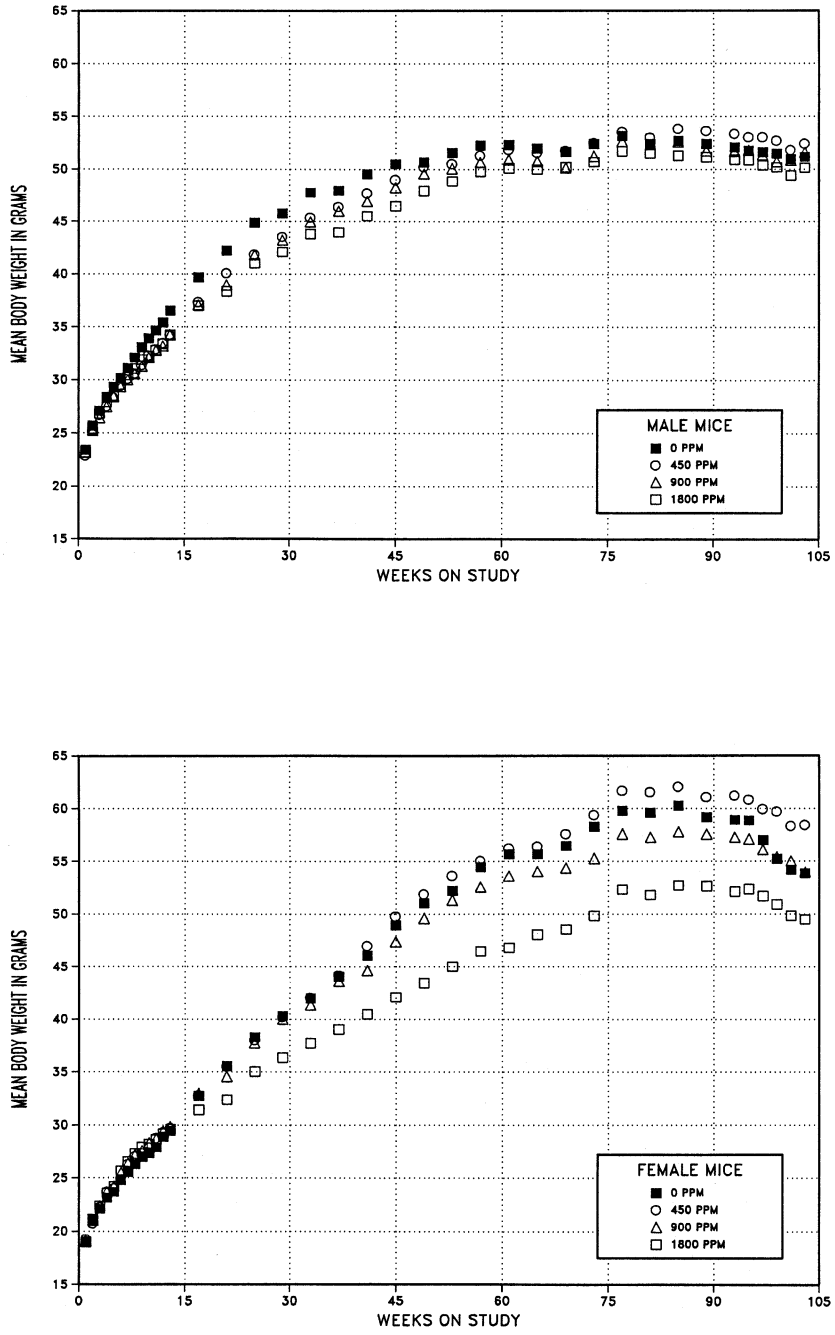


FIGURE 4
Growth Curves for Male and Female Mice Exposed to Methyl Isobutyl Ketone by Inhalation for 2 Years

TABLE 7
Mean Body Weights and Survival of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

Weeks on Study	Chamber Control		450 ppm			900 ppm			1,800 ppm		
	Av. Wt. (g)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors	Av. Wt. (g)	Wt. (% of controls)	No. of Survivors
1	23.5	50	22.9	97	50	23.2	99	50	23.2	99	50
2	25.7	50	25.2	98	50	25.3	98	50	25.4	99	50
3	27.1	50	26.7	99	50	26.4	97	50	26.8	99	50
4	28.4	50	27.5	97	50	27.4	97	50	27.9	98	50
5	29.3	50	28.3	97	50	28.4	97	49	28.5	97	50
6	30.2	50	29.4	97	50	29.3	97	49	29.6	98	50
7	31.1	50	30.0	97	50	30.0	97	49	30.4	98	50
8	32.1	50	30.6	95	50	30.6	95	49	31.0	97	50
9	33.1	50	31.4	95	50	31.3	95	49	31.9	96	50
10	33.9	50	32.3	95	50	32.1	95	49	32.2	95	50
11	34.7	50	32.9	95	50	32.7	94	49	32.8	95	50
12	35.4	50	33.5	95	50	33.2	94	49	33.4	94	50
13	36.5	50	34.3	94	50	34.2	94	49	34.2	94	50
17	39.7	50	37.3	94	50	37.1	94	49	37.0	93	50
21	42.2	50	40.1	95	50	39.0	92	49	38.4	91	50
25	44.9	50	41.9	93	50	41.8	93	49	41.0	91	50
29	45.8	50	43.5	95	50	43.2	94	49	42.1	92	50
33	47.8	50	45.4	95	50	45.0	94	49	43.8	92	50
37	48.0	50	46.4	97	50	46.0	96	49	44.0	92	50
41	49.6	50	47.7	96	50	47.0	95	49	45.5	92	50
45	50.5	50	49.0	97	50	48.3	96	49	46.5	92	50
49	50.7	50	50.2	99	50	49.6	98	49	48.0	95	50
53	51.6	50	50.5	98	50	50.1	97	49	48.9	95	50
57	52.3	50	51.3	98	50	50.6	97	49	49.8	95	50
61	52.3	50	51.9	99	50	50.9	97	48	50.1	96	50
65	52.0	50	51.6	99	50	50.7	98	48	50.0	96	49
69	51.7	50	51.8	100	50	50.1	97	47	50.2	97	49
73	52.4	49	52.5	100	49	51.2	98	45	50.7	97	49
77	53.2	49	53.5	101	49	52.6	99	42	51.7	97	48
81	52.4	49	53.0	101	49	52.3	100	41	51.5	98	47
85	52.7	49	53.8	102	47	52.6	100	41	51.3	97	47
89	52.4	45	53.6	102	47	51.7	99	40	51.1	98	43
93	52.1	44	53.4	103	47	51.7	99	39	50.9	98	42
95	51.7	44	53.0	103	46	51.8	100	38	50.9	99	41
97	51.6	43	53.0	103	45	51.3	99	38	50.4	98	41
99	51.5	41	52.7	102	44	50.7	98	38	50.2	98	40
101	51.0	41	51.8	102	44	50.9	100	36	49.4	97	40
103	51.2	40	52.4	102	43	51.6	101	35	50.1	98	38
Mean for weeks											
1-13	30.8		29.6	96		29.5	96		29.8	97	
14-52	46.6		44.6	96		44.1	95		42.9	92	
53-103	52.0		52.5	101		51.3	99		50.5	97	

TABLE 8
Mean Body Weights and Survival of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

Weeks on Study	Chamber Control		450 ppm			900 ppm			1,800 ppm		
	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	19.1	50	19.2	101	50	19.1	100	50	19.0	100	50
2	21.1	50	20.7	98	50	21.0	100	50	21.1	100	50
3	22.1	50	22.3	101	50	22.4	101	50	22.4	101	50
4	23.2	50	23.7	102	49	23.7	102	50	23.6	102	50
5	23.7	50	24.0	101	49	24.2	102	50	24.2	102	50
6	24.8	50	24.9	100	49	25.5	103	50	25.7	104	50
7	25.5	50	26.3	103	49	26.4	104	50	26.6	104	50
8	26.3	50	27.0	103	49	27.2	103	50	27.3	104	50
9	27.0	50	27.3	101	49	27.5	102	50	27.9	103	50
10	27.3	50	27.9	102	49	28.3	104	50	28.2	103	50
11	27.9	50	28.8	103	49	28.7	103	50	28.6	103	50
12	28.9	50	29.3	101	49	29.4	102	49	29.2	101	50
13	29.4	50	29.7	101	49	29.9	102	49	29.6	101	50
17	32.7	50	32.8	100	49	33.0	101	49	31.4	96	50
21	35.6	50	35.5	100	49	34.6	97	49	32.4	91	50
25	38.3	50	38.0	99	49	37.7	98	49	35.0	91	50
29	40.3	49	40.2	100	49	40.0	99	49	36.4	90	50
33	42.0	49	42.1	100	49	41.3	98	49	37.7	90	50
37	44.0	49	44.2	101	49	43.6	99	49	39.0	89	50
41	46.1	49	47.0	102	49	44.7	97	49	40.5	88	50
45	48.9	49	49.8	102	49	47.4	97	49	42.1	86	50
49	51.1	49	51.9	102	49	49.6	97	49	43.4	85	49
53	52.2	49	53.6	103	49	51.3	98	49	45.0	86	49
57	54.5	48	55.0	101	49	52.6	97	49	46.5	85	49
61	55.7	48	56.2	101	49	53.6	96	49	46.8	84	49
65	55.7	48	56.4	101	49	54.0	97	49	48.0	86	48
69	56.5	48	57.6	102	49	54.4	96	49	48.5	86	48
73	58.3	48	59.4	102	49	55.3	95	49	49.9	86	48
77	59.8	48	61.7	103	48	57.6	96	48	52.3	88	47
81	59.6	47	61.5	103	48	57.3	96	47	51.8	87	47
85	60.3	45	62.0	103	48	57.8	96	46	52.7	87	47
89	59.2	45	61.1	103	47	57.6	97	46	52.6	89	46
93	58.9	44	61.2	104	44	57.3	97	45	52.1	89	45
95	58.9	43	60.8	103	44	57.1	97	44	52.4	89	45
97	57.0	43	59.9	105	43	56.1	98	43	51.7	91	45
99	55.2	41	59.7	108	41	55.4	100	42	50.9	92	44
101	54.2	39	58.3	108	40	55.0	102	39	49.8	92	44
103	53.9	36	58.4	108	37	54.0	100	39	49.5	92	41
Mean for weeks											
1-13	25.1		25.5	101		25.6	102		25.6	102	
14-52	42.1		42.4	101		41.3	98		37.5	90	
53-103	56.9		58.9	104		55.4	97		50.0	88	

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 liver was the primary site of methyl isobutyl ketone-related toxicity. The incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) were increased in all exposed groups of males and in 900 and 1,800 ppm females, and the incidences in the 1,800 ppm groups were significantly greater than those in the chamber controls (Tables 9, C3, and D3). The incidences of hepatocellular adenoma in all exposed groups of males and the 900 and 1,800 ppm females were at the upper limit or exceeded the historical control ranges for chamber controls given NTP-2000 diet (Tables 9, C4, and D4). The incidence of hepatocellular carcinoma in females was increased at 1,800 ppm; although not statistically significant, the incidence exceeded the historical control range. The incidences of hepatocellular adenoma or carcinoma (combined) in males exposed to 1,800 ppm and females exposed to 900 or 1,800 ppm also exceeded the historical control ranges. The incidences of eosinophilic foci were increased in all exposed groups of female mice, and the differences from the chamber controls were significant in the 450 and 1,800 ppm groups.

The histologic appearance of the hepatocellular proliferative lesions was consistent with those commonly observed as spontaneous lesions in mice. Hepatocellular adenomas were discrete, variably sized, circumscribed masses with variable compression of the adjacent normal parenchyma. Adenomas were composed of well-differentiated hepatocytes with evidence of mild cellular pleomorphism. Hepatic cords were irregular and abruptly impacted the adjacent parenchyma at right angles. Hepatocellular carcinomas were expansive masses characterized by irregular borders and a trabecular pattern with hepatic cords greater than three to four cells wide; the neoplastic hepatocytes varied from well-differentiated to markedly atypical with enlarged hyperchromatic atypical nuclei and one or more prominent nuclei. Eosinophilic foci consisted of enlarged hepatocytes with ground-glass appearing cytoplasm; larger foci sometimes caused slight compression of the adjacent parenchyma.

Lung: Exposure to methyl isobutyl ketone resulted in significantly decreased incidences alveolar/bronchiolar adenoma in 900 ppm males (chamber control, 9/50; 450 ppm, 5/50; 900 ppm, 1/50; 1,800 ppm, 5/50) and of alveolar/bronchiolar adenoma or carcinoma (combined) in 450 and 900 ppm males (14/50, 5/50, 3/50, 10/50) compared to the chamber controls (Tables C1 and C3). The incidences of these neoplasms in all exposed male groups were less than the ranges in historical chamber controls given NTP-2000 diet [adenoma: 74/349 (21% ± 6%), range 12%-26%; adenoma or carcinoma (combined): 115/349 (33% ± 6%), range 26%-44%]. These decreased incidences were not related to exposure, occurred only in male mice, and were considered to be spurious and not related to exposure to methyl isobutyl ketone.

GENETIC TOXICOLOGY

Methyl isobutyl ketone (100 to 6,667 µg/plate) was not mutagenic in *Salmonella typhimurium* strains TA97, TA98, TA100, or TA1535, when tested with and without 10% or 30% hamster or rat liver metabolic activation enzymes (Table E1; Zeiger *et al.*, 1992).

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Male				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus[a]	3	4	5	8
Hepatocellular Adenoma[b]				
Overall rate[c]	17/50 (34%)	25/50 (50%)	23/50 (46%)	34/50 (68%)
Adjusted rate[d]	36.4%	52.0%	51.9%	71.9%
Terminal rate[e]	16/40 (40%)	22/42 (52%)	17/35 (49%)	28/37 (76%)
First incidence (days)	678	582	471	551
Poly-3 test[f]	P<0.001	P=0.090	P=0.097	P<0.001
Hepatocellular Carcinoma[g]	12	12	10	9
Hepatocellular Adenoma or Carcinoma[h]				
Overall rate	27/50 (54%)	34/50 (68%)	28/50 (56%)	37/50 (74%)
Adjusted rate	56.1%	68.3%	61.6%	77.3%
Terminal rate	22/40 (55%)	27/42 (64%)	20/35 (57%)	28/37 (76%)
First incidence (days)	482	493	471	551
Poly-3 test	P=0.028	P=0.146	P=0.368	P=0.019

TABLE 9
Incidences of Neoplasms and Nonneoplastic Lesions of the Liver in Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Female				
Number Examined Microscopically	50	50	50	50
Eosinophilic Focus	4	11*	10	14**
Hepatocellular Adenoma[i]				
Overall rate	13/50 (26%)	15/50 (30%)	20/50 (40%)	23/50 (46%)
Adjusted rate	28.8%	32.4%	43.1%	49.3%
Terminal rate	11/35 (31%)	11/37 (30%)	17/39 (44%)	20/38 (53%)
First incidence (days)	715	687	673	705
Poly-3 test	P=0.016	P=0.442	P=0.111	P=0.033
Hepatocellular Carcinoma[j]	6	5	6	11
Hepatocellular Adenoma or Carcinoma[k]				
Overall rate	17/50 (34%)	17/50 (34%)	22/50 (44%)	27/50 (54%)
Adjusted rate	37.1%	36.4%	46.9%	57.6%
Terminal rate	12/35 (34%)	12/37 (32%)	18/39 (46%)	22/38 (58%)
First incidence (days)	586	598	567	687
Poly-3 test	P=0.013	P=0.556N	P=0.228	P=0.035

* 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] Historical incidence for 2-year inhalation studies with chamber controls given NTP-2000 diet (mean ± standard deviation): 134/350 (38.3% ± 6.3%); range, 30%-46%
[c] Number of animals with neoplasm per number of animals with liver 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 incidences 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 lower incidence in an exposure group is indicated by **N**.
[g] Historical incidence: 85/350 (24.3% ± 4.8%); range, 18%-32%
[h] Historical incidence: 196/350 (56.0% ± 6.2%); range, 50%-68%
[i] Historical incidence: 78/347 (22.5% ± 8.1%); range, 12%-35%
[j] Historical incidence: 37/347 (10.7% ± 1.8%); range, 8%-12%
[k] Historical incidence: 108/347 (31.1% ± 6.8%); range, 22%-39%

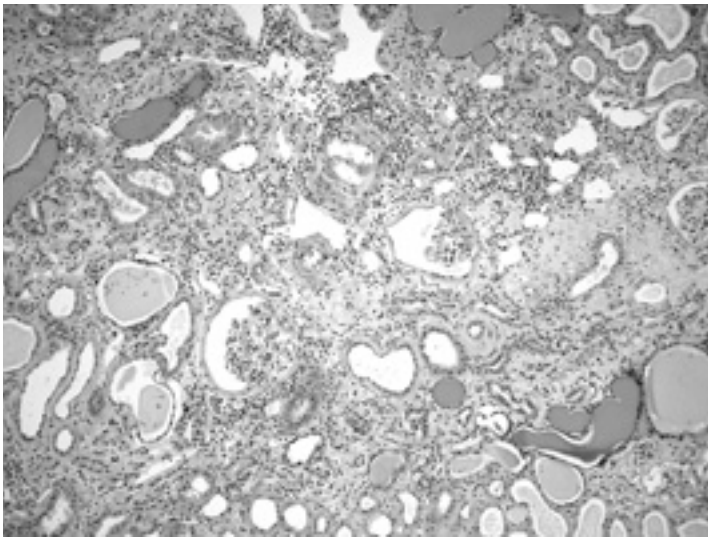


PLATE 1
Marked nephropathy in the kidney of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. Note the dilated tubules containing homogenous proteinaceous casts, glomeruli with dilated Bowman's space, marked interstitial fibrosis, and inflammatory cell infiltrates. H&E; 10×

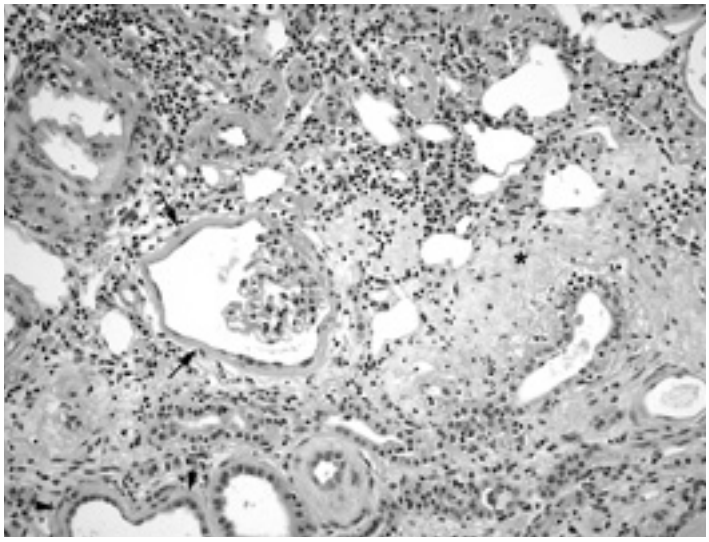


PLATE 2
Higher magnification of Plate 1. Note several renal tubules with thickened basement membranes (arrowheads), glomerulus with dilated Bowman's space and thickened basement membrane (arrows), marked interstitial fibrosis (asterisk), and mononuclear inflammatory cell infiltrates. H&E; 20×

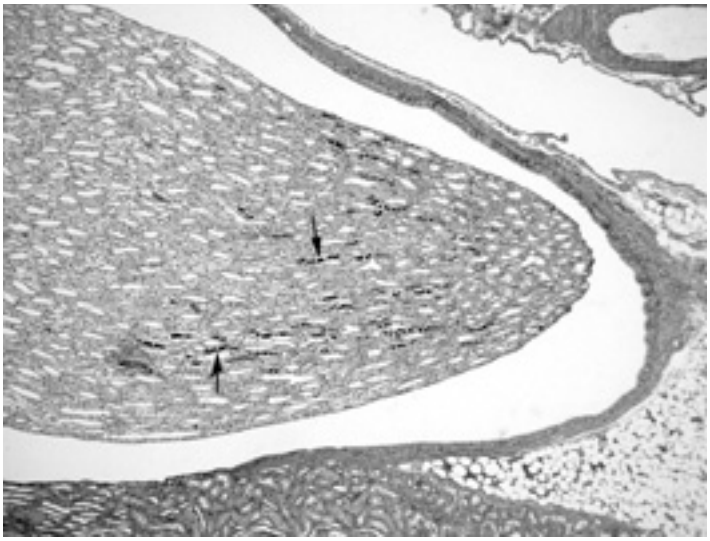


PLATE 3
Linear mineralization (arrows) in the renal papilla of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. H&E; 4×

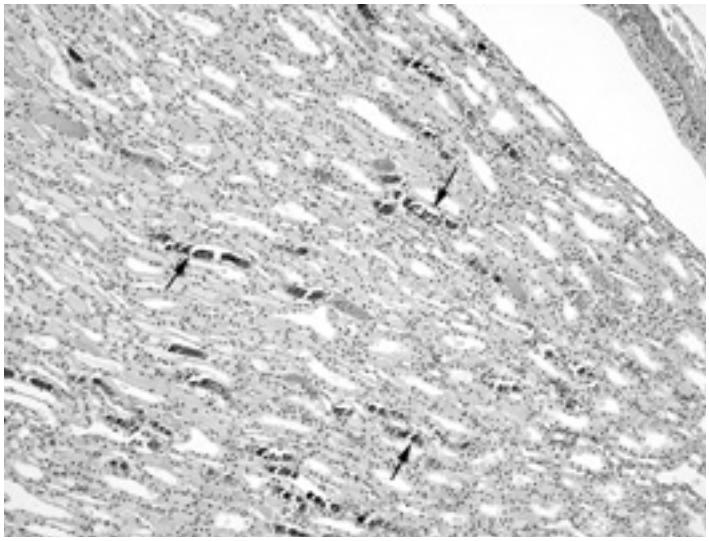


PLATE 4
Higher magnification of Plate 3. Deposits of mineral appear as linear lamellated intraluminal or intracellular concretions (arrows) within the collecting tubules of the renal papilla. H&E; 10×

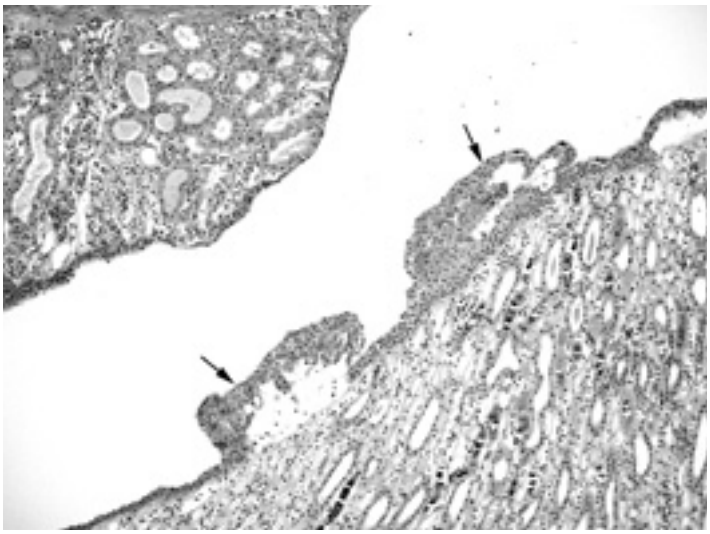


PLATE 5
Transitional epithelial hyperplasia in the kidney of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. Hyperplasia (arrows) occurs as focal papillary thickening of the transitional epithelium lining the renal pelvis, which projects into the urinary space. H&E; 10×

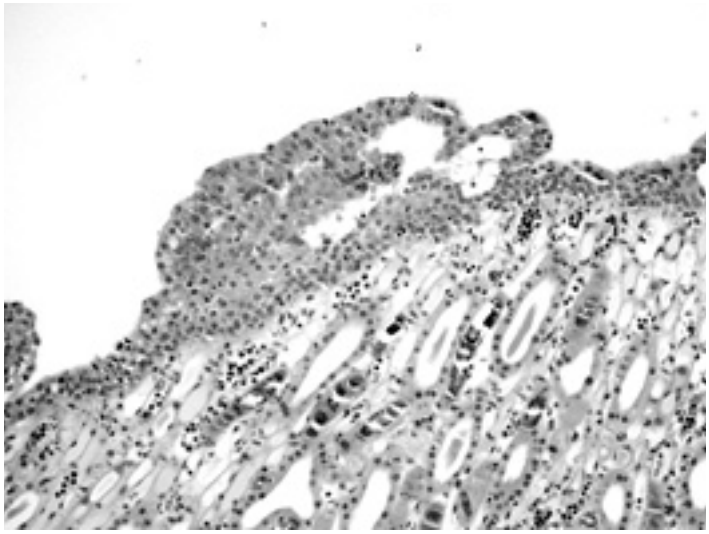


PLATE 6
Higher magnification of Plate 5. Note the linear deposits of mineral within the collecting ducts of the renal papilla. H&E; 20×

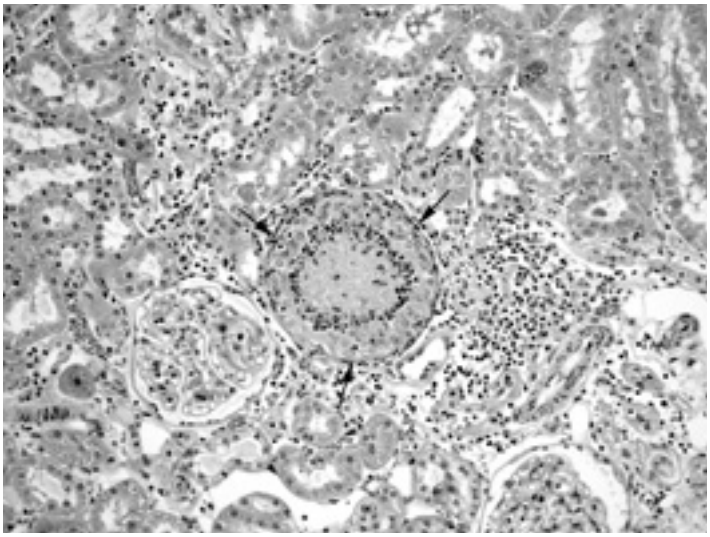


PLATE 7
Renal tubule epithelial hyperplasia in the kidney of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. The small focus of renal tubule hyperplasia (arrows) is surrounded by normal renal tubules. H&E; 20×

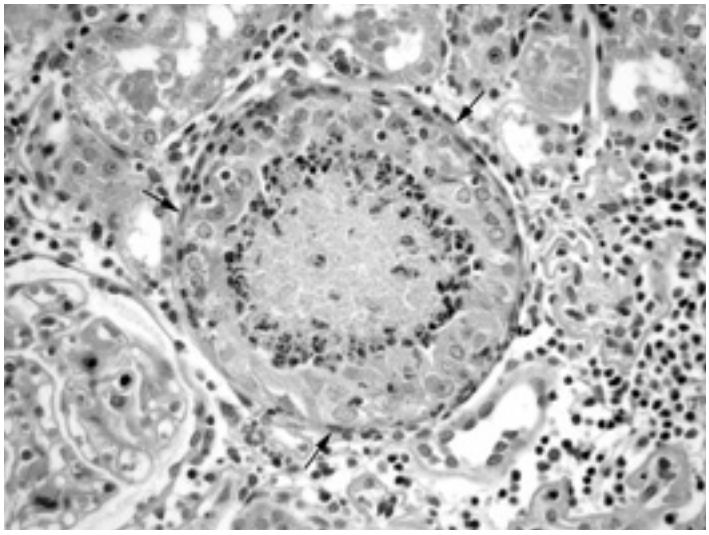


PLATE 8
Higher magnification of Plate 7. The hyperplastic tubule has maintained its tubule shape and is still contained within an intact basement membrane (arrows). The normal, single layer of epithelial cells has been replaced by hyperplastic epithelial cells showing very little pleomorphism. Note the central area of necrosis within the hyperplastic tubule. H&E; 40×

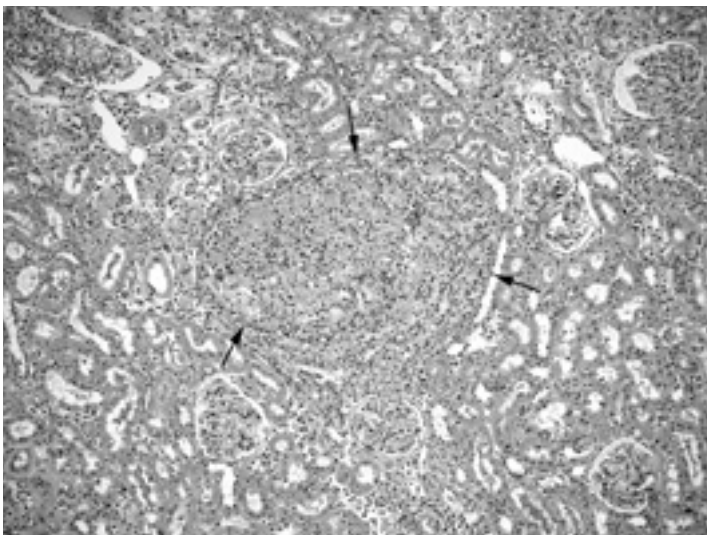


PLATE 9
Renal tubule adenoma (arrows) in the kidney of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. The adenoma is well circumscribed and greater than five normal-sized renal tubules in diameter. H&E; 10×

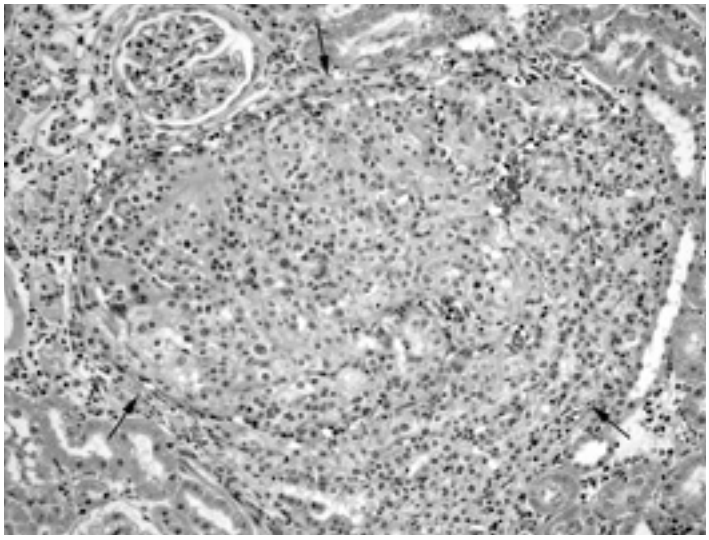


PLATE 10
Higher magnification of Plate 9. The adenoma (arrows) is characterized by a solid-growth pattern of pleomorphic cells arranged in small nests separated by delicate vascular septae. Some of the cells are vacuolated. There is partial loss of basement membrane integrity and focal slight compression of the surrounding renal parenchyma. H&E; 20×

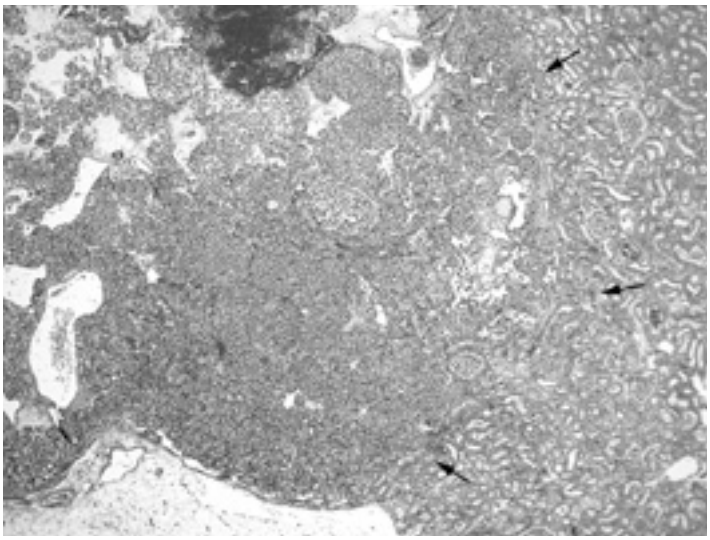


PLATE 11
Renal tubule carcinoma in the kidney of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. The carcinoma (left of arrows) is highly cellular and has effaced the renal parenchyma. H&E; 4×

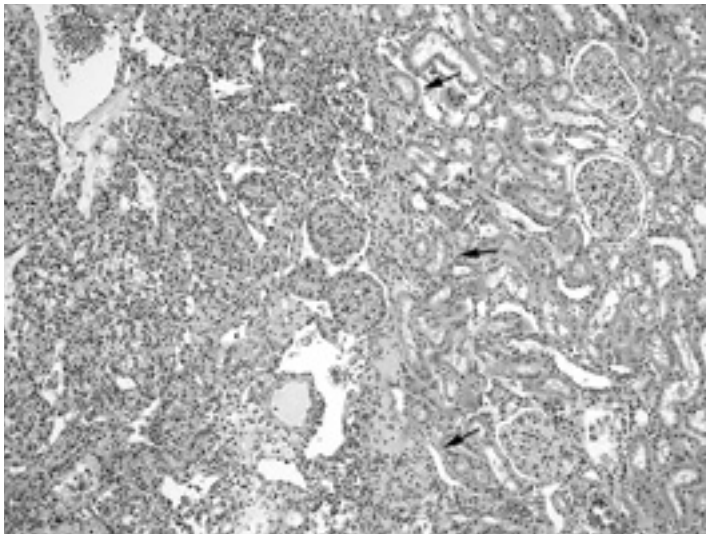


PLATE 12
Higher magnification of Plate 11. The carcinoma (left of arrows) has a pleomorphic growth pattern with the neoplastic cells forming tubules, cords, and solid areas. H&E; 10×

DISCUSSION AND CONCLUSIONS

The toxicology of methyl isobutyl ketone has been extensively studied. However, in spite of its high production volume and exposure profile, there are no reports in the literature that investigate the effects of chronic inhalation exposure to methyl isobutyl ketone. In order to complement the safety information available for this compound, the National Cancer Institute and the United States Environmental Protection Agency (USEPA) nominated methyl isobutyl ketone to the National Toxicology Program for toxicity and carcinogenicity studies.

A series of prechronic studies (Bushy Run Research Center, 1983; Phillips *et al*., 1987) served as the basis for selection of the exposure concentrations used for these 2-year studies. Male and female F344/N rats and $B6C3F_1$ mice were exposed by whole body inhalation to methyl isobutyl ketone concentrations of 0, 100, 500, or 2,000 ppm, 6 hours/day for 14 days. Although treatment-related changes in body weights did not occur, the liver weights of exposed male and female rats and kidney weights of male rats exposed to 500 or 2,000 ppm were increased. Similar liver weight changes occurred in female mice. Histological examination revealed the presence of tubular epithelial regeneration and hyaline droplet accumulation in the kidneys of male rats exposed to 500 or 2,000 ppm. In addition, an increased number of mitotic figures were detected in the livers of two of six male and one of six female rats in the 2,000 ppm groups.

In a subsequent subchronic study, Phillips *et al*. (1987) exposed animals via inhalation to concentrations of 0, 50, 250, or 1,000 ppm methyl isobutyl ketone, 6 hours/day, 5 days per week for 14 weeks. The only microscopic finding reported was an increase in the incidence and extent of hyaline droplet accumulation within the epithelial cells of the proximal tubules in the kidneys of male rats exposed to 250 or 1,000 ppm. Similar to the results observed in the 2-week study, liver and kidney weights were significantly increased in animals exposed to 250 or 1,000 ppm; however, no statistically significant differences were observed in body weights throughout the study.

Although substantial pathologic changes or neurotoxic effects were not found in animals exposed to 2,000 or 1,000 ppm methyl isobutyl ketone, it was anticipated that 2,000 ppm would probably exceed the maximum tolerated dose for a 2-year exposure period. Therefore, 1,800 ppm was selected as the highest exposure concentration for the current studies. The other exposure concentrations were spaced by half to detect potential exposure-related relationships.

In the current 2-year study, exposure of male rats to 1,800 ppm methyl isobutyl ketone resulted in decreased survival compared to that of the chamber controls. Malignant and benign proliferative lesions in the kidney of male rats and increased incidences of chronic nephropathy in all exposed groups of male and female rats indicated that the kidney was the target organ for methyl isobutyl ketone. Although chronic nephropathy is one of the most commonly recognized spontaneous lesions in the rat (Seely *et al*., 2002), this condition can be exacerbated by chemical exposure, leading to increased incidences and average severities of this spontaneous disease (Lock and Hard, 2004).

In the current study, although chronic nephropathy was observed in almost all male rats including the chamber controls, nephropathy was most severe in the 1,800 ppm group. The average severity of nephropathy was moderate in the 1,800 ppm group while the average severity in the chamber control group was mild. Although chronic nephropathy as a syndrome is more prevalent and severe in male rats, there were exposure-related increased incidences of minimal to mild chronic nephropathy in all exposed groups of females.

