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.

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## SUMMARY

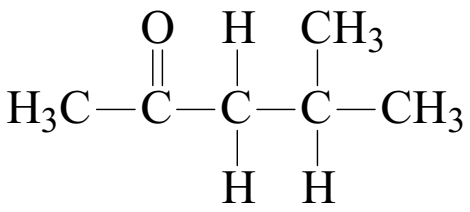
**Background**
Methyl isobutyl ketone has many industrial uses, including as a solvent for paints and lacquers and in dry cleaning. We studied methyl isobutyl ketone to determine if it caused cancer in rats or mice.

**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 $\alpha$2u-globulin accumulation in male rats and nephropathy in female rats.

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* 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)<br><br>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.

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## 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.

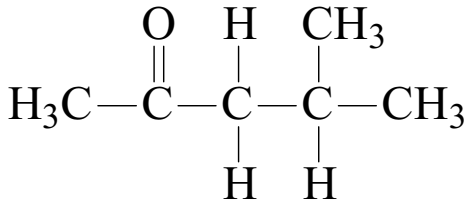
Dr. Giesy, the second principal reviewer, also agreed with the proposed conclusions and asked if the doses may have been too high.

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 dry-cleaning 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

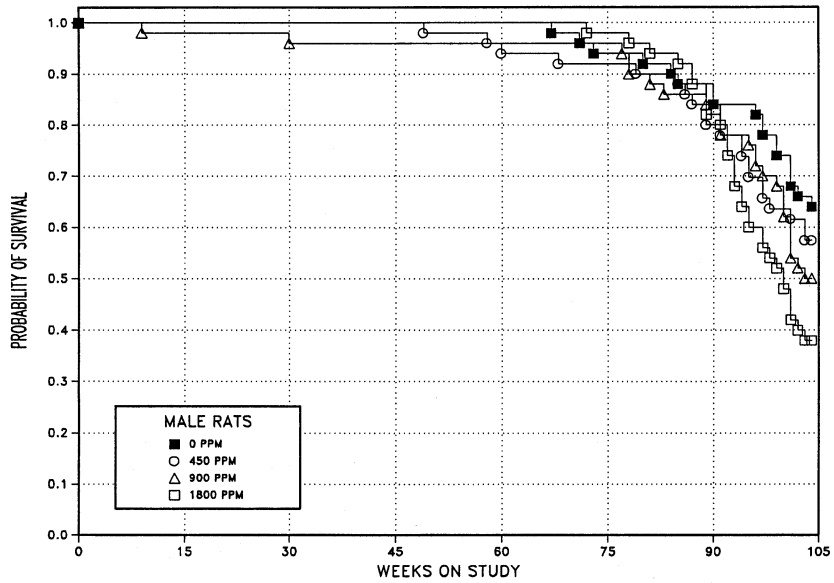
### *Survival*

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



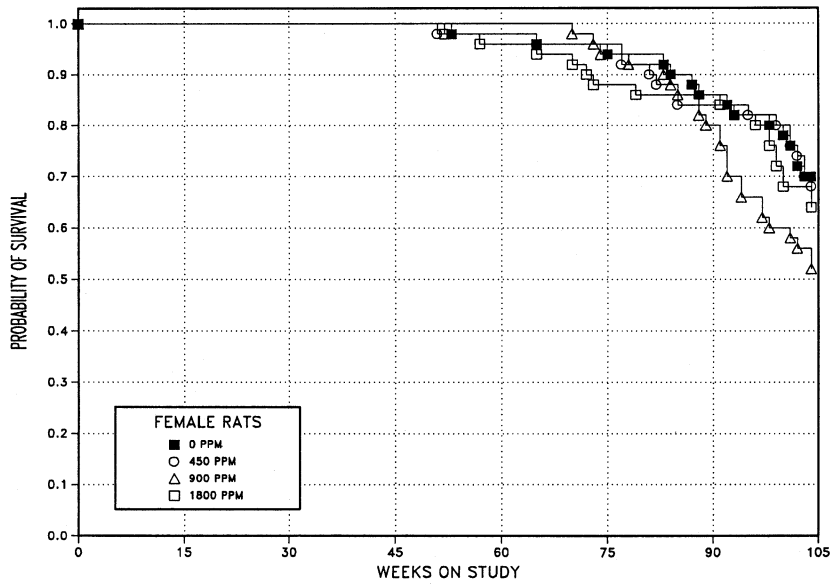




**FIGURE 1**
**Kaplan-Meier Survival Curves for Male and Female Rats Exposed to Methyl Isobutyl Ketone by Inhalation for 2 Years**

### *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.

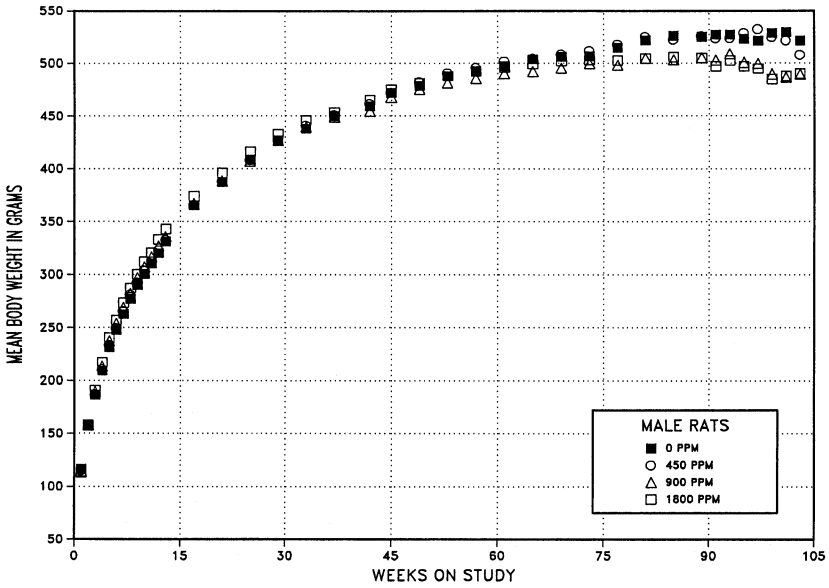
Similar, sporadic lesions have been observed in F344/N rats in six other NTP inhalation or dermal exposure studies at three different laboratories. In all these studies, the single common factor is that the animals were housed individually. No such episodes have been observed in concurrent dosed feed, 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 | |



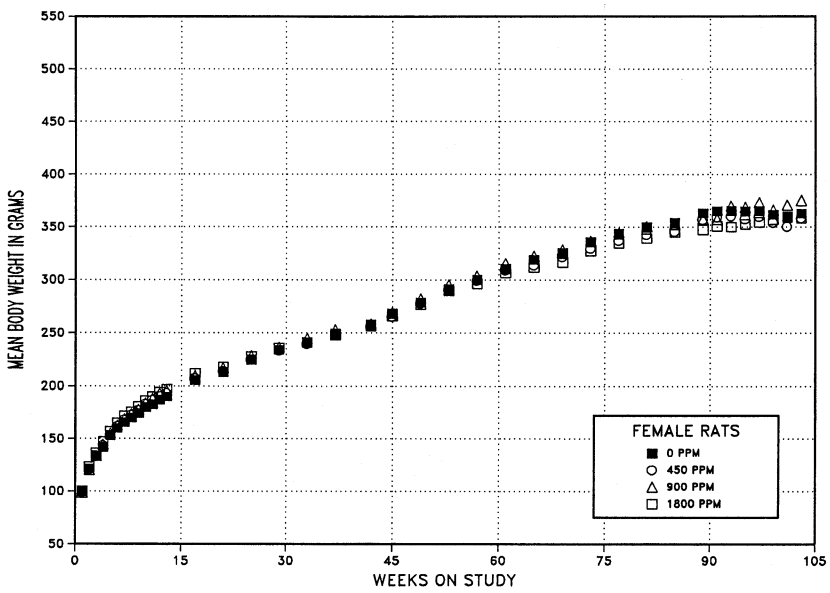




**FIGURE 2**
**Growth Curves for Male and Female Rats Exposed to Methyl Isobutyl Ketone by Inhalation for 2 Years**

## *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 $\alpha$2u-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

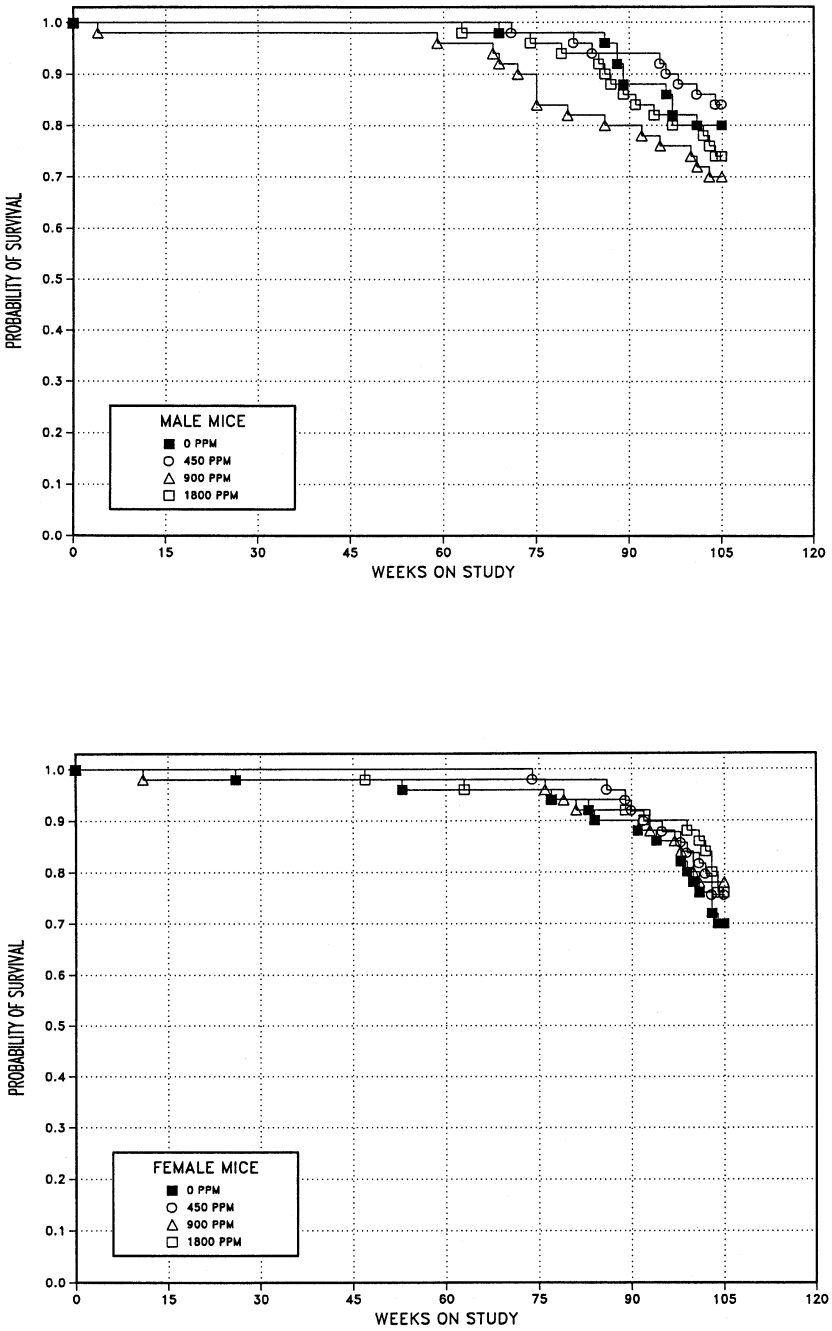
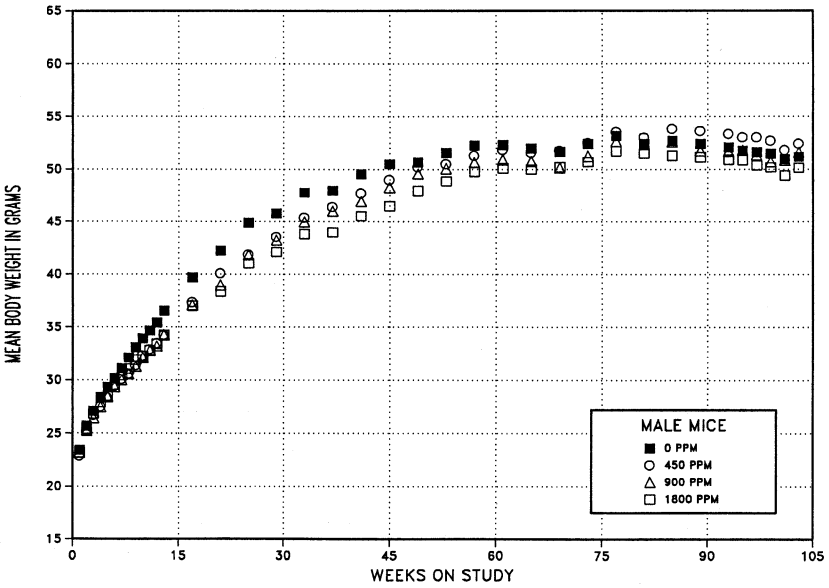



**FIGURE 3**
**Kaplan-Meier Survival Curves for Male and Female Mice Exposed to Methyl Isobutyl Ketone by Inhalation for 2 Years**



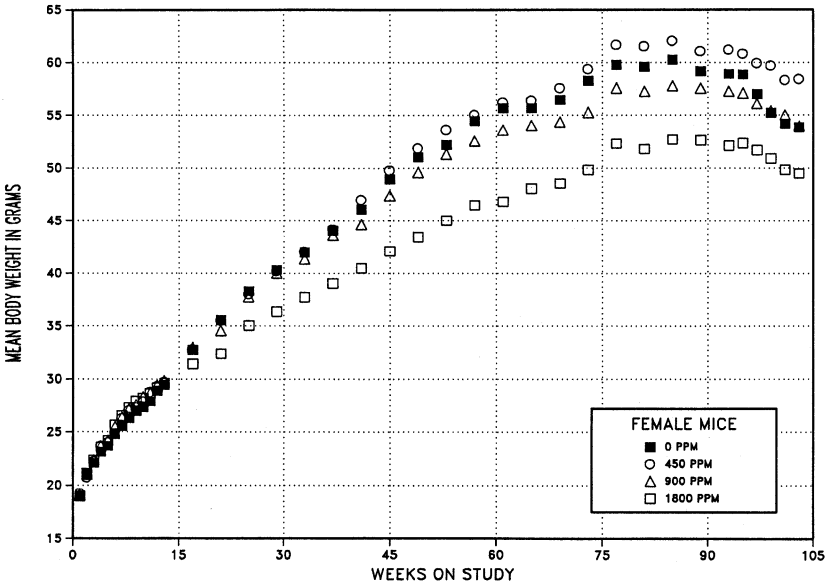




**FIGURE 4**
**Growth Curves for Male and Female Mice Exposed to Methyl Isobutyl Ketone by Inhalation for 2 Years**

**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%

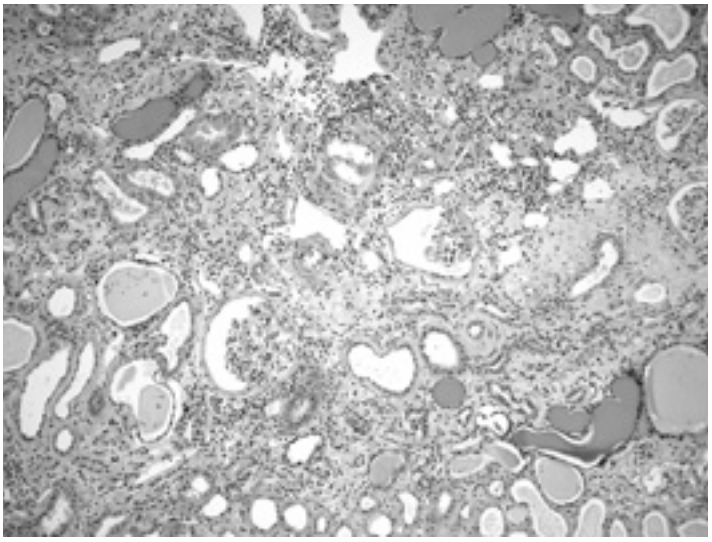


**Plate 1**
Marked nephropathy in the kidney of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. Note the dilated tubules containing homogenous proteinaceous casts, glomeruli with dilated Bowman's space, marked interstitial fibrosis, and inflammatory cell infiltrates.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

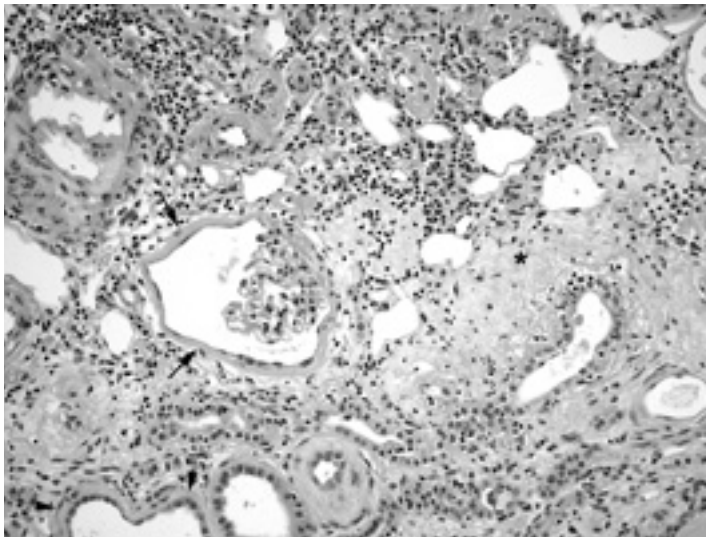


**Plate 2**
Higher magnification of Plate 1. Note several renal tubules with thickened basement membranes (arrowheads), glomerulus with dilated Bowman's space and thickened basement membrane (arrows), marked interstitial fibrosis (asterisk), and mononuclear inflammatory cell infiltrates. H&E; 20×

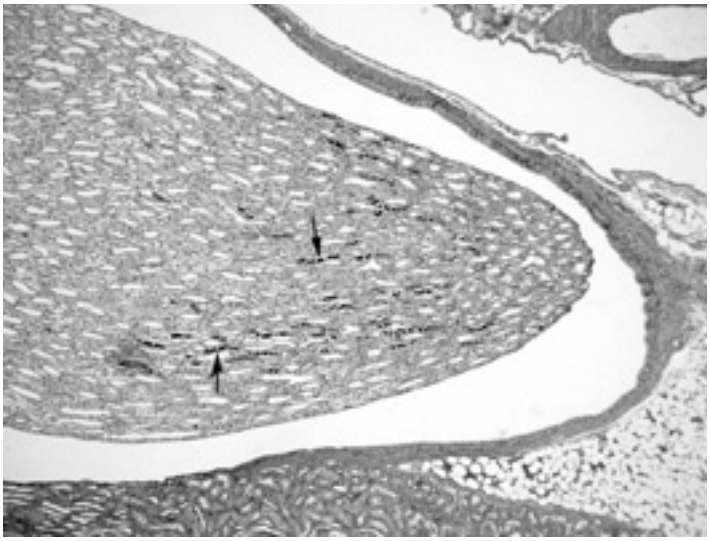


**Plate 3**
Linear mineralization (arrows) in the renal papilla of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. H&E; 4×

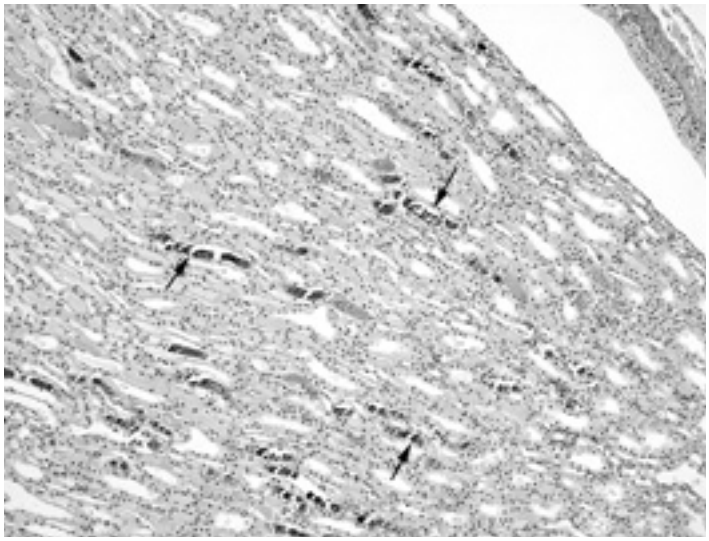


**Plate 4**
Higher magnification of Plate 3. Deposits of mineral appear as linear lamellated intraluminal or intracellular concretions (arrows) within the collecting tubules of the renal papilla. H&E; 10×