Increased incidences of exposure-related renal tubule hyperplasia and renal tubule adenomas, and the occurrence of renal tubule carcinomas in the current 2-year study provide some evidence of carcinogenicity of methyl isobutyl ketone in male rats. In the standard single-section evaluation of the kidney, males exposed to 900 or 1,800 ppm had marginal increased incidences of renal tubule adenoma, carcinoma, and adenoma or carcinoma (combined). Subsequent extended evaluation of

kidney step sections in male rats revealed additional incidences of renal tubule adenomas in all groups. The extended evaluation also revealed additional incidences of renal tubule hyperplasia in all exposed groups of males with the incidence in the 1,800 ppm group significantly increased compared to the chamber control group. However, no additional renal tubule carcinomas were identified. Two female rats in the 1,800 ppm group developed renal mesenchymal tumors. Although these rare neoplasms have not been previously observed in chamber controls, the occurrence of only two neoplasms makes the relationship to methyl isobutyl ketone exposure unclear.

The variety of kidney lesions described in the literature after subchronic exposures to methyl isobutyl ketone suggests that the tumorigenic effect observed in the kidney in the current 2-year study may be related to a form of nephropathy known as α2u-globulin nephropathy, a spontaneous renal syndrome that is commonly seen in male rats. In α2u-globulin nephropathy, renal toxicity is associated with the accumulation of hyaline protein droplets in the cytoplasm of the proximal tubule epithelium (Montgomery and Seely, 1990). The physiopathology, diagnostic characteristics, and relevance of this syndrome in human risk assessment have been extensively discussed in the literature (USEPA, 1991; IARC, 1999). Briefly, the xenobiotic or its metabolites bind reversibly and specifically with the protein α2u-globulin, which is synthesized predominantly in the liver under multihormonal, but mainly androgen, control. The poorly hydrolyzable complex is freely filtered across the glomerulus and reabsorbed in the proximal tubules where it accumulates within the cytoplasmic phagolysosomes. This accumulation eventually overloads the tubule cell resulting in a cycle of cytotoxicity, apoptosis, cell death, and a compensatory increase in cell proliferation that, if chronic, may lead to the promotion of neoplasia (Swenberg *et al*., 1989; Borghoff *et al*., 1990). It has also been proposed that α2u-globulin may serve as a vector to increase the delivery of a toxicant or protoxicant to proximal tubule cells, so that nephrotoxicity occurs not from the abnormal accumulation and degradation of α2u-globulin, but because chemical levels are elevated in the renal tubules (Melnick, 1992).

The USEPA (1991) has proposed the fulfillment of a specific set of criteria to establish a link between α2u-globulin nephropathy and renal tumorigenesis. The criteria include increases in the number and size of hyaline droplets in renal proximal tubule epithelial cells of treated male rats; that the accumulating protein in the hyaline droplets is α2u-globulin; and a pathologic sequence of renal tubule lesions including formation of linear casts, linear mineralization of the papillary tubule, and renal tubule hyperplasia. Results from the current 2-year study show exposure-related and significantly increased incidences of minimal to mild linear mineralization of the renal papilla tubule epithelium in all groups of exposed male rats, indicating that methyl isobutyl ketone meets at least one of the required criteria. In addition, there were increased incidences of transitional epithelial hyperplasia in the renal pelvis of male rats exposed to 900 or 1,800 ppm. Minimal hyaline droplet accumulation was observed in two 900 ppm and two 1,800 ppm male rats that died relatively early in the study. Although the hallmarks of α2u-globulin syndrome are the increases in the size and number of lysosomes filled with α2u-globulin, the increase in hyaline droplets diminishes with age and is not expected to be detectable in aged rats in a 2-year study (USEPA, 1991).

As previously mentioned, published studies have suggested an association between the α2u-globulin syndrome and the nephrotoxicity of methyl isobutyl ketone. Phillips *et al*. (1987) reported characteristic hyaline droplets in the kidneys of Fischer 344 male rats exposed via inhalation to 250 or 1,000 ppm methyl isobutyl ketone for 14 weeks. Similarly, increased absolute and relative kidney weights of male (but not female) rats and histologic changes suggestive of nephropathy were clearly present in Sprague-Dawley rats exposed to 1,000 or 2,000 ppm methyl isobutyl ketone for at least 70 days (Nemec *et al*., 2004). However, α2u-globulin levels were not measured in either of these studies. Although the variety of pathologic changes described in exposed male rats in the current 2-year study are characteristic of the spectrum of lesions described in the α2u-globulin-induced nephropathy, the exposure-related increased incidences of chronic nephropathy in the female rats indicate that the exposure-related nephropathy also occurred independent of the α2u-globulin mechanism. Female rats produce scant if any hepatic α2u-globulin and thus do not develop α2u-globulin nephropathy (MacInnes *et al*., 1986; Chatterjee *et al*., 1989; Lehman-McKeeman and Caudill, 1992). Additional research is needed to characterize the binding of methyl isobutyl ketone to α2u-globulin and to clarify the role of α2u-globulin in the observed tumor outcome in male rats in the current 2-year study.

Other findings reported in male rats included a positive trend in the incidence of mononuclear cell leukemia. Incidences of this common neoplasm in the chamber control group of animals were not different from those observed in the chamber controls in the historical database. Although the incidences were statistically significant in the highest exposure group, the strength of the

response was insufficient to allow a definitive association with chemical exposure.

In addition, exposed male rats exhibited exposure-related increased incidences of adrenal medulla hyperplasia, as well as increased incidences of benign or malignant pheochromocytomas. Nemec *et al.* (2004) reported significant changes in adrenal gland weights of Sprague-Dawley male rats exposed to 2,000 ppm methyl isobutyl ketone for 70 days. In the current study, the incidences of pheochromocytomas were not statistically significant, were within the historical control range, and the incidences of adrenal hyperplasia were statistically significant only in the highest exposure group. Because the biological significance of this finding is not certain, these slight increases were not considered to be related to exposure.

Exposure to concentrations of 450, 900, or 1,800 ppm methyl isobutyl ketone did not cause notable in-life toxicity in either sex of B6C3F$_1$ mice. No clinical signs related to chemical exposure were recorded, and the survival of exposed animals was comparable to that of the chamber controls. Although females exposed to 1,800 ppm had consistently lower mean body weights after approximately 4 months on study, the mean body weights of the other exposed groups of males and females were similar to those of the chamber controls throughout the study.

In the current 2-year study in mice, increased incidences of eosinophilic foci of the liver occurred in all groups of females, with significantly increased incidences in the 450 and 1,800 ppm groups. Hepatic foci are more frequently observed in mice treated with hepatocarcinogens than untreated controls, and although there is evidence linking these lesions to the development of hepatocellular neoplasms, their exact role in hepatocarcinogenesis is still uncertain (Harada *et al*., 1999). In general, these lesions precede the development of hepatic neoplasms and may increase in incidence and multiplicity with time and administration of liver carcinogens. However, while some foci progress to neoplasia, others regress when the inciting carcinogenic stimulus is removed.

In addition, hepatocellular adenomas and carcinomas were diagnosed in all exposed groups of male and female mice in the current 2-year study. In males and females exposed to 1,800 ppm, there were significantly increased incidences of hepatocellular adenoma, and the incidences exceeded the historical control ranges. Of particular interest was the number of mice of both sexes that exhibited multiple hepatocellular adenomas in the 1,800 ppm groups (30% vs. 12% for males and 28% vs. 2% for females). Although hepatocellular adenoma is the most frequent spontaneous liver neoplasm in B6C3F$_1$ mice, the number of neoplasms detected in mice exposed to 1,800 ppm and the positive trends in the multiplicity observed in exposed males and females provide some evidence of carcinogenic effect of methyl isobutyl ketone in mice.

Findings reported in the current study are consistent with those from subchronic studies suggesting the liver as the target organ of methyl isobutyl ketone-related toxicity in mice. Exposure to vapor concentrations of 2,000 ppm methyl isobutyl ketone for 14 days resulted in increased hepatic mitosis in female mice (Phillips *et al*., 1987). The liver was again recognized as a target organ in the subsequent 14-week study, in which males exposed to 1,000 ppm had a slight but statistically significant increase in absolute and/or relative liver weight; however, no gross or microscopic hepatic lesions were observed in any group (Phillips *et al*., 1987). More recently, Nemec *et al*. (2004) reported exposure-related increases in absolute and relative liver weights of male and female Sprague-Dawley rats exposed to 2000 ppm methyl isobutyl ketone for 70 days and correlating exposure-related centrilobular hepatocellular hypertrophy in males exposed to 500, 1,000, or 2,000 ppm. The significance of hepatocellular hypertrophy in the liver carcinogenic response is not completely understood. Although it has been considered an adaptive response to excessive metabolic load (Schulte-Hermann, 1974), histologic evaluation of the results from the current 2-year study did not find evidence of hepatocellular hypertrophy in livers of mice chronically exposed to methyl isobutyl ketone. A recent survey of 111 NTP studies over a 10-year period identified hepatocellular hypertrophy as the best single predictor of liver cancer (Allen *et al.,* 2004).

Methyl isobutyl ketone induces various cytochrome P450 isozymes, which may explain the liver lesions found in mice exposed to this chemical. The highest induction was in isozymes that were inducible by either phenobarbital or β-naphthoflavone (Lapadula *et al*., 1991). Two metabolites, 2-methyl-2-pentanol and 2-hydroxymethyl isobutyl ketone, were reported to be more potent than methyl isobutyl ketone for enhancing chloroform-induced hepatotoxicity (Vezina *et al*., 1990).

Both methyl isobutyl ketone and its metabolites have potentiated intrahepatic cholestasis induced by taurolithocholic acid, a combination of manganese and bilirubin, and manganese alone (Vezina and Plaa, 1988). Finally, Raymond and Plaa (1995b) reported increases in two additional isozymes associated with increased aminopyrine *N*-demethylation activity in both liver and kidney, and increased benzphetamine *N*-demethylation activity in the liver.

CONCLUSIONS

Under the conditions of these 2-year studies, there was *some evidence of carcinogenic activity** of methyl isobutyl ketone in male F344/N rats based on increased incidences of renal tubule neoplasms. Increased incidences of mononuclear cell leukemia in 1,800 ppm male F344/N rats may have been related to methyl isobutyl ketone exposure. There was *equivocal evidence of carcinogenic activity* of methyl isobutyl ketone in female F344/N rats based on the occurrence of renal mesenchymal tumors in the 1,800 ppm group. There was *some evidence of carcinogenic activity* of methyl isobutyl ketone in male and female $B6C3F_1$ mice based on increased incidences of liver neoplasms.

Exposure to methyl isobutyl ketone resulted in nonneoplastic lesions of the kidney characteristic of α2u-globulin accumulation in male rats and nephropathy in female rats.

---

* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and public discussion on this Technical Report appears on page 12.

REFERENCES

Abou-Donia, M.B., Lapadula, D.M., Campbell, G., and Timmons, P.R. (1985). The synergism of *n*-hexane-induced neurotoxicity by methyl isobutyl ketone following subchronic (90 days) inhalation in hens: Induction of hepatic microsomal cytochrome P-450. *Toxicol. Appl. Pharmacol.* **81**, 1-16.

The Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra (1993). Vol. 1, 2nd ed., p. 633(C). Aldrich Chemical Co., Inc., Milwaukee, WI.

The Aldrich Library of FT-IR Collection (1997). Vol. 1, 2nd ed., p. 642(A). Aldrich Chemical Co., Inc., Milwaukee, WI.

Allen, D.G., Pearse, G., Haseman, J.K., and Maronpot, R.R. (2004). Prediction of rodent carcinogenesis: An evaluation of prechronic liver lesions as forecasters of liver tumors in NTP carcinogenicity studies. *Toxicol. Pathol*. **32**, 393-401.

American Conference of Governmental Industrial Hygenists (ACGIH) (2005). *TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*. ACGIH, Cincinnati, OH.

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.

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.

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

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 $\alpha_{2\mu}$-globulin nephropathy. *Annu. Rev. Pharmacol. Toxicol*. **30**, 349-367.

Brown, K.W., and Donnelly, K.C. (1988). An estimation of the risk associated with the organic constituents of hazardous and municipal waste landfill leachates. *Hazardous Waste Hazardous Mater.* **5**, 1-30.

Bushy Run Research Center (1983). Methyl Isobutyl Ketone. Ninety-day Inhalation Study on Rats and Mice. Project Report 46-504.

Chatterjee, B., Demyan, W.F., Song, C.S., Garg, B.D., and Roy, A.K. (1989). Loss of androgenic induction of $\alpha_{2\mu}$-globulin gene family in the liver of NIH black rats. *Endocrinology* **125**, 1385-1388.

Chemical Manufacturers Association (CMA) (1997). Dossier, SIDS Profile Summary, and SIAR for MIBK. CMA, Washington, DC.

Chemical Market Reporter (CMR) (2004). Schnell Publishing Co., Inc., New York.

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

Commission of the European Communities (CEC) (1976). Analysis of Organic Micropollutants in Water. CEC, Luxembourg.

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.

David, R.M., Bernard, L.G., Banton, M.I., Tyler, T.R., Topping, D.C., Gill, M.W., and O'Donoghue, J.L. (1999). The effect of repeated methyl isobutyl ketone vapor exposure on schedule-controlled operant behavior in rats. *Neurotoxicology* **20**, 583-593.

De Ceaurriz, J.C., Micillino, J.C., Bonnet, P., and Guenier, J.P. (1981). Sensory irritation caused by various industrial airborne chemicals. *Toxicol. Lett.* **9**, 137-143.

Dick, R.B., Krieg, E.F., Jr., Setzer, J., and Taylor, B. (1992). Neurobehavioral effects from acute exposures to methyl isobutyl ketone and methyl ethyl ketone. *Fundam. Appl. Toxicol.* **19**, 453-473.

DiVincenzo, G.D., Kaplan, C.J., and Dedinas, J. (1976). Characterization of the metabolites of methyl *n*-butyl ketone, methyl iso-butyl ketone, and methyl ethyl ketone in guinea pig serum and their clearance. *Toxicol. Appl. Pharmacol*. **36**, 511-522.

Dodd, D.E., Longo, L.C., and Eisler, D.L. (1982). Nine-day vapour inhalation study on rats and mice. Bushy Run Research Center, Report 45-501, submitted to U.S. Environmental Protection Agency. Chemical Manufacturers Association, Washington, DC.

Duguay, A.B., and Plaa, G.L. (1995). Tissue concentrations of methyl isobutyl ketone, methyl *n*-butyl ketone and their metabolites after oral or inhalation exposure. *Toxicol. Lett.* **75**, 51-58.

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

Francis, A.J., Iden, G.T., Nine, B.J., and Chang, C.K. (1980). Characterization of organics in leachates from low level radioactive waste disposal sites. *Nucl. Technol.* **50**, 158-163.

Frostling, H., Hoff, A., Jacobsson, S., Pfaffli, P., Vainiotalo, S., and Zitting, A. (1984). Analytical, occupational and toxicologic aspects of the degradation products of polypropylene plastics. *Scand. J. Work Environ. Health* **10**, 163-169.

Furia, T.E., and Bellanca, N., Eds. (1975). *Fenaroli's Handbook of Flavor Ingredients*, 2nd ed. CRC Press, Inc., Cleveland, OH.

Gagnon, P., Mergler, D., and Lapare, S. (1994). Olfactory adaptation, threshold shift and recovery at low levels of exposure to methyl isobutyl ketone (MIBK). *Neurotoxicology* **15**, 637-642.

Garman, J.R., Freund, T., and Lawless, E.W. (1987). Testing for groundwater contamination at hazardous waste sites. *Chromatogr. Sci.* **25**, 328-344.

Granvil, C.P., Sharkawi, M., and Plaa, G.L. (1994). Metabolic fate of methyl *n*-butyl ketone, methyl isobutyl ketone and their metabolites in mice. *Toxicol. Lett.* **70**, 263-267.

Hampton, C.V., Pierson, W.R., Harvey, T.M., Updegrove, W.S., and Marano, R.S. (1982). Hydrocarbon gases emitted from vehicles on the road. 1. A qualitative gas chromatography/mass spectroscopy survey. *Environ. Sci. Technol.* **16**, 287-298.

Harada, T., Enomoto, A., Boorman, G.A., and Maronpot, R.R. (1999). Liver and gallbladder. In *Pathology of the Mouse. Reference and Atlas* (R.R. Maronpot, G.A. Boorman, and B.W. Gaul, Eds.), pp. 119-183. Cache River Press, Vienna, IL.

Hard, G.C., Alden, C.L., Stula, E.F., and Trump, B.F. (1995). Proliferative lesions of the kidney in rats. In *Guides for Toxicologic Pathology*. STP/ARP/AFIP, Washington, DC.

Hjelm, E.W., Hagberg, M., Iregren, A., and Lof, A. (1990). Exposure to methyl isobutyl ketone: Toxicokinetics and occurrence of irritative and CNS symptoms in man. *Int. Arch. Occup. Environ. Health* **62**, 19-26.

Hjelm, E.W., Boman, A., Fernstrom, P., Hagberg, M., and Johanson, G. (1991). Percutaneous uptake and kinetics of methyl isobutyl ketone (MIBK) in the guinea-pig. *Toxicol. Lett.* **56**, 79-86.

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

International Agency for Research on Cancer (IARC) (1999). Concensus report. In *Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis* (C.C. Capen, E. Dybing, J.M. Rice, and J.D. Willbourn, Eds.). IARC Scientific Publication No.-147. IARC, Lyon, France.

International Labour Office (ILO) (1971). Encyclopedia of Occupational Health and Safety. McGraw Hill, New York.

International Programme on Chemical Safety (IPCS) (1990). Environmental Health Criteria 117: Methyl Isobutyl Ketone. World Health Organization, Geneva, Switzerland.

Iregren, A., Tesarz, M., and Wigaeushjelm, E. (1993). Human experimental MIBK exposure: Effects on heart rate, performance, and symptoms. *Environ. Res.* **63**, 101-108.

Johnson, W., Jr. (2004). Safety assessment of MIBK (methyl isobutyl ketone). *Int. J. Toxicol.* **23** (Suppl. 1), 29-57.

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

Krasavage, W.J., O'Donoghue, J.L., and DiVicenzo, G.D. (1982). Methyl isobutyl ketone. In *Patty's Industrial Hygiene and Toxicology* (G.D. Clayton and F.E. Clayton, Eds.), Vol.-2E, pp. 4747-4751. John Wiley and Sons, New York.

Krishnan, K., Brodeur, J., Plaa, G.L., and Charbonneau, M. (1992). Modulation of hexachlorobenzene-induced hepatic porphyria by methyl isobutyl ketone in the rat. *Toxicol. Lett.* **61**, 167-174.

Lande, S.S., Durkin, P.R., Christopher, D.H., Howard, P.H., and Saxena, J. (1976). Investigation of selected potential environmental contaminants: Ketones solvents. NTIS Public Report #252970.

Lapadula, D.M., Habig, C., Gupta, R.P., and Abou-Donia, M.B. (1991). Induction of cytochrome P450 isozymes by simultaneous inhalation exposure of hens to *n*-hexane and methyl isobutyl ketone (MiBK). *Biochem. Pharmacol.* **41**, 877-883.

Lehman-McKeeman, L.D., and Caudill, D. (1992). Biochemical basis for mouse resistance to hyaline droplet nephropathy: Lack of relevance of the $\alpha_{2\mu}$-globulin superfamily in this male rat-specific syndrome. *Toxicol. Appl. Pharmacol*. **112**, 214-221.

Lock, E.A., and Hard, G.C. (2004). Chemically induced renal tubule tumors in the laboratory rat and mouse: Review of the NCI/NTP database and categorization of renal carcinogens based on mechanistic information. *Crit. Rev. Toxicol*. **34**, 211-299.

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.

MacEwen, J.D., Vernot, E.H., and Haun, C.C. (1971). Effects of 90-day continuous exposure to methyl isobutyl ketone on dogs, monkeys, and rats. AD Report, ISS No.-730291, U.S. National Technical Information Service, Springfield, VA.

MacInnes, J.I., Nozik, E.S., and Kurtz, D.T. (1986). Tissue-specific expression of the rat alpha$_{2\mu}$ globulin gene family. *Mol. Cell. Biol*. **6**, 3563-3567.

Malysheva, M.V. (1988). The effect of the methods of cutaneous administration of methyl isobutyl ketone on its toxicity. *Gig. Sanit.* **10**, 79-80.

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 the chemically induced protein droplet ($\alpha_{2\mu}$-globulin) nephropathy in renal carcinogenesis. *Regul. Toxicol. Pharmacol*. **16**, 111-125.

The Merck Index (1989). 11th ed., (S. Budavri, Ed.). Merck and Company, Rahway, NJ.

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.

Montgomery, C.A., Jr., and Seely, J.C. (1990). Kidney. In *Pathology of the Fischer Rat. Reference and Atlas* (G.A. Boorman, S.L. Eustis, M.R. Elwell, C.A. Montgomery, Jr., and W.F. Mackenzie, Eds.), pp. 127-153. Academic Press, Inc., San Diego.

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 of Standards and Technology (NIST), Environmental Protection Agency (EPA), National Institute of Health (NIH) Mass Spectral Database (1994). Standard reference database 1A, standard reference data program. U.S. Department of Commerce, Gaithersburg, MD.

National Technical Information Service (NTIS) (1985). Scientific Literature Review of Aliphatic Ketones, Secondary Alcohols and Related Esters in Flavor Usage. Vol.-I, Part-2, PB85-141059. NTIS, Washington, DC.

Nemec, M., Pitt, J., Topping, D., Gingell, R., Pavkov, K., Rauckman, E., and Harris, S. (2004). Inhalation two-generation reproductive toxicity study of methyl isobutyl ketone in rats. *Intl. J. Toxicol*. **23**, 127-143.

O'Donoghue, J.L., Haworth, S.R., Curren, R.D., Kirby, P.E., Lawlor, T., Moran, E.J., Phillips, R.D., Putnam, D.L., Rogers-Back, A.M., Slesinski, R.S., and Thilagar, A. (1988). Mutagenicity studies on ketone solvents: Methyl ethyl ketone, methyl isobutyl ketone, and isophorone. *Mutat. Res.* **206**, 149-161.

Osol, A., Chase, G.D., Gennaro, A.R., Gibson, M.R., Granberg, C.B., Harvey, S.C., King, R.E., Martin, A.N., Swinyard, E.A., and Zink, G.L., Eds. (1980). *Remington's Pharmaceutical Sciences*. Philadelphia College of Pharmacy and Science, Philadelphia.

Pellizzari, E.D., Hartwell, T.D., Harris, B.S.H., Waddell, R.D., Whitaker, D.A., and Erickson, M.D. (1982). Purgeable organic compounds in mothers' milk. *Bull. Environ. Contam. Toxicol.* **28**, 322-328.

Phillips, R.D., Moran, E.J., Dodd, D.E., Fowler, E.H., Kary, C.D., and O'Donoghue, J. (1987). A 14-week vapor inhalation toxicity study of methyl isobutyl ketone. *Fundam. Appl. Toxicol.* **9**, 380-388.

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

Plaa, G.L., and Ayotte, P. (1985). Taurolithocholate-induced intrahepatic cholestasis: Potentiation by methyl isobutyl ketone and methyl *n*-butyl ketone in rats. *Toxicol. Appl. Pharmacol.* **80**, 228-234.

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.

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.

Raymond, P., and Plaa, G.L. (1995a). Ketone potentiation of haloalkane-induced hepato- and nephrotoxicity. I. Dose-response relationships. *J. Toxicol. Environ. Health* **45**, 465-480.

Raymond, P., and Plaa, G.L. (1995b). Ketone potentiation of haloalkane-induced hepato- and nephrotoxicity. II. Implication of monooxygenases. *J. Toxicol. Environ. Health* **46**, 317-328.

Ruth, J.H. (1986). Odor thresholds and irritation levels of several chemical substances: A review. *Am. Ind. Hyg. Assoc. J.* **47**, A142-A151.

Sawhney, B.L., and Kozloski, R.P. (1984). Organic pollutants in leachates from landfill sites. *J. Environ. Qual.* **13**, 349-352.

Schulte-Hermann, R. (1974). Induction of liver growth by xenobiotic compounds and other stimuli. *Crit. Rev. Toxicol*. **3**, 97-158.

Seely, J.C., Haseman, J.K., Nyska, A., Wolf, D.C., Everitt, J.I., and Hailey, J.R. (2002). The effect of chronic progressive nephropathy on the incidence of renal tubule cell neoplasms in control male F344 rats. *Toxicol. Pathol*. **30**, 681-686.

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

Swann, R.L., Laskowski, D.A., McCall, P.J., Vanderkuy, K., and Dishburger, H.J. (1983). A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. *Residues Rev.* **85**, 17-28.

Swenberg, J.A., Short, B., Borghoff, S., Strasser, J., and Charbonneau, M. (1989). The comparative pathobiology of $\alpha_{2\mu}$-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.

Topping, D.C., et al. (2001). Ketones of six to thirteen carbons. In *Patty's Toxicology* (E. Bingham, B. Cohrssen, and C.H. Powell, Eds.), Vol. 6. John Wiley and Sons, New York.

Tyl, R.W., France, K.A., Fisher, L.C., Pritts, I.M., Tyler, T.R., Phillips, R.D., and Moran, E.J. (1987). Developmental toxicity evaluation of inhaled methyl isobutyl ketone in Fischer 344 rats and CD-1 mice. *Fundamen. Appl. Toxicol.* **8**, 310-327.

U.S. Environmental Protection Agency (USEPA) (1991). Alpha$_{2\mu}$-globulin: Association with chemically induced renal toxicity and neoplasia in the male rat. EPA 625/3-91/019F. Risk Assessment Forum. U.S. EPA, Washington, DC.

Vernot, E.H., MacEwen, J.D., and Harris, E.S. (1971). Continuous Exposure of Animals to Methyl Isobutyl Ketone Vapors. AD Report, ISS No. 751443, p. 11. National Technical Information Service, Springfield, VA.

Verschueren, K. (1983). *Handbook of Environmental Data on Organic Chemicals*, 2nd ed., pp. 459-461. Van Nostrand Reinhold Co., New York.

Vezina, M., and Plaa, G.L. (1988). Methyl isobutyl ketone metabolites and potentitation of the cholestasis induced in rats by a manganese-bilirubin combination or manganese alone. *Toxicol. Appl. Pharmacol*. **92**, 419-427.

Vezina, M., Kobusch, A.B., du Souich, P., Greselin, E., and Plaa, G.L. (1990). Potentiation of chloroform-induced hepatotoxicity by methyl isobutyl ketone and two metabolites. *Can. J. Physiol. Pharmacol*. **68**, 1055-1061.

Whitehead, L.W., Ball, G.L., Fine, L.J., and Langolf, G.D. (1984). Solvent vapor exposures in booth spray painting and spray glueing, and associated operations. *Am. Ind. Hyg. Assoc. J.* **45**, 767-772.

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.

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 METHYL ISOBUTYL KETONE

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone[a]

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death		1		
Moribund	14	16	21	29
Natural deaths	4	5	4	2
Survivors				
Terminal sacrifice	32	28	25	19
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, rectum	(49)	(48)	(50)	(50)
Adenoma			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Hepatocellular adenoma	1 (2%)			1 (2%)
Histiocytic sarcoma		2 (4%)		
Oral mucosa	(2)			
Squamous cell carcinoma	1 (50%)			
Pancreas	(50)	(48)	(50)	(50)
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Sarcoma, metastatic, lung		1 (2%)		
Schwannoma malignant	1 (2%)			
Endocrine System				
Adrenal cortex	(50)	(48)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Adrenal medulla	(50)	(48)	(50)	(50)
Pheochromocytoma malignant		2 (4%)	1 (2%)	2 (4%)
Pheochromocytoma benign	7 (14%)	4 (8%)	6 (12%)	11 (22%)
Bilateral, pheochromocytoma benign	1 (2%)	3 (6%)	4 (8%)	1 (2%)
Islets, pancreatic	(50)	(48)	(50)	(50)
Adenoma	3 (6%)	4 (8%)	1 (2%)	1 (2%)
Carcinoma	4 (8%)	2 (4%)	2 (4%)	1 (2%)
Pituitary gland	(50)	(49)	(50)	(50)
Adenoma	35 (70%)	29 (59%)	30 (60%)	29 (58%)
Thyroid gland	(50)	(48)	(50)	(50)
C-cell, adenoma	1 (2%)	4 (8%)		4 (8%)
C-cell, carcinoma	2 (4%)	3 (6%)		1 (2%)
Follicular cell, carcinoma	1 (2%)	2 (4%)	2 (4%)	
General Body System				
Peritoneum	(48)	(46)	(49)	(49)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Genital System				
Epididymis	(50)	(49)	(50)	(50)
Preputial gland	(50)	(49)	(50)	(50)
Carcinoma	1 (2%)		1 (2%)	
Testes	(50)	(50)	(50)	(50)
Bilateral, interstitial cell, adenoma	28 (56%)	34 (68%)	37 (74%)	38 (76%)
Interstitial cell, adenoma	14 (28%)	8 (16%)	7 (14%)	10 (20%)
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Histiocytic sarcoma		1 (2%)		
Lymph node	(7)	(7)	(12)	(15)
Deep cervical, carcinoma, metastatic, thyroid gland		1 (14%)		1 (7%)
Lymph node, bronchial	(11)	(13)	(12)	(7)
Carcinoma, metastatic, thyroid gland			1 (8%)	
Sarcoma, metastatic, lung		1 (8%)		
Lymph node, mandibular	(1)	(1)	(3)	(2)
Lymph node, mesenteric	(50)	(48)	(50)	(50)
Lymph node, mediastinal	(41)	(44)	(46)	(44)
Carcinoma, metastatic, thyroid gland		1 (2%)		
Sarcoma, metastatic, lung		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Histiocytic sarcoma		1 (2%)		
Schwannoma malignant, metastatic, heart	1 (2%)			
Thymus	(49)	(47)	(50)	(49)
Carcinoma, metastatic, thyroid gland		1 (2%)		
Schwannoma malignant, metastatic, heart	1 (2%)			
Integumentary System				
Mammary gland	(49)	(49)	(50)	(50)
Carcinoma	2 (4%)	1 (2%)		1 (2%)
Fibroadenoma	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Skin	(50)	(49)	(50)	(50)
Basal cell adenoma				1 (2%)
Basal cell carcinoma		1 (2%)		
Fibrous histiocytoma				1 (2%)
Keratoacanthoma			1 (2%)	
Sarcoma		1 (2%)		1 (2%)
Squamous cell papilloma			1 (2%)	
Sebaceous gland, adenoma	1 (2%)			1 (2%)
Subcutaneous tissue, fibroma	4 (8%)	1 (2%)	2 (4%)	2 (4%)
Subcutaneous tissue, fibrosarcoma	1 (2%)	2 (4%)		
Musculoskeletal System				
Skeletal muscle	(3)	(3)	(4)	(6)
Sarcoma, metastatic, lung		1 (33%)		
Schwannoma malignant, metastatic, heart	1 (33%)			

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Nervous System				
Brain	(50)	(49)	(50)	(50)
Glioma malignant		1 (2%)		
Granular cell tumor malignant			1 (2%)	
Respiratory System				
Larynx	(50)	(48)	(50)	(50)
Carcinoma, metastatic, thyroid gland		1 (2%)		
Lung	(50)	(49)	(50)	(50)
Alveolar/bronchiolar carcinoma				2 (4%)
Carcinoma, metastatic, mammary gland		1 (2%)		
Carcinoma, metastatic, thyroid gland			1 (2%)	
Carcinoma, metastatic, Zymbal's gland				1 (2%)
Fibrosarcoma, metastatic, skin	1 (2%)			
Schwannoma malignant, metastatic, heart	1 (2%)			
Mediastinum, sarcoma		2 (4%)		
Mediastinum, schwannoma malignant, metastatic, heart	1 (2%)			
Pleura	(50)	(49)	(50)	(50)
Schwannoma malignant, metastatic, heart	1 (2%)			
Special Senses System				
Eye	(49)	(45)	(46)	(48)
Carcinoma, metastatic, oral mucosa	1 (2%)			
Zymbal's gland	(1)			(2)
Carcinoma	1 (100%)			2 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Renal tubule, adenoma			2 (4%)	3 (6%)
Renal tubule, carcinoma		1 (2%)		2 (4%)
Urinary bladder	(50)	(48)	(50)	(50)
Leiomyoma				1 (2%)
Transitional epithelium, papilloma	1 (2%)			1 (2%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma		2 (4%)		
Leukemia mononuclear	25 (50%)	26 (52%)	32 (64%)	35 (70%)
Mesothelioma malignant	1 (2%)	1 (2%)		1 (2%)

TABLE A1
Summary of the Incidence of Neoplasms in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	50	48	49	50
Total primary neoplasms	139	136	133	154
Total animals with benign neoplasms	50	47	47	49
Total benign neoplasms	99	89	94	105
Total animals with malignant neoplasms	31	35	34	41
Total malignant neoplasms	40	47	39	49
Total animals with metastatic neoplasms	3	3	1	2
Total metastatic neoplasms	8	9	2	2

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

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

+: 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 Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	0 1 3	0 2 0	0 2 2	0 2 4	0 2 9	0 3 0	0 3 3	0 4 4	0 4 6	0 5 0	0 0 3	0 0 7	0 1 0	0 1 6	0 1 8	0 2 1	0 2 6	0 3 1	0 3 2	0 3 4	0 3 6	0 4 0	0 4 3	0 4 8	0 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X																			1
Mesentery		+				+				+				+			+					+				10
Oral mucosa																										2
Squamous cell carcinoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue	+																									1
Tooth																										1
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign		X		X	X																		X			7
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				3
Carcinoma					X				X																	4
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X	X	X	X	X	X		X	X	X		X		X			X		X		X	X			35
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																										1
C-cell, carcinoma				X																						2
Follicular cell, carcinoma							X																			1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tissue NOS																					+					1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	4 6 8	4 9 2	5 0 5	5 5 4	5 5 8	5 9 2	6 2 4	6 2 9	6 7 1	6 7 9	6 7 9	6 8 7	6 8 7	7 0 1	7 0 2	7 0 2	7 1 3	7 2 3	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6
Carcass ID Number	0 4 5	0 4 2	0 3 9	0 4 7	0 3 5	0 2 8	0 2 5	0 1 4	0 3 8	0 0 8	0 4 1	0 1 5	0 2 7	0 1 7	0 1 9	0 3 7	0 0 6	0 2 3	0 0 1	0 0 2	0 0 4	0 0 5	0 0 9	0 1 1	0 1 2
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						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							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	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Schwannoma malignant, metastatic, heart						X																			
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, heart						X																			
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																					X				
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																					X				
Subcutaneous tissue, fibrosarcoma																									X
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+										+									
Schwannoma malignant, metastatic, heart						X																			
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																+									
Spinal cord																+									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	726	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	01 13	00 20	00 22	00 24	00 29	00 30	00 33	00 44	00 46	00 50	00 03	00 07	00 10	01 16	01 18	02 21	02 26	03 01	03 32	03 34	03 36	04 00	04 43	04 48	04 49	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	X	28
Interstitial cell, adenoma		X	X	X									X						X		X					14
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	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	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	M	+	M	+	+	+	+	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma		X																								1
Schwannoma malignant, metastatic, heart																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Schwannoma malignant, metastatic, heart																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																	X									2
Fibroadenoma					X	X																				2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sebaceous gland, adenoma													X													1
Subcutaneous tissue, fibroma												X						X				X				4
Subcutaneous tissue, fibrosarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle										+																3
Schwannoma malignant, metastatic, heart																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve										+																2
Spinal cord										+																2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	4 6 8	4 9 2	5 0 5	5 5 4	5 5 8	5 9 2	6 2 4	6 2 9	6 7 1	6 7 9	6 7 9	6 8 7	6 8 7	7 0 1	7 0 2	7 0 2	7 1 3	7 2 3	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6
Carcass ID Number	0 4 5	0 4 2	0 3 9	0 4 7	0 3 5	0 2 8	0 2 5	0 1 4	0 1 3	0 0 8	0 4 1	0 1 5	0 2 7	0 1 7	0 1 9	0 3 7	0 0 6	0 2 3	0 1 1	0 0 2	0 0 4	0 0 5	0 0 9	0 1 1	0 1 2
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic, skin																									X
Schwannoma malignant, metastatic, heart						X																			
Mediastinum, schwannoma malignant, metastatic, heart						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant, metastatic, heart						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, oral mucosa																X									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lacrimal gland						+																			
Zymbal's gland					+																				
Carcinoma					X																				
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma													X												
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X	X			X		X	X	X	X	X	X	X	X				X			X	X		X	
Mesothelioma malignant																									

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	726	726	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	01 13	01 20	01 22	01 24	01 29	01 30	01 33	01 44	01 46	01 50	01 03	01 07	01 10	01 16	01 18	01 21	01 26	01 31	01 32	01 34	01 36	01 40	01 43	01 48	01 49	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrosarcoma, metastatic, skin																										1
Schwannoma malignant, metastatic, heart																										1
Mediastinum, schwannoma malignant, metastatic, heart																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant, metastatic, heart																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	49
Carcinoma, metastatic, oral mucosa																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lacrimal gland																										1
Zymbal's gland																										1
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X			X	X		X			X			X		X			X			X	X			25
Mesothelioma malignant														X												1