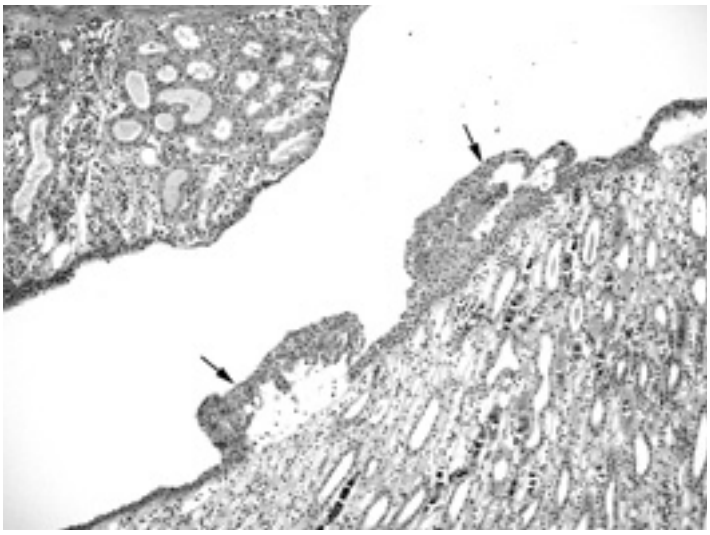


**Plate 5**
Transitional epithelial hyperplasia in the kidney of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. Hyperplasia (arrows) occurs as focal papillary thickening of the transitional epithelium lining the renal pelvis, which projects into the urinary space.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

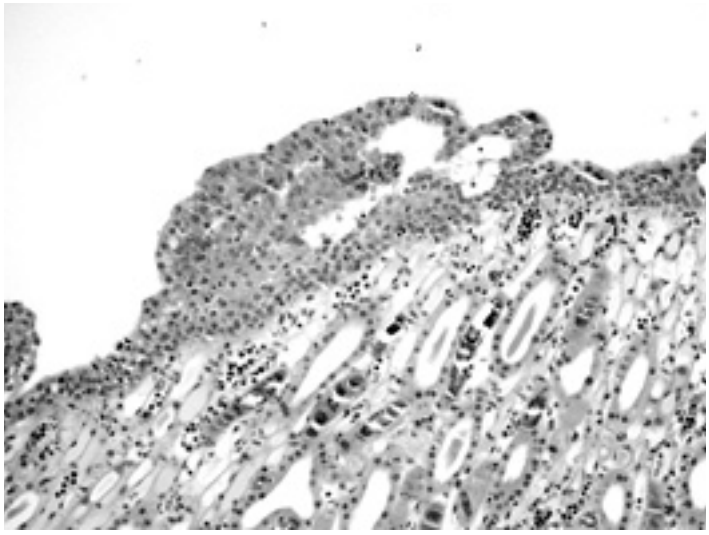


**Plate 6**
Higher magnification of Plate 5. Note the linear deposits of mineral within the collecting ducts of the renal papilla. H&E; 20×

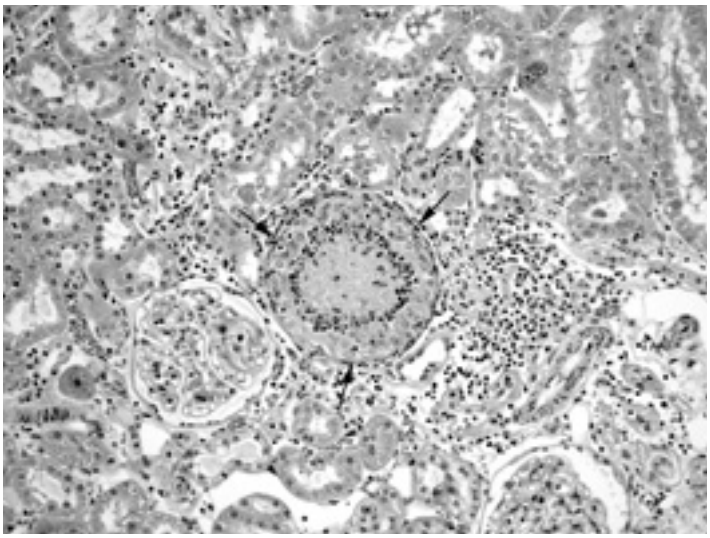


**Plate 7**
Renal tubule epithelial hyperplasia in the kidney of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. The small focus of renal tubule hyperplasia (arrows) is surrounded by normal renal tubules. H&E; 20×

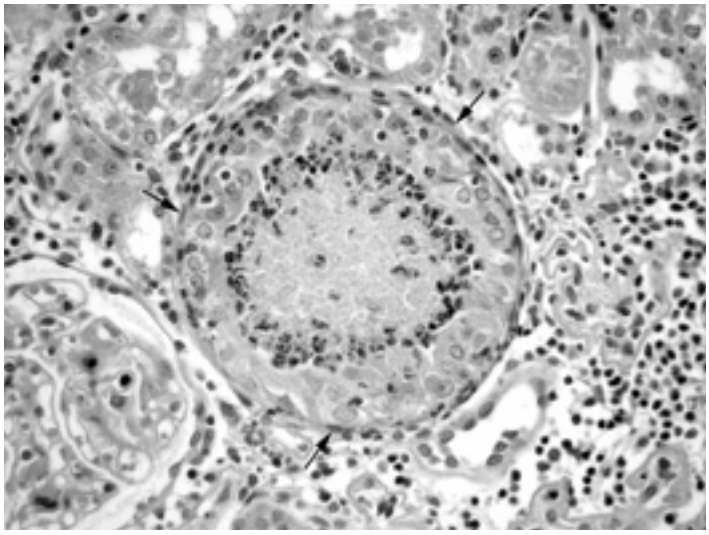


**Plate 8**
Higher magnification of Plate 7. The hyperplastic tubule has maintained its tubule shape and is still contained within an intact basement membrane (arrows). The normal, single layer of epithelial cells has been replaced by hyperplastic epithelial cells showing very little pleomorphism. Note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

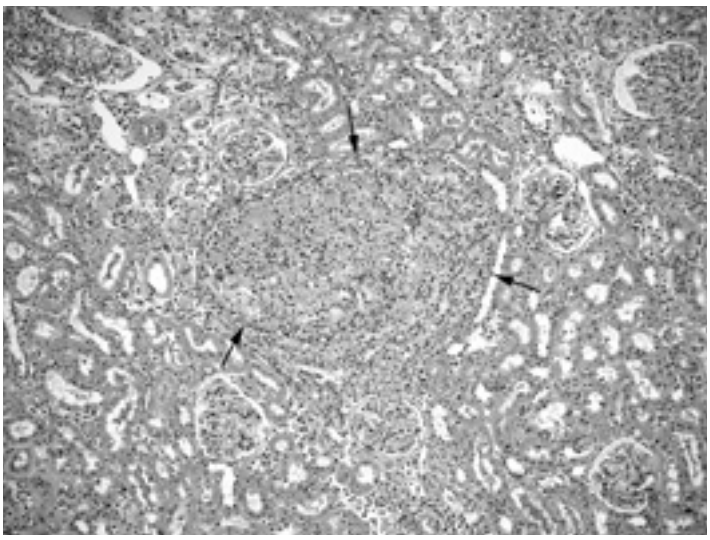


**Plate 9**
Renal tubule adenoma (arrows) in the kidney of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. The adenoma is well circumscribed and greater than five normal-sized renal tubules in diameter. H&E; 10×

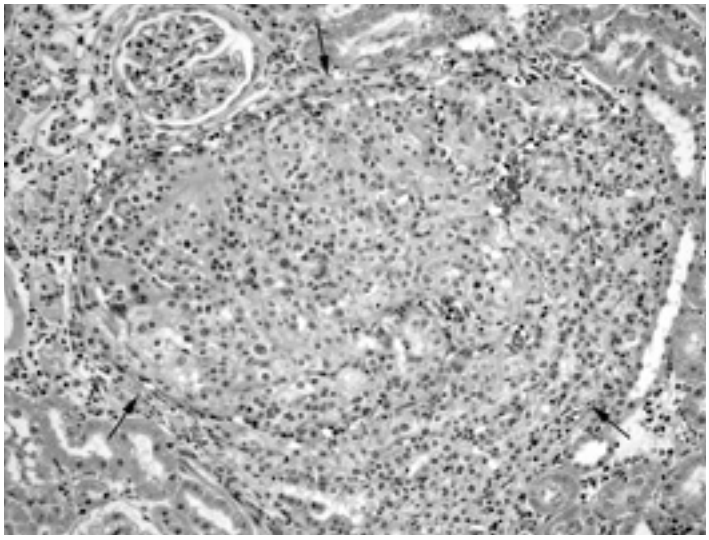


**Plate 10**
Higher magnification of Plate 9. The adenoma (arrows) is characterized by a solid-growth pattern of pleomorphic cells arranged in small nests separated by delicate vascular septae. Some of the cells are vacuolated. There is partial loss of basement membrane integrity and focal slight compression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

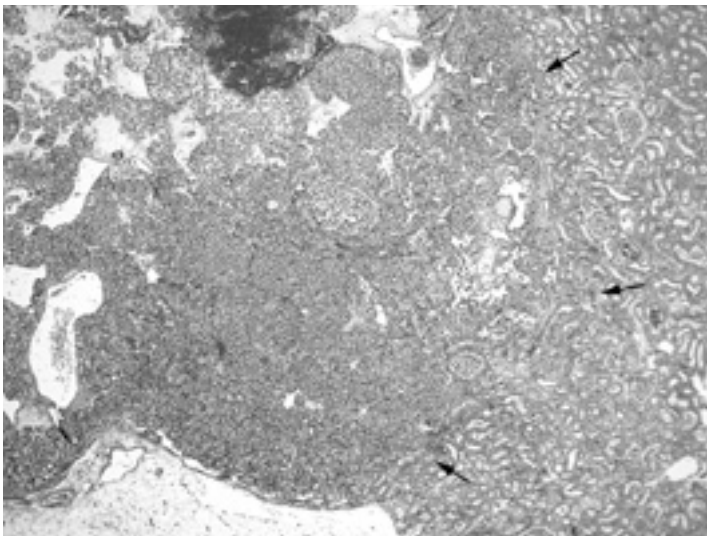


**Plate 11**
Renal tubule carcinoma in the kidney of a male F344/N rat exposed to 1,800 ppm methyl isobutyl ketone by inhalation for 2 years. The carcinoma (left of arrows) is highly cellular and has effaced the renal parenchyma. H&E; 4×