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	726	726	726	726	726	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	21 11	21 12	21 17	22 20	22 23	22 24	22 27	23 30	23 36	23 38	24 43	24 45	24 48	21 14	21 16	21 18	22 28	23 31	23 32	23 34	23 35	24 40	24 41	24 44	Total Tissues/ Tumors
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																		X							2
Mesentery	+								+							+	+		+						12
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue														+											1
Cardiovascular System																									
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, lung																									1
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																									1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pheochromocytoma malignant																									2
Pheochromocytoma benign																	X	X					X	X	4
Bilateral, pheochromocytoma benign	X							X																	3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma			X								X						X						X		4
Carcinoma																		X	X						2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X	X	X		X	X	X				X	X	X		X	X	X		X	X		X	X	X	29
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell, adenoma			X					X				X								X					4
C-cell, carcinoma										X							X								3
Follicular cell, carcinoma									X																2
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	46

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	3 3 8	4 0 5	4 2 0	4 7 1	5 5 1	5 9 5	6 0 2	6 0 9	6 1 8	6 2 1	6 2 1	6 3 7	6 5 4	6 5 8	6 5 9	6 6 4	6 7 4	6 7 7	6 8 5	7 0 5	7 2 0	7 2 1	7 2 6	7 2 6	7 2 6
Carcass ID Number	2 1 1 3	2 1 1 9	2 1 2 5	2 2 4 2	2 2 5 0	2 2 0 3	2 2 4 6	2 2 1 1	2 2 4 9	2 2 0 1	2 2 2 6	2 2 2 2	2 2 1 5	2 2 4 7	2 2 2 9	2 2 1 0	2 2 3 9	2 2 0 6	2 2 3 7	2 2 0 7	2 2 0 8	2 2 0 5	2 2 0 2	2 2 0 4	2 2 0 9
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bilateral, interstitial cell, adenoma				X	X	X	X	X			X					X		X	X		X	X	X		X
Interstitial cell, adenoma										X			X	X			X			X					
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Lymph node															+		+			+		+			+
Deep cervical, carcinoma, metastatic, thyroid gland																									
Lymph node, bronchial	M	M	+	M	+	M	M	M	M	+	A	M	M	M	M	+	M	M	M	+	+	+	M	M	M
Sarcoma, metastatic, lung					X																				
Lymph node, mandibular	M	M	M	M	M	M	M	M	M	M	A	M	M	M	M	M	+	M	M	M	M	M	M	M	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Lymph node, mediastinal	M	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	M	+	+	+
Carcinoma, metastatic, thyroid gland																									
Sarcoma, metastatic, lung					X																				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Thymus	+	+	+	+	+	M	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma															X										
Sarcoma				X																					
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, fibrosarcoma																			X						
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle					+	+																			
Sarcoma, metastatic, lung					X																				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Glioma malignant						X																			
Peripheral nerve					+	+																			
Spinal cord					+	+																			

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	726	726	726	726	726	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	21 11	21 12	21 17	22 10	22 23	22 24	22 27	23 10	23 36	23 38	24 43	24 45	24 48	21 14	21 16	21 18	22 28	23 11	23 12	23 33	23 34	23 35	24 40	24 41	24 44	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			X		X	X	X		34
Interstitial cell, adenoma																	X			X		X					8
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Lymph node								+									+										7
Deep cervical, carcinoma, metastatic, thyroid gland																	X										1
Lymph node, bronchial	M	M	M	M	M	M	M	+	M	+	M	M	M	M	M	M	+	M	M	M	+	M	+	+	M		13
Sarcoma, metastatic, lung																											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		1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		44
Carcinoma, metastatic, thyroid gland																	X										1
Sarcoma, metastatic, lung																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
Carcinoma, metastatic, thyroid gland																	X										1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Carcinoma	X																										1
Fibroadenoma																								X	X		2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Basal cell carcinoma																											1
Sarcoma																											1
Subcutaneous tissue, fibroma																								X			1
Subcutaneous tissue, fibrosarcoma											X																2
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Skeletal muscle														+													3
Sarcoma, metastatic, lung																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Glioma malignant																											1
Peripheral nerve														+													3
Spinal cord														+													3

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	3 3 8	4 0 5	4 2 0	4 7 1	5 5 1	5 9 5	6 0 2	6 0 9	6 1 8	6 2 1	6 2 1	6 3 7	6 5 4	6 5 8	6 5 9	6 6 4	6 7 4	6 7 7	6 8 5	7 0 5	7 2 0	7 2 1	7 2 6	7 2 6	7 2 6
Carcass ID Number	2 1 3	2 1 9	2 2 5	2 4 2	2 5 0	2 0 3	2 4 6	2 2 1	2 4 9	2 0 1	2 2 1	2 2 2	2 1 5	2 4 7	2 2 9	2 1 0	2 3 9	2 0 6	2 3 7	2 0 7	2 0 8	2 0 5	2 0 2	2 0 4	2 0 9
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																									
Lung	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, mammary gland																									
Mediastinum, sarcoma	X				X																				
Nose	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	I	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma								X																	
Leukemia mononuclear						X	X				X				X	X	X		X	X	X	X	X	X	X
Mesothelioma malignant																									X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	2 1 1	2 1 2	2 1 7	2 2 0	2 2 3	2 2 4	2 2 7	2 3 0	2 3 6	2 3 8	2 4 3	2 4 5	2 4 8	2 1 4	2 1 6	2 1 8	2 2 8	2 3 1	2 3 2	2 3 3	2 3 4	2 3 5	2 4 0	2 4 1	2 4 4	Total Tissues/ Tumors

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	
Carcass ID Number	4 0 3	4 0 8	4 1 2	4 1 9	4 2 1	4 2 4	4 3 0	4 3 6	4 4 0	4 4 8	4 0 1	4 0 2	4 0 5	4 0 6	4 0 7	4 2 3	4 2 7	4 3 1	4 3 4	4 3 5	4 3 7	4 3 8	4 4 2	4 4 5	4 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+		+		+	+						+									+				9
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																				1
Pheochromocytoma benign					X														X						X	6
Bilateral, pheochromocytoma benign												X					X									4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma										X																2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X	X	X	X		X	X	X		X	X	X	X		X			X	X	X		X			30
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, carcinoma									X																	2
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+			+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																	X									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	X	X			X	X	X	X	37
Interstitial cell, adenoma							X				X									X	X					7

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	0 5 7	2 0 5	5 3 9	5 4 0	5 4 4	5 6 7	5 8 0	6 1 9	6 3 3	6 3 7	6 3 7	6 6 0	6 6 7	6 7 0	6 7 7	6 8 8	6 9 5	6 9 5	6 9 5	7 0 2	7 0 2	7 0 7	7 0 7	7 1 3	7 2 1
Carcass ID Number	4 2 2	4 1 5	4 4 6	4 4 1	4 3 2	4 4 3	4 0 4	4 1 3	4 2 5	4 1 0	4 2 0	4 2 9	4 2 6	4 1 7	4 3 9	4 2 8	4 0 9	4 1 8	4 5 0	4 1 1	4 1 4	4 1 6	4 4 7	4 4 4	4 3 3
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	+	+	+
Carcinoma, metastatic, thyroid gland																					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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma													X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+					+									+				
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor malignant																									
Peripheral nerve							+					+									+				
Spinal cord				+			+					+									+				
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, thyroid gland																					X				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																	X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	726	726	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	40 03	40 08	41 02	41 09	42 01	42 24	43 00	43 06	44 00	44 08	40 01	40 02	40 05	40 06	40 07	42 23	42 37	43 01	43 14	43 15	43 17	43 18	44 02	44 45	44 49	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+											+									12
Lymph node, bronchial	M	M	M	M	M	+	+	M	M	M	+	M	+	M	+	M	M	M	M	M	M	M	M	M	M	12
Carcinoma, metastatic, thyroid gland																										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	3
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroadenoma													X													2
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma												X														1
Squamous cell papilloma									X																	1
Subcutaneous tissue, fibroma																			X	X						2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle													+													4
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor malignant																	X									1
Peripheral nerve													+													4
Spinal cord													+													5
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, thyroid gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	I	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	46
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma											X															2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	0 5 7	2 0 5	5 3 9	5 4 0	5 4 4	5 6 7	5 8 0	6 1 9	6 3 3	6 3 7	6 3 7	6 6 0	6 6 7	6 7 0	6 7 7	6 8 8	6 9 5	6 9 5	6 9 5	7 0 2	7 0 2	7 0 7	7 0 7	7 1 3	7 2 1
Carcass ID Number	4 2 2	4 1 5	4 4 6	4 4 1	4 3 2	4 4 3	4 0 4	4 1 3	4 2 5	4 1 0	4 2 0	4 2 9	4 2 6	4 1 7	4 3 9	4 2 8	4 0 9	4 1 8	4 5 0	4 1 1	4 1 4	4 1 6	4 4 7	4 4 4	4 4 3
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	X

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	726	726	726	726	726	726	726	726	726	726	726	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	727	
Carcass ID Number	40 3	40 8	41 2	41 9	42 1	42 4	43 0	43 6	44 0	44 8	40 1	40 2	40 5	40 6	40 7	42 3	42 7	43 1	43 4	43 5	43 7	43 8	44 2	44 5	44 9	Total Tissues/ Tumors
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X				X		X		X	X	X		X	X		X		X	X		X			X			32

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

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

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	6 9 4	7 0 2	7 0 5	7 0 6	7 1 2	7 1 9	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	
Carcass ID Number	6 4 8	6 1 1	6 1 7	6 4 0	6 2 0	6 4 3	6 0 6	6 1 0	6 1 4	6 1 5	6 1 9	6 2 5	6 2 8	6 2 9	6 3 4	6 3 5	6 3 8	6 3 9	6 4 4	6 4 7	6 4 9	6 0 2	6 0 4	6 3 3	6 3 6	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										1
Mesentery																+		+								7
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															X	2
Pheochromocytoma benign					X	X	X				X									X		X				11
Bilateral, pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Carcinoma																								X		1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X		X	X				X	X		X	X	X		X		X		X		X	X	X	X		29
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma												X								X	X					4
C-cell, carcinoma																										1
General Body System																										
Peritoneum	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Genital System																										
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	X	X	X	X	X	38
Interstitial cell, adenoma									X	X						X										10

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	4 9 8	5 4 4	5 6 7	5 9 5	6 0 4	6 0 9	6 2 1	6 2 2	6 2 3	6 3 6	6 3 8	6 3 8	6 3 9	6 4 5	6 4 5	6 4 9	6 5 2	6 5 3	6 5 9	6 6 5	6 7 4	6 7 7	6 8 1	6 9 3	6 9 4
Carcass ID Number	6 0 3	6 2 6	6 2 7	6 1 8	6 3 7	6 1 2	6 3 0	6 2 2	6 3 1	6 2 4	6 0 8	6 0 9	6 2 1	6 0 1	6 3 2	6 4 2	6 5 0	6 4 1	6 0 7	6 1 3	6 0 5	6 2 3	6 1 6	6 4 6	6 4 5
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node			+				+	+		+		+	+			+	+				+				
Deep cervical, carcinoma, metastatic, thyroid gland												X													
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	M
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Fibrous histiocytoma																									
Sarcoma																									
Sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle											+													+	
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																								+	
Spinal cord																								+	
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, Zymbal's gland				X																					
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland				+																					
Carcinoma				X																					

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	6 9 4	7 0 2	7 0 5	7 0 6	7 1 2	7 1 9	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	
Carcass ID Number	6 4 8	6 1 1	6 1 7	6 4 0	6 2 0	6 4 3	6 0 6	6 1 0	6 1 4	6 1 5	6 1 9	6 2 5	6 2 8	6 2 9	6 3 4	6 3 5	6 3 8	6 3 9	6 4 4	6 4 7	6 4 9	6 0 2	6 0 4	6 3 3	6 3 6	Total Tissues/ Tumors
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node				+		+	+							+									+		+	15
Deep cervical, carcinoma, metastatic, thyroid gland																										1
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	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	2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	M	+	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma															X											1
Fibroadenoma														X												1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																		X								1
Fibrous histiocytoma			X																							1
Sarcoma								X																		1
Sebaceous gland, adenoma													X													1
Subcutaneous tissue, fibroma						X				X																2
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle														+			+		+						+	6
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve														+			+		+						+	5
Spinal cord														+			+		+						+	5
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma													X					X								2
Carcinoma, metastatic, Zymbal's gland																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	I	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland																					+					2
Carcinoma																					X					2

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	4 9 8	5 4 4	5 6 7	5 9 5	6 0 4	6 0 9	6 2 1	6 2 2	6 2 3	6 3 6	6 3 8	6 3 8	6 3 9	6 4 5	6 4 5	6 4 9	6 5 2	6 5 3	6 5 9	6 6 5	6 7 4	6 7 7	6 8 1	6 9 3	6 9 4
Carcass ID Number	6 0 3	6 2 6	6 2 7	6 1 8	6 3 7	6 1 2	6 3 0	6 2 2	6 3 1	6 2 4	6 0 8	6 0 9	6 2 1	6 0 1	6 3 2	6 4 2	6 5 0	6 4 1	6 0 7	6 1 3	6 0 5	6 2 3	6 1 6	6 4 6	6 4 5
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Renal tubule, adenoma																									
Renal tubule, carcinoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Transitional epithelium, papilloma																							X		
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	X
Mesothelioma malignant									X																

TABLE A2
Individual Animal Tumor Pathology of Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	6 9 4	7 0 2	7 0 5	7 0 6	7 1 2	7 1 9	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 6	7 2 7	7 2 7	7 2 7	
Carcass ID Number	6 4 8	6 1 1	6 1 7	6 4 0	6 2 0	6 4 3	6 0 6	6 1 0	6 1 4	6 1 5	6 1 9	6 2 5	6 2 8	6 2 9	6 3 4	6 3 5	6 3 8	6 3 9	6 4 4	6 4 7	6 4 9	6 0 2	6 0 4	6 3 3	6 3 6	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, adenoma						X															X	X				3
Renal tubule, carcinoma																						X			X	2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																									X	1
Transitional epithelium, papilloma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X	X	X	X	X	X			X		X		X		X	X					X		X	X	35
Mesothelioma malignant																										1

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	8/50 (16%)	7/48 (15%)	10/50 (20%)	12/50 (24%)
Adjusted rate[b]	17.8%	17.3%	23.4%	27.7%
Terminal rate[c]	6/32 (19%)	6/28 (21%)	5/25 (20%)	4/19 (21%)
First incidence (days)	671	654	637	609
Poly-3 test[d]	P=0.120	P=0.585N	P=0.353	P=0.197
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	8/50 (16%)	9/48 (19%)	11/50 (22%)	14/50 (28%)
Adjusted rate	17.8%	22.0%	25.7%	32.3%
Terminal rate	6/32 (19%)	6/28 (21%)	6/25 (24%)	6/19 (32%)
First incidence (days)	671	654	637	609
Poly-3 test	P=0.062	P=0.415	P=0.262	P=0.090
Kidney: Renal Tubule Adenoma (Single Sections)				
Overall rate	0/50 (0%)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted rate	0.0%	0.0%	4.7%	7.3%
Terminal rate	0/32 (0%)	0/28 (0%)	1/25 (4%)	2/19 (11%)
First incidence (days)	—[e]	—[f]	695	719
Poly-3 test	P=0.024		P=0.225	P=0.106
Kidney: Renal Tubule Adenoma (Step Sections)				
Overall rate	2/50 (4%)	3/50 (6%)	1/50 (2%)	7/50 (14%)
Adjusted rate	4.5%	7.2%	2.4%	16.8%
Terminal rate	1/32 (3%)	2/28 (7%)	0/25 (0%)	5/19 (26%)
First incidence (days)	713	677	695	677
Poly-3 test	P=0.029	P=0.473	P=0.519N	P=0.062
Kidney: Renal Tubule Adenoma (Single and Step Sections)				
Overall rate	2/50 (4%)	3/50 (6%)	3/50 (6%)	10/50 (20%)
Adjusted rate	4.5%	7.2%	7.1%	24.0%
Terminal rate	1/32 (3%)	2/28 (7%)	1/25 (4%)	7/19 (37%)
First incidence (days)	713	677	695	677
Poly-3 test	P=0.002	P=0.473	P=0.477	P=0.009
Kidney: Renal Tubule Adenoma or Carcinoma (Single Sections)				
Overall rate	0/50 (0%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted rate	0.0%	2.4%	4.7%	9.7%
Terminal rate	0/32 (0%)	1/28 (4%)	1/25 (4%)	3/19 (16%)
First incidence (days)	—	726 (T)	695	719
Poly-3 test	P=0.018	P=0.487	P=0.225	P=0.051
Kidney: Renal Tubule Adenoma or Carcinoma (Single and Step Sections)				
Overall rate	2/50 (4%)	4/50 (8%)	3/50 (6%)	11/50 (22%)
Adjusted rate	4.5%	9.5%	7.1%	26.4%
Terminal rate	1/32 (3%)	3/28 (11%)	1/25 (4%)	8/19 (42%)
First incidence (days)	713	677	695	677
Poly-3 test	P<0.001	P=0.309	P=0.477	P=0.004
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	4/50 (8%)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted rate	9.0%	7.2%	4.7%	4.8%
Terminal rate	4/32 (13%)	3/28 (11%)	1/25 (4%)	2/19 (11%)
First incidence (days)	726 (T)	726 (T)	667	726 (T)
Poly-3 test	P=0.267N	P=0.535N	P=0.360N	P=0.371N

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Pancreatic Islets: Adenoma				
Overall rate	3/50 (6%)	4/48 (8%)	1/50 (2%)	1/50 (2%)
Adjusted rate	6.7%	9.9%	2.4%	2.4%
Terminal rate	2/32 (6%)	4/28 (14%)	0/25 (0%)	0/19 (0%)
First incidence (days)	554	726 (T)	713	652
Poly-3 test	P=0.152N	P=0.439	P=0.329N	P=0.334N
Pancreatic Islets: Carcinoma				
Overall rate	4/50 (8%)	2/48 (4%)	2/50 (4%)	1/50 (2%)
Adjusted rate	9.0%	5.0%	4.7%	2.4%
Terminal rate	3/32 (9%)	2/28 (7%)	1/25 (4%)	1/19 (5%)
First incidence (days)	701	726 (T)	580	726 (T)
Poly-3 test	P=0.145N	P=0.385N	P=0.358N	P=0.202N
Pancreatic Islets: Adenoma or Carcinoma				
Overall rate	7/50 (14%)	6/48 (13%)	3/50 (6%)	2/50 (4%)
Adjusted rate	15.5%	14.9%	7.0%	4.8%
Terminal rate	5/32 (16%)	6/28 (21%)	1/25 (4%)	1/19 (5%)
First incidence (days)	554	726 (T)	580	652
Poly-3 test	P=0.045N	P=0.588N	P=0.181N	P=0.099N
Pituitary Gland: Adenoma				
Overall rate	35/50 (70%)	29/49 (59%)	30/50 (60%)	29/50 (58%)
Adjusted rate	72.5%	66.4%	67.1%	63.2%
Terminal rate	21/32 (66%)	20/28 (71%)	16/25 (64%)	12/19 (63%)
First incidence (days)	492	595	580	498
Poly-3 test	P=0.207N	P=0.341N	P=0.365N	P=0.222N
Skin (Subcutaneous Tissue): Fibroma				
Overall rate	4/50 (8%)	1/50 (2%)	2/50 (4%)	2/50 (4%)
Adjusted rate	9.0%	2.4%	4.8%	4.8%
Terminal rate	4/32 (13%)	1/28 (4%)	2/25 (8%)	1/19 (5%)
First incidence (days)	726 (T)	726 (T)	726 (T)	719
Poly-3 test	P=0.354N	P=0.198N	P=0.363N	P=0.371N
Skin (Subcutaneous Tissue): Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma				
Overall rate	1/50 (2%)	3/50 (6%)	0/50 (0%)	2/50 (4%)
Adjusted rate	2.3%	7.0%	0.0%	4.8%
Terminal rate	1/32 (3%)	1/28 (4%)	0/25 (0%)	1/19 (5%)
First incidence (days)	726 (T)	471	—	705
Poly-3 test	P=0.527	P=0.290	P=0.511N	P=0.475
Skin (Subcutaneous Tissue): Fibrous Histiocytoma, Fibroma, Fibrosarcoma, or Sarcoma				
Overall rate	5/50 (10%)	4/50 (8%)	2/50 (4%)	4/50 (8%)
Adjusted rate	11.2%	9.4%	4.8%	9.7%
Terminal rate	5/32 (16%)	2/28 (7%)	2/25 (8%)	2/19 (11%)
First incidence (days)	726 (T)	471	726 (T)	705
Poly-3 test	P=0.439N	P=0.527N	P=0.239N	P=0.544N
Testes: Adenoma				
Overall rate	42/50 (84%)	42/50 (84%)	44/50 (88%)	48/50 (96%)
Adjusted rate	86.5%	90.3%	94.4%	97.6%
Terminal rate	29/32 (91%)	26/28 (93%)	25/25 (100%)	19/19 (100%)
First incidence (days)	468	471	539	498
Poly-3 test	P=0.015	P=0.393	P=0.149	P=0.036

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Thyroid Gland (C-Cell): Adenoma				
Overall rate	1/50 (2%)	4/48 (8%)	0/50 (0%)	4/50 (8%)
Adjusted rate	2.3%	9.9%	0.0%	9.6%
Terminal rate	1/32 (3%)	4/28 (14%)	0/25 (0%)	3/19 (16%)
First incidence (days)	726 (T)	726 (T)	—	674
Poly-3 test	P=0.206	P=0.149	P=0.511N	P=0.158
Thyroid Gland (C-Cell): Carcinoma				
Overall rate	2/50 (4%)	3/48 (6%)	0/50 (0%)	1/50 (2%)
Adjusted rate	4.5%	7.4%	0.0%	2.4%
Terminal rate	2/32 (6%)	2/28 (7%)	0/25 (0%)	0/19 (0%)
First incidence (days)	726 (T)	658	—	638
Poly-3 test	P=0.254N	P=0.458	P=0.250N	P=0.523N
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	3/50 (6%)	7/48 (15%)	0/50 (0%)	5/50 (10%)
Adjusted rate	6.7%	17.3%	0.0%	12.0%
Terminal rate	3/32 (9%)	6/28 (21%)	0/25 (0%)	3/19 (16%)
First incidence (days)	726 (T)	658	—	638
Poly-3 test	P=0.490	P=0.120	P=0.129N	P=0.322
All Organs: Mononuclear Cell Leukemia				
Overall rate	25/50 (50%)	26/50 (52%)	32/50 (64%)	35/50 (70%)
Adjusted rate	52.0%	59.1%	67.0%	72.6%
Terminal rate	13/32 (41%)	16/28 (57%)	13/25 (52%)	9/19 (47%)
First incidence (days)	468	595	205	544
Poly-3 test	P=0.016	P=0.314	P=0.096	P=0.027
All Organs: Benign Neoplasms				
Overall rate	50/50 (100%)	47/50 (94%)	47/50 (94%)	49/50 (98%)
Adjusted rate	100.0%	99.0%	99.1%	99.0%
Terminal rate	32/32 (100%)	28/28 (100%)	25/25 (100%)	19/19 (100%)
First incidence (days)	468	471	539	498
Poly-3 test	P=0.563N	P=0.968N	P=0.901N	P=0.862N
All Organs: Malignant Neoplasms				
Overall rate	31/50 (62%)	35/50 (70%)	34/50 (68%)	41/50 (82%)
Adjusted rate	63.7%	74.4%	70.5%	84.4%
Terminal rate	17/32 (53%)	19/28 (68%)	14/25 (56%)	14/19 (74%)
First incidence (days)	468	338	205	544
Poly-3 test	P=0.018	P=0.177	P=0.312	P=0.015

TABLE A3
Statistical Analysis of Primary Neoplasms in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	50/50 (100%)	48/50 (96%)	49/50 (98%)	50/50 (100%)
Adjusted rate	100.0%	99.2%	100.0%	100.0%
Terminal rate	32/32 (100%)	28/28 (100%)	25/25 (100%)	19/19 (100%)
First incidence (days)	468	338	205	498
Poly-3 test	P=0.972	P=0.992N	P=1.000N	—

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, kidney, pancreatic islets, pituitary 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 the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group
[f] Value of statistic cannot be computed.

TABLE A4a
Historical Incidence of Renal Tubule Neoplasms in Untreated Male F344/N Rats[a]

Study	Incidence in Controls		
	Adenoma	Cacinoma	Adenoma or Carcinoma
Historical Incidence in Chamber Controls Given NTP-2000 Diet			
Decalin	1/50	0/50	1/50
Divinylbenzene	0/50	0/50	0/50
Indium phosphide	0/50	0/50	0/50
Methyl isobutyl ketone	0/50	0/50	0/50
Naphthalene	0/49	0/49	0/49
Propylene glycol mono-*t*-butyl ether	1/50	0/50	1/50
Stoddard solvent (Type IIC)	0/50	1/50	1/50
Vanadium pentoxide	1/50	0/50	1/50
Overall Historical Incidence: Inhalation Studies			
Total (%)	3/399 (0.8%)	1/399 (0.3%)	4/399 (1.0%)
Mean ± standard deviation	0.8% ± 1.0%	0.3% ± 0.7%	1.0% ± 1.1%
Range	0%-2%	0%-2%	0%-2%
Overall Historical Incidence: All Routes			
Total (%)	6/1,448 (0.4%)	1/1,448 (0.1%)	7/1,448 (0.5%)
Mean ± standard deviation	0.5% ± 0.9%	0.1% ± 0.4%	0.5% ± 0.9%
Range	0%-2%	0%-2%	0%-2%

[a] Data as of January 28, 2005

TABLE A4b
Historical Incidence of Mononuclear Cell Leukemia in Untreated Male F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence in Chamber Controls Given NTP-2000 Diet	
Decalin	19/50
Divinylbenzene	22/50
Indium phosphide	16/50
Methyl isobutyl ketone	25/50
Naphthalene	26/49
Propylene glycol mono-*t*-butyl ether	33/50
Stoddard solvent (Type IIC)	25/50
Vanadium pentoxide	22/50
Overall Historical Incidence: Inhalation Studies	
Total (%)	188/399 (47.1%)
Mean ± standard deviation	47.1% ± 10.3%
Range	32%-66%
Overall Historical Incidence: All Routes	
Total (%)	622/1,459 (42.6%)
Mean ± standard deviation	41.4% ± 12.3%
Range	22%-68%

[a] Data as of January 28, 2005

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone[a]

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death		1		
Moribund	14	16	21	29
Natural deaths	4	5	4	2
Survivors				
Terminal sacrifice	32	28	25	19
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(48)	(48)	(50)	(50)
Ulcer		1 (2%)		2 (4%)
Intestine small, ileum	(48)	(47)	(48)	(49)
Diverticulum			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			1 (2%)
Basophilic focus	11 (22%)	5 (10%)	13 (26%)	4 (8%)
Clear cell focus	14 (28%)	13 (26%)	17 (34%)	9 (18%)
Degeneration, cystic	1 (2%)		1 (2%)	3 (6%)
Eosinophilic focus	2 (4%)	6 (12%)	10 (20%)	9 (18%)
Hemorrhage			1 (2%)	
Hepatodiaphragmatic nodule	3 (6%)	6 (12%)	7 (14%)	7 (14%)
Inflammation, granulomatous		1 (2%)		
Mixed cell focus	1 (2%)		2 (4%)	1 (2%)
Necrosis	1 (2%)	6 (12%)	1 (2%)	
Vacuolization cytoplasmic	4 (8%)	2 (4%)	2 (4%)	
Bile duct, cyst	1 (2%)			
Bile duct, hyperplasia		3 (6%)	4 (8%)	4 (8%)
Bile duct, inflammation, suppurative		1 (2%)		
Centrilobular, necrosis	1 (2%)	1 (2%)	1 (2%)	4 (8%)
Hepatocyte, regeneration		2 (4%)	1 (2%)	4 (8%)
Periportal, inflammation, chronic		1 (2%)		
Mesentery	(10)	(12)	(9)	(7)
Necrosis	10 (100%)	12 (100%)	9 (100%)	7 (100%)
Oral mucosa	(2)			
Pharyngeal, hyperplasia, squamous	1 (50%)			
Pancreas	(50)	(48)	(50)	(50)
Hemorrhage			1 (2%)	
Necrosis		1 (2%)		
Acinus, atrophy	4 (8%)	7 (15%)	5 (10%)	2 (4%)
Artery, thrombosis		1 (2%)		
Salivary glands	(50)	(48)	(50)	(50)
Hyperplasia		1 (2%)		
Stomach, forestomach	(50)	(48)	(50)	(50)
Hyperplasia, squamous			1 (2%)	1 (2%)
Ulcer	3 (6%)	1 (2%)	6 (12%)	6 (12%)
Stomach, glandular	(50)	(48)	(50)	(50)
Erosion	1 (2%)	1 (2%)	2 (4%)	3 (6%)
Ulcer				1 (2%)
Serosa, fibrosis			1 (2%)	

[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 Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Alimentary System (continued)				
Tongue	(1)	(1)		
Epithelium, hyperplasia	1 (100%)	1 (100%)		
Tooth	(1)			
Peridontal tissue, inflammation	1 (100%)			
Cardiovascular System				
Heart	(50)	(49)	(50)	(50)
Cardiomyopathy	14 (28%)	9 (18%)	12 (24%)	8 (16%)
Atrium, thrombosis	2 (4%)	4 (8%)	3 (6%)	1 (2%)
Myocardium, mineralization	1 (2%)			
Pericardium, fibrosis			1 (2%)	
Pericardium, inflammation, chronic			1 (2%)	
Valve, inflammation, suppurative		1 (2%)		
Endocrine System				
Adrenal cortex	(50)	(48)	(50)	(50)
Atrophy	1 (2%)		1 (2%)	
Hyperplasia			1 (2%)	
Necrosis				1 (2%)
Vacuolization cytoplasmic	7 (14%)	3 (6%)	6 (12%)	3 (6%)
Adrenal medulla	(50)	(48)	(50)	(50)
Atrophy	1 (2%)			
Hemorrhage	1 (2%)			
Hyperplasia	13 (26%)	18 (38%)	18 (36%)	24 (48%)
Thrombosis			1 (2%)	
Islets, pancreatic	(50)	(48)	(50)	(50)
Hyperplasia		1 (2%)		1 (2%)
Parathyroid gland	(49)	(48)	(49)	(50)
Hyperplasia		1 (2%)		
Pituitary gland	(50)	(49)	(50)	(50)
Angiectasis			1 (2%)	
Atrophy	1 (2%)			
Cyst	1 (2%)	1 (2%)		1 (2%)
Hemorrhage	4 (8%)	1 (2%)		1 (2%)
Hyperplasia	8 (16%)	8 (16%)	9 (18%)	9 (18%)
Thyroid gland	(50)	(48)	(50)	(50)
C-cell, hyperplasia	4 (8%)	3 (6%)	5 (10%)	1 (2%)
Follicle, cyst	1 (2%)	1 (2%)		1 (2%)
Follicular cell, hyperplasia	1 (2%)			
General Body System				
None				

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Genital System				
Preputial gland	(50)	(49)	(50)	(50)
Cyst	1 (2%)	2 (4%)		
Hyperplasia	1 (2%)	2 (4%)		3 (6%)
Inflammation, granulomatous				1 (2%)
Inflammation, suppurative			1 (2%)	
Prostate	(50)	(49)	(50)	(50)
Inflammation, suppurative	3 (6%)	1 (2%)		2 (4%)
Seminal vesicle	(50)	(49)	(50)	(50)
Hyperplasia		1 (2%)		
Testes	(50)	(50)	(50)	(50)
Germinal epithelium, atrophy	10 (20%)	8 (16%)	8 (16%)	15 (30%)
Interstitial cell, hyperplasia	4 (8%)	3 (6%)	1 (2%)	3 (6%)
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(50)
Hyperplasia, reticulum cell		1 (2%)		
Myelofibrosis		1 (2%)		
Lymph node	(7)	(7)	(12)	(15)
Infiltration cellular, histiocyte			1 (8%)	
Deep cervical, hemorrhage		1 (14%)		
Deep cervical, infiltration cellular, histiocyte	1 (14%)			
Deep cervical, pigmentation				1 (7%)
Pancreatic, ectasia	2 (29%)			
Pancreatic, pigmentation			1 (8%)	
Renal, ectasia			1 (8%)	
Lymph node, bronchial	(11)	(13)	(12)	(7)
Angiectasis	1 (9%)			
Ectasia	3 (27%)	2 (15%)	1 (8%)	
Hemorrhage		1 (8%)		
Infiltration cellular, histiocyte	1 (9%)	1 (8%)		
Pigmentation	1 (9%)	1 (8%)		
Lymph node, mesenteric	(50)	(48)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)		1 (2%)	
Lymph node, mediastinal	(41)	(44)	(46)	(44)
Angiectasis		1 (2%)		
Hemorrhage	1 (2%)			
Hyperplasia, lymphoid			1 (2%)	1 (2%)
Infiltration cellular, histiocyte			1 (2%)	
Pigmentation		1 (2%)		1 (2%)
Spleen	(50)	(50)	(50)	(50)
Accessory spleen	2 (4%)	1 (2%)		1 (2%)
Fibrosis	2 (4%)	5 (10%)	3 (6%)	8 (16%)
Hemorrhage	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Necrosis	4 (8%)	4 (8%)	6 (12%)	4 (8%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Integumentary System				
Mammary gland	(49)	(49)	(50)	(50)
Galactocele	5 (10%)		1 (2%)	3 (6%)
Skin	(50)	(49)	(50)	(50)
Cyst epithelial inclusion	3 (6%)	3 (6%)		4 (8%)
Hyperkeratosis	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Hyperplasia, focal, squamous			1 (2%)	
Inflammation, acute		1 (2%)		
Inflammation, granulomatous			1 (2%)	2 (4%)
Sebaceous gland, hyperplasia	1 (2%)			
Subcutaneous tissue, fibrosis		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Hyperostosis	1 (2%)			
Cranium, maxilla, fracture		1 (2%)		
Tibia, fracture				1 (2%)
Skeletal muscle	(3)	(3)	(4)	(6)
Hemorrhage				1 (17%)
Nervous System				
Brain	(50)	(49)	(50)	(50)
Compression	8 (16%)	8 (16%)	3 (6%)	6 (12%)
Hemorrhage	5 (10%)	3 (6%)	6 (12%)	4 (8%)
Spinal cord	(2)	(3)	(5)	(5)
Gliosis			1 (20%)	
Inflammation			1 (20%)	
Neuron, degeneration			1 (20%)	
Respiratory System				
Larynx	(50)	(48)	(50)	(50)
Foreign body	2 (4%)	3 (6%)	6 (12%)	4 (8%)
Inflammation, suppurative		2 (4%)	2 (4%)	2 (4%)
Epiglottis, hyperplasia			1 (2%)	
Epiglottis, metaplasia, squamous		1 (2%)		
Lung	(50)	(49)	(50)	(50)
Hemorrhage	2 (4%)	5 (10%)	5 (10%)	
Inflammation, chronic	4 (8%)		2 (4%)	
Inflammation, suppurative		2 (4%)	1 (2%)	
Thrombosis		1 (2%)		
Alveolar epithelium, hyperplasia	4 (8%)	7 (14%)	4 (8%)	4 (8%)
Alveolar epithelium, metaplasia, squamous	1 (2%)			
Alveolus, emphysema	2 (4%)			
Alveolus, infiltration cellular, histiocyte	10 (20%)	5 (10%)	6 (12%)	6 (12%)
Alveolus, pigmentation		1 (2%)		
Bronchiole, hyperplasia				1 (2%)
Bronchiole, alveolus, foreign body		1 (2%)		
Interstitium, fibrosis	2 (4%)		3 (6%)	1 (2%)