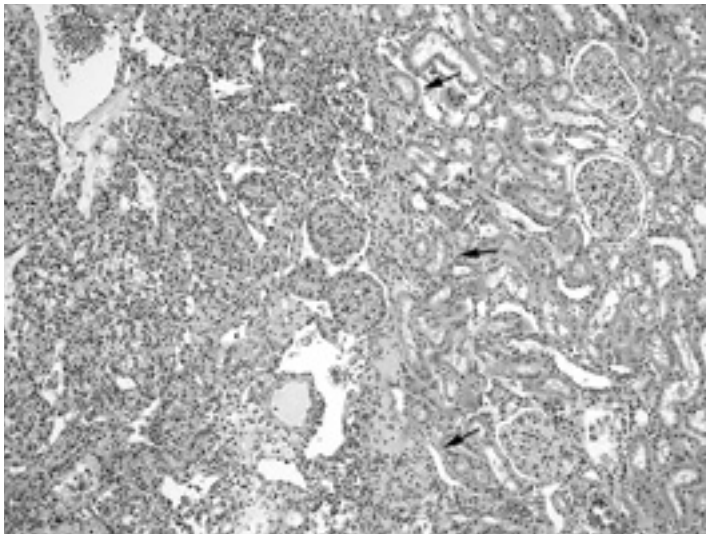


**Plate 12**
Higher magnification of Plate 11. The carcinoma (left of arrows) has a pleomorphic growth pattern with the neoplastic cells forming tubules, cords, and solid areas. H&E; 10×

# 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 $\alpha$2u-globulin accumulation in male rats and nephropathy in female rats.

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* 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.

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# APPENDIX A
# SUMMARY OF LESIONS IN MALE RATS IN THE 2-YEAR INHALATION STUDY OF METHYL ISOBUTYL KETONE


| | | |
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**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** | 468 | 492 | 505 | 554 | 588 | 592 | 624 | 629 | 671 | 679 | 679 | 687 | 687 | 701 | 702 | 702 | 713 | 723 | 726 | 726 | 726 | 726 | 726 | 726 | 726 |
| **Carcass ID Number** | 045 | 042 | 039 | 047 | 035 | 028 | 025 | 014 | 038 | 008 | 041 | 015 | 027 | 017 | 019 | 037 | 006 | 023 | 001 | 002 | 004 | 005 | 009 | 011 | 012 |
| **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** | 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 | |
| **Carcass ID Number** | 013 | 020 | 022 | 024 | 029 | 030 | 033 | 044 | 046 | 050 | 003 | 007 | 010 | 016 | 018 | 021 | 026 | 031 | 032 | 034 | 036 | 040 | 043 | 048 | 049 | 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** | 468 | 492 | 505 | 554 | 588 | 592 | 624 | 629 | 671 | 679 | 679 | 687 | 687 | 701 | 702 | 702 | 713 | 723 | 726 | 726 | 726 | 726 | 726 | 726 | 726 |
| **Carcass ID Number** | 045 | 042 | 039 | 047 | 035 | 028 | 025 | 014 | 038 | 008 | 041 | 015 | 027 | 017 | 019 | 037 | 006 | 023 | 001 | 002 | 004 | 005 | 009 | 011 | 012 |
| **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 | |
| **Carcass ID Number** | 013 | 020 | 022 | 024 | 029 | 030 | 033 | 044 | 046 | 050 | 003 | 007 | 010 | 016 | 018 | 021 | 026 | 031 | 032 | 034 | 036 | 040 | 043 | 048 | 049 | 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** | 468 | 492 | 505 | 554 | 588 | 592 | 624 | 629 | 671 | 679 | 679 | 687 | 687 | 701 | 702 | 702 | 713 | 723 | 726 | 726 | 726 | 726 | 726 | 726 | 726 |
| **Carcass ID Number** | 045 | 042 | 039 | 047 | 035 | 028 | 025 | 014 | 038 | 008 | 041 | 015 | 027 | 017 | 019 | 037 | 006 | 023 | 001 | 002 | 004 | 005 | 009 | 011 | 012 |
| **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 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | |
| **Carcass ID Number** | 013 | 020 | 022 | 024 | 029 | 030 | 033 | 044 | 046 | 050 | 003 | 007 | 010 | 016 | 018 | 021 | 026 | 031 | 032 | 034 | 036 | 040 | 043 | 048 | 049 | 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** | 338 | 405 | 420 | 471 | 551 | 595 | 602 | 609 | 618 | 621 | 621 | 637 | 654 | 658 | 659 | 664 | 674 | 677 | 685 | 705 | 720 | 721 | 726 | 726 | 726 |
| **Carcass ID Number** | 213 | 219 | 225 | 242 | 250 | 203 | 246 | 221 | 249 | 201 | 226 | 222 | 215 | 247 | 229 | 210 | 239 | 206 | 237 | 207 | 208 | 205 | 202 | 204 | 209 |
| **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 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | |
| **Carcass ID Number** | 211 | 212 | 217 | 220 | 223 | 224 | 227 | 230 | 236 | 238 | 243 | 245 | 248 | 214 | 216 | 218 | 228 | 231 | 232 | 233 | 234 | 235 | 240 | 241 | 244 | 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 | 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** | 338 | 405 | 420 | 471 | 551 | 595 | 602 | 609 | 618 | 621 | 621 | 637 | 654 | 658 | 659 | 664 | 674 | 677 | 685 | 705 | 720 | 721 | 726 | 726 | 726 |
| **Carcass ID Number** | 213 | 219 | 225 | 242 | 250 | 203 | 246 | 221 | 249 | 201 | 226 | 222 | 215 | 247 | 229 | 210 | 239 | 206 | 237 | 207 | 208 | 205 | 202 | 204 | 209 |
| **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 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | |
| **Carcass ID Number** | 211 | 212 | 217 | 220 | 223 | 224 | 227 | 230 | 236 | 238 | 243 | 245 | 248 | 214 | 216 | 218 | 228 | 231 | 232 | 233 | 234 | 235 | 240 | 241 | 244 | 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** | 338 | 405 | 420 | 471 | 551 | 595 | 602 | 609 | 618 | 621 | 621 | 637 | 654 | 658 | 659 | 664 | 674 | 677 | 685 | 705 | 720 | 721 | 726 | 726 | 726 |
| **Carcass ID Number** | 213 | 219 | 225 | 242 | 250 | 203 | 246 | 221 | 249 | 201 | 226 | 222 | 215 | 247 | 229 | 210 | 239 | 206 | 237 | 207 | 208 | 205 | 202 | 204 | 209 |
| **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** | 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** | 211 | 212 | 217 | 220 | 223 | 224 | 227 | 230 | 236 | 238 | 243 | 245 | 248 | 214 | 216 | 218 | 228 | 231 | 232 | 233 | 234 | 235 | 240 | 241 | 244 | 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** | 057 | 205 | 539 | 540 | 544 | 567 | 580 | 619 | 633 | 637 | 637 | 660 | 667 | 670 | 677 | 688 | 695 | 695 | 695 | 702 | 702 | 707 | 707 | 713 | 721 |
| **Carcass ID Number** | 422 | 415 | 446 | 441 | 432 | 443 | 404 | 413 | 425 | 410 | 420 | 429 | 426 | 417 | 439 | 428 | 409 | 418 | 450 | 411 | 414 | 416 | 447 | 444 | 433 |
| **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** | 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 | |
| **Carcass ID Number** | 403 | 408 | 412 | 419 | 421 | 424 | 430 | 436 | 440 | 448 | 401 | 402 | 405 | 406 | 407 | 423 | 427 | 431 | 434 | 435 | 437 | 438 | 442 | 445 | 449 | 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** | 057 | 205 | 539 | 540 | 544 | 567 | 580 | 619 | 633 | 637 | 637 | 660 | 667 | 670 | 677 | 688 | 695 | 695 | 695 | 702 | 702 | 707 | 707 | 713 | 721 |
| **Carcass ID Number** | 422 | 415 | 446 | 441 | 432 | 443 | 404 | 413 | 425 | 410 | 420 | 429 | 426 | 417 | 439 | 428 | 409 | 418 | 450 | 411 | 414 | 416 | 447 | 444 | 433 |
| **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 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | |
| **Carcass ID Number** | 403 | 408 | 412 | 419 | 421 | 424 | 430 | 436 | 440 | 448 | 401 | 402 | 405 | 406 | 407 | 423 | 427 | 431 | 434 | 435 | 437 | 438 | 442 | 445 | 449 | 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** | 057 | 205 | 539 | 540 | 544 | 567 | 580 | 619 | 633 | 637 | 637 | 660 | 667 | 670 | 677 | 688 | 695 | 695 | 695 | 702 | 702 | 707 | 707 | 713 | 721 |
| **Carcass ID Number** | 422 | 415 | 446 | 441 | 432 | 443 | 404 | 413 | 425 | 410 | 420 | 429 | 426 | 417 | 439 | 428 | 409 | 418 | 450 | 411 | 414 | 416 | 447 | 444 | 433 |
| **Systemic Lesions** | | | | | | | | | | | | | | | | | | | | | | | | | |
| Multiple organs | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear | | X | X | X | X | X | | X | | X | X | X | X | X | | X | | X | X | | X | X | X | X | X |