TABLE A5
Summary of the Incidence of Nonneoplastic Lesions in Male Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Respiratory System (continued)				
Nose	(50)	(49)	(50)	(50)
Foreign body	1 (2%)	3 (6%)	4 (8%)	7 (14%)
Inflammation, suppurative	4 (8%)	8 (16%)	4 (8%)	10 (20%)
Goblet cell, hyperplasia	1 (2%)	1 (2%)		5 (10%)
Nasolacrimal duct, inflammation, suppurative		1 (2%)	1 (2%)	1 (2%)
Respiratory epithelium, hyperplasia	4 (8%)	1 (2%)	3 (6%)	3 (6%)
Pleura	(50)	(49)	(50)	(50)
Fibrosis	3 (6%)			
Inflammation, chronic	6 (12%)		6 (12%)	4 (8%)
Mesothelium, hyperplasia			1 (2%)	1 (2%)
Trachea	(50)	(48)	(50)	(50)
Inflammation, suppurative		2 (4%)		
Epithelium, hyperplasia		1 (2%)		
Special Senses System				
Eye	(49)	(45)	(46)	(48)
Anterior chamber, hemorrhage		1 (2%)		
Anterior chamber, inflammation, suppurative		1 (2%)		
Cornea, hyperplasia				1 (2%)
Lens, cataract	7 (14%)	6 (13%)	3 (7%)	2 (4%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Infarct			4 (8%)	3 (6%)
Nephropathy	42 (84%)	45 (90%)	47 (94%)	50 (100%)
Papilla, mineralization	1 (2%)	6 (12%)	22 (44%)	29 (58%)
Pelvis, dilatation		1 (2%)		
Pelvis, transitional epithelium, hyperplasia	1 (2%)	5 (10%)	6 (12%)	19 (38%)
Renal tubule, accumulation, hyaline droplet			2 (4%)	2 (4%)
Renal tubule, cyst	1 (2%)	1 (2%)	1 (2%)	
Renal tubule, hyperplasia	1 (2%)	11 (22%)	3 (6%)	18 (36%)
Renal tubule, pigmentation				1 (2%)
Transitional epithelium, hyperplasia				1 (2%)
Urinary bladder	(50)	(48)	(50)	(50)
Calculus, microscopic observation only	1 (2%)	2 (4%)	2 (4%)	
Transitional epithelium, hyperplasia		1 (2%)		

APPENDIX B
SUMMARY OF LESIONS IN FEMALE RATS IN THE 2-YEAR INHALATION STUDY OF METHYL ISOBUTYL KETONE

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone[a]

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	14	14	20	15
Natural deaths	1	2	4	3
Survivors				
Died last week of study		1		
Terminal sacrifice	35	33	26	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(49)	(49)	(50)
Adenoma				1 (2%)
Liver	(50)	(50)	(50)	(50)
Carcinoma, metastatic, adrenal cortex		1 (2%)		
Hepatocellular adenoma		1 (2%)	1 (2%)	
Histiocytic sarcoma				1 (2%)
Mesentery	(18)	(17)	(15)	(15)
Histiocytic sarcoma				1 (7%)
Schwannoma malignant		1 (6%)		
Oral mucosa		(1)		
Squamous cell carcinoma		1 (100%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Carcinoma		1 (2%)		
Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma malignant		1 (2%)	1 (2%)	
Pheochromocytoma benign	3 (6%)		2 (4%)	2 (4%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Adenoma				1 (2%)
Pituitary gland	(49)	(50)	(50)	(50)
Adenoma	24 (49%)	28 (56%)	26 (52%)	30 (60%)
Carcinoma			1 (2%)	
Thyroid gland	(50)	(50)	(50)	(50)
Bilateral, c-cell, adenoma		1 (2%)		
C-cell, adenoma	3 (6%)	1 (2%)	2 (4%)	2 (4%)
C-cell, carcinoma	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Follicular cell, adenoma	1 (2%)		1 (2%)	
General Body System				
None				

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Genital System				
Clitoral gland	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)	3 (6%)	1 (2%)	3 (6%)
Ovary	(50)	(50)	(50)	(50)
Cystadenocarcinoma			1 (2%)	
Cystadenocarcinoma, metastatic, ovary			1 (2%)	
Granulosa cell tumor benign				1 (2%)
Thecoma malignant				1 (2%)
Uterus	(50)	(50)	(50)	(50)
Carcinoma				1 (2%)
Hemangioma				1 (2%)
Histiocytic sarcoma	1 (2%)			
Leiomyosarcoma		1 (2%)		
Polyp stromal	11 (22%)	4 (8%)	7 (14%)	13 (26%)
Polyp stromal, multiple				1 (2%)
Sarcoma stromal	1 (2%)			1 (2%)
Bilateral, polyp stromal		1 (2%)	1 (2%)	
Cervix, polyp stromal	1 (2%)			
Serosa, hemangioma		1 (2%)		
Vagina	(2)			(1)
Histiocytic sarcoma	1 (50%)			
Sarcoma	1 (50%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Lymph mode	(1)	(2)	(2)	(3)
Deep cervical, carcinoma, metastatic, thyroid gland			1 (50%)	1 (33%)
Lymph node, bronchial	(9)	(12)	(8)	(7)
Carcinoma, metastatic, thyroid gland		1 (8%)		1 (14%)
Cystadenocarcinoma, metastatic, ovary			1 (13%)	
Sarcoma, metastatic, skin				1 (14%)
Lymph node, mandibular	(1)		(2)	(1)
Lymph node, mesenteric	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Lymph node, mediastinal	(46)	(44)	(46)	(49)
Carcinoma, metastatic, Zymbal's gland				1 (2%)
Cystadenocarcinoma, metastatic, ovary			1 (2%)	
Spleen	(50)	(50)	(50)	(50)
Histiocytic sarcoma				1 (2%)
Thymus	(47)	(49)	(49)	(49)
Cystadenocarcinoma, metastatic, ovary			1 (2%)	
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Carcinoma	5 (10%)	8 (16%)	6 (12%)	4 (8%)
Fibroadenoma	17 (34%)	11 (22%)	18 (36%)	10 (20%)
Fibroadenoma, multiple	5 (10%)	8 (16%)	7 (14%)	8 (16%)
Skin	(50)	(50)	(50)	(50)
Basal cell carcinoma		1 (2%)		
Schwannoma malignant				1 (2%)
Squamous cell papilloma			1 (2%)	
Subcutaneous tissue, fibroma			1 (2%)	
Subcutaneous tissue, fibrosarcoma		1 (2%)		

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Cranium, carcinoma, metastatic, pituitary gland			1 (2%)	
Skeletal muscle	(10)	(5)	(8)	(14)
Cystadenocarcinoma, metastatic, ovary			1 (13%)	
Sarcoma			1 (13%)	
Schwannoma malignant		1 (20%)		
Nervous System				
Brain	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Pineal gland, adenoma		1 (2%)		
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)	1 (2%)		
Carcinoma, metastatic, clitoral gland			1 (2%)	1 (2%)
Carcinoma, metastatic, thyroid gland			1 (2%)	1 (2%)
Carcinoma, metastatic, Zymbal's gland				1 (2%)
Carcinoma, metastatic, adrenal cortex		1 (2%)		
Cystadenocarcinoma, metastatic, ovary			1 (2%)	
Pheochromocytoma malignant, metastatic, adrenal medulla			1 (2%)	
Sarcoma, metastatic, skin				1 (2%)
Mediastinum, schwannoma malignant, metastatic, mesentery		1 (2%)		
Special Senses System				
Harderian gland	(50)	(50)	(50)	(50)
Sarcoma			1 (2%)	
Zymbal's gland			(3)	(1)
Carcinoma			2 (67%)	1 (100%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Cystadenocarcinoma, metastatic, ovary			1 (2%)	
Mesenchymal tumor malignant				2 (4%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	2 (4%)			1 (2%)
Leukemia mononuclear	14 (28%)	21 (42%)	12 (24%)	16 (32%)

TABLE B1
Summary of the Incidence of Neoplasms in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Neoplasm Summary				
Total animals with primary neoplasms[c]	46	46	49	47
Total primary neoplasms	91	99	94	103
Total animals with benign neoplasms	44	39	40	40
Total benign neoplasms	66	58	67	70
Total animals with malignant neoplasms	22	27	22	25
Total malignant neoplasms	25	41	27	33
Total animals with metastatic neoplasms		3	5	4
Total metastatic neoplasms		4	12	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 B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	3 7 0	4 5 4	5 2 3	5 7 6	5 8 3	6 0 6	6 1 6	6 4 3	6 5 0	6 8 5	6 9 6	7 0 7	7 0 9	7 1 4	7 1 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8
Carcass ID Number	1 4 4 6	1 2 3	1 0 5	1 2 7	1 1 1	1 3 5	1 0 2	1 4 5	1 0 1	1 2 6	1 1 3	1 1 5	1 3 9	1 4 7	1 0 8	1 1 7	1 1 8	1 2 1	1 2 8	1 3 2	1 3 8	1 4 8	1 0 4	1 0 6	1 0 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 benign								X				X	X												
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma						X	X	X		X	X		X	X	X	X	X	X			X			X	
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																		X							
C-cell, carcinoma																									
Follicular cell, adenoma																									
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: 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 Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	10909	11010	11104	12202	13101	13303	13404	13606	13707	14000	14303	14404	14703	11203	11606	11909	12000	12404	12505	12909	13000	14101	14202	14409	15000	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesentery		+		+		+					+			+							+		+	+	+	18
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																										3
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	46
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Adenoma	X	X	X						X						X			X	X	X	X		X		X	24
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma									X													X				3
C-cell, carcinoma											X															1
Follicular cell, adenoma														X												1
General Body System																										
Peritoneum	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	3 7 0	4 5 4	5 2 3	5 7 6	5 8 3	6 0 6	6 1 6	6 4 3	6 5 0	6 8 5	6 9 6	7 0 7	7 0 9	7 1 4	7 1 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8
Carcass ID Number	1 4 4 6	1 2 6 3	1 0 0 5	1 2 5 7	1 1 6 1	1 3 6 5	1 0 6 2	1 4 6 5	1 0 6 1	1 2 6 6	1 1 6 3	1 1 6 5	1 3 6 9	1 4 6 7	1 0 6 8	1 1 6 7	1 1 6 8	1 2 6 1	1 2 6 8	1 3 6 2	1 3 6 8	1 4 6 8	1 0 6 4	1 0 6 6	1 0 6 7
Genital System																								
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																						X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																						
Polyp stromal	X		X		X															X			X	X
Sarcoma stromal																	X							
Cervix, polyp stromal								X																
Vagina		+																						
Histiocytic sarcoma		X																						
Sarcoma																								
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
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	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma						X																		
Fibroadenoma									X	X			X		X		X		X	X		X		
Fibroadenoma, multiple																							X	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle								+							+								+	
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																	
Peripheral nerve								+							+								+	
Spinal cord								+							+								+	

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	10109	11010	11104	11202	11301	11333	11434	11636	11737	11840	11943	12044	12103	12212	12316	12419	12520	12624	12725	12929	13030	13241	13442	13449	13550	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Polyp stromal	X			X									X							X				X		11
Sarcoma stromal																										1
Cervix, polyp stromal																										1
Vagina				+																						2
Histiocytic sarcoma																										1
Sarcoma				X																						1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										1
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	9
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	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma			X						X													X			X	5
Fibroadenoma				X	X	X				X	X	X	X								X			X		17
Fibroadenoma, multiple			X				X							X					X							5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle		+		+	+	+						+									+		+			10
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Peripheral nerve		+		+	+	+						+									+		+			10
Spinal cord		+		+	+	+						+									+		+			10

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	3 7 0	4 5 4	5 2 3	5 7 6	5 8 3	6 0 6	6 1 6	6 4 3	6 5 0	6 8 5	6 9 6	7 0 7	7 0 9	7 1 4	7 1 6	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8
Carcass ID Number	1 4 4 6	1 2 3	1 0 5	1 2 7	1 1 1	1 3 5	1 0 2	1 4 5	1 0 1	1 2 6	1 1 3	1 1 5	1 3 9	1 4 7	1 0 8	1 1 7	1 1 8	1 2 1	1 2 8	1 3 2	1 3 8	1 4 8	1 0 4	1 0 6	1 0 7
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Ear																	+							
Eye	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X					X																	
Leukemia mononuclear					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 Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	10909	11010	11104	11222	11331	11333	11334	11336	11337	11440	11443	11444	11445	11032	11126	11169	11190	11204	11224	11225	11229	11230	11241	11242	11249	11250		Total Tissues/ Tumors
Respiratory System																												
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma														X														1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Special Senses System																												
Ear																												1
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary System																												
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Systemic Lesions																												
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																												2
Leukemia mononuclear			X				X	X		X									X								14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	33 30	33 39	34 42	34 45	34 47	34 49	30 01	00 13	00 04	00 06	00 07	00 08	01 10	12 00	22 05	22 58	23 31	33 12	33 23	33 34	33 36	33 38	44 44	44 46	44 48	Total Tissues/ Tumors
Alimentary System																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, adrenal cortex																											1
Hepatocellular adenoma																											1
Mesentery			+		+			+	+	+					+	+	+	+	+			+		+			17
Schwannoma malignant																											1
Oral mucosa																											1
Squamous cell carcinoma																											1
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
Carcinoma																											1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant	X																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	M	M	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	+	+	+	M	+		40
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma	X		X		X		X				X				X	X	X	X	X	X		X		X	X		28
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bilateral, C-cell, adenoma																											1
C-cell, adenoma					X																						1
C-cell, carcinoma																											1
General Body System																											
Peritoneum	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	3 5 6	4 5 5	5 3 7	5 3 9	5 6 2	5 6 9	5 9 4	5 9 5	6 6 5	6 9 3	7 0 7	7 0 7	7 1 2	7 1 8	7 2 1	7 2 2	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	3 1 7	3 2 7	3 5 0	3 1 2	3 0 9	3 3 7	3 2 4	3 1 6	3 1 5	3 4 0	3 1 4	3 2 9	3 4 3	3 3 5	3 4 1	3 1 8	3 0 2	3 0 5	3 1 1	3 1 3	3 1 9	3 2 1	3 2 2	3 2 3	3 2 6
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																					X				
Polyp stromal								X				X													
Bilateral, polyp stromal																									
Serosa, hemangioma																									
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
Carcinoma, metastatic, thyroid gland																						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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma				X		X		X		X	X									X					
Fibroadenoma				X			X		X		X			X					X						
Fibroadenoma, multiple										X													X		
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma												X													
Subcutaneous tissue, fibrosarcoma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle	+																	+			+				
Schwannoma malignant	X																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pineal gland, adenoma																									
Peripheral nerve																		+			+				
Spinal cord																		+			+				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	33 30	33 39	34 42	44 45	34 47	34 49	30 01	00 13	00 04	00 06	00 07	00 08	01 10	20	22 25	22 58	23 31	33 12	33 23	33 34	33 36	33 38	34 44	44 46	34 48	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma															X							X	X			3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																										1
Polyp stromal						X					X															4
Bilateral, polyp stromal				X																						1
Serosa, hemangioma										X																1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node						+																				2
Lymph node, bronchial	M	M	M	+	M	M	M	M	M	M	M	M	M	M	+	+	M	M	M	M	M	M	+	M	M	12
Carcinoma, metastatic, thyroid gland																										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
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	44
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma							X															X				8
Fibroadenoma		X								X				X	X						X					11
Fibroadenoma, multiple	X		X		X							X				X	X									8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Subcutaneous tissue, fibrosarcoma																							X			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle												+					+									5
Schwannoma malignant																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pineal gland, adenoma																					X					1
Peripheral nerve												+					+									4
Spinal cord												+					+									4

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	3 5 6	4 5 5	5 3 7	5 3 9	5 6 2	5 6 9	5 9 4	5 9 5	6 6 5	6 9 3	7 0 7	7 0 7	7 1 2	7 1 8	7 2 1	7 2 2	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	3 1 7	3 2 7	3 5 0	3 1 2	3 0 9	3 3 7	3 2 4	3 1 6	3 1 5	3 4 0	3 1 4	3 2 9	3 4 3	3 3 5	3 4 1	3 1 8	3 0 2	3 0 5	3 1 1	3 1 3	3 1 9	3 2 1	3 2 2	3 2 3	3 2 6
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Carcinoma, metastatic, adrenal cortex															X										
Mediastinum, schwannoma malignant, metastatic, mesentery	X																								
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X			X	X			X	X	X			X	X		X		X	X	X			

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	33030	33039	33442	34455	34457	34459	30101	30013	30034	30046	30067	30078	31010	32200	32255	32288	32331	33312	33323	33334	33366	33388	34445	34466	34468	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																									1
Carcinoma, metastatic, adrenal cortex																										1
Mediastinum, schwannoma malignant, metastatic, mesentery																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear							+																			1
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			21

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	4 8 9	5 0 9	5 1 3	5 4 6	5 8 1	5 8 2	5 9 0	6 1 4	6 1 6	6 2 1	6 3 6	6 3 7	6 4 2	6 4 2	6 4 3	6 5 3	6 5 3	6 7 4	6 7 7	6 8 4	7 0 2	7 1 4	7 2 6	7 2 6	7 2 7
Carcass ID Number	5 4 8	5 2 4	5 4 7	5 2 8	5 0 1	5 3 3	5 4 0	5 4 3	5 2 0	5 1 4	5 4 2	5 2 7	5 0 7	5 3 7	5 4 9	5 1 2	5 1 3	5 1 0	5 1 1	5 3 0	5 2 3	5 2 5	5 0 9	5 1 8	5 0 3
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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 malignant																									
Pheochromocytoma benign																						X			
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X	X	X	X	X	X		X	X	X		X			X	X	X	X		X		X	X
Carcinoma																							X		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, adenoma																	X								
C-cell, carcinoma													X												
Follicular cell, adenoma																									
General Body System																									
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8	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	5 4 1	5 0 2	5 0 4	5 0 5	5 0 6	5 0 8	5 1 5	5 1 6	5 2 2	5 2 6	5 3 1	5 3 8	5 3 9	5 4 4	5 4 6	5 5 0	5 1 7	5 1 9	5 2 1	5 2 9	5 3 2	5 3 4	5 3 5	5 3 6	5 4 5	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma										X																1
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 malignant																									X	1
Pheochromocytoma benign																				X						2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma					X			X		X		X	X	X			X		X					X		26
Carcinoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma	X																									2
C-cell, carcinoma																										1
Follicular cell, adenoma									X																	1
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	4 8 9	5 0 9	5 1 3	5 4 6	5 8 1	5 8 2	5 9 0	6 1 4	6 1 6	6 2 1	6 3 6	6 3 7	6 4 2	6 4 2	6 4 3	6 5 3	6 5 3	6 7 4	6 7 7	6 8 4	7 0 2	7 1 4	7 2 6	7 6	7 2 7
Carcass ID Number	5 4 8	5 2 4	5 4 7	5 2 8	5 0 1	5 3 3	5 4 0	5 4 3	5 2 0	5 1 4	5 4 2	5 2 7	5 0 7	5 3 7	5 4 9	5 1 2	5 1 3	5 1 0	5 1 1	5 3 0	5 2 3	5 2 5	5 0 9	5 1 8	5 0 3
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenocarcinoma		X																							
Cystadenocarcinoma, metastatic, ovary		X																							
Oviduct																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp stromal					X							X							X						
Bilateral, polyp stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node													+		+										
Deep cervical, carcinoma, metastatic, thyroid gland													X												
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
Cystadenocarcinoma, metastatic, ovary		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
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenocarcinoma, metastatic, ovary		X																							
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenocarcinoma, metastatic, ovary		X																							
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																X		X							
Fibroadenoma				X			X	X	X						X		X			X					
Fibroadenoma, multiple											X							X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Subcutaneous tissue, fibroma																									
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cranium, carcinoma, metastatic, pituitary gland																							X		
Skeletal muscle	+	+																+		+			+		
Cystadenocarcinoma, metastatic, ovary		X																							
Sarcoma	X																								
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve																		+		+			+		
Spinal cord																		+		+			+		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	
Carcass ID Number	54 41	50 12	50 04	50 05	50 06	50 08	51 15	51 16	52 22	52 26	53 31	53 38	53 39	54 44	54 46	55 00	51 17	51 19	52 21	52 29	53 32	53 34	53 35	53 36	54 45	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma									X																	1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenocarcinoma																										1
Cystadenocarcinoma, metastatic, ovary																										1
Oviduct										+																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Polyp stromal					X													X	X	X						7
Bilateral, polyp stromal													X													1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										2
Deep cervical, carcinoma, metastatic, thyroid gland																										1
Lymph node, bronchial	+	M	+	M	M	M	M	M	M	M	M	+	+	M	M	M	M	M	M	M	M	M	M	M	M	8
Cystadenocarcinoma, metastatic, ovary																										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	2
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, mediastinal	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	46
Cystadenocarcinoma, metastatic, ovary																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cystadenocarcinoma, metastatic, ovary																										1
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma		X		X										X							X					6
Fibroadenoma	X	X					X		X	X	X	X	X							X			X		X	18
Fibroadenoma, multiple			X		X	X															X		X			7
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																					X					1
Subcutaneous tissue, fibroma							X																			1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cranium, carcinoma, metastatic, pituitary gland																										1
Skeletal muscle				+													+								+	8
Cystadenocarcinoma, metastatic, ovary																										1
Sarcoma																										1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve				+													+								+	6
Spinal cord				+													+								+	6

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	4 8 9	5 0 9	5 1 3	5 4 6	5 8 1	5 8 2	5 9 0	6 1 4	6 1 6	6 2 1	6 3 6	6 3 7	6 4 2	6 4 2	6 4 3	6 5 3	6 5 3	6 7 4	6 7 7	6 8 4	7 0 2	7 1 4	7 2 6	7 2 6	7 2 7
Carcass ID Number	5 4 8	5 2 4	5 4 7	5 2 8	5 0 1	5 3 3	5 4 0	5 4 3	5 2 0	5 1 4	5 4 2	5 2 7	5 0 7	5 3 7	5 4 9	5 1 2	5 1 3	5 1 0	5 1 1	5 3 0	5 2 3	5 2 5	5 0 9	5 1 8	5 0 3
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, clitoral gland																									
Carcinoma, metastatic, thyroid gland													X												
Cystadenocarcinoma, metastatic, ovary		X																							
Pheochromocytoma malignant, metastatic, adrenal medulla																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Ear									+																
Eye	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma	X																								
Zymbal's gland													+												
Carcinoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenocarcinoma, metastatic, ovary		X																							
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear												X	X		X		X			X	X				

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	727	728	728	728	728	728	728	728	728	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	
Carcass ID Number	54101	50102	50004	50005	50006	50008	51015	51016	51022	52026	53031	53038	53039	54044	54046	55050	51017	51119	52021	52029	53032	53034	53035	53036	54045	Total Tissues/ Tumors
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, clitoral gland									X																	1
Carcinoma, metastatic, thyroid gland																										1
Cystadenocarcinoma, metastatic, ovary																										1
Pheochromocytoma malignant, metastatic, adrenal medulla																									X	1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Ear								+																		2
Eye	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Zymbal's gland											+						+									3
Carcinoma																	X									2
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenocarcinoma, metastatic, ovary																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X												X	X			X						X		12

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

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

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	71 19	72 25	72 26	73 30	73 36	73 39	74 41	70 02	70 08	70 09	71 02	71 15	71 16	71 17	72 20	72 22	72 23	72 27	72 29	73 31	74 40	74 43	74 46	74 47	75 50	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																						X				1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Mesentery		+				+	+			+		+	+	+					+				+			15
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																								+		2
Cardiovascular System																										
Blood vessel	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign																					X					2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																X										1
Parathyroid gland	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X	X	X		X	X	X		X	X	X				X		X	X	X		X	X	X	X		30
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, adenoma																X										2
C-cell, carcinoma																							X			2
General Body System																										
Peritoneum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tissue NOS							+						+													2

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	3 6 4	3 9 8	4 5 4	4 8 9	4 9 9	5 0 6	5 4 8	6 3 7	6 5 1	6 6 7	6 8 1	6 8 1	6 9 1	6 9 2	6 9 5	6 9 5	7 2 3	7 2 6	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	7 3 4	7 2 1	7 3 8	7 0 7	7 0 1	7 2 8	7 4 2	7 4 5	7 3 2	7 4 4	7 1 8	7 3 3	7 3 7	7 4 8	7 1 1	7 4 9	7 0 5	7 0 1	7 2 4	7 3 5	7 0 3	7 0 4	7 0 6	7 1 3	7 1 4
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor benign																									
Thecoma malignant						X																			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma	X																								
Hemangioma																									
Polyp stromal		X									X											X	X		X
Polyp stromal, multiple																									
Sarcoma stromal															X										
Vagina										+															
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node					+								+				+								
Deep cervical, carcinoma, metastatic, thyroid gland																	X								
Lymph node, bronchial	M	M	M	M	+	+	M	M	M	M	M	M	M	M	M	M	+	M	+	M	M	M	M	+	M
Carcinoma, metastatic, thyroid gland																	X								
Sarcoma, metastatic, skin						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
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, Zymbal's gland																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																						
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																							X		
Fibroadenoma					X													X	X	X					
Fibroadenoma, multiple												X									X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Schwannoma malignant						X																			
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle							+	+	+	+	+						+						+		

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	71 19	72 25	72 26	73 30	73 36	73 39	74 41	70 02	70 08	70 09	71 12	71 15	71 16	71 17	72 20	72 22	72 23	72 27	72 29	73 31	74 40	74 43	74 46	74 47	75 50	Total Tissues/ Tumors
Genital System																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma				X					X			X														3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign																							X			1
Thecoma malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Hemangioma																					X					1
Polyp stromal						X			X							X	X		X	X			X		X	13
Polyp stromal, multiple																		X								1
Sarcoma stromal																										1
Vagina																										1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node																										3
Deep cervical, carcinoma, metastatic, thyroid gland																										1
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	M	7
Carcinoma, metastatic, thyroid gland																										1
Sarcoma, metastatic, skin																										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	1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node, mediastinal	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, Zymbal's gland																				X						1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma					X																		X	X		4
Fibroadenoma	X			X			X									X	X		X							10
Fibroadenoma, multiple		X			X				X			X			X					X						8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Schwannoma malignant																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+			+		+			+						+				+	+						14

TABLE B2
Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	3 6 4	3 9 8	4 5 4	4 8 9	4 9 9	5 0 6	5 4 8	6 3 7	6 5 1	6 6 7	6 8 1	6 8 1	6 9 1	6 9 2	6 9 5	6 9 5	7 2 3	7 2 6	7 2 7	7 2 7	7 2 8	7 2 8	7 2 8	7 2 8	7 2 8
Carcass ID Number	7 3 4	7 2 1	7 3 8	7 0 7	7 0 1	7 1 0	7 2 8	7 4 2	7 4 5	7 3 2	7 4 4	7 4 1 8	7 3 3	7 3 7	7 4 8	7 1 1	7 4 9	7 0 5	7 0 1	7 2 4	7 3 5	7 0 3	7 0 4	7 0 6	7 1 3	7 1 4
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Peripheral nerve							+	+	+	+	+						+							+		
Spinal cord							+	+	+	+	+						+							+		
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, clitoral gland																										
Carcinoma, metastatic, thyroid gland																	X									
Carcinoma, metastatic, Zymbal's gland																										
Sarcoma, metastatic, skin						X																				
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																										
Eye	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Zymbal's gland																										
Carcinoma																										
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesenchymal tumor malignant																										
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X																							
Leukemia mononuclear					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 Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	728	728	728	728	728	728	728	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	
Carcass ID Number	71 19	72 25	72 26	73 30	73 36	73 39	74 01	70 02	70 08	70 09	71 12	71 15	71 16	71 17	72 20	72 22	72 23	72 27	72 29	73 31	74 40	74 43	74 46	74 47	75 50	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Peripheral nerve	+			+		+			+						+				+	+						14
Spinal cord	+			+		+			+						+				+	+						14
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, clitoral gland									X																	1
Carcinoma, metastatic, thyroid gland																										1
Carcinoma, metastatic, Zymbal's gland																				X						1
Sarcoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pleura	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Zymbal's gland																				+						1
Carcinoma																				X						1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesenchymal tumor malignant						X							X													2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Leukemia mononuclear					X											X	X			X			X	X	X	16

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Adrenal Medulla: Benign Pheochromocytoma				
Overall rate[a]	3/50 (6%)	0/50 (0%)	2/50 (4%)	2/50 (4%)
Adjusted rate[b]	6.6%	0.0%	4.8%	4.6%
Terminal rate[c]	0/35 (0%)	0/34 (0%)	1/26 (4%)	2/32 (6%)
First incidence (days)	643	—[e]	714	727 (T)
Poly-3 test[d]	P=0.590N	P=0.122N	P=0.534N	P=0.522N
Adrenal Medulla: Benign or Malignant Pheochromocytoma				
Overall rate	3/50 (6%)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted rate	6.6%	2.3%	7.1%	4.6%
Terminal rate	0/35 (0%)	1/34 (3%)	2/26 (8%)	2/32 (6%)
First incidence (days)	643	727 (T)	714	727 (T)
Poly-3 test	P=0.543N	P=0.311N	P=0.627	P=0.522N
Clitoral Gland: Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	3/50 (6%)
Adjusted rate	2.2%	6.7%	2.4%	7.0%
Terminal rate	1/35 (3%)	3/34 (9%)	1/26 (4%)	3/32 (9%)
First incidence (days)	727 (T)	727 (T)	727 (T)	727 (T)
Poly-3 test	P=0.295	P=0.303	P=0.746	P=0.292
Mammary Gland: Fibroadenoma				
Overall rate	22/50 (44%)	19/50 (38%)	25/50 (50%)	18/50 (36%)
Adjusted rate	48.5%	41.2%	55.5%	40.9%
Terminal rate	18/35 (51%)	13/34 (38%)	16/26 (62%)	15/32 (47%)
First incidence (days)	650	539	546	499
Poly-3 test	P=0.371N	P=0.312N	P=0.321	P=0.303N
Mammary Gland: Carcinoma				
Overall rate	5/50 (10%)	8/50 (16%)	6/50 (12%)	4/50 (8%)
Adjusted rate	11.1%	17.3%	14.1%	9.3%
Terminal rate	4/35 (11%)	3/34 (9%)	4/26 (15%)	4/32 (13%)
First incidence (days)	606	539	653	727 (T)
Poly-3 test	P=0.357N	P=0.291	P=0.455	P=0.529N
Mammary Gland: Fibroadenoma or Carcinoma				
Overall rate	26/50 (52%)	24/50 (48%)	29/50 (58%)	21/50 (42%)
Adjusted rate	56.8%	51.0%	64.0%	47.7%
Terminal rate	21/35 (60%)	16/34 (47%)	19/26 (73%)	18/32 (56%)
First incidence (days)	606	539	546	499
Poly-3 test	P=0.300N	P=0.363N	P=0.308	P=0.254N
Pituitary Gland: Adenoma				
Overall rate	24/49 (49%)	28/50 (56%)	26/50 (52%)	30/50 (60%)
Adjusted rate	52.9%	57.4%	55.0%	65.5%
Terminal rate	16/34 (47%)	17/34 (50%)	10/26 (39%)	20/32 (63%)
First incidence (days)	606	455	513	489
Poly-3 test	P=0.141	P=0.406	P=0.500	P=0.150
Pituitary Gland: Adenoma or Carcinoma				
Overall rate	24/49 (49%)	28/50 (56%)	27/50 (54%)	30/50 (60%)
Adjusted rate	52.9%	57.4%	57.1%	65.5%
Terminal rate	16/34 (47%)	17/34 (50%)	10/26 (39%)	20/32 (63%)
First incidence (days)	606	455	513	489
Poly-3 test	P=0.135	P=0.406	P=0.419	P=0.150

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Thyroid Gland (C-Cell): Adenoma				
Overall rate	3/50 (6%)	2/50 (4%)	2/50 (4%)	2/50 (4%)
Adjusted rate	6.7%	4.5%	4.7%	4.6%
Terminal rate	3/35 (9%)	2/34 (6%)	1/26 (4%)	1/32 (3%)
First incidence (days)	727 (T)	727 (T)	653	651
Poly-3 test	P=0.446N	P=0.503N	P=0.527N	P=0.514N
Thyroid Gland (C-Cell): Adenoma or Carcinoma				
Overall rate	4/50 (8%)	3/50 (6%)	3/50 (6%)	4/50 (8%)
Adjusted rate	8.9%	6.7%	7.1%	9.2%
Terminal rate	4/35 (11%)	3/34 (9%)	1/26 (4%)	2/32 (6%)
First incidence (days)	727 (T)	727 (T)	642	651
Poly-3 test	P=0.518	P=0.503N	P=0.529N	P=0.627
Uterus: Stromal Polyp				
Overall rate	12/50 (24%)	5/50 (10%)	8/50 (16%)	14/50 (28%)
Adjusted rate	25.5%	11.1%	18.6%	31.7%
Terminal rate	8/35 (23%)	3/34 (9%)	5/26 (19%)	12/32 (38%)
First incidence (days)	370	595	581	398
Poly-3 test	P=0.139	P=0.063N	P=0.299N	P=0.336
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	13/50 (26%)	5/50 (10%)	8/50 (16%)	15/50 (30%)
Adjusted rate	27.6%	11.1%	18.6%	33.8%
Terminal rate	9/35 (26%)	3/34 (9%)	5/26 (19%)	12/32 (38%)
First incidence (days)	370	595	581	398
Poly-3 test	P=0.130	P=0.039N	P=0.224N	P=0.337
All Organs: Mononuclear Cell Leukemia				
Overall rate	14/50 (28%)	21/50 (42%)	12/50 (24%)	16/50 (32%)
Adjusted rate	30.3%	44.4%	27.6%	35.0%
Terminal rate	9/35 (26%)	12/34 (35%)	6/26 (23%)	8/32 (25%)
First incidence (days)	583	356	637	499
Poly-3 test	P=0.526N	P=0.115	P=0.480N	P=0.399
All Organs: Benign Neoplasms				
Overall rate	44/50 (88%)	39/50 (78%)	40/50 (80%)	40/50 (80%)
Adjusted rate	90.3%	79.5%	83.4%	84.6%
Terminal rate	31/35 (89%)	26/34 (77%)	22/26 (85%)	28/32 (88%)
First incidence (days)	370	455	513	398
Poly-3 test	P=0.380N	P=0.109N	P=0.233N	P=0.288N
All Organs: Malignant Neoplasms				
Overall rate	22/50 (44%)	27/50 (54%)	22/50 (44%)	25/50 (50%)
Adjusted rate	46.5%	55.5%	48.6%	52.7%
Terminal rate	15/35 (43%)	15/34 (44%)	11/26 (42%)	14/32 (44%)
First incidence (days)	454	356	489	364
Poly-3 test	P=0.400	P=0.247	P=0.503	P=0.345

TABLE B3
Statistical Analysis of Primary Neoplasms in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	46/50 (92%)	46/50 (92%)	49/50 (98%)	47/50 (94%)
Adjusted rate	92.9%	92.0%	98.0%	94.0%
Terminal rate	32/35 (91%)	30/34 (88%)	25/26 (96%)	29/32 (91%)
First incidence (days)	370	356	489	364
Poly-3 test	P=0.405	P=0.581N	P=0.226	P=0.576

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for adrenal gland, 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 comparisons between the chamber controls and that exposed group. The Poly-3 test accounts for the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

TABLE B4
Historical Incidence of Malignant Mesenchymal Tumor of the Kidney in Untreated Female F344/N Rats[a]

Study	Incidence in Controls
Historical Incidence in Chamber Controls Given NTP-2000 Diet	
Decalin	0/50
Divinylbenzene	0/50
Indium phosphide	0/50
Methyl isobutyl ketone	0/50
Naphthalene	0/48
Propylene glycol mono-*t*-butyl ether	0/49
Stoddard solvent (Type IIC)	0/49
Vanadium pentoxide	0/50
Overall Historical Incidence: Inhalation Studies	
Total (%)	0/396 (0.0%)
Overall Historical Incidence: All Routes	
Total (%)	0/1,453 (0.0%)

[a] Data as of January 28, 2005

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone[a]

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	14	14	20	15
Natural deaths	1	2	4	3
Survivors				
Died last week of study		1		
Terminal sacrifice	35	33	26	32
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(50)	(49)	(49)	(50)
Foreign body	1 (2%)			
Intestine small, duodenum	(50)	(50)	(49)	(50)
Foreign body	1 (2%)			
Intestine small, jejunum	(50)	(49)	(49)	(49)
Necrosis	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Basophilic focus	36 (72%)	24 (48%)	26 (52%)	20 (40%)
Clear cell focus	11 (22%)	10 (20%)	11 (22%)	7 (14%)
Eosinophilic focus	3 (6%)		1 (2%)	2 (4%)
Hepatodiaphragmatic nodule	8 (16%)	12 (24%)	9 (18%)	5 (10%)
Inflammation, granulomatous		1 (2%)		
Mixed cell focus	1 (2%)	3 (6%)		
Necrosis			2 (4%)	3 (6%)
Vacuolization cytoplasmic	3 (6%)	3 (6%)	5 (10%)	4 (8%)
Hepatocyte, regeneration	1 (2%)	1 (2%)	2 (4%)	2 (4%)
Serosa, fibrosis		1 (2%)		
Mesentery	(18)	(17)	(15)	(15)
Fibrosis	1 (6%)			
Hemorrhage		1 (6%)		
Inflammation, granulomatous			1 (7%)	
Necrosis	18 (100%)	15 (88%)	15 (100%)	14 (93%)
Pancreas	(50)	(50)	(50)	(50)
Cyst				1 (2%)
Acinus, atrophy	1 (2%)	1 (2%)	1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperkeratosis	1 (2%)			
Hyperplasia, squamous		2 (4%)	2 (4%)	
Necrosis		1 (2%)		
Ulcer	2 (4%)		1 (2%)	1 (2%)
Tongue	(1)	(1)	(3)	(2)
Epithelium, hyperplasia	1 (100%)	1 (100%)	3 (100%)	2 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Atrium, thrombosis		1 (2%)		

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

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hyperplasia		1 (2%)	1 (2%)	
Vacuolization cytoplasmic	9 (18%)	4 (8%)	13 (26%)	9 (18%)
Adrenal medulla	(50)	(50)	(50)	(50)
Atrophy		1 (2%)		
Hyperplasia		2 (4%)		
Necrosis				1 (2%)
Islets, pancreatic	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)	1 (2%)		1 (2%)
Pituitary gland	(49)	(50)	(50)	(50)
Cyst	3 (6%)	6 (12%)	4 (8%)	3 (6%)
Hemorrhage		2 (4%)	2 (4%)	3 (6%)
Hyperplasia	11 (22%)	11 (22%)	8 (16%)	10 (20%)
Thyroid gland	(50)	(50)	(50)	(50)
Cyst				1 (2%)
C-cell, hyperplasia	4 (8%)	2 (4%)	2 (4%)	5 (10%)
Follicular cell, hyperplasia				1 (2%)
General Body System				
None				
Genital System				
Clitoral gland	(50)	(50)	(50)	(50)
Cyst	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Hyperplasia	1 (2%)	3 (6%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)	1 (2%)		
Ovary	(50)	(50)	(50)	(50)
Cyst	6 (12%)	10 (20%)	7 (14%)	4 (8%)
Cyst, multiple	1 (2%)			
Uterus	(50)	(50)	(50)	(50)
Cyst	1 (2%)			
Decidual reaction	1 (2%)			
Hemorrhage	1 (2%)		1 (2%)	2 (4%)
Necrosis	2 (4%)			1 (2%)
Thrombosis				1 (2%)
Endometrium, hyperplasia	1 (2%)	2 (4%)	3 (6%)	3 (6%)
Endometrium, inflammation, suppurative	1 (2%)			
Myometrium, hyperplasia				1 (2%)
Vagina	(2)			(1)
Muscularis, hyperplasia				1 (100%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Hematopoietic System				
Bone marrow	(50)	(50)	(50)	(50)
Myelofibrosis				1 (2%)
Lymph node	(1)	(2)	(2)	(3)
Pancreatic, hemorrhage		1 (50%)		
Lymph node, bronchial	(9)	(12)	(8)	(7)
Ectasia	2 (22%)			
Hemorrhage		1 (8%)		
Hyperplasia, lymphoid		2 (17%)		
Pigmentation	1 (11%)	2 (17%)		
Lymph node, mediastinal	(46)	(44)	(46)	(49)
Angiectasis		1 (2%)		
Spleen	(50)	(50)	(50)	(50)
Accessory spleen			1 (2%)	1 (2%)
Fibrosis		1 (2%)		
Hemorrhage	1 (2%)		1 (2%)	
Inflammation, granulomatous		1 (2%)		
Necrosis	1 (2%)			1 (2%)
Integumentary System				
Mammary gland	(50)	(50)	(50)	(50)
Galactocele	1 (2%)	1 (2%)		1 (2%)
Epithelium, hyperplasia		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Cyst epithelial inclusion	1 (2%)	1 (2%)		1 (2%)
Hyperkeratosis	1 (2%)			
Hyperplasia, focal, squamous		1 (2%)		
Inflammation, acute		2 (4%)		
Ulcer	1 (2%)	1 (2%)		2 (4%)
Musculoskeletal System				
None				
Nervous System				
Brain	(50)	(50)	(50)	(50)
Compression	8 (16%)	11 (22%)	10 (20%)	7 (14%)
Gliosis			1 (2%)	
Hemorrhage	5 (10%)	4 (8%)	10 (20%)	5 (10%)
Necrosis			1 (2%)	2 (4%)
Thrombosis	1 (2%)			
Cerebrum, pigmentation	1 (2%)			
Spinal cord	(10)	(4)	(6)	(14)
Cyst epithelial inclusion				1 (7%)
Hemorrhage				1 (7%)

TABLE B5
Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Respiratory System				
Larynx	(50)	(50)	(50)	(50)
Foreign body	1 (2%)	2 (4%)	3 (6%)	2 (4%)
Inflammation, chronic	1 (2%)	1 (2%)		
Inflammation, suppurative			1 (2%)	2 (4%)
Epiglottis, hyperplasia			1 (2%)	
Epiglottis, metaplasia, squamous		1 (2%)	2 (4%)	2 (4%)
Lung	(50)	(50)	(50)	(50)
Foreign body			1 (2%)	
Hemorrhage				1 (2%)
Inflammation, chronic	2 (4%)	10 (20%)	7 (14%)	4 (8%)
Inflammation, granulomatous			1 (2%)	
Alveolar epithelium, hyperplasia	3 (6%)	5 (10%)	2 (4%)	6 (12%)
Alveolar epithelium, metaplasia, squamous		1 (2%)		1 (2%)
Alveolus, emphysema	1 (2%)			
Alveolus, infiltration cellular, histiocyte	13 (26%)	2 (4%)	5 (10%)	11 (22%)
Alveolus, pigmentation			1 (2%)	
Bronchiole, hyperplasia	1 (2%)	2 (4%)	2 (4%)	3 (6%)
Interstitium, fibrosis	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Nose	(50)	(50)	(50)	(50)
Foreign body		2 (4%)	2 (4%)	1 (2%)
Inflammation, suppurative		1 (2%)	6 (12%)	
Goblet cell, hyperplasia			2 (4%)	1 (2%)
Nasolacrimal duct, inflammation, suppurative	5 (10%)	2 (4%)	2 (4%)	
Olfactory epithelium, degeneration, hyaline	1 (2%)		1 (2%)	2 (4%)
Respiratory epithelium, degeneration, hyaline	9 (18%)	3 (6%)	8 (16%)	9 (18%)
Respiratory epithelium, hyperplasia		2 (4%)	2 (4%)	
Pleura	(50)	(50)	(50)	(50)
Fibrosis	12 (24%)	7 (14%)	4 (8%)	5 (10%)
Inflammation, chronic	7 (14%)	7 (14%)	1 (2%)	1 (2%)
Mesothelium, hyperplasia	1 (2%)			
Special Senses System				
Eye	(49)	(50)	(48)	(49)
Inflammation, suppurative		1 (2%)	2 (4%)	
Cornea, inflammation, suppurative			1 (2%)	
Lens, cataract	2 (4%)	3 (6%)	4 (8%)	4 (8%)
Urinary System				
Kidney	(50)	(50)	(50)	(50)
Infarct				1 (2%)
Nephropathy	19 (38%)	35 (70%)	38 (76%)	44 (88%)
Papilla, mineralization	3 (6%)	5 (10%)	3 (6%)	3 (6%)
Pelvis, transitional epithelium, hyperplasia	1 (2%)	1 (2%)		1 (2%)
Pelvis, transitional epithelium, mineralization	9 (18%)	6 (12%)	7 (14%)	2 (4%)
Renal tubule, cyst		1 (2%)		1 (2%)
Renal tubule, hyperplasia	1 (2%)	1 (2%)		1 (2%)
Urinary bladder	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)			

APPENDIX C
SUMMARY OF LESIONS IN MALE MICE IN THE 2-YEAR INHALATION STUDY OF METHYL ISOBUTYL KETONE

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone[a]

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	9	6	12	9
Natural deaths	1	2	3	4
Survivors				
Died last week of study			1	
Terminal sacrifice	40	42	34	37
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, cecum	(49)	(48)	(47)	(47)
Intestine small, duodenum	(49)	(48)	(45)	(47)
Adenoma	1 (2%)		1 (2%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Intestine small, jejunum	(49)	(48)	(47)	(47)
Adenoma		1 (2%)		
Intestine small, ileum	(49)	(48)	(48)	(47)
Carcinoma		1 (2%)		1 (2%)
Liver	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Hemangioma	1 (2%)			
Hemangiosarcoma	2 (4%)	1 (2%)	2 (4%)	
Hepatoblastoma		1 (2%)		
Hepatocellular carcinoma	10 (20%)	11 (22%)	8 (16%)	7 (14%)
Hepatocellular carcinoma, multiple	2 (4%)	1 (2%)	2 (4%)	2 (4%)
Hepatocellular adenoma	11 (22%)	14 (28%)	11 (22%)	19 (38%)
Hepatocellular adenoma, multiple	6 (12%)	11 (22%)	12 (24%)	15 (30%)
Hepatocholangiocarcinoma	5 (10%)	2 (4%)		
Histiocytic sarcoma	1 (2%)		1 (2%)	1 (2%)
Sarcoma, metastatic, bone	1 (2%)			
Mesentery	(9)	(3)	(3)	(4)
Sarcoma, metastatic, salivary glands				1 (25%)
Pancreas	(49)	(50)	(49)	(50)
Hepatocellular carcinoma, metastatic, liver			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver	2 (4%)			
Histiocytic sarcoma			1 (2%)	
Salivary glands	(50)	(50)	(48)	(50)
Sarcoma				1 (2%)
Stomach, forestomach	(50)	(49)	(49)	(50)
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma				1 (2%)
Stomach, glandular	(49)	(49)	(49)	(49)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver	2 (4%)	2 (4%)		
Sarcoma, metastatic, bone	1 (2%)			

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Hepatocholangiocarcinoma, metastatic, liver	2 (4%)			
Sarcoma, metastatic, bone	1 (2%)			
Capsule, adenoma	2 (4%)		1 (2%)	1 (2%)
Adrenal medulla	(50)	(50)	(49)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Ganglioneuroma			1 (2%)	
Pheochromocytoma malignant	1 (2%)			
Islets, pancreatic	(49)	(50)	(49)	(50)
Adenoma	1 (2%)	1 (2%)		3 (6%)
Pituitary gland	(50)	(47)	(48)	(49)
Astrocytoma malignant, metastatic, brain			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Pars distalis, adenoma				1 (2%)
Thyroid gland	(50)	(49)	(50)	(50)
Follicular cell, adenoma		1 (2%)		
Follicular cell, carcinoma		1 (2%)		
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Prostate	(50)	(49)	(49)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Sarcoma, metastatic, bone	1 (2%)			
Seminal vesicle	(50)	(50)	(49)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Interstitial cell, adenoma		2 (4%)		
Hematopoietic System				
Bone marrow	(50)	(49)	(50)	(49)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Hemangiosarcoma				1 (2%)
Lymph node			(1)	(2)
Lymph node, bronchial	(39)	(35)	(37)	(39)
Hepatocholangiocarcinoma, metastatic, liver	1 (3%)	2 (6%)		
Sarcoma, metastatic, bone	1 (3%)			
Lymph node, mandibular	(37)	(36)	(32)	(34)
Hepatocholangiocarcinoma, metastatic, liver	1 (3%)			
Histiocytic sarcoma			1 (3%)	
Sarcoma, metastatic, salivary glands				1 (3%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Hematopoietic System (continued)				
Lymph node, mesenteric	(49)	(48)	(48)	(48)
Sarcoma, metastatic, bone	1 (2%)			
Lymph node, mediastinal	(42)	(38)	(36)	(38)
Hepatocholangiocarcinoma, metastatic, liver	3 (7%)	2 (5%)		
Sarcoma, metastatic, bone	1 (2%)			
Spleen	(50)	(50)	(49)	(49)
Hemangiosarcoma	1 (2%)			
Histiocytic sarcoma			1 (2%)	
Thymus	(42)	(44)	(44)	(47)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		
Sarcoma, metastatic, bone	1 (2%)			
Thymoma malignant	1 (2%)			
Integumentary System				
Skin	(50)	(50)	(49)	(50)
Subcutaneous tissue, fibrosarcoma				1 (2%)
Subcutaneous tissue, fibrous histiocytoma	1 (2%)			1 (2%)
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, histiocytic sarcoma			1 (2%)	
Subcutaneous tissue, sarcoma, metastatic, bone	1 (2%)			
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Sarcoma	1 (2%)			
Sarcoma, metastatic, bone	1 (2%)			
Skeletal muscle	(3)	(2)		
Hepatocholangiocarcinoma, metastatic, liver	2 (67%)	2 (100%)		
Sarcoma, metastatic, bone	1 (33%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Astrocytoma malignant			1 (2%)	
Histiocytic sarcoma			1 (2%)	
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	8 (16%)	5 (10%)	1 (2%)	5 (10%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma	5 (10%)	1 (2%)	3 (6%)	4 (8%)
Alveolar/bronchiolar carcinoma, multiple				1 (2%)
Carcinoma, metastatic, harderian gland		1 (2%)		
Hepatocellular carcinoma, metastatic, liver	7 (14%)	5 (10%)	3 (6%)	5 (10%)
Hepatocholangiocarcinoma, metastatic, liver	3 (6%)	2 (4%)		
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, bone	1 (2%)			
Sarcoma, metastatic, salivary glands				1 (2%)

TABLE C1
Summary of the Incidence of Neoplasms in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(50)
Fibrous histiocytoma, metastatic, skin				1 (2%)
Histiocytic sarcoma			1 (2%)	
Sarcoma, metastatic, bone	1 (2%)			
Pleura	(1)			
Hepatocholangiocarcinoma, metastatic, liver	1 (100%)			
Special Senses System				
Eye	(49)	(48)	(49)	(49)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Harderian gland	(50)	(49)	(50)	(50)
Adenoma	5 (10%)	4 (8%)	5 (10%)	7 (14%)
Carcinoma	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Histiocytic sarcoma			1 (2%)	
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Alveolar/bronchiolar carcinoma, metastatic, lung	1 (2%)			
Fibrous histiocytoma, metastatic, skin				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	1 (2%)			
Sarcoma, metastatic, bone	1 (2%)			
Renal tubule, carcinoma		1 (2%)		
Ureter				(1)
Transitional epithelium, carcinoma				1 (100%)
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)	1 (2%)
Lymphoma malignant	1 (2%)	3 (6%)	1 (2%)	2 (4%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	45	41	36	45
Total primary neoplasms	69	63	52	79
Total animals with benign neoplasms	27	32	29	37
Total benign neoplasms	36	39	32	53
Total animals with malignant neoplasms	29	21	16	20
Total malignant neoplasms	33	24	20	26
Total animals with metastatic neoplasms	12	8	4	7
Total metastatic neoplasms	46	19	5	12

[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 Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	4 8 2	5 9 2	6 1 2	6 1 4	6 1 8	6 2 2	6 6 6	6 7 6	6 7 8	7 0 4	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
Carcass ID Number	0 0 3	0 4 4	0 0 7	0 0 5	0 2 1	0 4 5	0 3 7	0 3 4	0 0 2	0 3 2	0 0 1	0 0 6	0 1 1	0 1 5	0 1 8	0 1 9	0 2 0	0 2 2	0 2 7	0 2 9	0 3 0	0 3 8	0 4 1	0 4 7	0 5 0
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Intestine small, jejunum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma						X																			
Hemangiosarcoma	X																								
Hepatocellular carcinoma	X			X						X	X	X		X								X			
Hepatocellular carcinoma, multiple							X								X										
Hepatocellular adenoma									X							X				X	X		X		
Hepatocellular adenoma, multiple											X							X							
Hepatocholangiocarcinoma			X		X	X															X				X
Histiocytic sarcoma		X																							
Sarcoma, metastatic, bone							X																		
Mesentery									+								+	+					+		
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver			X		X																				
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver			X		X																				
Sarcoma, metastatic, bone							X																		
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver			X		X																				
Sarcoma, metastatic, bone							X																		
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																								X	
Pheochromocytoma malignant													X												

+: 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 Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	
Carcass ID Number	00404	00510	00612	00714	00817	00923	01024	01125	01228	01335	01436	01540	01642	01743	01844	01946	02048	02149	02208	02309	02413	02516	02616	02731	02833	02933	03039	Total Tissues/ Tumors
Alimentary System																												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	I	+	+	+	+	+	+	+	+	43
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma															X													1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																												1
Hemangiosarcoma																						X						2
Hepatocellular carcinoma						X			X																		X	10
Hepatocellular carcinoma, multiple																												2
Hepatocellular adenoma		X			X	X							X							X					X			11
Hepatocellular adenoma, multiple			X												X		X	X										6
Hepatocholangiocarcinoma																												5
Histiocytic sarcoma																												1
Sarcoma, metastatic, bone																												1
Mesentery	+		+	+							+						+											9
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																												2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																												
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																												2
Sarcoma, metastatic, bone																												1
Endocrine System																												
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																												2
Sarcoma, metastatic, bone																												1
Capsule, adenoma																	X								X			2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																												1
Pheochromocytoma malignant																												1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	4 8 2	5 9 8	6 1 2	6 1 4	6 1 8	6 2 2	6 2 6	6 6 7	6 7 6	7 0 8	7 0 4	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
Carcass ID Number	0 0 3	0 4 4	0 0 7	0 0 5	0 2 1	0 4 5	0 3 7	0 3 4	0 0 2	0 3 2	0 0 1	0 0 6	0 1 1	0 1 5	0 1 8	0 1 9	0 2 0	0 2 2	0 2 7	0 2 9	0 3 0	0 3 8	0 4 1	0 4 7	0 5 0
Endocrine System (continued)																									
Islets, pancreatic	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	M	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	M	+	+	M	+	+	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver					X																				
Histiocytic sarcoma		X																							
Penis											+														
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver			X																						
Sarcoma, metastatic, bone							X																		
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver					X																				
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, bronchial	M	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Hepatocholangiocarcinoma, metastatic, liver					X																				
Sarcoma, metastatic, bone							X																		
Lymph node, mandibular	+	+	+	+	+	M	+	M	+	+	+	+	+	M	M	+	+	+	+	+	M	+	M	+	+
Hepatocholangiocarcinoma, metastatic, liver			X																						
Lymph node, mesenteric	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, bone							X																		
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	M	+	+
Hepatocholangiocarcinoma, metastatic, liver			X		X	X																			
Sarcoma, metastatic, bone							X																		
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Thymus	M	+	+	M	M	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver			X																						
Sarcoma, metastatic, bone							X																		
Thymoma malignant																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

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 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 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	0 0 4	0 1 0	0 1 2	0 1 4	0 1 7	0 2 3	0 2 4	0 2 5	0 2 8	0 3 5	0 3 6	0 4 0	0 4 2	0 4 3	0 4 6	0 4 8	0 4 9	0 0 8	0 0 9	0 1 3	0 1 6	0 2 6	0 3 1	0 3 3	0 3 9	Total Tissues/ Tumors
Endocrine System (continued)																										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma																								X		1
Parathyroid gland	+	+	M	+	M	+	+	+	+	+	M	+	M	M	M	+	M	M	M	M	+	+	+	M	+	32
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, bone																										1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node, bronchial	+	+	+	+	M	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	M	M	M	39
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, bone																										1
Lymph node, mandibular	M	+	M	+	+	M	+	M	M	+	+	+	I	+	+	+	+	+	+	M	+	+	+	+	+	37
Hepatocholangiocarcinoma, metastatic, liver																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, metastatic, bone																										1
Lymph node, mediastinal	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	+	M	+	42
Hepatocholangiocarcinoma, metastatic, liver																										3
Sarcoma, metastatic, bone																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																									1
Thymus	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	42
Hepatocholangiocarcinoma, metastatic, liver																										1
Sarcoma, metastatic, bone																										1
Thymoma malignant							X																			1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	4 8 2	5 9 2	6 1 2	6 1 4	6 1 8	6 2 2	6 2 6	6 7 6	6 7 8	7 0 4	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
Carcass ID Number	0 0 3	0 4 4	0 0 7	0 0 5	0 2 1	0 4 5	0 3 7	0 3 4	0 3 2	0 3 2	0 3 1	0 0 6	0 1 1	0 1 5	0 1 8	0 1 9	0 2 0	0 2 2	0 2 7	0 2 9	0 3 0	0 3 8	0 4 1	0 4 7	0 5 0
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, fibrous histiocytoma								X																	
Subcutaneous tissue, sarcoma, metastatic, bone							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma							X																		
Sarcoma, metastatic, bone							X																		
Skeletal muscle			+		+		+																		
Hepatocholangiocarcinoma, metastatic, liver			X		X																				
Sarcoma, metastatic, bone							X																		
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma											X							X							
Alveolar/bronchiolar adenoma, multiple							X																		
Alveolar/bronchiolar carcinoma																X			X				X		
Hepatocellular carcinoma, metastatic, liver	X			X						X	X				X							X			
Hepatocholangiocarcinoma, metastatic, liver			X		X	X																			
Histiocytic sarcoma		X																							
Sarcoma, metastatic, bone							X																		
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, bone							X																		
Pleura						+																			
Hepatocholangiocarcinoma, metastatic, liver						X																			
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver					X																				
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma		X										X													
Carcinoma																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	
Carcass ID Number	00014	00110	00112	00114	00117	00123	00224	00225	00228	00235	00336	00340	00442	00443	00446	00448	00449	00508	00909	00913	00916	00926	00931	00933	00939	Total Tissues/ Tumors
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	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrous histiocytoma																												1
Subcutaneous tissue, sarcoma, metastatic, bone																												1
Musculoskeletal System																												
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																												1
Sarcoma, metastatic, bone																												1
Skeletal muscle																												3
Hepatocholangiocarcinoma, metastatic, liver																												2
Sarcoma, metastatic, bone																												1
Nervous System																												
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																												
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma		X		X	X					X		X		X														8
Alveolar/bronchiolar adenoma, multiple																												1
Alveolar/bronchiolar carcinoma											X																X	5
Hepatocellular carcinoma, metastatic, liver						X																						7
Hepatocholangiocarcinoma, metastatic, liver																												3
Histiocytic sarcoma																												1
Sarcoma, metastatic, bone																												1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, bone																												1
Pleura																												1
Hepatocholangiocarcinoma, metastatic, liver																												1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																												
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																												1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma							X									X		X										5
Carcinoma														X												X		2

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	482	589	612	614	618	622	626	676	708	704	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	00303	00434	00047	00055	00221	00445	00337	00334	00302	00322	00301	00306	00311	00315	00318	00319	00320	00322	00327	00329	00330	00338	00341	00447	00450
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic, lung																								X		
Hepatocholangiocarcinoma, metastatic, liver					X																					
Histiocytic sarcoma		X																								
Sarcoma, metastatic, bone							X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma		X																								
Lymphoma malignant																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

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 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 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	0 0 4	0 1 0	0 1 2	0 1 4	0 1 7	0 2 3	0 2 4	0 2 5	0 2 8	0 3 5	0 3 6	0 4 0	0 4 2	0 4 3	0 4 6	0 4 8	0 4 9	0 0 8	0 0 9	0 1 3	0 1 6	0 2 6	0 3 1	0 3 3	0 3 9	Total Tissues/ Tumors
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma, metastatic, lung																										1
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Sarcoma, metastatic, bone																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant																									X	1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	
Carcass ID Number	25 00	20 06	20 08	21 11	21 16	21 18	22 23	23 33	23 36	23 38	23 39	24 42	24 45	24 46	24 47	20 03	20 04	21 15	22 24	22 25	23 00	23 02	23 35	24 00	24 01	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	I	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocholangiocarcinoma, metastatic, liver																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma	X																									1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatoblastoma																										1
Hepatocellular carcinoma							X	X												X				X		11
Hepatocellular carcinoma, multiple			X																							1
Hepatocellular adenoma	X			X	X							X	X	X			X	X				X			X	14
Hepatocellular adenoma, multiple			X				X		X	X	X													X		11
Hepatocholangiocarcinoma																										2
Mesentery						+																				3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocholangiocarcinoma, metastatic, liver																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										2
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma						X																				1
Parathyroid gland	M	+	M	+	+	M	+	+	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	M	+	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma															X											1
Follicular cell, carcinoma																								X		1
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	731	
Carcass ID Number	25 00	20 06	20 08	21 11	21 16	21 18	22 33	23 33	23 36	23 38	23 39	24 02	24 45	24 46	24 47	20 13	20 04	21 15	22 24	22 25	23 30	23 32	23 35	24 40	24 41	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																									X	2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, bronchial	+	+	M	+	+	+	+	+	+	+	+	+	M	+	M	+	M	M	+	M	M	M	+	M	+	35
Hepatocholangiocarcinoma, metastatic, liver																										2
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	M	+	M	M	M	M	+	+	+	M	M	+	+	+	M	36
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Lymph node, mediastinal	M	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	M	M	+	M	+	M	+	+	38
Hepatocholangiocarcinoma, metastatic, liver																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Hepatocholangiocarcinoma, metastatic, liver																										1
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
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Hepatocholangiocarcinoma, metastatic, liver																										2
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																									5
Alveolar/bronchiolar carcinoma																										1
Carcinoma, metastatic, harderian gland						X																				1
Hepatocellular carcinoma, metastatic, liver			X																							5
Hepatocholangiocarcinoma, metastatic, liver																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

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

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	731	
Carcass ID Number	250	206	208	211	216	218	223	233	236	238	239	242	245	246	247	203	204	215	224	225	230	232	235	240	241	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma	X	X		X																						4
Carcinoma						X																				1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Renal tubule, carcinoma				X																						1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant				X								X		X												3

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	0262	4122	4721	4880	5001	5119	5220	5220	5254	6002	6039	6599	6698	7011	7117	7229	7229	7229	7229	7229	7229	7229	7229	7229	7229
Carcass ID Number	4440	4022	4022	4080	4004	4047	4446	4448	4412	4425	4406	4411	4417	4136	4343	4033	4099	4114	4116	4128	4229	4331	4333	4337	4339
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	A	+	M	+	M	+	+	A	A	+	+	+	+	+	+	I	+	M	+	+	+	A	+	M
Intestine large, colon	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	A	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine small, duodenum	+	A	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Adenoma																		X							
Intestine small, jejunum	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Hepatocellular carcinoma				X						X				X					X						
Hepatocellular carcinoma, multiple											X												X		
Hepatocellular adenoma			X						X			X					X	X							
Hepatocellular adenoma, multiple											X			X	X				X		X	X		X	
Histiocytic sarcoma							X																		
Mesentery																		+			+				
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma							X																		
Salivary glands	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth								+																	
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma													X												
Adrenal medulla	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ganglioneuroma																									
Islets, pancreatic	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	+	M	M	M	M	+	M	+	+	+	+	M	M	+	+	+	+	+	I	M	+	M	+
Pituitary gland	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+
Astrocytoma malignant, metastatic, brain		X																							
Histiocytic sarcoma							X																		
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	
Carcass ID Number	44040	44045	44049	44050	44001	44005	44010	44015	44018	44019	44020	44021	44023	44024	44026	44027	44030	44038	44042	44070	44113	44133	44132	44134	44135	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	39
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		2
Hepatocellular carcinoma	X				X																		X	X		8
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma							X			X				X		X		X					X			11
Hepatocellular adenoma, multiple	X		X			X					X		X													12
Histiocytic sarcoma																										1
Mesentery								+																		3
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metastatic, liver					X																					1
Histiocytic sarcoma																										1
Salivary glands	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Capsule, adenoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ganglioneuroma				X																						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	M	M	+	M	+	M	M	M	+	+	M	+	+	M	+	+	+	+	M	I	+	29
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Astrocytoma malignant, metastatic, brain																										1
Histiocytic sarcoma																										1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	0262	4129	4721	4801	5019	5197	5220	5220	5554	6029	6359	6599	6908	7017	7129	7229	7229	7229	7229	7229	7229	7229	7229	7229	7229
Carcass ID Number	4404	4022	4022	4208	4004	4047	4466	4148	4122	4125	4206	4141	4177	4136	4403	4033	4009	4114	4166	4228	4299	4331	4337	4337	4339
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node																									
Lymph node, bronchial	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	M	M	+	+	+	+
Lymph node, mandibular	+	M	+	M	+	M	+	M	A	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M
Histiocytic sarcoma							X																		
Lymph node, mesenteric	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mediastinal	+	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	M
Spleen	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Thymus	+	M	+	M	+	+	+	+	A	+	+	+	+	+	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											
Subcutaneous tissue, histiocytic sarcoma							X																		
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma malignant		X																							
Histiocytic sarcoma							X																		
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma												X													
Hepatocellular carcinoma, metastatic, liver											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																		
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	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 1	7 3 1	7 3 1	7 3 1	7 3 1	7 3 1	
Carcass ID Number	4 4 0	4 4 5	4 4 9	4 5 0	4 0 1	4 0 5	4 1 0	4 1 5	4 1 8	4 1 9	4 2 0	4 2 1	4 2 3	4 2 4	4 2 6	4 2 7	4 3 0	4 3 8	4 4 2	4 0 7	4 1 1	4 1 3	4 3 2	4 3 4	4 3 5	Total Tissues/ Tumors
Genital System																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node													+													1
Lymph node, bronchial	+	+	M	+	+	M	+	+	+	+	+	+	+	+	M	M	M	M	M	+	+	+	+	+	+	37
Lymph node, mandibular	+	+	+	+	+	+	M	+	M	M	M	+	+	M	M	M	+	+	+	M	+	+	M	+	M	32
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	M	M	M	+	+	+	36
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Thymus	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	44
Integumentary System																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Subcutaneous tissue, hemangiosarcoma																										1
Subcutaneous tissue, histiocytic sarcoma																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma malignant																										1
Histiocytic sarcoma																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma						X																				1
Alveolar/bronchiolar carcinoma						X													X							3
Hepatocellular carcinoma, metastatic, liver	X				X																					3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	0262	4121	4171	4480	5001	5119	5220	5220	5254	6029	6039	6599	6981	7017	7129	7229	7229	7229	7229	7229	7229	7229	7229	7229
Carcass ID Number	44042	40242	42278	40084	40047	44476	44468	41282	12025	20661	40417	41763	43443	40033	40094	41146	41168	42289	43391	43313	43377	43379		
Special Senses System																								
Eye	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma				X																X				X
Carcinoma																								
Histiocytic sarcoma							X																	
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma							X																	
Lymphoma malignant																								

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	729	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	
Carcass ID Number	44040	44045	44049	44050	44001	44005	44010	44015	44018	44019	44020	44021	44023	44024	44026	44027	44030	44038	44042	44007	44011	44013	44032	44034	44035		Total Tissues/ Tumors
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma																				X	X						5
Carcinoma																			X								1
Histiocytic sarcoma																											1
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Histiocytic sarcoma																											1
Lymphoma malignant													X														1

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	4 4 1	5 1 3	5 5 1	5 9 3	6 0 1	6 0 7	6 1 7	6 3 7	6 5 6	6 7 8	7 1 0	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
Carcass ID Number	6 0 1	6 3 3	6 0 7	6 3 1	6 4 7	6 1 3	6 2 9	6 1 8	6 4 6	6 3 9	6 0 2	6 1 2	6 3 6	6 0 3	6 1 0	6 1 6	6 1 7	6 1 9	6 2 0	6 2 3	6 3 0	6 3 4	6 3 5	6 3 7	6 4 1
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	A	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	A	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma													X												
Intestine small, jejunum	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	A	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin		X																							
Hepatocellular carcinoma			X					X				X													
Hepatocellular carcinoma, multiple				X							X														
Hepatocellular adenoma							X	X		X			X		X	X	X	X			X			X	
Hepatocellular adenoma, multiple			X		X														X	X		X	X		X
Histiocytic sarcoma						X																			
Mesentery						+			+																
Sarcoma, metastatic, salivary glands						X																			
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma						X																			
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Squamous cell papilloma																									
Stomach, glandular	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X										X					
Parathyroid gland	+	+	+	M	+	+	+	M	+	+	+	M	+	M	+	M	+	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																									
None																									

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	
Carcass ID Number	64343	64434	64499	60066	60008	60099	61011	61144	61155	62022	62244	62288	63032	63388	64545	64488	65040	60445	60055	62211	62255	62266	62277	64401	64402	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	M	+	45
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																			X							1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																										1
Hepatocellular carcinoma							X			X		X									X					7
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma			X	X		X		X								X		X	X	X				X		19
Hepatocellular adenoma, multiple	X	X					X		X	X		X		X							X					15
Histiocytic sarcoma																										1
Mesentery										+	+															4
Sarcoma, metastatic, salivary glands																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma					X																					1
Squamous cell papilloma											X															1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma				X																						1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																				X						3
Parathyroid gland	+	+	+	+	+	+	+	+	M	+	+	I	+	+	+	M	M	M	+	M	+	+	+	M	+	37
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma													X													1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
None																										

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	441	513	551	593	601	607	617	637	656	678	710	711	725	729	729	729	729	729	729	729	729	729	729	729	729
Carcass ID Number	60013	60337	60311	63417	64173	61239	62188	61446	64369	63902	60122	61326	60301	61066	61167	61197	62203	62303	63304	63345	63357	63475	63541	64141	64141
Genital System																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis										+															
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hematopoietic System																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin		X																							
Hemangiosarcoma																									
Lymph node											+														
Lymph node, bronchial	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	M	+	+	+	M	+	M	+	+
Lymph node, mandibular	M	+	+	+	+	+	+	M	M	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+
Sarcoma, metastatic, salivary glands						X																			
Lymph node, mesenteric	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	M	M	+	+	I	+	M	+
Spleen	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	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, fibrosarcoma							X																		
Subcutaneous tissue, fibrous histiocytoma		X																							
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X													X			X		
Alveolar/bronchiolar carcinoma						X																			
Alveolar/bronchiolar carcinoma, multiple																									
Hepatocellular carcinoma, metastatic, liver				X				X			X	X													
Sarcoma, metastatic, salivary glands						X																			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	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 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	6 4 4 3	6 4 4 4	6 4 4 9	6 0 0 6	6 0 0 8	6 0 0 9	6 1 1 1	6 1 1 4	6 1 1 5	6 2 2 2	6 2 2 4	6 2 2 8	6 3 3 2	6 3 3 8	6 4 4 5	6 4 4 8	6 5 0 0	6 0 0 4	6 0 0 5	6 2 2 1	6 2 2 5	6 2 2 6	6 2 2 7	6 4 4 0	6 4 4 2	Total Tissues/ Tumors
Genital System																											
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis																											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrous histiocytoma, metastatic, skin																											1
Hemangiosarcoma																										X	1
Lymph node																+											2
Lymph node, bronchial	+	M	+	+	M	+	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	39
Lymph node, mandibular	+	+	+	M	M	M	M	+	M	+	+	+	M	+	+	+	+	M	+	+	M	M	M	+	+		34
Sarcoma, metastatic, salivary glands																											1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph node, mediastinal	M	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	M	+	+	M	M	+	+	+	+	+	38
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	47
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	M	
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrosarcoma																											1
Subcutaneous tissue, fibrous histiocytoma																											1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Respiratory System																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X																		X					5
Alveolar/bronchiolar carcinoma					X							X					X										4
Alveolar/bronchiolar carcinoma, multiple																							X				1
Hepatocellular carcinoma, metastatic, liver																						X					5
Sarcoma, metastatic, salivary glands																											1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2
Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	4 4 1	5 1 3	5 5 1	5 9 3	6 0 1	6 0 7	6 1 7	6 3 7	6 5 6	6 7 8	7 1 0	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
Carcass ID Number	6 0 1	6 3 3	6 0 7	6 3 1	6 4 7	6 1 3	6 2 9	6 1 8	6 4 6	6 3 9	6 0 2	6 1 2	6 3 6	6 0 3	6 1 0	6 1 6	6 1 7	6 1 9	6 2 0	6 2 3	6 3 0	6 3 4	6 3 5	6 3 7	6 4 1
Special Senses System																									
Eye	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma			X	X																	X				
Carcinoma																									
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrous histiocytoma, metastatic, skin		X																							
Ureter																						+			
Transitional epithelium, carcinoma																						X			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	729	729	729	730	730	730	730	730	730	730	730	730	730	730	730	730	730	730	731	731	731	731	731	731	731	731	
Carcass ID Number	64343	64449	64496	60066	60088	60091	61011	61145	61152	62224	62248	62328	63385	64548	64588	65040	60045	60211	62215	62266	62427	64042	64412		Total Tissues/ Tumors
Special Senses System																											
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma		X				X		X				X															7
Carcinoma					X	X																					2
Urinary System																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibrous histiocytoma, metastatic, skin																											1
Ureter																											1
Transitional epithelium, carcinoma																											1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																											
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Lymphoma malignant																X											2