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

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **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 | |
| **Carcass ID Number** | 403 | 408 | 412 | 419 | 421 | 424 | 430 | 436 | 440 | 448 | 401 | 402 | 405 | 406 | 407 | 423 | 427 | 431 | 434 | 435 | 437 | 438 | 442 | 445 | 449 | 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** | 498 | 544 | 567 | 595 | 604 | 609 | 621 | 622 | 623 | 636 | 638 | 638 | 639 | 645 | 645 | 649 | 652 | 653 | 659 | 665 | 674 | 677 | 681 | 693 | 694 |
| **Carcass ID Number** | 603 | 626 | 627 | 618 | 637 | 612 | 630 | 622 | 631 | 624 | 608 | 609 | 621 | 601 | 632 | 642 | 650 | 641 | 607 | 613 | 605 | 623 | 616 | 646 | 645 |
| **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** | 694 | 702 | 705 | 706 | 712 | 719 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 727 | 727 | 727 | 727 | |
| **Carcass ID Number** | 648 | 611 | 617 | 640 | 620 | 643 | 606 | 610 | 614 | 615 | 619 | 625 | 628 | 629 | 634 | 635 | 638 | 639 | 644 | 647 | 649 | 602 | 604 | 633 | 636 | 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** | 498 | 544 | 567 | 595 | 604 | 609 | 621 | 622 | 623 | 636 | 638 | 638 | 639 | 645 | 645 | 649 | 652 | 653 | 659 | 665 | 674 | 677 | 681 | 693 | 694 |
| **Carcass ID Number** | 603 | 626 | 627 | 618 | 637 | 612 | 630 | 622 | 631 | 624 | 608 | 609 | 621 | 601 | 632 | 642 | 650 | 641 | 607 | 613 | 605 | 623 | 616 | 646 | 645 |
| **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** | 694 | 702 | 705 | 706 | 712 | 719 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 727 | 727 | 727 | 727 | |
| **Carcass ID Number** | 648 | 611 | 617 | 640 | 620 | 643 | 606 | 610 | 614 | 615 | 619 | 625 | 628 | 629 | 634 | 635 | 638 | 639 | 644 | 647 | 649 | 602 | 604 | 633 | 636 | 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** | 498 | 544 | 567 | 595 | 604 | 609 | 621 | 622 | 623 | 636 | 638 | 638 | 639 | 645 | 645 | 649 | 652 | 653 | 659 | 665 | 674 | 677 | 681 | 693 | 694 |
| **Carcass ID Number** | 603 | 626 | 627 | 618 | 637 | 612 | 630 | 622 | 631 | 624 | 608 | 609 | 621 | 601 | 632 | 642 | 650 | 641 | 607 | 613 | 605 | 623 | 616 | 646 | 645 |
| **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** | 694 | 702 | 705 | 706 | 712 | 719 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 726 | 727 | 727 | 727 | 727 | | |
| **Carcass ID Number** | 648 | 611 | 617 | 640 | 620 | 643 | 606 | 610 | 614 | 615 | 619 | 625 | 628 | 629 | 634 | 635 | 638 | 639 | 644 | 647 | 649 | 602 | 604 | 633 | 636 | 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 . . . . . 94

**TABLE B2** Individual Animal Tumor Pathology of Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone . . . . . 98

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**TABLE B5** Summary of the Incidence of Nonneoplastic Lesions in Female Rats in the 2-Year Inhalation Study of Methyl Isobutyl Ketone . . . . . 126

**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** | 370 | 454 | 523 | 576 | 583 | 606 | 616 | 643 | 650 | 685 | 696 | 707 | 709 | 714 | 716 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 728 | 728 | 728 |
| **Carcass ID Number** | 146 | 123 | 105 | 127 | 111 | 135 | 102 | 145 | 101 | 126 | 113 | 115 | 139 | 147 | 108 | 117 | 118 | 121 | 128 | 132 | 138 | 148 | 104 | 106 | 107 |
| **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 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | |
| **Carcass ID Number** | 109 | 110 | 114 | 122 | 131 | 133 | 134 | 136 | 137 | 140 | 143 | 144 | 103 | 112 | 116 | 119 | 120 | 124 | 125 | 129 | 130 | 141 | 142 | 149 | 150 | 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** | 370 | 454 | 523 | 576 | 583 | 606 | 616 | 643 | 650 | 685 | 696 | 707 | 709 | 714 | 716 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 728 | 728 | 728 |
| **Carcass ID Number** | 146 | 123 | 105 | 127 | 111 | 135 | 102 | 145 | 101 | 126 | 113 | 115 | 139 | 147 | 108 | 117 | 118 | 121 | 128 | 132 | 138 | 148 | 104 | 106 | 107 |
| **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 | + | 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 | | | | | | 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** | 109 | 110 | 114 | 122 | 131 | 133 | 134 | 136 | 137 | 140 | 143 | 144 | 103 | 112 | 116 | 119 | 120 | 124 | 125 | 129 | 130 | 141 | 142 | 149 | 150 | 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** | 370 | 454 | 523 | 576 | 583 | 606 | 616 | 643 | 650 | 685 | 696 | 707 | 709 | 714 | 716 | 727 | 727 | 727 | 727 | 727 | 727 | 727 | 728 | 728 | 728 | 728 |
| **Carcass ID Number** | 146 | 123 | 105 | 127 | 111 | 135 | 102 | 145 | 101 | 126 | 113 | 115 | 139 | 147 | 108 | 117 | 118 | 121 | 128 | 132 | 138 | 148 | 104 | 106 | 107 |
| **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 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | |
| **Carcass ID Number** | 109 | 110 | 114 | 122 | 131 | 133 | 134 | 136 | 137 | 140 | 143 | 144 | 103 | 112 | 116 | 119 | 120 | 124 | 125 | 129 | 130 | 141 | 142 | 149 | 150 | 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** | 356 | 455 | 537 | 539 | 562 | 569 | 594 | 595 | 665 | 693 | 707 | 707 | 712 | 718 | 721 | 722 | 728 | 728 | 728 | 728 | 728 | 728 | 728 | 728 | 728 |
| **Carcass ID Number** | 317 | 327 | 350 | 312 | 309 | 337 | 324 | 316 | 315 | 340 | 314 | 329 | 343 | 335 | 341 | 318 | 302 | 305 | 311 | 313 | 319 | 321 | 322 | 323 | 326 |
| **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 | |
| **Carcass ID Number** | 330 | 339 | 342 | 345 | 347 | 349 | 301 | 303 | 304 | 306 | 307 | 308 | 310 | 320 | 325 | 328 | 331 | 332 | 333 | 334 | 336 | 338 | 344 | 346 | 348 | 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** | 356 | 455 | 537 | 539 | 562 | 569 | 594 | 595 | 665 | 693 | 707 | 707 | 712 | 718 | 721 | 722 | 728 | 728 | 728 | 728 | 728 | 728 | 728 | 728 | 728 |
| **Carcass ID Number** | 317 | 327 | 350 | 312 | 309 | 337 | 324 | 316 | 315 | 340 | 314 | 329 | 343 | 335 | 341 | 318 | 302 | 305 | 311 | 313 | 319 | 321 | 322 | 323 | 326 |
| **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** | 330 | 339 | 342 | 345 | 347 | 349 | 301 | 303 | 304 | 306 | 307 | 308 | 310 | 320 | 325 | 328 | 331 | 332 | 333 | 334 | 336 | 338 | 344 | 346 | 348 | 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** | 356 | 455 | 537 | 539 | 562 | 569 | 594 | 595 | 665 | 693 | 707 | 707 | 712 | 718 | 721 | 722 | 728 | 728 | 728 | 728 | 728 | 728 | 728 | 728 | 728 |
| **Carcass ID Number** | 317 | 327 | 350 | 312 | 309 | 337 | 324 | 316 | 315 | 340 | 314 | 329 | 343 | 335 | 341 | 318 | 302 | 305 | 311 | 313 | 319 | 321 | 322 | 323 | 326 |
| **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** | 330 | 339 | 342 | 345 | 347 | 349 | 301 | 303 | 304 | 306 | 307 | 308 | 310 | 320 | 325 | 328 | 331 | 332 | 333 | 334 | 336 | 338 | 344 | 346 | 348 | 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** | 489 | 509 | 513 | 546 | 581 | 582 | 590 | 614 | 616 | 621 | 636 | 637 | 642 | 642 | 643 | 653 | 653 | 674 | 677 | 684 | 702 | 714 | 726 | 726 | 727 |
| **Carcass ID Number** | 548 | 524 | 547 | 528 | 501 | 533 | 540 | 543 | 520 | 514 | 542 | 527 | 507 | 537 | 549 | 512 | 513 | 510 | 511 | 530 | 523 | 525 | 509 | 518 | 503 |
| **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** | 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** | 541 | 502 | 504 | 505 | 506 | 508 | 515 | 516 | 522 | 526 | 531 | 538 | 539 | 544 | 546 | 550 | 517 | 519 | 521 | 529 | 532 | 534 | 535 | 536 | 545 | 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** | 489 | 509 | 513 | 546 | 581 | 582 | 590 | 614 | 616 | 621 | 636 | 637 | 642 | 642 | 643 | 653 | 653 | 674 | 677 | 684 | 702 | 714 | 726 | 726 | 727 |
| **Carcass ID Number** | 548 | 524 | 547 | 528 | 501 | 533 | 540 | 543 | 520 | 514 | 542 | 527 | 507 | 537 | 549 | 512 | 513 | 510 | 511 | 530 | 523 | 525 | 509 | 518 | 503 |
| **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 |
| 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 |
| 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** | 541 | 502 | 504 | 505 | 506 | 508 | 515 | 516 | 522 | 526 | 531 | 538 | 539 | 544 | 546 | 550 | 517 | 519 | 521 | 529 | 532 | 534 | 535 | 536 | 545 | 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** | 489 | 509 | 513 | 546 | 581 | 582 | 590 | 614 | 616 | 621 | 636 | 637 | 642 | 642 | 643 | 653 | 653 | 674 | 677 | 684 | 702 | 714 | 726 | 726 | 727 |
| **Carcass ID Number** | 548 | 524 | 547 | 528 | 501 | 533 | 540 | 543 | 520 | 514 | 542 | 527 | 507 | 537 | 549 | 512 | 513 | 510 | 511 | 530 | 523 | 525 | 509 | 518 | 503 |
| **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** | 541 | 502 | 504 | 505 | 506 | 508 | 515 | 516 | 522 | 526 | 531 | 538 | 539 | 544 | 546 | 550 | 517 | 519 | 521 | 529 | 532 | 534 | 535 | 536 | 545 | 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** | 364 | 398 | 454 | 489 | 499 | 506 | 548 | 637 | 651 | 667 | 681 | 681 | 691 | 692 | 695 | 695 | 723 | 726 | 727 | 727 | 728 | 728 | 728 | 728 | 728 | 728 |
| **Carcass ID Number** | 734 | 721 | 738 | 707 | 710 | 728 | 742 | 745 | 732 | 744 | 718 | 733 | 737 | 748 | 711 | 749 | 705 | 701 | 724 | 735 | 703 | 704 | 706 | 713 | 714 |
| **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** | 719 | 725 | 726 | 730 | 736 | 739 | 741 | 702 | 708 | 709 | 712 | 715 | 716 | 717 | 720 | 722 | 723 | 727 | 729 | 731 | 740 | 743 | 746 | 747 | 750 | 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** | 364 | 398 | 454 | 489 | 499 | 506 | 548 | 637 | 651 | 667 | 681 | 681 | 691 | 692 | 695 | 695 | 723 | 726 | 727 | 727 | 728 | 728 | 728 | 728 | 728 | 728 |
| **Carcass ID Number** | 734 | 721 | 738 | 707 | 710 | 728 | 442 | 445 | 732 | 744 | 718 | 733 | 733 | 748 | 711 | 749 | 705 | 701 | 724 | 735 | 703 | 704 | 706 | 713 | 714 |
| **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** | 719 | 725 | 726 | 730 | 736 | 739 | 741 | 702 | 708 | 709 | 712 | 715 | 716 | 717 | 720 | 722 | 723 | 727 | 729 | 731 | 740 | 743 | 746 | 747 | 750 | 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** | 364 | 398 | 454 | 489 | 499 | 506 | 548 | 637 | 651 | 667 | 681 | 681 | 691 | 692 | 695 | 695 | 723 | 726 | 727 | 727 | 728 | 728 | 728 | 728 | 728 | 728 |
| **Carcass ID Number** | 734 | 721 | 738 | 707 | 710 | 728 | 742 | 745 | 732 | 744 | 718 | 733 | 737 | 748 | 711 | 749 | 705 | 701 | 724 | 735 | 703 | 704 | 706 | 713 | 714 |
| **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 | |
| **Carcass ID Number** | 719 | 725 | 726 | 730 | 736 | 739 | 741 | 702 | 708 | 709 | 712 | 715 | 716 | 717 | 720 | 722 | 723 | 727 | 729 | 731 | 740 | 743 | 746 | 747 | 750 | 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 . . . . . 132