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Harderian Gland: Adenoma				
Overall rate[a]	5/50 (10%)	4/50 (8%)	5/50 (10%)	7/50 (14%)
Adjusted rate[b]	10.6%	8.4%	11.6%	15.1%
Terminal rate[c]	4/40 (10%)	4/42 (10%)	4/35 (11%)	5/37 (14%)
First incidence (days)	598	729 (T)	480	551
Poly-3 test[d]	P=0.238	P=0.493N	P=0.574	P=0.370
Harderian Gland: Adenoma or Carcinoma				
Overall rate	7/50 (14%)	5/50 (10%)	6/50 (12%)	8/50 (16%)
Adjusted rate	14.9%	10.5%	14.0%	17.3%
Terminal rate	6/40 (15%)	5/42 (12%)	5/35 (14%)	6/37 (16%)
First incidence (days)	598	729 (T)	480	551
Poly-3 test	P=0.341	P=0.372N	P=0.568N	P=0.489
Liver: Hepatocellular Adenoma				
Overall rate	17/50 (34%)	25/50 (50%)	23/50 (46%)	34/50 (68%)
Adjusted rate	36.4%	52.0%	51.9%	71.9%
Terminal rate	16/40 (40%)	22/42 (52%)	17/35 (49%)	28/37 (76%)
First incidence (days)	678	582	471	551
Poly-3 test	P<0.001	P=0.090	P=0.097	P<0.001
Liver: Hepatocellular Carcinoma				
Overall rate	12/50 (24%)	12/50 (24%)	10/50 (20%)	9/50 (18%)
Adjusted rate	25.0%	24.4%	22.8%	19.2%
Terminal rate	8/40 (20%)	8/42 (19%)	6/35 (17%)	4/37 (11%)
First incidence (days)	482	493	480	551
Poly-3 test	P=0.271N	P=0.566N	P=0.498N	P=0.333N
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma				
Overall rate	27/50 (54%)	34/50 (68%)	28/50 (56%)	37/50 (74%)
Adjusted rate	56.1%	68.3%	61.6%	77.3%
Terminal rate	22/40 (55%)	27/42 (64%)	20/35 (57%)	28/37 (76%)
First incidence (days)	482	493	471	551
Poly-3 test	P=0.028	P=0.146	P=0.368	P=0.019
Liver: Hepatocellular Carcinoma or Hepatoblastoma				
Overall rate	12/50 (24%)	13/50 (26%)	10/50 (20%)	9/50 (18%)
Adjusted rate	25.0%	26.4%	22.8%	19.2%
Terminal rate	8/40 (20%)	9/42 (21%)	6/35 (17%)	4/37 (11%)
First incidence (days)	482	493	480	551
Poly-3 test	P=0.245N	P=0.528	P=0.498N	P=0.333N
Liver: Hepatocellular Adenoma, Hepatocellular Carcinoma, or Hepatoblastoma				
Overall rate	27/50 (54%)	35/50 (70%)	28/50 (56%)	37/50 (74%)
Adjusted rate	56.1%	70.3%	61.6%	77.3%
Terminal rate	22/40 (55%)	28/42 (67%)	20/35 (57%)	28/37 (76%)
First incidence (days)	482	493	471	551
Poly-3 test	P=0.033	P=0.102	P=0.368	P=0.019
Liver: Hepatocholangiocarcinoma				
Overall rate	5/50 (10%)	2/50 (4%)	0/50 (0%)	0/50 (0%)
Adjusted rate	10.5%	4.2%	0.0%	0.0%
Terminal rate	2/40 (5%)	0/42 (0%)	0/35 (0%)	0/37 (0%)
First incidence (days)	612	582	—[e]	—
Poly-3 test	P=0.008N	P=0.212N	P=0.042N	P=0.035N

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	9/50 (18%)	5/50 (10%)	1/50 (2%)	5/50 (10%)
Adjusted rate	19.3%	10.5%	2.4%	10.9%
Terminal rate	8/40 (20%)	4/42 (10%)	1/35 (3%)	4/37 (11%)
First incidence (days)	666	661	729 (T)	617
Poly-3 test	P=0.146N	P=0.181N	P=0.013N	P=0.205N
Lung: Alveolar/bronchiolar Carcinoma				
Overall rate	5/50 (10%)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted rate	10.8%	2.1%	7.1%	10.9%
Terminal rate	5/40 (13%)	1/42 (2%)	2/35 (6%)	4/37 (11%)
First incidence (days)	729 (T)	729 (T)	659	607
Poly-3 test	P=0.369	P=0.097N	P=0.407N	P=0.620
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	14/50 (28%)	5/50 (10%)	3/50 (6%)	10/50 (20%)
Adjusted rate	29.9%	10.5%	7.1%	21.7%
Terminal rate	13/40 (33%)	4/42 (10%)	2/35 (6%)	8/37 (22%)
First incidence (days)	666	661	659	607
Poly-3 test	P=0.326N	P=0.016N	P=0.005N	P=0.250N
Pancreatic Islets: Adenoma				
Overall rate	1/49 (2%)	1/50 (2%)	0/49 (0%)	3/50 (6%)
Adjusted rate	2.2%	2.1%	0.0%	6.6%
Terminal rate	1/40 (3%)	1/42 (2%)	0/35 (0%)	2/37 (5%)
First incidence (days)	729 (T)	729 (T)	—	678
Poly-3 test	P=0.153	P=0.755N	P=0.520N	P=0.300
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	6.4%	2.1%	7.0%	2.2%
Terminal rate	2/40 (5%)	0/42 (0%)	1/35 (3%)	1/37 (3%)
First incidence (days)	482	565	639	729 (T)
Poly-3 test	P=0.336N	P=0.300N	P=0.615	P=0.320N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	4/50 (8%)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted rate	8.4%	2.1%	7.0%	2.2%
Terminal rate	2/40 (5%)	0/42 (0%)	1/35 (3%)	1/37 (3%)
First incidence (days)	482	565	639	729 (T)
Poly-3 test	P=0.213N	P=0.176N	P=0.559N	P=0.194N
All Organs: Malignant Lymphoma				
Overall rate	1/50 (2%)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted rate	2.2%	6.3%	2.4%	4.4%
Terminal rate	1/40 (3%)	3/42 (7%)	1/35 (3%)	1/37 (3%)
First incidence (days)	729 (T)	729 (T)	729 (T)	710
Poly-3 test	P=0.509	P=0.313	P=0.739	P=0.492
All Organs: Benign Neoplasms				
Overall rate	27/50 (54%)	32/50 (64%)	29/50 (58%)	37/50 (74%)
Adjusted rate	56.5%	66.2%	64.2%	77.5%
Terminal rate	23/40 (58%)	28/42 (67%)	21/35 (60%)	30/37 (81%)
First incidence (days)	598	582	471	551
Poly-3 test	P=0.021	P=0.220	P=0.289	P=0.021

TABLE C3
Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
All Organs: Malignant Neoplasms				
Overall rate	29/50 (58%)	21/50 (42%)	16/50 (32%)	20/50 (40%)
Adjusted rate	58.2%	42.1%	35.1%	41.4%
Terminal rate	20/40 (50%)	15/42 (36%)	9/35 (26%)	12/37 (32%)
First incidence (days)	482	493	412	513
Poly-3 test	P=0.075N	P=0.078N	P=0.018N	P=0.070N
All Organs: Benign or Malignant Neoplasms				
Overall rate	45/50 (90%)	41/50 (82%)	36/50 (72%)	45/50 (90%)
Adjusted rate	90.0%	82.0%	76.5%	91.9%
Terminal rate	35/40 (88%)	33/42 (79%)	25/35 (71%)	34/37 (92%)
First incidence (days)	482	493	412	513
Poly-3 test	P=0.372	P=0.194N	P=0.061N	P=0.506

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, and pancreatic islets; 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 the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in an exposure group is indicated by **N**.
[e] Not applicable; no neoplasms in animal group

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

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Chamber Controls Given NTP-2000 Diet			
Decalin	22/50	10/50	28/50
Divinylbenzene	22/50	13/50	30/50
Indium phosphide	17/50	11/50	26/50
Methyl isobutyl ketone	17/50	12/50	27/50
Propylene glycol mono-*t*-butyl ether	18/50	9/50	25/50
Stoddard solvent (Type IIC)	23/50	16/50	34/50
Vanadium pentoxide	15/50	14/50	26/50
Overall Historical Incidence: Inhalation Studies			
Total (%)	134/350 (38.3%)	85/350 (24.3%)	196/350 (56.0%)
Mean ± standard deviation	38.3% ± 6.3%	24.3% ± 4.8%	56.0% ± 6.2%
Range	30%-46%	18%-32%	50%-68%
Overall Historical Incidence: All Routes			
Total (%)	490/1,506 (32.5%)	344/1,506 (22.8%)	745/1,506 (49.5%)
Mean ± standard deviation	32.6% ± 12.7%	22.9% ± 10.0%	49.5% ± 17.8%
Range	12%-63%	8%-46%	20%-85%

[a] Data as of January 28, 2005

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone[a]

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Moribund	9	6	12	9
Natural deaths	1	2	3	4
Survivors				
Died last week of study			1	
Terminal sacrifice	40	42	34	37
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(43)	(44)	(39)	(45)
Infiltration cellular, polymorphonuclear		1 (2%)		
Intestine large, rectum	(50)	(48)	(49)	(49)
Hemorrhage			1 (2%)	
Inflammation, acute	1 (2%)			
Intestine large, cecum	(49)	(48)	(47)	(47)
Hemorrhage			1 (2%)	
Intestine small, duodenum	(49)	(48)	(45)	(47)
Ulcer	1 (2%)			
Intestine small, jejunum	(49)	(48)	(47)	(47)
Cyst				1 (2%)
Peyer's patch, hyperplasia	1 (2%)	1 (2%)	2 (4%)	
Intestine small, ileum	(49)	(48)	(48)	(47)
Inflammation, acute				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis	1 (2%)			1 (2%)
Basophilic focus	8 (16%)	5 (10%)	4 (8%)	8 (16%)
Clear cell focus	22 (44%)	13 (26%)	13 (26%)	20 (40%)
Eosinophilic focus	3 (6%)	4 (8%)	5 (10%)	8 (16%)
Hepatodiaphragmatic nodule			1 (2%)	
Infarct		1 (2%)		
Inflammation, chronic				1 (2%)
Inflammation, granulomatous	1 (2%)		1 (2%)	
Mixed cell focus	1 (2%)		1 (2%)	1 (2%)
Necrosis	5 (10%)	1 (2%)	2 (4%)	7 (14%)
Tension lipidosis	4 (8%)	3 (6%)	3 (6%)	1 (2%)
Thrombosis			1 (2%)	
Bile duct, cyst		1 (2%)		
Bile duct, hyperplasia	1 (2%)			
Hepatocyte, erythrophagocytosis				1 (2%)
Hepatocyte, vacuolization cytoplasmic	1 (2%)		2 (4%)	1 (2%)
Mesentery	(9)	(3)	(3)	(4)
Fat, necrosis	9 (100%)	3 (100%)	3 (100%)	3 (75%)
Salivary glands	(50)	(50)	(48)	(50)
Inflammation, acute	1 (2%)			
Stomach, forestomach	(50)	(49)	(49)	(50)
Hyperplasia, squamous	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Inflammation	1 (2%)	2 (4%)	3 (6%)	
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 Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Alimentary System (continued)				
Stomach, glandular	(49)	(49)	(49)	(49)
Hyperplasia	1 (2%)			
Necrosis	1 (2%)		1 (2%)	
Tooth			(1)	
Malformation			1 (100%)	
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	10 (20%)	8 (16%)	2 (4%)	10 (20%)
Inflammation, suppurative				1 (2%)
Thrombosis	2 (4%)		3 (6%)	1 (2%)
Artery, inflammation, chronic active	2 (4%)			
Endocrine System				
Adrenal cortex	(50)	(50)	(49)	(50)
Hyperplasia	13 (26%)	18 (36%)	13 (27%)	9 (18%)
Hypertrophy	26 (52%)	30 (60%)	26 (53%)	14 (28%)
Adrenal medulla	(50)	(50)	(49)	(50)
Hyperplasia	1 (2%)	1 (2%)	3 (6%)	
Islets, pancreatic	(49)	(50)	(49)	(50)
Hyperplasia	1 (2%)	2 (4%)		1 (2%)
Pituitary gland	(50)	(47)	(48)	(49)
Pars distalis, hyperplasia	1 (2%)		2 (4%)	
Thyroid gland	(50)	(49)	(50)	(50)
Follicular cell, hyperplasia	4 (8%)	4 (8%)	6 (12%)	8 (16%)
General Body System				
None				
Genital System				
Epididymis	(50)	(50)	(50)	(50)
Granuloma sperm	2 (4%)		2 (4%)	1 (2%)
Infiltration cellular, polymorphonuclear		1 (2%)		
Inflammation, granulomatous		1 (2%)		
Penis	(1)	(1)		(1)
Inflammation, acute		1 (100%)		1 (100%)
Preputial gland	(50)	(50)	(50)	(50)
Ectasia	2 (4%)	3 (6%)		1 (2%)
Inflammation, chronic active		1 (2%)		2 (4%)
Prostate	(50)	(49)	(49)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)		
Seminal vesicle	(50)	(50)	(49)	(50)
Dilatation	1 (2%)			
Inflammation, chronic active	1 (2%)	1 (2%)		1 (2%)
Testes	(50)	(50)	(50)	(50)
Atrophy	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Thrombosis			1 (2%)	
Interstitial cell, hyperplasia	1 (2%)		1 (2%)	2 (4%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Hematopoietic System				
Lymph node, bronchial	(39)	(35)	(37)	(39)
Hyperplasia, lymphoid			1 (3%)	
Lymph node, mandibular	(37)	(36)	(32)	(34)
Hyperplasia, lymphoid			1 (3%)	
Lymph node, mesenteric	(49)	(48)	(48)	(48)
Infiltration cellular, histiocyte				1 (2%)
Lymph node, mediastinal	(42)	(38)	(36)	(38)
Hyperplasia, lymphoid			1 (3%)	
Spleen	(50)	(50)	(49)	(49)
Hematopoietic cell proliferation	2 (4%)	1 (2%)	1 (2%)	3 (6%)
Integumentary System				
Skin	(50)	(50)	(49)	(50)
Inflammation, acute	1 (2%)			
Inflammation, chronic active		2 (4%)	1 (2%)	
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Atrophy			1 (2%)	
Hyperostosis	1 (2%)			
Joint, cartilage, hyperplasia	1 (2%)			
Nervous System				
Brain	(50)	(50)	(50)	(50)
Hemorrhage				1 (2%)
Hydrocephalus			1 (2%)	
Necrosis	2 (4%)			
Respiratory System				
Lung	(50)	(50)	(50)	(50)
Congestion, chronic	1 (2%)			
Hemorrhage		1 (2%)		
Hyperplasia		1 (2%)		
Inflammation, chronic active			1 (2%)	
Pigmentation			1 (2%)	
Thrombosis			1 (2%)	
Alveolar epithelium, hyperplasia	7 (14%)	5 (10%)	5 (10%)	2 (4%)
Alveolus, infiltration cellular, histiocyte	1 (2%)	1 (2%)	3 (6%)	
Bronchiole, hyperplasia	1 (2%)	2 (4%)	3 (6%)	2 (4%)

TABLE C5
Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Respiratory System (continued)				
Nose	(50)	(50)	(50)	(50)
Hyperplasia	1 (2%)			
Inflammation, suppurative	4 (8%)	1 (2%)	3 (6%)	2 (4%)
Glands, hyperplasia	33 (66%)	32 (64%)	24 (48%)	26 (52%)
Olfactory epithelium, atrophy			1 (2%)	
Olfactory epithelium, degeneration, hyaline	1 (2%)	1 (2%)	2 (4%)	
Olfactory epithelium, necrosis			1 (2%)	
Respiratory epithelium, degeneration, hyaline		1 (2%)	3 (6%)	
Respiratory epithelium, hyperplasia			1 (2%)	
Respiratory epithelium, metaplasia	9 (18%)	11 (22%)	13 (26%)	6 (12%)
Special Senses System				
Eye	(49)	(48)	(49)	(49)
Cataract				1 (2%)
Degeneration			1 (2%)	1 (2%)
Cornea, inflammation, acute		1 (2%)		
Cornea, inflammation, chronic active		2 (4%)		
Cornea, mineralization				1 (2%)
Retina, atrophy	1 (2%)			
Harderian gland	(50)	(49)	(50)	(50)
Hyperplasia	3 (6%)	4 (8%)	1 (2%)	2 (4%)
Hypertrophy	1 (2%)			
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Cyst			1 (2%)	
Inflammation, suppurative	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Metaplasia, osseous	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Nephropathy	41 (82%)	45 (90%)	40 (82%)	43 (86%)
Renal tubule, hyperplasia	2 (4%)	2 (4%)	1 (2%)	
Urinary bladder	(50)	(49)	(49)	(50)
Hemorrhage				1 (2%)
Inflammation, chronic active	1 (2%)			
Inflammation, suppurative		1 (2%)		

APPENDIX D
SUMMARY OF LESIONS IN FEMALE MICE IN THE 2-YEAR INHALATION STUDY OF METHYL ISOBUTYL KETONE

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone[a]

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidental death		1		
Moribund	10	9	6	9
Natural deaths	5	3	5	3
Survivors				
Terminal sacrifice	35	37	39	38
Animals examined microscopically	50	50	50	50
Alimentary System				
Gallbladder	(42)	(44)	(34)	(40)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Intestine large, colon	(48)	(48)	(49)	(49)
Intestine large, rectum	(47)	(48)	(48)	(49)
Sarcoma, metastatic, skin	1 (2%)			
Intestine large, cecum	(46)	(48)	(47)	(49)
Adenoma		1 (2%)		
Histiocytic sarcoma			1 (2%)	
Intestine small, duodenum	(47)	(48)	(47)	(48)
Adenoma	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Intestine small, jejunum	(48)	(47)	(47)	(48)
Carcinoma			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Intestine small, ileum	(48)	(47)	(47)	(47)
Histiocytic sarcoma			1 (2%)	
Liver	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)	2 (4%)	1 (2%)	
Hepatoblastoma	1 (2%)			
Hepatocellular carcinoma	3 (6%)	4 (8%)	4 (8%)	11 (22%)
Hepatocellular carcinoma, multiple	3 (6%)	1 (2%)	2 (4%)	
Hepatocellular adenoma	11 (22%)	10 (20%)	12 (24%)	9 (18%)
Hepatocellular adenoma, multiple	2 (4%)	5 (10%)	8 (16%)	14 (28%)
Hepatocholangiocarcinoma	1 (2%)	1 (2%)		
Histiocytic sarcoma	2 (4%)		1 (2%)	5 (10%)
Mesentery	(11)	(11)	(13)	(8)
Hemangiosarcoma, metastatic, spleen			1 (8%)	
Hemangiosarcoma, metastatic, uterus			1 (8%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (9%)		
Histiocytic sarcoma				1 (13%)
Sarcoma, metastatic, skin	1 (9%)			
Pancreas	(50)	(50)	(49)	(50)
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)	1 (2%)		
Histiocytic sarcoma	2 (4%)		1 (2%)	1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Carcinoma	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (2%)			
Squamous cell carcinoma				1 (2%)
Squamous cell papilloma	1 (2%)		3 (6%)	

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Alimentary System (continued)				
Stomach, glandular	(49)	(50)	(48)	(49)
Tooth	(1)			(1)
Histiocytic sarcoma				1 (100%)
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Hemangioma			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver	2 (4%)			
Histiocytic sarcoma	1 (2%)		1 (2%)	1 (2%)
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic, liver				1 (2%)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (2%)		1 (2%)	2 (4%)
Adrenal medulla	(50)	(50)	(49)	(49)
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma				1 (2%)
Pheochromocytoma benign	2 (4%)			1 (2%)
Islets, pancreatic	(50)	(50)	(49)	(50)
Carcinoma				1 (2%)
Parathyroid gland	(28)	(33)	(30)	(36)
Adenoma			1 (3%)	
Pituitary gland	(50)	(49)	(48)	(49)
Histiocytic sarcoma			1 (2%)	1 (2%)
Pars distalis, adenoma	7 (14%)	9 (18%)	4 (8%)	6 (12%)
Pars intermedia, adenoma			2 (4%)	
Thyroid gland	(50)	(50)	(49)	(48)
C-cell, adenoma				1 (2%)
C-cell, carcinoma	1 (2%)			
Follicular cell, carcinoma	1 (2%)			
General Body System				
Peritoneum		(2)	(1)	
Hemangiosarcoma, metastatic, spleen		1 (50%)		
Hepatocholangiocarcinoma, metastatic, liver		1 (50%)		

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Genital System				
Clitoral gland	(45)	(42)	(41)	(42)
Hemangiosarcoma, metastatic, spleen		1 (2%)		
Ovary	(49)	(50)	(48)	(50)
Cystadenoma		2 (4%)	1 (2%)	3 (6%)
Histiocytic sarcoma	2 (4%)		1 (2%)	
Uterus	(50)	(50)	(49)	(50)
Carcinoma	1 (2%)			1 (2%)
Hemangioma			1 (2%)	
Hemangiosarcoma	1 (2%)		2 (4%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (2%)		1 (2%)	3 (6%)
Leiomyoma		1 (2%)	1 (2%)	1 (2%)
Polyp stromal	3 (6%)	2 (4%)	2 (4%)	
Polyp stromal, multiple		1 (2%)		
Sarcoma stromal	1 (2%)			
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Hemangiosarcoma, metastatic, spleen	1 (2%)	1 (2%)		
Histiocytic sarcoma	3 (6%)		1 (2%)	1 (2%)
Lymph node	(7)	(3)	(9)	(5)
Iliac, histiocytic sarcoma			1 (11%)	
Lumbar, hemangiosarcoma			1 (11%)	
Lumbar, histiocytic sarcoma				1 (20%)
Pancreatic, hepatocholangiocarcinoma, metastatic, liver	1 (14%)			
Renal, histiocytic sarcoma	1 (14%)			
Lymph node, bronchial	(44)	(41)	(39)	(37)
Hepatocholangiocarcinoma, metastatic, liver	2 (5%)	1 (2%)		
Histiocytic sarcoma	1 (2%)			1 (3%)
Lymph node, mandibular	(40)	(42)	(39)	(38)
Histiocytic sarcoma			1 (3%)	1 (3%)
Lymph node, mesenteric	(50)	(49)	(49)	(47)
Hemangiosarcoma, metastatic, uterus			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Histiocytic sarcoma	2 (4%)		1 (2%)	1 (2%)
Lymph node, mediastinal	(46)	(40)	(38)	(41)
Carcinoma, metastatic, skin			1 (3%)	
Hepatocholangiocarcinoma, metastatic, liver	2 (4%)	1 (3%)		
Histiocytic sarcoma	2 (4%)			1 (2%)
Spleen	(50)	(50)	(49)	(50)
Hemangiosarcoma	1 (2%)	2 (4%)	2 (4%)	1 (2%)
Hemangiosarcoma, metastatic, uterus			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver		1 (2%)		
Histiocytic sarcoma	1 (2%)		1 (2%)	2 (4%)
Thymus	(49)	(47)	(46)	(46)
Histiocytic sarcoma	1 (2%)			

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Integumentary System				
Mammary gland	(50)	(49)	(50)	(49)
Carcinoma	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Skin	(50)	(50)	(50)	(50)
Basal cell carcinoma			1 (2%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (2%)			
Sarcoma	1 (2%)			
Subcutaneous tissue, fibrosarcoma			1 (2%)	
Subcutaneous tissue, fibrous histiocytoma	2 (4%)	1 (2%)		1 (2%)
Subcutaneous tissue, hemangioma				1 (2%)
Subcutaneous tissue, hemangiosarcoma			1 (2%)	
Subcutaneous tissue, hemangiosarcoma, metastatic, spleen	1 (2%)			
Subcutaneous tissue, histiocytic sarcoma	1 (2%)			
Subcutaneous tissue, liposarcoma			1 (2%)	
Subcutaneous tissue, sarcoma	1 (2%)	1 (2%)		3 (6%)
Subcutaneous tissue, sarcoma, multiple				1 (2%)
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)			
Skeletal muscle	(1)	(2)	(3)	(2)
Carcinoma, metastatic, skin			1 (33%)	
Hemangiosarcoma, metastatic, spleen			1 (33%)	
Hepatocholangiocarcinoma, metastatic, liver	1 (100%)	1 (50%)		
Histiocytic sarcoma				1 (50%)
Sarcoma			1 (33%)	
Nervous System				
Brain	(50)	(50)	(50)	(50)
Histiocytic sarcoma	1 (2%)		1 (2%)	1 (2%)
Respiratory System				
Larynx	(50)	(50)	(49)	(50)
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	2 (4%)	1 (2%)	1 (2%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)			
Alveolar/bronchiolar carcinoma		2 (4%)	1 (2%)	1 (2%)
Carcinoma, metastatic, skin			1 (2%)	
Carcinoma, metastatic, thyroid gland	1 (2%)			
Hemangiosarcoma, metastatic, uterus			1 (2%)	
Hepatocellular carcinoma, metastatic, liver	4 (8%)	1 (2%)	1 (2%)	1 (2%)
Hepatocholangiocarcinoma, metastatic, liver	2 (4%)	1 (2%)		
Histiocytic sarcoma	3 (6%)		1 (2%)	2 (4%)
Nose	(50)	(50)	(50)	(49)
Histiocytic sarcoma	1 (2%)		1 (2%)	
Pleura			(1)	
Carcinoma, metastatic, skin			1 (100%)	
Trachea	(50)	(50)	(49)	(50)

TABLE D1
Summary of the Incidence of Neoplasms in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Special Senses System				
Eye	(49)	(48)	(49)	(50)
Histiocytic sarcoma			1 (2%)	
Harderian gland	(49)	(49)	(49)	(50)
Adenoma	6 (12%)	4 (8%)	2 (4%)	3 (6%)
Carcinoma	1 (2%)	3 (6%)	2 (4%)	3 (6%)
Histiocytic sarcoma			1 (2%)	
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Hepatocellular carcinoma, metastatic, liver	1 (2%)			
Hepatocholangiocarcinoma, metastatic, liver	2 (4%)			
Histiocytic sarcoma	2 (4%)		1 (2%)	3 (6%)
Urinary bladder	(50)	(50)	(49)	(50)
Histiocytic sarcoma			1 (2%)	
Sarcoma, metastatic, skin	1 (2%)			
Systemic Lesions				
Multiple organs[b]	(50)	(50)	(50)	(50)
Histiocytic sarcoma	3 (6%)		1 (2%)	6 (12%)
Lymphoma malignant	13 (26%)	5 (10%)	11 (22%)	13 (26%)
Neoplasm Summary				
Total animals with primary neoplasms[c]	42	40	40	42
Total primary neoplasms	75	60	73	84
Total animals with benign neoplasms	29	29	30	33
Total benign neoplasms	37	37	39	40
Total animals with malignant neoplasms	30	22	28	31
Total malignant neoplasms	38	23	34	44
Total animals with metastatic neoplasms	9	3	4	1
Total metastatic neoplasms	27	19	11	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 D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	1 7 7	3 6 8	5 3 7	5 7 8	5 8 6	6 3 2	6 5 3	6 8 1	6 8 4	6 9 1	6 9 7	7 0 6	7 1 5	7 1 5	7 2 4	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
Carcass ID Number	1 3 8	1 3 0	1 5 0	1 0 8	1 0 1 4	1 3 9	1 4 3	1 4 7	1 4 5	1 0 4	1 1 5	1 4 6	1 0 5	1 2 2	1 0 2	1 1 9	1 2 3	2 2 6	1 3 6	1 0 3	1 0 6	1 0 7	1 0 9	1 1 3	1 1 7
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	+	A	+	+	A	+	+	A	A	+	+	+	+	+	+	+	+	+	M	+	+
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic, skin																									
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	A	A	M	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	A	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																					X				
Intestine small, jejunum	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma									X																
Hepatoblastoma														X											
Hepatocellular carcinoma														X											
Hepatocellular carcinoma, multiple					X					X					X										
Hepatocellular adenoma													X	X					X			X			X
Hepatocellular adenoma, multiple																				X					
Hepatocholangiocarcinoma				X																					
Histiocytic sarcoma												X													
Mesentery			+						+	+								+			+			+	
Sarcoma, metastatic, skin																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver				X																					
Histiocytic sarcoma										X															
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma								X																	
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Squamous cell papilloma																	X								
Stomach, glandular	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth												+													
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic, liver															X										
Hepatocholangiocarcinoma, metastatic, liver				X										X											
Histiocytic sarcoma										X															

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 2 4	1 2 9	1 3 2	1 3 4	1 4 0	1 4 4	1 4 8	1 4 9	1 0 1	1 1 0	1 1 1	1 1 2	1 1 6	1 1 8	1 2 0	1 2 1	1 2 5	1 2 7	1 2 8	1 3 1	1 3 3	1 3 5	1 3 7	1 4 1	1 4 2	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Sarcoma, metastatic, skin																					X					1
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatoblastoma																										1
Hepatocellular carcinoma			X											X												3
Hepatocellular carcinoma, multiple																										3
Hepatocellular adenoma								X	X					X			X					X			X	11
Hepatocellular adenoma, multiple																			X							2
Hepatocholangiocarcinoma																										1
Histiocytic sarcoma							X																			2
Mesentery		+		+			+							+								+				11
Sarcoma, metastatic, skin																					X					1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma							X																			2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma							X																			1
Squamous cell papilloma																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Hepatocholangiocarcinoma, metastatic, liver																										2
Histiocytic sarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	1 7 7	3 6 8	5 3 7	5 7 8	5 8 6	6 3 2	6 5 3	6 8 1	6 8 4	6 9 1	6 9 7	7 0 6	7 1 5	7 1 5	7 2 4	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
Carcass ID Number	1 3 8	1 3 0	1 5 0	1 0 8	1 0 1 4	1 3 9	1 4 3	1 4 7	1 4 5	1 0 4	1 1 5	1 4 6	1 0 5	1 2 2	1 0 2	1 1 9	1 2 3	1 2 6	1 3 6	1 0 3	1 0 6	1 0 7	1 0 9	1 1 3	1 1 7
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																									
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																			X						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	M	+	M	M	M	+	+	M	+	M	M	M	+	+	+	M	+	+	+	M	+	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma																				X		X			
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell, carcinoma									X																
Follicular cell, carcinoma																							X		
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+
Ovary	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X															
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Hemangiosarcoma																									
Histiocytic sarcoma																									
Polyp stromal					X											X						X			
Sarcoma stromal																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen																									
Histiocytic sarcoma										X		X													
Lymph node				+						+				+								+			
Pancreatic, hepatocholangiocarcinoma, metastatic, liver				X																					
Renal, histiocytic sarcoma										X															
Lymph node, bronchial	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Hepatocholangiocarcinoma, metastatic, liver				X										X											
Histiocytic sarcoma										X															
Lymph node, mandibular	+	+	+	M	+	+	M	+	+	+	+	+	M	+	M	+	I	+	+	M	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver				X																					
Histiocytic sarcoma										X															
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver				X										X											
Histiocytic sarcoma										X															

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 2 4	1 2 9	1 3 2	1 3 4	1 4 0	1 4 4	1 4 8	1 4 9	1 0 1	1 1 0	1 1 1	1 1 2	1 1 6	1 1 8	1 2 0	1 2 1	1 2 5	1 2 7	1 2 8	1 3 1	1 3 3	1 3 5	1 3 7	1 4 1	1 4 2	Total Tissues/ Tumors
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma							X																			1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma benign									X																	2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	M	M	M	M	+	+	+	M	+	+	M	M	+	+	+	+	I	+	M	M	M	28
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pars distalis, adenoma	X				X	X							X					X								7
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell, carcinoma																										1
Follicular cell, carcinoma																										1
General Body System																										
None																										
Genital System																										
Clitoral gland	+	I	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma							X																			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																							X			1
Hemangiosarcoma			X																							1
Histiocytic sarcoma							X																			1
Polyp stromal																										3
Sarcoma stromal															X											1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																						X				1
Histiocytic sarcoma							X																			3
Lymph node				+										+										+		7
Pancreatic, hepatocholangiocarcinoma, metastatic, liver																										1
Renal, histiocytic sarcoma																										1
Lymph node, bronchial	+	+	+	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	44
Hepatocholangiocarcinoma, metastatic, liver																										2
Histiocytic sarcoma																										1
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	+	40
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Histiocytic sarcoma							X																			2
Lymph node, mediastinal	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	+	+	+	M	+	+	46
Hepatocholangiocarcinoma, metastatic, liver																										2
Histiocytic sarcoma							X																			2

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	1 7 7	3 6 8	5 3 7	5 7 8	5 8 6	6 3 2	6 5 3	6 8 1	6 8 4	6 9 1	6 9 7	7 0 6	7 1 5	7 1 5	7 2 4	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
Carcass ID Number	1 3 3 8	1 3 3 0	1 5 0 0	1 0 0 8	1 0 1 4	1 3 9 9	1 4 3 3	1 4 4 7	1 4 4 5	1 4 0 4	1 4 1 5	1 4 4 6	1 4 0 5	1 2 0 2	1 2 0 2	1 2 1 9	1 2 2 3	1 2 2 6	1 3 6 6	1 3 0 3	1 3 0 6	1 3 0 7	1 3 0 9	1 3 1 3	1 3 1 7
Hematopoietic System (continued)																								
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Histiocytic sarcoma																								
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X														
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma												X												
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver														X										
Sarcoma											X													
Subcutaneous tissue, fibrous histiocytoma					X																			
Subcutaneous tissue, hemangiosarcoma, metastatic, spleen																								
Subcutaneous tissue, histiocytic sarcoma												X												
Subcutaneous tissue, sarcoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma										X														
Skeletal muscle				+																				
Hepatocholangiocarcinoma, metastatic, liver				X																				
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X				X							X						
Alveolar/bronchiolar adenoma, multiple																								
Carcinoma, metastatic, thyroid gland																							X	
Hepatocellular carcinoma, metastatic, liver					X					X					X									
Hepatocholangiocarcinoma, metastatic, liver				X										X										
Histiocytic sarcoma										X		X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma																								
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 2 4	1 2 9	1 3 2	1 3 4	1 4 0	1 4 4	1 4 8	1 4 9	1 0 1	1 1 0	1 1 1	1 1 2	1 1 6	1 1 8	1 2 0	1 2 1	1 2 5	1 2 7	1 2 8	1 3 1	1 3 3	1 3 5	1 3 7	1 4 1	1 4 2	Total Tissues/ Tumors
Hematopoietic System (continued)																											
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																						X					1
Histiocytic sarcoma							X																				1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																											1
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																											1
Sarcoma																											1
Subcutaneous tissue, fibrous histiocytoma																		X									2
Subcutaneous tissue, hemangiosarcoma, metastatic, spleen																						X					1
Subcutaneous tissue, histiocytic sarcoma																											1
Subcutaneous tissue, sarcoma																					X						1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																											1
Skeletal muscle																											1
Hepatocholangiocarcinoma, metastatic, liver																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma							X																				1
Respiratory System																											
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																											3
Alveolar/bronchiolar adenoma, multiple														X													1
Carcinoma, metastatic, thyroid gland																											1
Hepatocellular carcinoma, metastatic, liver			X																								4
Hepatocholangiocarcinoma, metastatic, liver																											2
Histiocytic sarcoma							X																				3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma							X																				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: Chamber Control

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

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	1 2 4	1 2 9	1 3 2	1 3 4	1 4 0	1 4 4	1 4 8	1 4 9	1 0 1	1 1 0	1 1 1	1 1 2	1 1 6	1 1 8	1 2 0	1 2 1	1 2 5	1 2 7	1 2 8	1 3 1	1 3 3	1 3 5	1 3 7	1 4 1	1 4 2	Total Tissues/ Tumors
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma			X									X				X	X									6
Carcinoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver																										1
Hepatocholangiocarcinoma, metastatic, liver																										2
Histiocytic sarcoma							X																			2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic, skin																				X						1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma							X																			3
Lymphoma malignant		X		X									X	X					X						X	13

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	0212	0515	0598	0620	0628	0638	0662	0683	0687	0702	0710	0715	0715	0731	0731	0731	0731	0731	0731	0731	0732	0732	0732	0732
Carcass ID Number	35020	33304	33206	33001	33039	33033	33036	33024	33013	33127	33212	33223	33230	33050	33077	33118	33125	33229	33230	33302	33340	33400	33404	33409
Alimentary System																								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	M	M	+	I	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																						
Intestine large, colon	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma											X													
Intestine small, duodenum	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																						
Intestine small, jejunum	A	+	A	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																						
Intestine small, ileum	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																		X						
Hepatocellular carcinoma			X									X												
Hepatocellular carcinoma, multiple															X									
Hepatocellular adenoma									X				X		X		X				X			
Hepatocellular adenoma, multiple										X		X							X					
Hepatocholangiocarcinoma		X																						
Mesentery		+				+			+			+			+				+					
Hepatocholangiocarcinoma, metastatic, liver		X																						
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																						
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																						
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endocrine System																								
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																						
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																						
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	M	M	M	+	+	+	M	M	+	M	+	+	+	+	+	+	+	+	+	M	M	M
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Pars distalis, adenoma								X										X		X				
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
General Body System																								
Peritoneum		+								+														
Hemangiosarcoma, metastatic, spleen										X														
Hepatocholangiocarcinoma, metastatic, liver		X																						