**TABLE C2** Individual Animal Tumor Pathology of Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone . . . . . 136

**TABLE C3** Statistical Analysis of Primary Neoplasms in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone . . . . . 162

**TABLE C4** Historical Incidence of Hepatocellular Neoplasms in Untreated Male $B6C3F_1$ Mice . . . . . 165

**TABLE C5** Summary of the Incidence of Nonneoplastic Lesions in Male Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone . . . . . 166

**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** | 482 | 598 | 612 | 614 | 618 | 622 | 666 | 667 | 678 | 704 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 003 | 044 | 007 | 005 | 021 | 045 | 037 | 034 | 002 | 032 | 001 | 006 | 011 | 015 | 018 | 019 | 020 | 022 | 027 | 029 | 030 | 038 | 041 | 047 | 050 |
| **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 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | |
| **Carcass ID Number** | 004 | 010 | 012 | 014 | 017 | 023 | 024 | 025 | 028 | 035 | 036 | 040 | 042 | 043 | 046 | 048 | 049 | 008 | 009 | 013 | 016 | 026 | 031 | 033 | 039 | 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** | 482 | 598 | 612 | 614 | 618 | 622 | 666 | 676 | 678 | 704 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 003 | 044 | 007 | 005 | 021 | 045 | 037 | 034 | 002 | 032 | 001 | 006 | 011 | 015 | 018 | 019 | 020 | 022 | 027 | 029 | 030 | 038 | 041 | 047 | 050 |
| **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** | 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** | 004 | 010 | 012 | 014 | 017 | 023 | 024 | 025 | 028 | 035 | 036 | 040 | 042 | 043 | 046 | 048 | 049 | 008 | 009 | 013 | 016 | 026 | 031 | 033 | 039 | 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** | 482 | 598 | 612 | 614 | 618 | 622 | 666 | 667 | 678 | 704 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 003 | 044 | 007 | 005 | 021 | 045 | 037 | 034 | 002 | 032 | 001 | 016 | 011 | 015 | 018 | 019 | 020 | 022 | 027 | 029 | 030 | 038 | 041 | 047 | 050 |
| **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 | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 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 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | |
| **Carcass ID Number** | 004 | 010 | 012 | 014 | 017 | 023 | 024 | 025 | 028 | 035 | 036 | 040 | 042 | 043 | 046 | 048 | 049 | 008 | 009 | 013 | 016 | 026 | 031 | 033 | 039 | 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 | |
| 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 | 598 | 612 | 614 | 618 | 622 | 666 | 667 | 678 | 704 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 003 | 044 | 007 | 005 | 021 | 045 | 037 | 034 | 002 | 032 | 001 | 006 | 011 | 015 | 018 | 019 | 020 | 022 | 027 | 029 | 030 | 038 | 041 | 047 | 050 |
| **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** | 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** | 004 | 010 | 012 | 014 | 017 | 023 | 024 | 025 | 028 | 035 | 036 | 040 | 042 | 043 | 046 | 048 | 049 | 008 | 009 | 013 | 016 | 026 | 031 | 033 | 039 | 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** | 493 | 565 | 582 | 661 | 670 | 680 | 704 | 724 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 220 | 210 | 234 | 244 | 231 | 205 | 207 | 222 | 201 | 202 | 209 | 212 | 213 | 214 | 217 | 219 | 221 | 226 | 227 | 228 | 229 | 237 | 243 | 248 | 249 |
| **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 | 731 | 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 |
| **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** | 493 | 565 | 582 | 661 | 670 | 680 | 704 | 724 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 220 | 210 | 234 | 244 | 231 | 205 | 207 | 222 | 201 | 202 | 209 | 212 | 213 | 214 | 217 | 219 | 221 | 226 | 227 | 228 | 229 | 237 | 243 | 248 | 249 |
| **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 | 731 | 731 | 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 |
| **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** | 493 | 565 | 582 | 661 | 670 | 680 | 704 | 724 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 220 | 210 | 234 | 244 | 231 | 205 | 207 | 222 | 201 | 202 | 209 | 212 | 213 | 214 | 217 | 219 | 221 | 226 | 227 | 228 | 229 | 237 | 243 | 248 | 249 |
| **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 | 731 | 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** | 026 | 412 | 471 | 480 | 501 | 519 | 520 | 520 | 554 | 602 | 639 | 659 | 698 | 701 | 717 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 444 | 402 | 422 | 408 | 404 | 447 | 446 | 448 | 412 | 425 | 406 | 441 | 417 | 436 | 443 | 403 | 409 | 414 | 416 | 428 | 429 | 431 | 433 | 437 | 439 |
| **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** | 440 | 445 | 449 | 450 | 401 | 405 | 410 | 415 | 418 | 419 | 420 | 421 | 423 | 424 | 426 | 427 | 430 | 438 | 442 | 407 | 411 | 413 | 432 | 434 | 435 | 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** | 026 | 412 | 471 | 480 | 501 | 519 | 520 | 522 | 554 | 602 | 639 | 659 | 698 | 701 | 717 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 444 | 402 | 422 | 408 | 404 | 447 | 446 | 448 | 412 | 425 | 406 | 441 | 417 | 436 | 443 | 403 | 409 | 414 | 416 | 428 | 429 | 431 | 433 | 437 | 439 |
| **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** | 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** | 440 | 445 | 449 | 450 | 401 | 405 | 410 | 415 | 418 | 419 | 420 | 421 | 423 | 424 | 426 | 427 | 430 | 438 | 442 | 407 | 411 | 413 | 432 | 434 | 435 | 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** | 026 | 412 | 471 | 480 | 501 | 519 | 520 | 522 | 554 | 602 | 639 | 659 | 698 | 701 | 717 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 444 | 402 | 422 | 408 | 404 | 447 | 446 | 448 | 412 | 425 | 406 | 441 | 417 | 436 | 443 | 403 | 409 | 414 | 416 | 428 | 429 | 431 | 433 | 437 | 439 |
| **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 | 731 | 731 | 731 | 731 | 731 | 731 | |
| **Carcass ID Number** | 440 | 445 | 449 | 450 | 401 | 405 | 410 | 415 | 418 | 419 | 420 | 421 | 423 | 424 | 426 | 427 | 430 | 438 | 442 | 407 | 411 | 413 | 432 | 434 | 435 | 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** | 441 | 513 | 551 | 593 | 601 | 607 | 617 | 637 | 656 | 678 | 710 | 717 | 725 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 601 | 633 | 607 | 631 | 647 | 613 | 629 | 618 | 646 | 639 | 602 | 612 | 636 | 603 | 610 | 616 | 617 | 619 | 620 | 623 | 630 | 634 | 635 | 637 | 641 |
| **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** | 643 | 644 | 649 | 606 | 608 | 609 | 611 | 614 | 615 | 622 | 624 | 628 | 632 | 638 | 645 | 648 | 650 | 604 | 605 | 621 | 625 | 626 | 627 | 640 | 642 | 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 | 717 | 725 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 601 | 633 | 607 | 631 | 647 | 613 | 629 | 618 | 646 | 639 | 602 | 612 | 636 | 603 | 610 | 616 | 617 | 619 | 620 | 623 | 630 | 634 | 635 | 637 | 641 |
| **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** | 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** | 643 | 644 | 649 | 606 | 608 | 609 | 611 | 614 | 615 | 622 | 624 | 628 | 632 | 638 | 645 | 648 | 650 | 604 | 605 | 621 | 625 | 626 | 627 | 640 | 642 | 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 | |
| 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** | 441 | 513 | 551 | 593 | 601 | 607 | 617 | 637 | 656 | 678 | 710 | 717 | 725 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 | 729 |
| **Carcass ID Number** | 601 | 633 | 607 | 631 | 647 | 613 | 629 | 618 | 646 | 639 | 602 | 612 | 636 | 603 | 610 | 616 | 617 | 619 | 620 | 623 | 630 | 634 | 635 | 637 | 641 |
| **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 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | |
| **Carcass ID Number** | 643 | 644 | 649 | 606 | 608 | 609 | 611 | 614 | 615 | 622 | 624 | 628 | 632 | 638 | 645 | 648 | 650 | 604 | 605 | 621 | 625 | 626 | 627 | 640 | 642 | 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 . . . . . 173

**TABLE D2** Individual Animal Tumor Pathology of Female Mice in the 2-Year Inhalation Study of Methyl Isobutyl Ketone . . . . . 178

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**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** | 177 | 368 | 537 | 578 | 586 | 632 | 653 | 681 | 684 | 691 | 697 | 706 | 715 | 715 | 724 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 |
| **Carcass ID Number** | 138 | 130 | 150 | 108 | 114 | 139 | 143 | 147 | 145 | 104 | 115 | 146 | 105 | 122 | 102 | 119 | 123 | 126 | 136 | 103 | 106 | 107 | 109 | 113 | 117 |
| **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** | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | |
| **Carcass ID Number** | 124 | 129 | 132 | 134 | 140 | 144 | 148 | 149 | 101 | 110 | 111 | 112 | 116 | 118 | 120 | 121 | 125 | 127 | 128 | 131 | 133 | 135 | 137 | 141 | 142 | 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** | 177 | 368 | 537 | 578 | 586 | 632 | 653 | 681 | 684 | 691 | 697 | 706 | 715 | 715 | 724 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 |
| **Carcass ID Number** | 138 | 130 | 150 | 108 | 114 | 139 | 143 | 147 | 145 | 104 | 115 | 146 | 105 | 122 | 102 | 119 | 123 | 126 | 136 | 103 | 106 | 107 | 109 | 113 | 117 |
| **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** | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | |
| **Carcass ID Number** | 124 | 129 | 132 | 134 | 140 | 144 | 148 | 149 | 101 | 110 | 111 | 112 | 116 | 118 | 120 | 121 | 125 | 127 | 128 | 131 | 133 | 135 | 137 | 141 | 142 | 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** | 177 | 368 | 537 | 578 | 586 | 632 | 653 | 681 | 684 | 691 | 697 | 706 | 715 | 715 | 724 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 |
| **Carcass ID Number** | 138 | 130 | 150 | 108 | 114 | 139 | 143 | 147 | 145 | 104 | 115 | 146 | 105 | 122 | 102 | 119 | 123 | 126 | 136 | 103 | 106 | 107 | 109 | 113 | 117 |
| **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** | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | |
| **Carcass ID Number** | 124 | 129 | 132 | 134 | 140 | 144 | 148 | 149 | 101 | 110 | 111 | 112 | 116 | 118 | 120 | 121 | 125 | 127 | 128 | 131 | 133 | 135 | 137 | 141 | 142 | 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** | 177 | 368 | 537 | 578 | 586 | 632 | 653 | 681 | 684 | 691 | 697 | 706 | 715 | 715 | 724 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 |
| **Carcass ID Number** | 138 | 130 | 150 | 108 | 114 | 139 | 143 | 147 | 145 | 104 | 115 | 146 | 105 | 122 | 102 | 119 | 123 | 126 | 136 | 103 | 106 | 107 | 109 | 113 | 117 |
| **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** | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | |
| **Carcass ID Number** | 124 | 129 | 132 | 134 | 140 | 144 | 148 | 149 | 101 | 110 | 111 | 112 | 116 | 118 | 120 | 121 | 125 | 127 | 128 | 131 | 133 | 135 | 137 | 141 | 142 | 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** | 021 | 515 | 598 | 620 | 628 | 638 | 662 | 683 | 687 | 702 | 710 | 715 | 715 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 |
| **Carcass ID Number** | 350 | 334 | 326 | 301 | 339 | 333 | 336 | 324 | 313 | 327 | 312 | 322 | 323 | 305 | 307 | 318 | 325 | 329 | 330 | 332 | 343 | 303 | 304 | 306 | 309 |
| **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** | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | |
| **Carcass ID Number** | 316 | 317 | 320 | 321 | 328 | 331 | 335 | 337 | 340 | 341 | 344 | 345 | 346 | 347 | 302 | 308 | 310 | 311 | 314 | 315 | 319 | 338 | 342 | 348 | 349 | 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** | 021 | 515 | 598 | 620 | 628 | 638 | 662 | 683 | 687 | 702 | 710 | 715 | 715 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 |
| **Carcass ID Number** | 350 | 334 | 326 | 301 | 339 | 333 | 336 | 324 | 313 | 327 | 312 | 322 | 323 | 305 | 307 | 318 | 325 | 329 | 330 | 332 | 343 | 303 | 304 | 306 | 309 |
| **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** | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | |
| **Carcass ID Number** | 316 | 317 | 320 | 321 | 328 | 331 | 335 | 337 | 340 | 341 | 344 | 345 | 346 | 347 | 302 | 308 | 310 | 311 | 314 | 315 | 319 | 338 | 342 | 348 | 349 | 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** | 021 | 515 | 598 | 620 | 628 | 638 | 662 | 683 | 687 | 702 | 710 | 715 | 715 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 |
| **Carcass ID Number** | 350 | 334 | 326 | 301 | 339 | 333 | 336 | 324 | 313 | 327 | 312 | 322 | 323 | 305 | 307 | 318 | 325 | 329 | 330 | 332 | 343 | 303 | 304 | 306 | 309 |
| **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** | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | |
| **Carcass ID Number** | 316 | 317 | 320 | 321 | 328 | 331 | 335 | 337 | 340 | 341 | 344 | 345 | 346 | 347 | 302 | 308 | 310 | 311 | 314 | 315 | 319 | 338 | 342 | 348 | 349 | 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** | 075 | 530 | 551 | 567 | 648 | 648 | 673 | 684 | 695 | 696 | 701 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 |
| **Carcass ID Number** | 536 | 512 | 535 | 542 | 528 | 537 | 547 | 540 | 520 | 541 | 521 | 503 | 507 | 509 | 510 | 514 | 524 | 549 | 501 | 504 | 505 | 506 | 511 | 515 | 517 |
| **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** | 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 | |
| **Carcass ID Number** | 519 | 525 | 526 | 527 | 530 | 531 | 532 | 538 | 543 | 546 | 550 | 502 | 508 | 513 | 516 | 518 | 522 | 523 | 529 | 533 | 534 | 539 | 544 | 545 | 548 | 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** | 075 | 530 | 551 | 567 | 648 | 648 | 673 | 684 | 695 | 696 | 701 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 |
| **Carcass ID Number** | 536 | 512 | 535 | 542 | 528 | 537 | 547 | 540 | 520 | 541 | 521 | 503 | 507 | 509 | 510 | 514 | 524 | 549 | 501 | 504 | 505 | 506 | 511 | 515 | 517 |
| **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** | 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 | |
| **Carcass ID Number** | 519 | 525 | 526 | 527 | 530 | 531 | 532 | 538 | 543 | 546 | 550 | 502 | 508 | 513 | 516 | 518 | 522 | 523 | 529 | 533 | 534 | 539 | 544 | 545 | 548 | 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** | 075 | 530 | 551 | 567 | 648 | 648 | 673 | 684 | 695 | 696 | 701 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 | 732 |
| **Carcass ID Number** | 536 | 512 | 535 | 542 | 528 | 537 | 547 | 540 | 520 | 541 | 521 | 503 | 507 | 509 | 510 | 514 | 524 | 549 | 501 | 504 | 505 | 506 | 511 | 515 | 517 |
| **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 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | 733 | |
| **Carcass ID Number** | 519 | 525 | 526 | 527 | 530 | 531 | 532 | 538 | 543 | 546 | 550 | 502 | 508 | 513 | 516 | 518 | 522 | 523 | 529 | 533 | 534 | 539 | 544 | 545 | 548 | 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** | 329 | 435 | 535 | 617 | 643 | 687 | 705 | 714 | 715 | 719 | 722 | 724 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 | 732 |
| **Carcass ID Number** | 725 | 706 | 745 | 733 | 729 | 740 | 713 | 714 | 703 | 716 | 711 | 708 | 707 | 710 | 712 | 717 | 723 | 728 | 738 | 739 | 742 | 744 | 705 | 709 | 720 |
| **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** | 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** | 721 | 727 | 737 | 741 | 743 | 746 | 747 | 749 | 750 | 701 | 702 | 704 | 715 | 718 | 719 | 722 | 724 | 726 | 730 | 731 | 732 | 734 | 735 | 736 | 748 | 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** | 329 | 435 | 535 | 617 | 643 | 687 | 705 | 714 | 715 | 719 | 722 | 724 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 |
| **Carcass ID Number** | 725 | 706 | 745 | 733 | 729 | 740 | 713 | 714 | 703 | 716 | 711 | 708 | 707 | 710 | 712 | 717 | 723 | 728 | 738 | 739 | 742 | 744 | 705 | 709 | 720 |
| **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** | 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** | 721 | 727 | 737 | 741 | 743 | 746 | 747 | 749 | 750 | 701 | 702 | 704 | 715 | 718 | 719 | 722 | 724 | 726 | 730 | 731 | 732 | 734 | 735 | 736 | 748 | 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** | 329 | 435 | 535 | 617 | 643 | 687 | 705 | 714 | 715 | 719 | 722 | 724 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 731 | 732 | 732 | 732 |
| **Carcass ID Number** | 725 | 706 | 745 | 733 | 729 | 740 | 713 | 714 | 703 | 716 | 711 | 708 | 707 | 710 | 712 | 717 | 723 | 728 | 738 | 739 | 742 | 744 | 705 | 709 | 720 |
| **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** | 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** | 721 | 727 | 737 | 741 | 743 | 746 | 747 | 749 | 750 | 701 | 702 | 704 | 715 | 718 | 719 | 722 | 724 | 726 | 730 | 731 | 732 | 734 | 735 | 736 | 748 | 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

*SALMONELLA TYPHIMURIUM* MUTAGENICITY TEST PROTOCOL . . . . . 216
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# 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** (continued) | 0 | 26 ± 4.0 | 57 ± 1.3 | 26 ± 0.9 |
| | 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


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# 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.