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 1 1 6	3 1 1 7	3 1 2 0	3 2 2 1	3 2 2 8	3 3 1 1	3 3 3 5	3 3 3 7	3 4 4 0	3 4 4 1	3 4 4 4	3 4 4 5	3 4 4 6	3 4 4 7	3 4 0 2	3 4 0 8	3 4 1 0	3 4 1 1	3 4 1 4	3 4 1 5	3 4 1 9	3 4 3 8	3 4 4 2	3 4 4 8	3 4 4 9	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Hepatocholangiocarcinoma, metastatic, liver																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocholangiocarcinoma, metastatic, liver																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hepatocholangiocarcinoma, metastatic, liver																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma	X																									2
Hepatocellular carcinoma					X																X					4
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma	X												X		X	X						X				10
Hepatocellular adenoma, multiple					X	X																				5
Hepatocholangiocarcinoma																										1
Mesentery						+														+		+		+	+	11
Hepatocholangiocarcinoma, metastatic, liver																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	M	+	+	M	M	M	+	+	+	+	+	M	+	+	+	+	+	+	+	M	M	+	+	+	+	33
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma						X	X	X						X			X		X							9
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
General Body System																										
Peritoneum																										2
Hemangiosarcoma, metastatic, spleen																										1
Hepatocholangiocarcinoma, metastatic, liver																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	0212	0515	0598	0620	0628	0638	0662	0683	0687	0702	0710	0715	0715	0731	0731	0731	0731	0731	0731	0731	0732	0732	0732	0732
Carcass ID Number	35030	33034	33206	33301	33319	33333	33366	33324	33413	33427	33512	33622	33723	34005	34007	34118	34125	34229	34330	34432	34433	34440	34606	34609
Genital System																								
Clitoral gland	M	+	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	M	I	M	M	+	+	+
Hemangiosarcoma, metastatic, spleen										X														
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma										X														
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																						
Leiomyoma									X															
Polyp stromal																								
Polyp stromal, multiple					X																			
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, spleen										X														
Lymph node						+															+			
Lymph node, bronchial	+	+	+	+	M	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocholangiocarcinoma, metastatic, liver		X																						
Lymph node, mandibular	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node, mediastinal	M	+	M	+	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	
Hepatocholangiocarcinoma, metastatic, liver		X																						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X														
Hepatocholangiocarcinoma, metastatic, liver		X																						
Thymus	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																		X						
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrous histiocytoma																								
Subcutaneous tissue, sarcoma																								
Musculoskeletal System																								
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle		+																						
Hepatocholangiocarcinoma, metastatic, liver		X																						
Nervous System																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	3 1 6	3 1 7	3 2 0	3 2 1	3 2 8	3 3 1	3 3 5	3 3 7	3 4 0	3 4 1	3 4 4	3 4 5	3 4 6	3 4 7	3 4 0	3 0 2	3 0 8	3 1 0	3 1 1	3 1 4	3 1 5	3 1 9	3 3 8	3 4 2	3 4 8	3 4 9	Total Tissues/ Tumors
Genital System																											
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	42
Hemangiosarcoma, metastatic, spleen																											1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma								X																			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocholangiocarcinoma, metastatic, liver																											1
Leiomyoma																											1
Polyp stromal			X	X																							2
Polyp stromal, multiple																											1
Hematopoietic System																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma, metastatic, spleen																											1
Lymph node										+																	3
Lymph node, bronchial	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+		41
Hepatocholangiocarcinoma, metastatic, liver																											1
Lymph node, mandibular	M	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	M	+	42
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	40
Hepatocholangiocarcinoma, metastatic, liver																											1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma										X																	2
Hepatocholangiocarcinoma, metastatic, liver																											1
Thymus	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Integumentary System																											
Mammary gland	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma																											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrous histiocytoma		X																									1
Subcutaneous tissue, sarcoma																			X								1
Musculoskeletal System																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																				+							2
Hepatocholangiocarcinoma, metastatic, liver																											1
Nervous System																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

Number of Days on Study	0212	0515	0598	0620	0628	0638	0662	0683	0687	0702	0710	0715	0715	0731	0731	0731	0731	0731	0731	0731	0732	0732	0732	0732
Carcass ID Number	35020	35304	35026	35301	35039	35033	35036	35024	35013	35127	35212	35222	35230	35052	35077	35181	35125	35229	35230	35334	35400	35403	35600	35909
Respiratory System																								
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar carcinoma							X																	
Hepatocellular carcinoma, metastatic, liver												X												
Hepatocholangiocarcinoma, metastatic, liver		X																						
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																								
Eye	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X		
Carcinoma																								
Urinary System																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																								
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant				X										X			X				X			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 450 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	0705	5305	5551	5567	6448	6448	6673	6884	6905	6906	7001	7311	7311	7311	7311	7311	7311	7311	7312	7332	7332	7332	7332	7332	7332
Carcass ID Number	53616	51262	53555	54252	52828	53737	54477	54400	55220	54041	52211	50013	50037	50079	51090	51144	52449	54091	55044	50055	50056	51161	51515	51157	
Alimentary System																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	A	A	+	A	A	+	+	+	I	+	+	+	I	+	I	+	M	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Intestine small, duodenum	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																		X							
Intestine small, ileum	+	+	+	+	A	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Hepatocellular carcinoma				X																					
Hepatocellular carcinoma, multiple														X				X							
Hepatocellular adenoma							X	X			X				X					X		X	X		X
Hepatocellular adenoma, multiple														X				X							
Histiocytic sarcoma									X																
Mesentery							+				+			+	+	+								+	
Hemangiosarcoma, metastatic, spleen																									
Hemangiosarcoma, metastatic, uterus											X														
Pancreas	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma															X								X		
Stomach, glandular	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cardiovascular System																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Histiocytic sarcoma									X																
Endocrine System																									
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	M	M	A	+	+	+	M	+	M	+	M	M	+	+	+	M	+	+	+	+	+
Adenoma				X																					
Pituitary gland	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Pars distalis, adenoma										X													X		
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	5 1 1 9	5 2 2 5	5 2 2 6	5 2 2 7	5 3 3 0	5 3 3 1	5 3 3 2	5 3 3 8	5 4 4 3	5 4 4 6	5 5 0 0	5 5 0 2	5 5 0 8	5 5 1 3	5 5 1 6	5 5 1 8	5 5 2 2	5 5 2 3	5 5 2 9	5 5 3 3	5 5 3 4	5 5 3 9	5 5 4 4	5 5 4 5	5 5 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	M	I	M	I	+	I	+	+	+	+	+	+	+	+	I	I	+	+	+	I	+	+	+	+	34
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma																										1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Hepatocellular carcinoma	X						X				X															4
Hepatocellular carcinoma, multiple																										2
Hepatocellular adenoma									X				X			X					X					12
Hepatocellular adenoma, multiple						X	X			X	X							X					X			8
Histiocytic sarcoma																										1
Mesentery	+	+				+					+		+							+			+			13
Hemangiosarcoma, metastatic, spleen													X													1
Hemangiosarcoma, metastatic, uterus																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma													X													3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma				X																						1
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	M	+	M	M	M	M	M	+	+	M	+	M	+	+	+	+	+	+	+	M	+	M	+	30
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Histiocytic sarcoma																										1
Pars distalis, adenoma								X			X															4
Pars intermedia, adenoma					X																	X				2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	0 7 5	5 3 0	5 5 1	5 6 7	6 4 8	6 4 8	6 7 3	6 8 4	6 9 5	6 9 6	7 0 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	5 3 1 6	5 1 2	5 3 5	5 4 2	5 2 8	5 3 7	5 4 7	5 4 0	5 2 0	5 4 1	5 2 1	5 0 3	5 0 7	5 0 9	5 1 0	5 1 4	5 2 4	5 4 9	5 0 1	5 0 4	5 0 5	5 0 6	5 1 1	5 1 5	5 1 7
General Body System																								
Peritoneum																								
Genital System																								
Clitoral gland	+	M	+	+	M	+	+	+	+	+	I	+	M	+	M	+	+	+	+	+	+	+	M	+
Ovary	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																								
Histiocytic sarcoma									X															
Uterus	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																								
Hemangiosarcoma								X			X													
Histiocytic sarcoma									X															
Leiomyoma																								
Polyp stromal																								
Hematopoietic System																								
Bone marrow	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X															
Lymph node	+	+					+	+	+									+						
Iliac, histiocytic sarcoma									X															
Lumbar, hemangiosarcoma																								
Lymph node, bronchial	+	+	+	A	+	M	M	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	M	+	+	+	+	M	+	+	+	M	+	+	I	+	+	+	+	+	+	M	M	+	+
Histiocytic sarcoma									X															
Lymph node, mesenteric	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic, uterus											X													
Histiocytic sarcoma									X															
Lymph node, mediastinal	+	+	+	M	M	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M
Carcinoma, metastatic, skin						X																		
Spleen	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
Hemangiosarcoma, metastatic, uterus											X													
Histiocytic sarcoma									X															
Thymus	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																								
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																								X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma						X																		
Subcutaneous tissue, fibrosarcoma			X																					
Subcutaneous tissue, hemangiosarcoma																								
Subcutaneous tissue, liposarcoma																								

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	5 1 9	5 2 5	5 2 6	5 2 7	5 3 0	5 3 1	5 3 2	5 3 8	5 4 3	5 4 6	5 5 0	5 0 2	5 0 8	5 1 3	5 1 6	5 1 8	5 2 2	5 2 3	5 2 9	5 3 3	5 3 4	5 3 9	5 4 4	5 4 5	5 4 8	Total Tissues/ Tumors
General Body System																										
Peritoneum		+																								1
Genital System																										
Clitoral gland	M	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Ovary	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cystadenoma	X																									1
Histiocytic sarcoma																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma								X																		1
Hemangiosarcoma																										2
Histiocytic sarcoma																										1
Leiomyoma																			X							1
Polyp stromal											X												X			2
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Lymph node																			+					+	+	9
Iliac, histiocytic sarcoma																										1
Lumbar, hemangiosarcoma																									X	1
Lymph node, bronchial	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	M	+	+	39
Lymph node, mandibular	M	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	39
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma, metastatic, uterus																										1
Histiocytic sarcoma																										1
Lymph node, mediastinal	+	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	M	+	M	M	+	M	+	+	+	38
Carcinoma, metastatic, skin																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma													X				X									2
Hemangiosarcoma, metastatic, uterus																										1
Histiocytic sarcoma																										1
Thymus	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma																										1
Subcutaneous tissue, fibrosarcoma																										1
Subcutaneous tissue, hemangiosarcoma																					X					1
Subcutaneous tissue, liposarcoma																	X									1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	0735	5305	5551	5567	6428	6448	6673	6844	6905	6961	7011	7311	7311	7311	7311	7311	7311	7312	7322	7322	7322	7322	7322	7322	7322
Carcass ID Number	53616	51262	53525	54242	52428	53437	54477	54400	52400	54211	52211	50013	50077	50099	51010	51144	52449	54091	50014	50045	50056	50061	51141	51157	51117
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle						+																			
Carcinoma, metastatic, skin						X																			
Hemangiosarcoma, metastatic, spleen																									
Sarcoma																									
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Respiratory System																									
Larynx	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma				X																					
Alveolar/bronchiolar carcinoma																									
Carcinoma, metastatic, skin						X																			
Hemangiosarcoma, metastatic, uterus											X														
Hepatocellular carcinoma, metastatic, liver														X											
Histiocytic sarcoma									X																
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Pleura						+																			
Carcinoma, metastatic, skin						X																			
Trachea	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Harderian gland	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
Carcinoma						X																			
Histiocytic sarcoma									X																
Urinary System																									
Kidney	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Urinary bladder	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									X																
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma									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 Methyl Isobutyl Ketone: 900 ppm

Number of Days on Study	732	732	732	732	732	732	732	732	732	732	732	732	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	733	
Carcass ID Number	51 19	52 25	52 26	52 27	53 30	53 31	53 32	53 38	54 43	54 46	55 00	55 02	50 08	50 13	51 16	51 18	52 22	52 23	52 29	53 33	53 34	53 39	54 44	54 45	54 48	Total Tissues/ Tumors
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle			+										+													3
Carcinoma, metastatic, skin																										1
Hemangiosarcoma, metastatic, spleen													X													1
Sarcoma			X																							1
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma									X																	1
Carcinoma, metastatic, skin																										1
Hemangiosarcoma, metastatic, uterus																										1
Hepatocellular carcinoma, metastatic, liver																										1
Histiocytic sarcoma																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Pleura																										1
Carcinoma, metastatic, skin																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma							X																			2
Carcinoma																								X		2
Histiocytic sarcoma																										1
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymphoma malignant			X									X							X		X		X			11

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

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

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	7 2 1	7 2 7	7 3 7	7 4 1	7 4 3	7 4 6	7 4 7	7 4 9	7 5 0	7 0 1	7 0 2	7 0 4	7 1 5	7 1 8	7 1 9	7 2 2	7 2 4	7 2 6	7 3 0	7 3 1	7 3 2	7 3 4	7 3 5	7 3 6	7 4 8	Total Tissues/ Tumors
Alimentary System																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	+	+	+	+	+	I	+	M	+	+	M	+	+	+	+	M	+	+	+	+	M	+	40
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			X	X										X			X		X							11
Hepatocellular adenoma	X			X												X							X			9
Hepatocellular adenoma, multiple					X	X	X				X		X	X			X				X			X		14
Histiocytic sarcoma			X																							5
Mesentery														+								+	+	+		8
Histiocytic sarcoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																X										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth			+																							1
Histiocytic sarcoma			X																							1
Cardiovascular System																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Endocrine System																										
Adrenal cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic, liver				X																						1
Histiocytic sarcoma																										2
Adrenal medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1
Pheochromocytoma benign																										1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	M	M	+	M	M	M	+	M	+	+	36
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma			X																							1
Pars distalis, adenoma					X				X						X						X					6
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	48
C-cell, adenoma														X												1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	3 2 9	4 3 5	5 3 5	6 1 7	6 4 3	6 8 7	7 0 5	7 1 4	7 1 5	7 1 9	7 2 2	7 2 4	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
Carcass ID Number	7 2 5	7 0 6	7 0 4 5	7 3 3	7 2 9	7 4 0	7 1 3	7 1 4	7 0 3	7 1 6	7 1 1	7 0 8	7 0 7	7 1 0	7 1 2	7 1 7	7 2 3	7 2 8	7 3 8	7 3 9	7 4 2	7 4 4	7 0 5	7 0 9	7 2 0
General Body System																									
None																									
Genital System																									
Clitoral gland	+	+	+	+	+	+	+	M	+	M	+	M	+	+	+	M	+	+	M	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma															X										
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma											X														
Histiocytic sarcoma			X																						
Leiomyoma																									
Hematopoietic System																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Lymph node			+						+																
Lumbar, histiocytic sarcoma			X																						
Lymph node, bronchial	M	+	+	+	+	+	+	+	+	+	+	+	M	+	M	+	+	+	+	+	M	M	M	+	M
Histiocytic sarcoma						X																			
Lymph node, mandibular	+	M	+	+	M	+	M	M	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Lymph node, mesenteric	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X																			
Lymph node, mediastinal	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	M	+	+	+	M	+	+
Histiocytic sarcoma						X																			
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma							X																		
Histiocytic sarcoma											X	X													
Thymus	+	M	+	+	M	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Integumentary System																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma											X														
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Subcutaneous tissue, fibrous histiocytoma																									
Subcutaneous tissue, hemangioma				X																					
Subcutaneous tissue, sarcoma							X								X										
Subcutaneous tissue, sarcoma, multiple										X															
Musculoskeletal System																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle				+		+																			
Histiocytic sarcoma						X																			

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	7 2 1	7 2 7	7 3 7	7 4 1	7 4 3	7 4 6	7 4 7	7 4 9	7 5 0	7 0 1	7 0 2	7 0 4	7 1 5	7 1 8	7 1 9	7 2 2	7 2 4	7 2 6	7 3 0	7 3 1	7 3 2	7 3 4	7 3 5	7 3 6	7 4 8	Total Tissues/ Tumors
General Body System																										
None																										
Genital System																										
Clitoral gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	42
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma								X											X							3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																										1
Histiocytic sarcoma			X															X							3
Leiomyoma		X																								1
Hematopoietic System																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Lymph node		+													+							+				5
Lumbar, histiocytic sarcoma																										1
Lymph node, bronchial	M	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	+	M	+	M	+	+	+	+	+	37
Histiocytic sarcoma																										1
Lymph node, mandibular	+	M	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	M	+	+	38
Histiocytic sarcoma																										1
Lymph node, mesenteric	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Histiocytic sarcoma																										1
Lymph node, mediastinal	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M	+	M	+	+	+	M	41
Histiocytic sarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma																										2
Thymus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Integumentary System																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	49
Carcinoma																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Subcutaneous tissue, fibrous histiocytoma							X																			1
Subcutaneous tissue, hemangioma																										1
Subcutaneous tissue, sarcoma																								X		3
Subcutaneous tissue, sarcoma, multiple																										1
Musculoskeletal System																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Histiocytic sarcoma																										1

TABLE D2
Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	3 2 9	4 3 5	5 3 5	6 1 7	6 4 3	6 8 7	7 0 5	7 1 4	7 1 5	7 1 9	7 2 2	7 2 4	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
Carcass ID Number	7 2 5	7 0 6	7 0 4 5	7 3 3	7 3 2 9	7 4 0	7 1 1 3	7 1 1 4	7 0 3	7 1 3 6	7 1 1 1	7 0 1 8	7 0 0 7	7 1 1 0	7 1 1 2	7 1 2 7	7 2 2 3	7 2 3 8	7 3 3 8	7 3 3 9	7 4 4 2	7 4 4 4	7 0 0 5	7 0 0 9	7 2 0
Nervous System																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma											X														
Respiratory System																									
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma						X																			
Hepatocellular carcinoma, metastatic, liver																									
Histiocytic sarcoma											X														
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Special Senses System																									
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma	X																								
Carcinoma													X												
Urinary System																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma						X					X														
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Systemic Lesions																									
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma			X			X					X	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 Methyl Isobutyl Ketone: 1,800 ppm

Number of Days on Study	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 2	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	7 3 3	
Carcass ID Number	7 2 1	7 2 7	7 3 7	7 4 1	7 4 3	7 4 6	7 4 7	7 4 9	7 5 0	7 0 1	7 0 2	7 0 4	7 1 5	7 1 8	7 1 9	7 2 2	7 2 4	7 2 6	7 3 0	7 3 1	7 3 2	7 3 4	7 3 5	7 3 6	7 4 8	Total Tissues/ Tumors
Nervous System																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma																										1
Respiratory System																										
Larynx	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma													X													1
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver				X																						1
Histiocytic sarcoma			X																							2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Special Senses System																										
Eye	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																		X				X				3
Carcinoma														X			X									3
Urinary System																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma			X																							3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Systemic Lesions																										
Multiple organs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma			X															X								6
Lymphoma malignant		X							X	X			X									X	X			13

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Harderian Gland: Adenoma				
Overall rate[a]	6/50 (12%)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted rate[b]	13.2%	8.7%	4.4%	6.3%
Terminal rate[c]	4/35 (11%)	4/37 (11%)	1/39 (3%)	2/38 (5%)
First incidence (days)	586	731 (T)	695	329
Poly-3 test[d]	P=0.160N	P=0.365N	P=0.129N	P=0.223N
Harderian Gland: Carcinoma				
Overall rate	1/50 (2%)	3/50 (6%)	2/50 (4%)	3/50 (6%)
Adjusted rate	2.2%	6.5%	4.3%	6.5%
Terminal rate	0/35 (0%)	3/37 (8%)	1/39 (3%)	3/38 (8%)
First incidence (days)	715	731 (T)	648	731 (T)
Poly-3 test	P=0.317	P=0.312	P=0.509	P=0.316
Harderian Gland: Adenoma or Carcinoma				
Overall rate	7/50 (14%)	7/50 (14%)	4/50 (8%)	6/50 (12%)
Adjusted rate	15.4%	15.3%	8.6%	12.7%
Terminal rate	4/35 (11%)	7/37 (19%)	2/39 (5%)	5/38 (13%)
First incidence (days)	586	731 (T)	648	329
Poly-3 test	P=0.360N	P=0.609N	P=0.252N	P=0.471N
Liver: Hepatocellular Adenoma				
Overall rate	13/50 (26%)	15/50 (30%)	20/50 (40%)	23/50 (46%)
Adjusted rate	28.8%	32.4%	43.1%	49.3%
Terminal rate	11/35 (31%)	11/37 (30%)	17/39 (44%)	20/38 (53%)
First incidence (days)	715	687	673	705
Poly-3 test	P=0.016	P=0.442	P=0.111	P=0.033
Liver: Hepatocellular Carcinoma				
Overall rate	6/50 (12%)[e]	5/50 (10%)	6/50 (12%)	11/50 (22%)
Adjusted rate	13.1%	10.8%	12.9%	23.5%
Terminal rate	2/35 (6%)	3/37 (8%)	5/39 (13%)	7/38 (18%)
First incidence (days)	586	598	567	687
Poly-3 test	P=0.068	P=0.490N	P=0.610N	P=0.153
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma				
Overall rate	17/50 (34%)[e]	17/50 (34%)	22/50 (44%)	27/50 (54%)
Adjusted rate	37.1%	36.4%	46.9%	57.6%
Terminal rate	12/35 (34%)	12/37 (32%)	18/39 (46%)	22/38 (58%)
First incidence (days)	586	598	567	687
Poly-3 test	P=0.013	P=0.556N	P=0.228	P=0.035
Lung: Alveolar/bronchiolar Adenoma				
Overall rate	4/50 (8%)	2/50 (4%)	1/50 (2%)	1/50 (2%)
Adjusted rate	8.8%	4.4%	2.2%	2.2%
Terminal rate	2/35 (6%)	2/37 (5%)	0/39 (0%)	1/38 (3%)
First incidence (days)	653	731 (T)	567	731 (T)
Poly-3 test	P=0.108N	P=0.333N	P=0.172N	P=0.172N
Lung: Alveolar/bronchiolar Adenoma or Carcinoma				
Overall rate	4/50 (8%)	4/50 (8%)	2/50 (4%)	2/50 (4%)
Adjusted rate	8.8%	8.7%	4.3%	4.3%
Terminal rate	2/35 (6%)	3/37 (8%)	1/39 (3%)	1/38 (3%)
First incidence (days)	653	662	567	687
Poly-3 test	P=0.203N	P=0.635N	P=0.327N	P=0.325N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Ovary: Cystadenoma				
Overall rate	0/49 (0%)	2/50 (4%)	1/48 (2%)	3/50 (6%)
Adjusted rate	0.0%	4.4%	2.3%	6.5%
Terminal rate	0/35 (0%)	1/37 (3%)	1/38 (3%)	3/38 (8%)
First incidence (days)	—	702	731 (T)	731 (T)
Poly-3 test	P=0.109	P=0.242	P=0.496	P=0.125
Pituitary Gland (Pars Distalis): Adenoma				
Overall rate	7/50 (14%)	9/49 (18%)	4/48 (8%)	6/49 (12%)
Adjusted rate	15.6%	20.0%	9.0%	13.2%
Terminal rate	7/35 (20%)	8/36 (22%)	3/39 (8%)	6/38 (16%)
First incidence (days)	731 (T)	683	696	731 (T)
Poly-3 test	P=0.302N	P=0.393	P=0.268N	P=0.491N
Skin: Sarcoma				
Overall rate	2/50 (4%)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted rate	4.4%	2.2%	0.0%	8.6%
Terminal rate	1/35 (3%)	1/37 (3%)	0/39 (0%)	2/38 (5%)
First incidence (days)	697	731 (T)	—	705
Poly-3 test	P=0.167	P=0.494N	P=0.233N	P=0.352
Skin: Fibrous Histiocytoma, Fibrosarcoma, or Sarcoma				
Overall rate	4/50 (8%)	2/50 (4%)	1/50 (2%)	5/50 (10%)
Adjusted rate	8.8%	4.4%	2.2%	10.7%
Terminal rate	2/35 (6%)	2/37 (5%)	0/39 (0%)	3/38 (8%)
First incidence (days)	586	731 (T)	551	705
Poly-3 test	P=0.351	P=0.335N	P=0.173N	P=0.514
Stomach (Forestomach): Squamous Cell Papilloma				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted rate	2.2%	0.0%	6.5%	0.0%
Terminal rate	1/35 (3%)	0/37 (0%)	3/39 (8%)	0/38 (0%)
First incidence (days)	731 (T)	—	731 (T)	—
Poly-3 test	P=0.490N	P=0.496N	P=0.312	P=0.494N
Stomach (Forestomach): Squamous Cell Papilloma or Squamous Cell Carcinoma				
Overall rate	1/50 (2%)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted rate	2.2%	0.0%	6.5%	2.2%
Terminal rate	1/35 (3%)	0/37 (0%)	3/39 (8%)	1/38 (3%)
First incidence (days)	731 (T)	—	731 (T)	731 (T)
Poly-3 test	P=0.483	P=0.496N	P=0.312	P=0.753N
Uterus: Stromal Polyp				
Overall rate	3/50 (6%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	6.6%	6.5%	4.4%	0.0%
Terminal rate	2/35 (6%)	2/37 (5%)	2/39 (5%)	0/38 (0%)
First incidence (days)	586	628	731 (T)	—
Poly-3 test	P=0.069N	P=0.655N	P=0.496N	P=0.115N
Uterus: Stromal Polyp or Stromal Sarcoma				
Overall rate	4/50 (8%)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted rate	8.8%	6.5%	4.4%	0.0%
Terminal rate	3/35 (9%)	2/37 (5%)	2/39 (5%)	0/38 (0%)
First incidence (days)	586	628	731 (T)	—
Poly-3 test	P=0.035N	P=0.491N	P=0.333N	P=0.058N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
All Organs: Hemangiosarcoma				
Overall rate	3/50 (6%)	4/50 (8%)	7/50 (14%)	1/50 (2%)
Adjusted rate	6.6%	8.7%	15.2%	2.2%
Terminal rate	2/35 (6%)	3/37 (8%)	5/39 (13%)	0/38 (0%)
First incidence (days)	684	702	684	705
Poly-3 test	P=0.257N	P=0.510	P=0.166	P=0.295N
All Organs: Hemangioma or Hemangiosarcoma				
Overall rate	3/50 (6%)	4/50 (8%)	9/50 (18%)	2/50 (4%)
Adjusted rate	6.6%	8.7%	19.5%	4.3%
Terminal rate	2/35 (6%)	3/37 (8%)	7/39 (18%)	0/38 (0%)
First incidence (days)	684	702	684	617
Poly-3 test	P=0.433N	P=0.510	P=0.064	P=0.482N
All Organs: Histiocytic Sarcoma				
Overall rate	3/50 (6%)	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted rate	6.6%	0.0%	2.2%	12.7%
Terminal rate	1/35 (3%)	0/37 (0%)	0/39 (0%)	2/38 (5%)
First incidence (days)	691	—	695	535
Poly-3 test	P=0.050	P=0.116N	P=0.299N	P=0.265
All Organs: Malignant Lymphoma				
Overall rate	13/50 (26%)	5/50 (10%)	11/50 (22%)	13/50 (26%)
Adjusted rate	28.7%	10.8%	23.1%	26.9%
Terminal rate	11/35 (31%)	4/37 (11%)	8/39 (21%)	9/38 (24%)
First incidence (days)	653	620	75	329
Poly-3 test	P=0.349	P=0.027N	P=0.352N	P=0.517N
All Organs: Benign Neoplasms				
Overall rate	29/50 (58%)	29/50 (58%)	30/50 (60%)	33/50 (66%)
Adjusted rate	63.0%	61.8%	63.6%	68.8%
Terminal rate	24/35 (69%)	22/37 (60%)	24/39 (62%)	28/38 (74%)
First incidence (days)	586	628	567	329
Poly-3 test	P=0.276	P=0.538N	P=0.564	P=0.352
All Organs: Malignant Neoplasms				
Overall rate	30/50 (60%)	22/50 (44%)	28/50 (56%)	31/50 (62%)
Adjusted rate	63.6%	46.0%	56.8%	62.9%
Terminal rate	19/35 (54%)	16/37 (43%)	20/39 (51%)	21/38 (55%)
First incidence (days)	578	515	75	329
Poly-3 test	P=0.340	P=0.062N	P=0.317N	P=0.557N

TABLE D3
Statistical Analysis of Primary Neoplasms in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
All Organs: Benign or Malignant Neoplasms				
Overall rate	42/50 (84%)	40/50 (80%)	40/50 (80%)	42/50 (84%)
Adjusted rate	89.0%	82.2%	80.5%	84.5%
Terminal rate	31/35 (89%)	29/37 (78%)	30/39 (77%)	31/38 (82%)
First incidence (days)	578	515	75	329
Poly-3 test	P=0.387N	P=0.251N	P=0.184N	P=0.361N

(T) Terminal sacrifice
[a] Number of neoplasm-bearing animals/number of animals examined. Denominator is number of animals examined microscopically for liver, lung, ovary, 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 the differential mortality in animals that do not reach terminal sacrifice. A negative trend or a lower incidence in exposure group is indicated by **N**.
[e] A single hepatoblastoma occurred in an animal that also had a hepatocellular carcinoma.
[f] Not applicable; no neoplasms in animal group

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

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Chamber Controls Given NTP-2000 Diet			
Decalin	7/49	4/49	11/49
Divinylbenzene	17/49	5/49	19/49
Indium phosphide	12/50	6/50	18/50
Methyl isobutyl ketone	13/50	6/50	17/50
Propylene glycol mono-*t*-butyl ether	14/49	4/49	18/49
Stoddard solvent (Type IIC)	9/50	6/50	13/50
Vanadium pentoxide	6/50	6/50	12/50
Overall Historical Incidence: Inhalation Studies			
Total (%)	78/347 (22.5%)	37/347 (10.7%)	108/347 (31.1%)
Mean ± standard deviation	22.5% ± 8.1%	10.7% ± 1.8%	31.1% ± 6.8%
Range	12%-35%	8%-12%	22%-39%
Overall Historical Incidence: All Routes			
Total (%)	312/1,549 (20.1%)	128/1,549 (8.3%)	408/1,549 (26.3%)
Mean ± standard deviation	21.2% ± 13.4%	8.7% ± 5.8%	27.7% ± 15.5%
Range	6%-61%	0%-26%	8%-63%

[a] Data as of January 28, 2005

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone[a]

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Disposition Summary				
Animals initially in study	50	50	50	50
Early deaths				
Accidential death		1		
Moribund	10	9	6	9
Natural deaths	5	3	5	3
Survivors				
Terminal sacrifice	35	37	39	38
Animals examined microscopically	50	50	50	50
Alimentary System				
Intestine large, colon	(48)	(48)	(49)	(49)
Artery, inflammation, chronic active	1 (2%)			
Intestine large, rectum	(47)	(48)	(48)	(49)
Artery, inflammation, chronic active	1 (2%)			
Intestine large, cecum	(46)	(48)	(47)	(49)
Artery, inflammation, chronic active	1 (2%)	1 (2%)		
Intestine small, duodenum	(47)	(48)	(47)	(48)
Ulcer		1 (2%)		
Peyer's patch, hyperplasia				1 (2%)
Liver	(50)	(50)	(50)	(50)
Angiectasis			1 (2%)	
Basophilic focus	3 (6%)	2 (4%)	1 (2%)	3 (6%)
Clear cell focus	3 (6%)	4 (8%)	5 (10%)	2 (4%)
Cyst		1 (2%)		
Eosinophilic focus	4 (8%)	11 (22%)	10 (20%)	14 (28%)
Fatty change			1 (2%)	
Hematopoietic cell proliferation			2 (4%)	
Infarct		1 (2%)		
Infiltration cellular, mast cell	1 (2%)			
Inflammation, chronic		1 (2%)		2 (4%)
Mixed cell focus	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Necrosis	3 (6%)	1 (2%)	5 (10%)	1 (2%)
Tension lipidosis	1 (2%)	2 (4%)	3 (6%)	
Thrombosis	1 (2%)			
Bile duct, hyperplasia	1 (2%)			
Mesentery	(11)	(11)	(13)	(8)
Artery, inflammation, chronic active		1 (9%)		
Fat, hemorrhage	1 (9%)			
Fat, necrosis	9 (82%)	9 (82%)	11 (85%)	7 (88%)
Pancreas	(50)	(50)	(49)	(50)
Atrophy	3 (6%)		1 (2%)	
Basophilic focus			1 (2%)	
Inflammation, chronic active	1 (2%)		1 (2%)	
Necrosis, fatty			1 (2%)	
Artery, inflammation, chronic active		1 (2%)		
Duct, cyst	1 (2%)		1 (2%)	
Salivary glands	(50)	(50)	(50)	(50)
Atrophy				1 (2%)
Artery, inflammation, chronic active		1 (2%)		

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

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Alimentary System (continued)				
Stomach, forestomach	(50)	(50)	(50)	(50)
Hyperplasia, squamous	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Inflammation		1 (2%)		2 (4%)
Artery, inflammation, chronic active	2 (4%)			
Stomach, glandular	(49)	(50)	(48)	(49)
Metaplasia, hepatocyte			1 (2%)	
Necrosis				1 (2%)
Artery, inflammation, chronic active	2 (4%)			
Tooth	(1)			(1)
Malformation	1 (100%)			
Cardiovascular System				
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy	3 (6%)	6 (12%)	5 (10%)	3 (6%)
Inflammation, suppurative				1 (2%)
Artery, inflammation, chronic active	1 (2%)	2 (4%)		
Endocrine System				
Adrenal cortex	(50)	(50)	(50)	(50)
Hematopoietic cell proliferation			1 (2%)	
Hyperplasia	4 (8%)	3 (6%)	1 (2%)	2 (4%)
Hypertrophy	3 (6%)		3 (6%)	3 (6%)
Infiltration cellular, mononuclear cell				1 (2%)
Necrosis		1 (2%)		
Adrenal medulla	(50)	(50)	(49)	(49)
Hyperplasia	2 (4%)	2 (4%)	1 (2%)	
Islets, pancreatic	(50)	(50)	(49)	(50)
Hyperplasia			2 (4%)	1 (2%)
Pituitary gland	(50)	(49)	(48)	(49)
Pars distalis, angiectasis	1 (2%)	3 (6%)	3 (6%)	2 (4%)
Pars distalis, hyperplasia	10 (20%)	8 (16%)	13 (27%)	11 (22%)
Pars intermedia, hyperplasia	1 (2%)			
Thyroid gland	(50)	(50)	(49)	(48)
Cyst		1 (2%)		
Follicular cell, hyperplasia	7 (14%)	5 (10%)	11 (22%)	8 (17%)
General Body System				
Peritoneum		(2)	(1)	
Inflammation, suppurative			1 (100%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Genital System				
Ovary	(49)	(50)	(48)	(50)
Angiectasis		1 (2%)		
Cyst	14 (29%)	13 (26%)	13 (27%)	9 (18%)
Inflammation, suppurative				1 (2%)
Thrombosis	1 (2%)			
Artery, inflammation, chronic active	1 (2%)			1 (2%)
Uterus	(50)	(50)	(49)	(50)
Amyloid deposition	1 (2%)			
Angiectasis	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Hyperplasia, cystic		1 (2%)		
Infiltration cellular, mixed cell				1 (2%)
Inflammation, suppurative		1 (2%)	1 (2%)	1 (2%)
Metaplasia, squamous				1 (2%)
Necrosis		1 (2%)		
Thrombosis			1 (2%)	
Endometrium, hyperplasia, cystic	49 (98%)	48 (96%)	46 (94%)	49 (98%)
Hematopoietic System				
Bone marrow	(50)	(50)	(49)	(50)
Infiltration cellular, mast cell	1 (2%)			
Lymph node	(7)	(3)	(9)	(5)
Iliac, ectasia		1 (33%)		
Iliac, infiltration cellular, plasma cell	1 (14%)			
Lumbar, angiectasis		1 (33%)		
Lumbar, ectasia			1 (11%)	
Lumbar, infiltration cellular, plasma cell				1 (20%)
Renal, angiectasis		1 (33%)	1 (11%)	
Renal, ectasia	1 (14%)			
Renal, infiltration cellular, plasma cell				1 (20%)
Renal, artery, inflammation, chronic active		1 (33%)		
Lymph node, mandibular	(40)	(42)	(39)	(38)
Hyperplasia, lymphoid		2 (5%)		
Infiltration cellular, plasma cell				1 (3%)
Lymph node, mesenteric	(50)	(49)	(49)	(47)
Angiectasis				1 (2%)
Hyperplasia, lymphoid		1 (2%)		
Lymph node, mediastinal	(46)	(40)	(38)	(41)
Hyperplasia, lymphoid		1 (3%)		
Infiltration cellular, mast cell	1 (2%)			
Spleen	(50)	(50)	(49)	(50)
Hematopoietic cell proliferation	5 (10%)	1 (2%)	7 (14%)	5 (10%)
Infiltration cellular, mast cell	1 (2%)			

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Integumentary System				
Mammary gland	(50)	(49)	(50)	(49)
Hyperplasia		1 (2%)		
Skin	(50)	(50)	(50)	(50)
Foreign body		1 (2%)		
Hemorrhage	1 (2%)			
Inflammation, chronic active	2 (4%)	2 (4%)	5 (10%)	2 (4%)
Inflammation, suppurative		1 (2%)		
Musculoskeletal System				
Bone	(50)	(50)	(50)	(50)
Fracture		1 (2%)		
Hyperostosis			1 (2%)	
Infiltration cellular, mast cell	1 (2%)			
Skeletal muscle	(1)	(2)	(3)	(2)
Inflammation, suppurative		1 (50%)		
Artery, inflammation, chronic active				1 (50%)
Nervous System				
Brain	(50)	(50)	(50)	(50)
Meninges, infiltration cellular, mononuclear cell		1 (2%)	2 (4%)	2 (4%)
Respiratory System				
Larynx	(50)	(50)	(49)	(50)
Artery, inflammation, chronic active	1 (2%)		1 (2%)	
Respiratory epithelium, degeneration, hyaline			1 (2%)	
Lung	(50)	(50)	(50)	(50)
Infiltration cellular, mononuclear cell			1 (2%)	
Alveolar epithelium, hyperplasia	1 (2%)	5 (10%)	3 (6%)	5 (10%)
Alveolus, infiltration cellular, histiocyte	1 (2%)		2 (4%)	
Artery, mineralization		1 (2%)		
Bronchiole, hyperplasia		4 (8%)	2 (4%)	
Nose	(50)	(50)	(50)	(49)
Infiltration cellular, mast cell	1 (2%)			
Inflammation, suppurative	4 (8%)	3 (6%)	2 (4%)	
Artery, inflammation, chronic active	1 (2%)			
Glands, hyperplasia	23 (46%)	30 (60%)	23 (46%)	20 (41%)
Olfactory epithelium, atrophy		1 (2%)	1 (2%)	
Olfactory epithelium, degeneration, hyaline	8 (16%)	5 (10%)	4 (8%)	1 (2%)
Respiratory epithelium, degeneration, hyaline	24 (48%)	19 (38%)	20 (40%)	13 (27%)
Respiratory epithelium, metaplasia	3 (6%)	3 (6%)	6 (12%)	1 (2%)
Respiratory epithelium, metaplasia, squamous			1 (2%)	
Turbinate, necrosis			2 (4%)	
Trachea	(50)	(50)	(49)	(50)
Degeneration, hyaline			1 (2%)	

TABLE D5
Summary of the Incidence of Nonneoplastic Lesions in Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone

	Chamber Control	450 ppm	900 ppm	1,800 ppm
Special Senses System				
Eye	(49)	(48)	(49)	(50)
Cataract			1 (2%)	
Degeneration				1 (2%)
Cornea, inflammation, chronic active	1 (2%)	1 (2%)	3 (6%)	2 (4%)
Cornea, mineralization	1 (2%)			
Retina, atrophy	1 (2%)			
Harderian gland	(49)	(49)	(49)	(50)
Hyperplasia	1 (2%)	1 (2%)	2 (4%)	1 (2%)
Urinary System				
Kidney	(50)	(50)	(49)	(50)
Amyloid deposition	1 (2%)			
Cyst			1 (2%)	
Metaplasia, osseous	2 (4%)	2 (4%)	3 (6%)	2 (4%)
Nephropathy	22 (44%)	28 (56%)	26 (53%)	27 (54%)
Artery, inflammation, chronic active			1 (2%)	
Papilla, necrosis	1 (2%)			1 (2%)
Pelvis, dilatation			1 (2%)	
Renal tubule, hyperplasia				1 (2%)
Urinary bladder	(50)	(50)	(49)	(50)
Artery, inflammation, chronic active	1 (2%)			

APPENDIX E
GENETIC TOXICOLOGY

GENETIC TOXICOLOGY

SALMONELLA TYPHIMURIUM MUTAGENICITY TEST PROTOCOL

Testing was performed as reported by Zeiger *et al.* (1992). Methyl isobutyl ketone 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 methyl isobutyl ketone. The high dose was limited by toxicity. 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.