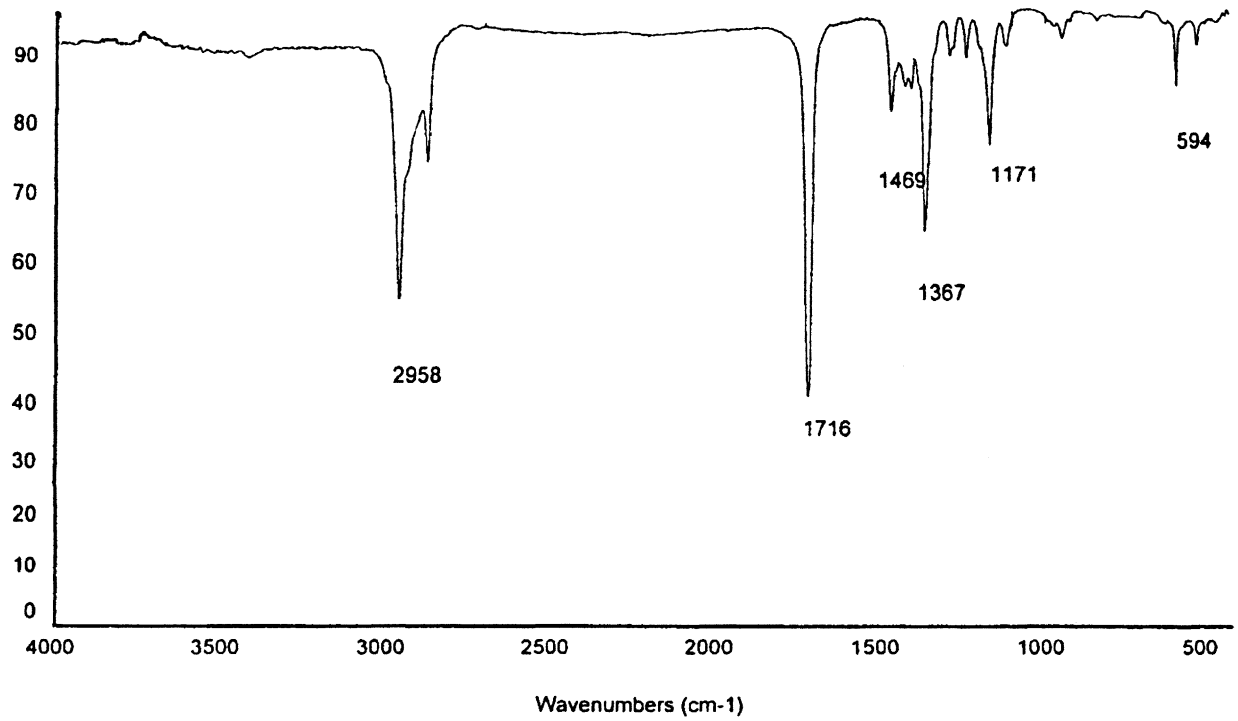


FIGURE F1
Infrared Absorption Spectrum of Methyl Isobutyl Ketone

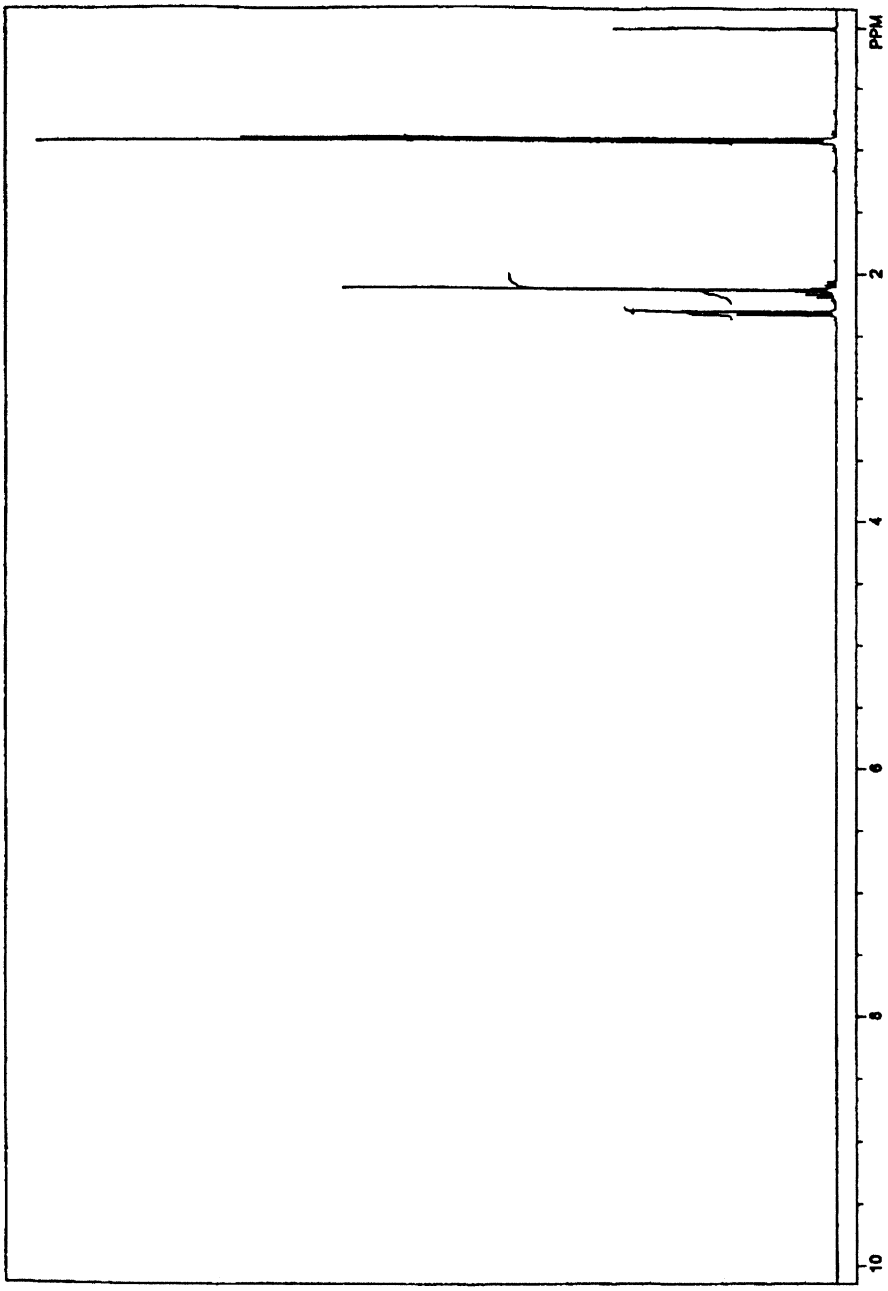


**FIGURE F2**
**Proton Nuclear Magnetic Resonance Spectrum of Methyl Isobutyl Ketone**

**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).

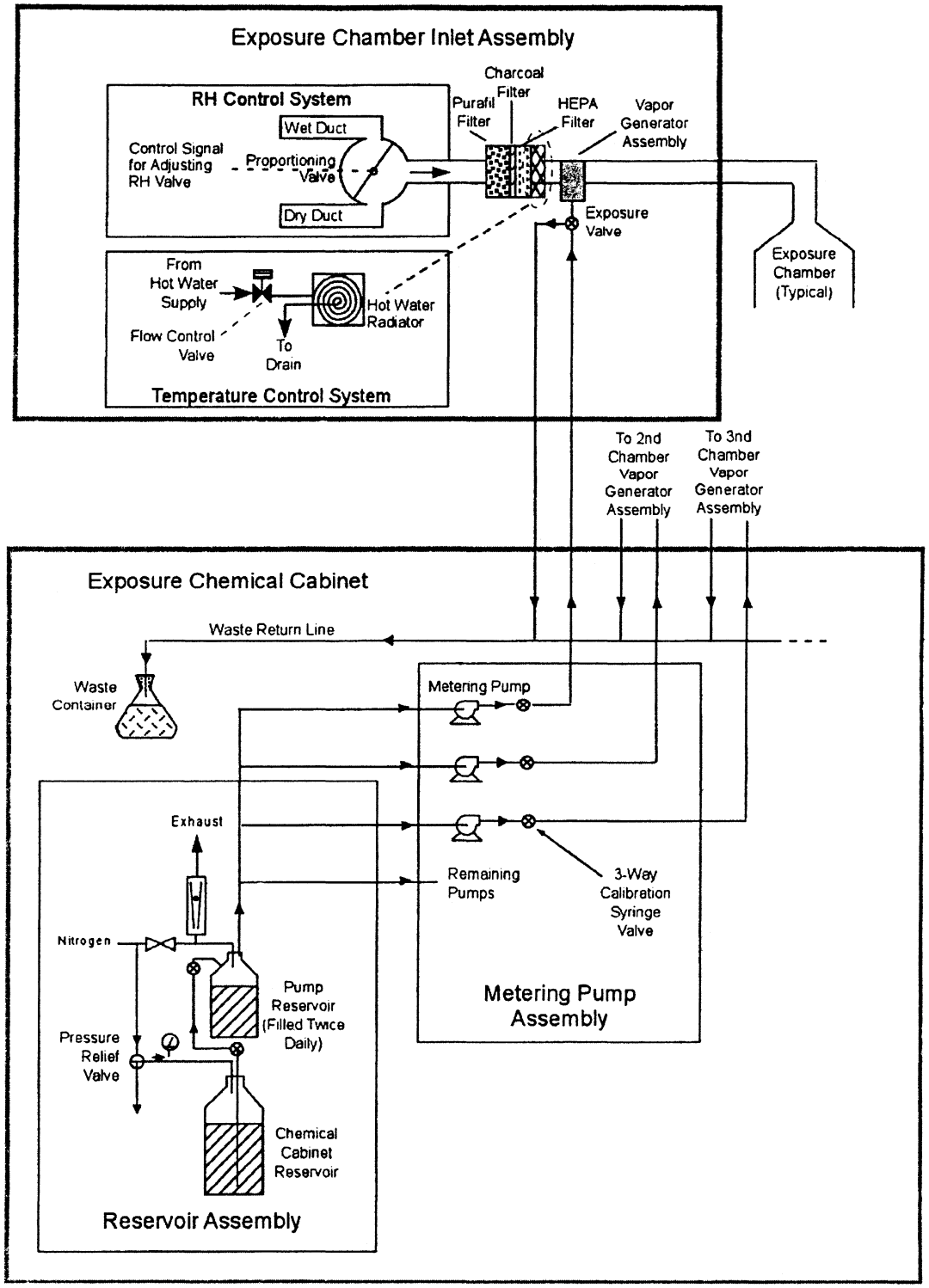


**FIGURE F3**
**Schematic of the Vapor Generation and Delivery System in the Inhalation Studies of Methyl Isobutyl Ketone**

**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

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TABLE G2 Vitamins and Minerals in NTP-2000 Rat and Mouse Ration . . . . . 230
TABLE G3 Nutrient Composition of NTP-2000 Rat and Mouse Ration . . . . . 231
TABLE G4 Contaminant Levels in NTP-2000 Rat and Mouse Ration . . . . . 232

**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

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# 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.