RESULTS

Methyl isobutyl ketone (100 to 6,667 µg/plate) was not mutagenic in *S. typhimurium* strains TA97, TA98, TA100, or TA1535, when tested with and without 10% or 30% hamster or rat liver metabolic activation enzymes (Table E1; Zeiger *et al.*, 1992).

TABLE E1
Mutagenicity of Methyl Isobutyl Ketone in *Salmonella typhimurium*[a]

Strain	Dose (µg/plate)	Revertants/Plate[b] -S9 Trial 1	-S9 Trial 2	+ hamster S9 10%	+ hamster S9 30%	+ rat S9 10%	+ rat S9 30%
TA100	0	89 ± 6.4	125 ± 2.4	118 ± 1.3	84 ± 6.4	124 ± 5.8	104 ± 3.0
	100	72 ± 5.5	121 ± 6.1	116 ± 4.5	94 ± 4.3	114 ± 4.5	100 ± 9.2
	333	83 ± 6.1	126 ± 3.3	111 ± 2.2	78 ± 5.8	109 ± 1.5	108 ± 10.1
	1,000	85 ± 7.3	106 ± 3.2	115 ± 11.5	95 ± 10.4	117 ± 3.6	99 ± 2.7
	3,333	77 ± 4.5	101 ± 8.1	102 ± 5.0	91 ± 3.3	111 ± 8.7	95 ± 3.1
	6,666		34 ± 17.0[c]	63 ± 5.0[c]		44 ± 21.7[c]	
	6,667	54 ± 4.2[c]			69 ± 5.7[c]		87 ± 4.5[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control[d]		327 ± 5.0	384 ± 25.0	515 ± 34.2	516 ± 19.5	1,915 ± 14.7	1,373 ± 24.6
TA1535	0	24 ± 1.2	26 ± 3.5	14 ± 1.2	11 ± 2.1	15 ± 2.0	11 ± 0.6
	100	17 ± 1.5	23 ± 3.6	17 ± 1.2	14 ± 2.2	9 ± 1.0	14 ± 3.0
	333	20 ± 1.9	24 ± 1.2	14 ± 3.1	11 ± 2.2	12 ± 4.4	13 ± 1.7
	1,000	18 ± 1.3	23 ± 0.6	17 ± 0.7	11 ± 1.5	10 ± 0.3	15 ± 1.3
	3,333	17 ± 2.1	24 ± 0.7	15 ± 0.3	13 ± 1.2	14 ± 2.7	12 ± 1.8
	6,666		15 ± 2.6[c]	8 ± 0.0[c]		9 ± 1.7[c]	
	6,667	6 ± 1.9[c]			8 ± 2.6[c]		11 ± 3.2[c]
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		369 ± 31.9	202 ± 4.3	68 ± 5.5	148 ± 7.9	378 ± 4.4	237 ± 12.7
TA97	0	81 ± 9.0	63 ± 1.2	98 ± 2.4	116 ± 9.4	95 ± 10.1	136 ± 6.7
	100	76 ± 6.7	65 ± 4.6	91 ± 5.6	123 ± 6.6	91 ± 7.2	131 ± 5.1
	333	67 ± 1.5	66 ± 0.3	98 ± 11.8	98 ± 10.2	95 ± 4.2	123 ± 8.7
	1,000	76 ± 4.2	67 ± 2.9	94 ± 6.4	109 ± 6.3	82 ± 3.2	114 ± 2.0
	3,333	76 ± 9.8		106 ± 0.9[c]	120 ± 3.8	107 ± 4.8	99 ± 2.7
	3,334		60 ± 5.0[c]				
	6,666	27 ± 15.0[c]		68 ± 7.0[c]	77 ± 4.0[c]	1 ± 1.0[c]	55 ± 10.0
	6,667		22 ± 16.7[c]				
Trial summary		Negative	Negative	Negative	Negative	Negative	Negative
Positive control		40 ± 7.0	136 ± 8.7	837 ± 16.8	1,020 ± 29.4	2,887 ± 38.8	1,124 ± 33.8

TABLE E1
Mutagenicity of Methyl Isobutyl Ketone in *Salmonella typhimurium*

Strain	Dose (µg/plate)	Revertants/Plate -S9 Trial 1	-S9 Trial 2	+ hamster S9 10%	+ hamster S9 30%
TA98	0	39 ± 2.0	19 ± 2.3	25 ± 2.6	46 ± 6.7
	100	46 ± 3.9	19 ± 1.5	33 ± 1.2	50 ± 4.9
	333	42 ± 1.2	21 ± 3.2	32 ± 5.9	52 ± 3.1
	1,000	42 ± 3.9	21 ± 2.7	20 ± 2.7	58 ± 5.9
	3,333	39 ± 1.2	20 ± 2.0	29 ± 1.7	59 ± 5.6
	6,666		9 ± 2.1[c]	21 ± 2.2[c]	
	6,667	12 ± 2.7[c]			30 ± 1.0[c]
Trial summary		Negative	Negative	Negative	Negative
Positive control		353 ± 6.9	362 ± 7.4	273 ± 6.7	156 ± 14.9

Strain	Dose (µg/plate)	+ rat S9 10%	+ rat S9 30%	+ rat S9 30%
TA98	0	26 ± 4.0	57 ± 1.3	26 ± 0.9
(continued)	100	30 ± 3.2	58 ± 9.9	32 ± 0.3
	333	33 ± 2.1	54 ± 2.0	34 ± 4.2
	1,000	30 ± 3.2	59 ± 3.8	24 ± 1.2
	3,333	32 ± 3.1	47 ± 5.0	24 ± 2.7
	6,666	17 ± 1.8[c]		
	6,667		27 ± 2.8[c]	25 ± 3.3[c]
Trial summary		Negative	Negative	Negative
Positive control		439 ± 20.5	370 ± 29.0	392 ± 2.6

[a] Study was performed at Microbiological Associates, Inc. The detailed protocol and these data are presented in Zeiger *et al*. (1992).
[b] 0 µg/plate was the solvent control.
[c] Revertants are presented as mean ± standard error from three plates.
[d] Slight toxicity
The positive controls in the absence of metabolic activation were sodium azide (TA100 and TA1535), 9-aminoacridine (TA97), and 4-nitro-*o*-phenlyenediamine (TA98). The positive control for metabolic activation with all strains was 2-aminoanthracene.

APPENDIX F
CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

CHEMICAL CHARACTERIZATION AND GENERATION OF CHAMBER CONCENTRATIONS

Procurement and Characterization of Methyl Isobutyl Ketone

Methyl isobutyl ketone was obtained from ChemCentral (Kent, WA) in one lot (81KL119800085). Identity and purity analyses were conducted by the analytical chemistry laboratory, Chemir/Polytech Laboratories, Inc. (Maryland Heights, MO). Purity and stability analyses were conducted by the study laboratory, Battelle Northwest Operations (Richland, WA). Elemental analyses were performed by Galbraith Laboratories, Inc. (Knoxville, TN).

The lot of the chemical, a colorless liquid, was identified as methyl isobutyl ketone by the analytical chemistry laboratory using infrared (IR) and proton nuclear magnetic resonance (NMR) spectroscopy. Infrared and NMR spectra were consistent with the structure of methyl isobutyl ketone and with literature spectra (*Aldrich* 1993, 1997). Representative IR and NMR spectra are presented in Figures F1 and F2.

The purity of the lot was determined by Galbraith Laboratories using elemental analysis and by the study laboratory using gas chromatography (GC) by systems A and B (Table F1).

Elemental analysis for carbon, hydrogen, and oxygen was in agreement with the theoretical values for methyl isobutyl ketone (*Merck*, 1989); nitrogen and sulfur were also detected at concentrations less than 0.1%. GC by system A indicated one major peak and three impurities. GC by system B was used to measure the area percent purity of the impurities greater than 0.1% relative to the major peak area. Three impurities were found to be 0.16%, 0.17%, and 0.11% relative to the major peak area, with a combined relative area of 0.44%. Samples taken from the top, middle, and bottom of one container were analyzed using GC by system A relative to a reference standard (Aldrich Chemical Co., Milwaukee, WI) of known purity, indicating a relative mean purity of greater than 99%. Subsequent purity analyses performed 30 days prior to the beginning of the study by the study laboratory using GC by system A on samples from five containers relative to a reference standard from the same lot indicated a relative purity greater than 99%. The overall purity was determined to be greater than 98%.

To identify the impurities, spectra of a mixture of possible impurity and/or degradation products were obtained by the study laboratory using GC by system B. The 0.16% impurity had the same retention time as 4-methyl-2-pentanol. By the use of GC/mass spectrometry (GC/MS) by system C, library searches (NIST/EPA/NIH, 1994), reference standards purchased from Aldrich Chemical Co., and standard addition, the first and third impurities were identified as 4-methyl-2-pentanol (0.16%) and *cis*-1,1,3,5-tetramethylcyclohexane (0.11%). Results from the second impurity's (0.17%) library search indicated 3,5,5-trimethylcyclohexene, but the retention time indicated it was neither 3,5,5-trimethylcyclohexene nor 2,3,3-trimethylcyclohexene; other trimethylcyclohexene isomers were not commercially available, so this impurity was not identified.

The bulk chemical was stored at room temperature, in 55-gallon metal drums. The stability and purity of methyl isobutyl ketone was monitored throughout the studies with GC system A; 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 F3. Methyl isobutyl ketone was pumped onto the heated surface of the generator where it was vaporized. For the 1,800 ppm chambers, glass fiber filter material (Type A/E, Gelman Sciences, Ann Arbor, MI) was wrapped around the generator cylinder to disperse the chemical over a larger area of the generator's surface. Generator output was controlled by the delivery rate of the chemical metering pump specific to each chamber and the generator temperature controller.

Precision metering pumps controlled flow to each chamber. In addition, a three-way valve, mounted upstream of all chamber flow-control valves, directed all chemical to the waste return line until the generation system was stable and exposures were ready to proceed. When the exposure started, the three-way valve was opened to allow the flow of methyl isobutyl ketone vapor to reach the chamber metering valves. Each metering valve, which was in the "off" position when exposures were not being conducted for that chamber, automatically opened to the established setting and allowed vapor to flow through individual temperature-controlled delivery lines to each exposure chamber. The vapor was then injected into the chamber inlet duct where it was further mixed and 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 condensation particle counter (Model 3022A, TSI Incorporated, St. Paul, MN) was used with and without animals in the exposure chambers to ensure that methyl isobutyl ketone vapor, and not aerosol, was produced. No particle counts above the minimum resolvable level (approximately 200 particles/cm^3) were detected.

Vapor Concentration Monitoring

Summaries of the chamber vapor concentrations are given in Table F2. The methyl isobutyl ketone concentrations in the exposure chambers were monitored by an on-line gas chromatograph (system D). Samples were drawn from each exposure chamber approximately every 28 minutes using a 16-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 methyl isobutyl ketone in nitrogen supplied by a standard generator (Kin-Tek, Precision Calibration Systems, La Marque, TX). The on-line gas chromatograph was calibrated monthly by a comparison of chamber concentration data to data from grab samples, which were collected with charcoal sampling tubes (ORBO™-101, Supelco, Bellefonte, PA), extracted with hexanes containing nonane as an internal standard, and analyzed by an off-line gas chromatograph (system E). The volumes of gas 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 methyl isobutyl ketone containing nonane as an internal standard in hexanes.

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. Prior to the beginning of the study, T_{90} and T_{10} values were measured in chambers without animals; T_{90} values ranged from 8 to 11 minutes, and T_{10} values were 9 minutes for all chambers. A T_{90} value of 12 minutes was selected for the studies. In the 2-year studies, with animals present, rat T_{90} values ranged from 8 to 12 minutes and T_{10} values ranged from 9 to 12 minutes; mouse T_{90} and T_{10} values were 11 minutes for all chambers.

The uniformity of methyl isobutyl ketone vapor concentration in the inhalation exposure chambers was measured without animals before the study began and every 3 months during the 2-year studies with animals present. The vapor concentration was measured using the on-line GC by system D with the automatic 16-port sample valve disabled to allow continuous monitoring from a single input line. Samples were collected from several positions in each chamber. Chamber concentration uniformity was maintained throughout the studies.

The persistence of methyl isobutyl ketone in the chamber after vapor delivery ended was determined by monitoring the concentration in the 1,800 ppm chamber in the 2-year studies with animals present in the chambers. In the 2-year studies, the concentration decreased to less than 1% of the target concentration within 26 minutes in the rat chamber and 23 minutes in the mouse chamber.

The stability of methyl isobutyl ketone in all exposure chambers (system D) and the generator and pump reservoirs (system A) was monitored during the studies using GC. Exposure chamber samples and generator and pump reservoir samples were collected on day 23 of the study; generator and pump reservoir samples were also collected at 3 and 6 months, with additional samples collected every subsequent 6-month period throughout the study, before reservoirs were emptied and cleaned. A second analysis was performed using GC by system F, using a polar column that permits resolution of compounds with similar boiling points but small differences in polarity. Exposure chamber stability was confirmed for 23 days and reservoir stability for 6 months. No degradation of the chemical was detected, and no impurities other than those present in the test chemical were detected.

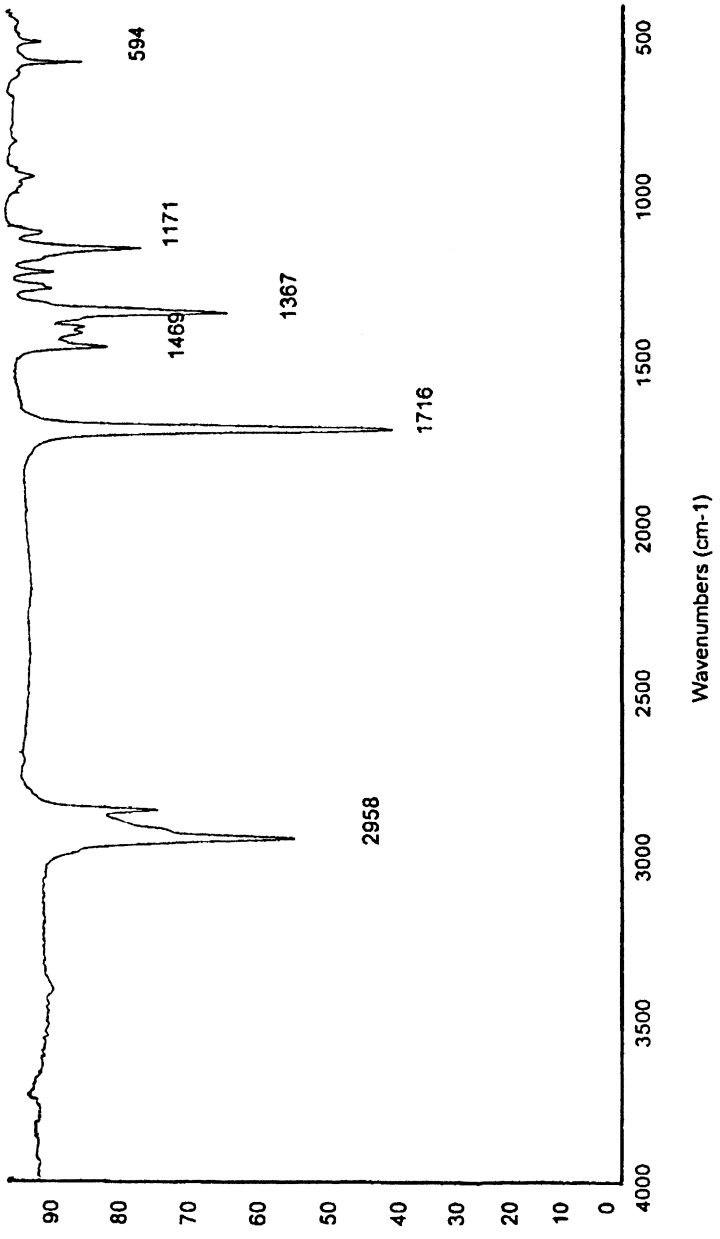


FIGURE F1
Infrared Absorption Spectrum of Methyl Isobutyl Ketone

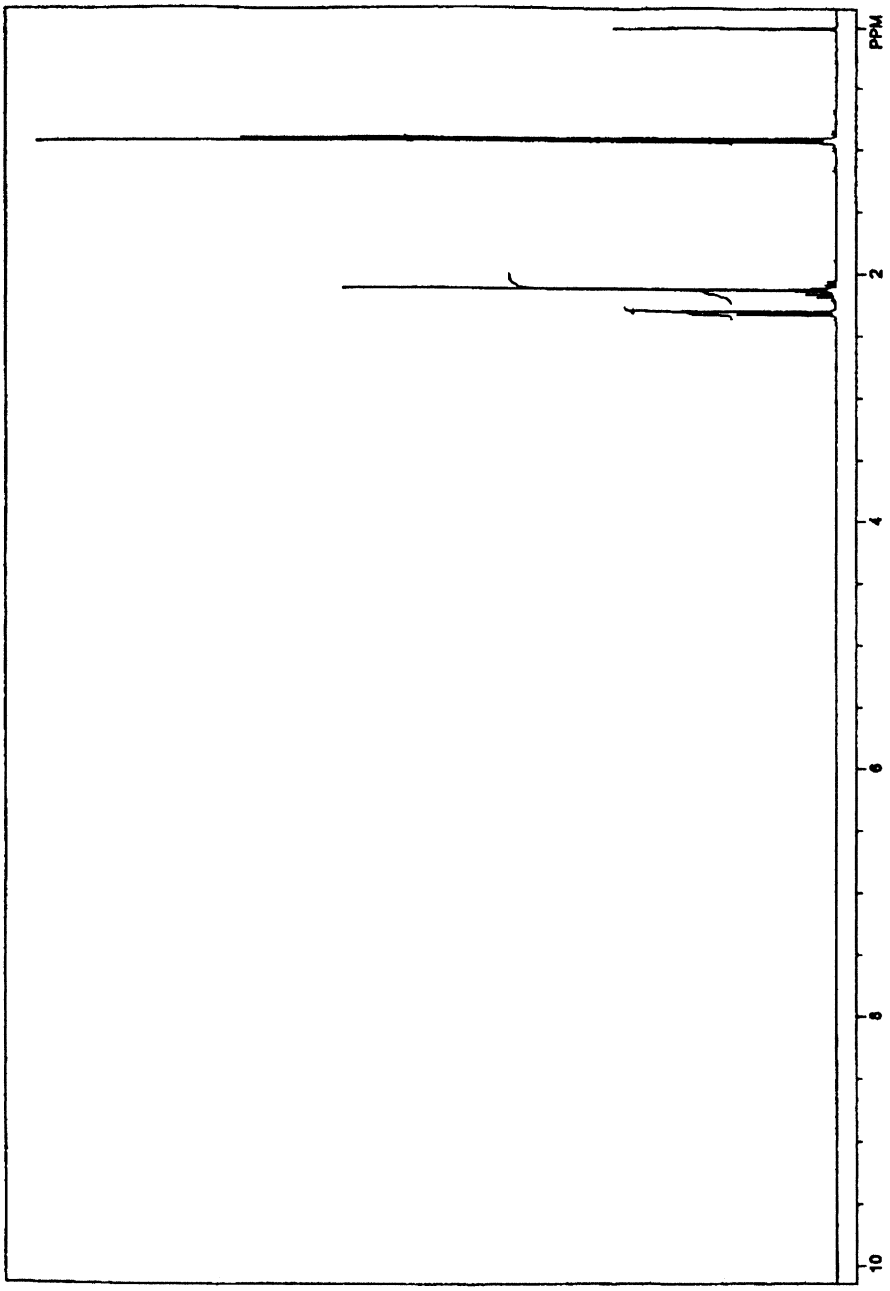


FIGURE F2
Proton Nuclear Magnetic Resonance Spectrum of Methyl Isobutyl Ketone

TABLE F1
Gas Chromatography Systems Used in the Inhalation Studies of Methyl Isobutyl Ketone[a]

Detection System	Column	Carrier Gas	Oven Temperature Program
System A			
Flame ionization	Rtx-5, 30 m × 0.25 mm, 1.0-µm film (Restek, Bellefonte, PA)	Helium at 24 PSI head pressure	40° C for 1 minute, then 6° C/minute to 140° C
System B			
Flame ionization	Rtx-5, 30 m × 0.25 mm, 1.0-µm film (Restek)	Helium at 24 PSI head pressure	45° C for 1 minute, then 5° C/minute to 250° C
System C			
Mass spectrometry	DB-5, 30 m × 0.25 mm, 0.25-µm film (J&W Scientific, Folsom, CA)	Helium at 5 PSI head pressure	35° C for 2 minutes, 2° C/minute to 50° C, then 25° C/minute to 150° C, held for 2 minutes
System D			
Flame ionization	DB-5, 15 m × 0.53 mm, 1.5-µm film (J&W Scientific)	Nitrogen at 20.0 mL/minute	Isothermal at 50° C
System E			
Flame ionization	DB-5, 30 m × 0.53 mm, 1.5-µm film (J&W Scientific)	Helium at 6 PSI head pressure	45° C for 1 minute, then 6° C/minute to 110° C
System F			
Flame ionization	DBWax-Etn, 30 m × 0.25 mm, 0.5-µm film (J&W Scientific)	Helium at 24 PSI head pressure	45° C for 1 minute, then 5° C/minute to 250° C

[a] Gas chromatographs were manufactured by Hewlett Packard (Palo Alto, CA).

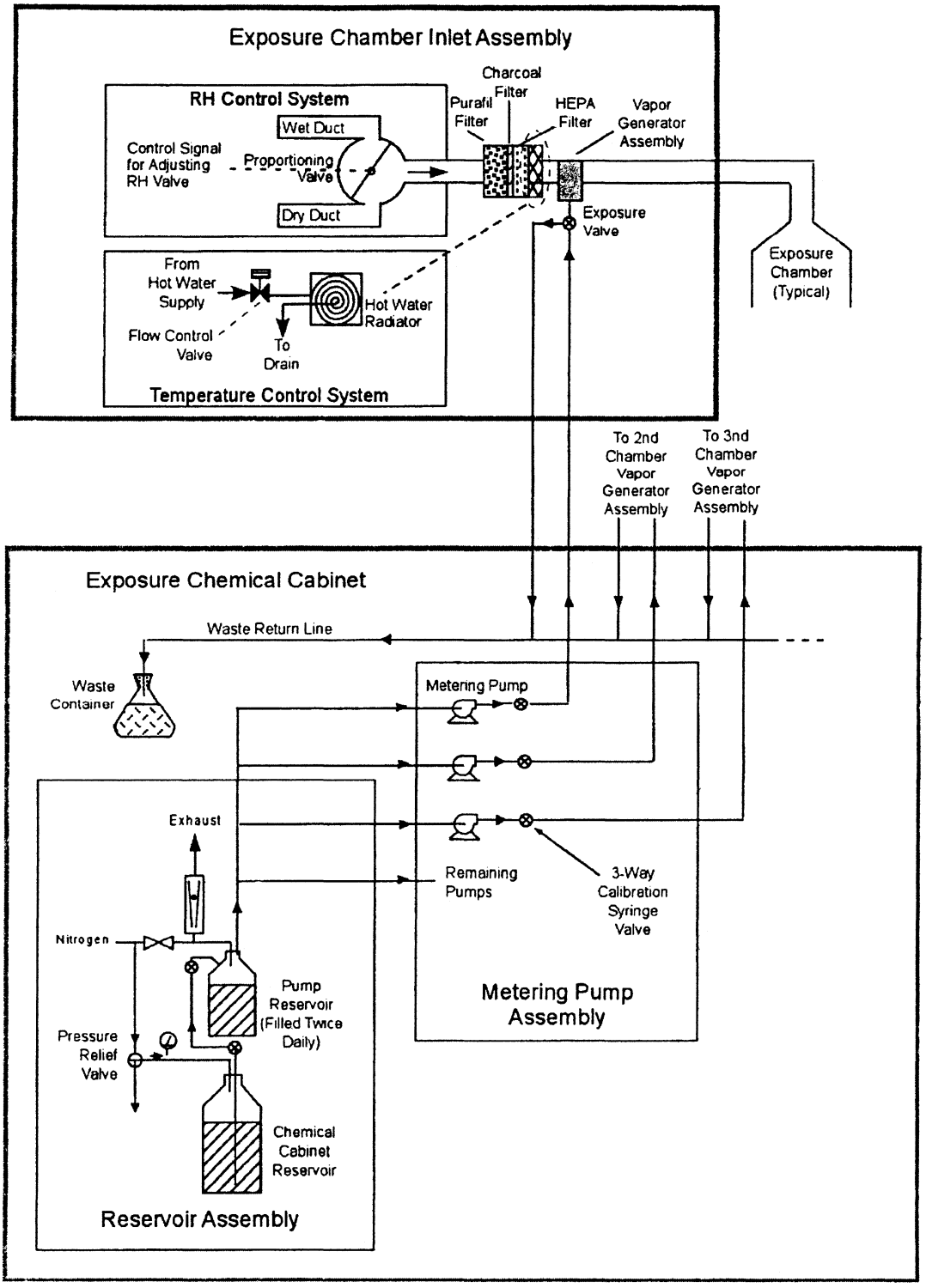


FIGURE F3
Schematic of the Vapor Generation and Delivery System in the Inhalation Studies of Methyl Isobutyl Ketone

TABLE F2
Summary of Chamber Concentrations in the 2-Year Inhalation Studies of Methyl Isobutyl Ketone

Target Concentration (ppm)	Total Number of Readings	Average Concentration[a] (ppm)
Rat Chambers		
450	6,898	451 ± 14
900	6,917	902 ± 22
1,800	6,978	1,806 ± 42
Mouse Chambers		
450	7,294	450 ± 10
900	7,356	899 ± 26
1,800	7,389	1,792 ± 48

[a] Mean ± standard deviation

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

TABLE G1
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 G2
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 G3
Nutrient Composition of NTP-2000 Rat and Mouse Ration

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Protein (% by weight)	14.1 ± 0.63	13.2 – 15.7	25
Crude fat (% by weight)	8.1 ± 0.29	7.6 – 8.6	25
Crude fiber (% by weight)	9.1 ± 0.55	8.0 – 10.5	25
Ash (% by weight)	5.2 ± 0.26	4.8 – 5.8	25
Amino Acids (% of total diet)			
Arginine	0.748 ± 0.053	0.670 – 0.850	12
Cystine	0.223 ± 0.027	0.150 – 0.250	12
Glycine	0.702 ± 0.043	0.620 – 0.750	12
Histidine	0.343 ± 0.023	0.310 – 0.390	12
Isoleucine	0.534 ± 0.041	0.430 – 0.590	12
Leucine	1.078 ± 0.059	0.960 – 1.140	12
Lysine	0.729 ± 0.065	0.620 – 0.830	12
Methionine	0.396 ± 0.053	0.260 – 0.460	12
Phenylalanine	0.611 ± 0.038	0.540 – 0.660	12
Threonine	0.492 ± 0.045	0.430 – 0.590	12
Tryptophan	0.129 ± 0.016	0.110 – 0.160	12
Tyrosine	0.378 ± 0.054	0.280 – 0.460	12
Valine	0.658 ± 0.049	0.550 – 0.710	12
Essential Fatty Acids (% of total diet)			
Linoleic	3.89 ± 0.278	3.49 – 4.54	12
Linolenic	0.30 ± 0.038	0.21 – 0.35	12
Vitamins			
Vitamin A (IU/kg)	4,672 ± 770	3,060 – 6,090	25
Vitamin D (IU/kg)	1,000[a]		
α–Tocopherol (ppm)	84.3 ± 17.06	52.0 – 110.0	12
Thiamine (ppm)[b]	7.1 ± 0.86	6.0 – 8.8	25
Riboflavin (ppm)	6.4 ± 2.11	4.20 – 11.20	12
Niacin (ppm)	78.6 ± 10.86	66.4 – 98.2	12
Pantothenic acid (ppm)	23.1 ± 3.61	17.4 – 29.1	12
Pyridoxine (ppm)[b]	8.88 ± 2.05	6.4 – 12.4	12
Folic acid (ppm)	1.84 ± 0.56	1.26 – 3.27	12
Biotin (ppm)	0.337 ± 0.13	0.225 – 0.704	12
Vitamin B_{12} (ppb)	64.8 ± 50.9	18.3 – 174.0	12
Choline (ppm)[b]	3,094 ± 292	2,700 – 3,790	12
Minerals			
Calcium (%)	1.040 ± 0.043	0.964 – 1.140	25
Phosphorus (%)	0.606 ± 0.037	0.552 – 0.701	25
Potassium (%)	0.668 ± 0.023	0.627 – 0.694	12
Chloride (%)	0.368 ± 0.033	0.300 – 0.423	12
Sodium (%)	0.189 ± 0.016	0.160 – 0.212	12
Magnesium (%)	0.200 ± 0.009	0.185 – 0.217	12
Sulfur (%)	0.176 ± 0.026	0.116 – 0.209	12
Iron (ppm)	177 ± 46.2	135 – 311	12
Manganese (ppm)	53.4 ± 6.42	42.1 – 63.1	12
Zinc (ppm)	52.5 ± 6.95	43.3 – 66.0	12
Copper (ppm)	6.64 ± 1.283	5.08 – 9.92	12
Iodine (ppm)	0.535 ± 0.242	0.233 – 0.972	12
Chromium (ppm)	0.545 ± 0.125	0.330 – 0.751	12
Cobalt (ppm)	0.23 ± 0.041	0.20 – 0.30	12

[a] From formulation
[b] As hydrochloride (thiamine and pyridoxine) or chloride (choline)

TABLE G4
Contaminant Levels in NTP-2000 Rat and Mouse Ration[a]

	Mean ± Standard Deviation[b]	Range	Number of Samples
Contaminants			
Arsenic (ppm)	0.22 ± 0.038	0.17 – 0.37	25
Cadmium (ppm)	0.04 ± 0.004	0.04 – 0.06	25
Lead (ppm)	0.09 ± 0.095	0.05 – 0.54	25
Mercury (ppm)	<0.02		25
Selenium (ppm)	0.22 ± 0.056	0.14 – 0.36	25
Aflatoxins (ppb)	<5.00		25
Nitrate nitrogen (ppm)[c]	12.1 ± 3.55	6.85 – 21.1	25
Nitrite nitrogen (ppm)[c]	<0.61		25
BHA (ppm)[d]	<1.0		25
BHT (ppm)[d]	<1.0		25
Aerobic plate count (CFU/g)	14 ± 13	10 – 70	25
Coliform (MPN/g)	2.9 ± 1.1	0.0 – 3.6	25
Escherichia coli (MPN/g)	<10		25
Salmonella (MPN/g)	Negative		25
Total nitrosoamines (ppb)[e]	4.7 ± 1.16	3.1 – 7.5	25
N-Nitrosodimethylamine (ppb)[e]	2.3 ± 0.53	1.2 – 3.2	25
N-Nitrosopyrrolidine (ppb)[e]	2.4 ± 1.14	1.0 – 5.1	25
Pesticides (ppm)			
α-BHC	<0.01		25
β-BHC	<0.02		25
γ-BHC	<0.01		25
δ-BHC	<0.01		25
Heptachlor	<0.01		25
Aldrin	<0.01		25
Heptachlor epoxide	<0.01		25
DDE	<0.01		25
DDD	<0.01		25
DDT	<0.01		25
HCB	<0.01		25
Mirex	<0.01		25
Methoxychlor	<0.05		25
Dieldrin	<0.01		25
Endrin	<0.01		25
Telodrin	<0.01		25
Chlordane	<0.05		25
Toxaphene	<0.10		25
Estimated PCBs	<0.20		25
Ronnel	<0.01		25
Ethion	<0.02		25
Trithion	<0.05		25
Diazinon	<0.10		25
Methyl chlorpyrifos	0.143 ± 0.094	0.020 – 0.418	25
Methyl parathion	<0.02		25
Ethyl parathion	<0.02		25
Malathion	0.181 ± 0.137	0.020 – 0.557	25
Endosulfan I	<0.01		25
Endosulfan II	<0.01		25
Endosulfan sulfate	<0.03		25

[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 H
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 five male and five female randomly selected sentinel rats and mice at 6, 12, and 18 months during the 2-year studies and from five male and five female randomly selected 1,800 ppm rats and mice at study termination. Blood from each animal was collected and allowed to clot, and the serum was separated. The samples were processed appropriately and sent to BioReliance (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	
ELISA	
Mycoplasma arthriditis	Study termination
Mycoplasma pulmonis	Study termination
PVM (pneumonia virus of mice)	6, 12, and 18 months, study termination
RCV/SDA (rat coronavirus/sialodacryoadenitis virus)	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

Method and Test	Time of Analysis
MICE	
ELISA	
Ectromelia virus	6, 12, and 18 months, study termination
EDIM (epizootic diarrhea of infant mice)	6, 12, and 18 months, study termination
GDVII (mouse encephalomyelitis virus)	6, 12, and 18 months, study termination
LCM (lymphocytic choriomeningitis virus)	6, 12, and 18 months, study termination
Mouse adenoma virus	6, 12, and 18 months, study termination
MCMV (mouse cytomegalovirus)	6, 12, and 18 months, study termination
MHV (mouse hepatitis virus)	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	
MCMV	Study termination
Parvovirus	6, 12, and 18 months, study termination

RESULTS

All serology tests were negative.

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
P.O. Box 12233, MD K2-05
Durham, NC 27709
Tel: 984-287-3211
ntpwebrequest@niehs.nih.gov

https://ntp.niehs.nih.gov

ISSN 2378-8925