NATIONAL TOXICOLOGY PROGRAM
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No. 291

TOXICOLOGY AND CARCINOGENESIS STUDIES OF ISOPHORONE

(CAS NO. 78-59-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

The NTP is made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT

ON THE

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(CAS NO. 78-59-1)

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(GAVAGE STUDIES)

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

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis Program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

Five categories of interpretative conclusions were adopted for use in June 1983 in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

These NTP Technical Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Technical Report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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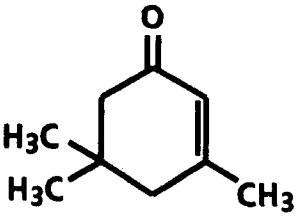

ISOPHORONE

(3,5,5-TRIMETHYL-2-CYCLOHEXEN-1-ONE)

CAS NO. 78-59-1

$C_9H_{14}O$ Molecular weight 138.2

ABSTRACT

Toxicology and carcinogenesis studies of isophorone (greater than 94% pure), a widely used solvent and chemical intermediate, were conducted by administering 0, 250, or 500 mg isophorone/kg body weight per day by gavage in corn oil to groups of 50 F344/N rats and 50 B6C3F_1 mice of each sex, 5 days per week for 103 weeks. Doses selected for the 2-year studies were based on 16-day studies in which rats and mice of each sex received doses of 0-2,000 mg/kg per day and on 13-week studies in which rats and mice of each sex received doses ranging from 0 to 1,000 mg/kg per day by gavage in corn oil. No chemically related gross or histopathologic effects were observed in the 16-day or 13-week studies, but 1/5 high dose male rats, 4/5 high dose female rats, and all high dose male and female mice died during the 16-day studies. During the 13-week studies, 1/10 high dose female rats and 3/10 high dose female mice died. The high dose for the 2-year studies was set at 500 mg/kg per day for each sex of rats and mice, based mainly on the deaths in the 13-week studies.

Throughout the 2-year study, the mean body weights of the high dose male rats averaged 5% lower than those of the vehicle controls. During the second year, the mean body weights of the female high dose rats averaged 8% lower than those of the vehicle controls, and the high dose female mice averaged 5% lower. The survival of high dose male rats was significantly lower than that of the vehicle controls after week 96 (final survival: vehicle control, 33/50; low dose, 33/50; high dose, 14/50). The survival of dosed female rats was poor (30/50; 23/50; 20/50), due in part to 20 gavage-related accidental deaths of dosed animals. The survival of male mice was also low (16/50; 16/50; 19/50), but there was a significant trend toward increased survival of dosed female mice relative to that of the vehicle controls (26/50; 35/50; 34/50).

Dosed male rats showed a variety of proliferative lesions of the kidney (tubular cell hyperplasia: 0/50; 1/50; 4/50; tubular cell adenoma: 0/50; 0/50; 2/50; tubular cell adenocarcinoma: 0/50; 3/50; 1/50; epithelial hyperplasia of the renal pelvis: 0/50; 5/50; 5/50). Dosed male rats also exhibited increased mineralization of the medullary collecting ducts (1/50; 31/50; 20/50), and low dose male rats showed a more severe nephropathy than is commonly seen in aging F344/N rats. Carcinomas of the preputial gland were increased in high dose male rats (0/50; 0/50; 5/50). With the exception of a moderate increase in nephropathy (21/50; 39/50; 32/50), female rats did not show chemically related increased incidences of neoplastic or nonneoplastic lesions.

In high dose male mice, isophorone exposure was associated with increased incidences of hepatocellular adenomas and carcinomas (18/48; 18/50; 29/50) and of mesenchymal tumors of the integumentary system (fibroma, fibrosarcoma, neurofibrosarcoma, or sarcoma: 6/48; 8/50; 14/50). An increased incidence of lymphomas or leukemias was noted in low dose male mice (8/48; 18/50; 5/50). Coagulative necrosis (3/48; 10/50; 11/50) and hepatocytomegaly (23/48; 39/50; 37/50) were observed more frequently in the livers of dosed male mice than in vehicle controls. No compound-related neoplastic or nonneoplastic lesions associated with isophorone exposure were seen in female mice.

Isophorone was not mutagenic in strains TA100, TA1535, TA1537, or TA98 of *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9. Isophorone was weakly mutagenic in the mouse L5178Y/TK$^{+/-}$ assay in the absence of S9; it was not tested in the presence of S9. Isophorone induced sister-chromatid exchanges in the absence of S9 in Chinese hamster ovary cells; it did not induce sister-chromatid exchanges in the presence of Aroclor 1254-induced male rat liver S9, and it did not induce chromosomal aberrations in Chinese hamster ovary cells in the presence or absence of S9.

An audit of the experimental data was conducted for the 2-year toxicology and carcinogenesis studies of isophorone. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenicity** of isophorone in male F344/N rats as shown by the occurrence of renal tubular cell adenomas and adenocarcinomas in animals given 250 or 500 mg/kg per day; carcinomas of the preputial gland were also observed at increased incidence in male rats given 500 mg/kg. There was *no evidence of carcinogenicity* in female F344/N rats given 250 or 500 mg/kg per day. For male B6C3F$_1$ mice, there was *equivocal evidence of carcinogenicity* of isophorone as shown by an increased incidence of hepatocellular adenomas or carcinomas (combined) and of mesenchymal tumors in the integumentary system in animals given 500 mg/kg per day and by an increase in malignant lymphomas in animals given 250 mg/kg per day. There was *no evidence of carcinogenicity* of isophorone in female B6C3F$_1$ mice given 250 or 500 mg/kg per day.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Isophorone is based on the 13-week studies that began in May 1979 and ended in August 1979 and on the 2-year studies that began in January 1980 and ended in January 1982 at Papanicolaou Cancer Research Institute.

National Toxicology Program
(Evaluated Experiment, Interpreted Results, and Reported Findings)

John R. Bucher, Ph.D., Chemical Manager

Gary A. Boorman, D.V.M., Ph.D.
David M. DeMarini, Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
C.W. Jameson, Ph.D.
William Kluwe, Ph.D.
E.E. McConnell, D.V.M.
G.N. Rao, D.V.M., Ph.D.
B.A. Schwetz, D.V.M., Ph.D.
Raymond W. Tennant, Ph.D.

NTP Pathology Working Group
(Evaluated Slides and Prepared Pathology Report on 2/17/83)

H. Solleveld, D.V.M., Ph.D. (NTP) (Chair)
G. Boorman, D.V.M., Ph.D. (NTP)
B. Gupta, B.V.Sc., D.V.M. (NTP)
S. Eustis, D.V.M., Ph.D. (NTP)
K. Morgan, D.V.M.
Chemical Industry Institute of Technology
M. Wolfe, D.V.M., Ph.D. (NTP)

Principal Contributors at Papanicolaou Cancer Research Institute
(Conducted Studies and Evaluated Tissues)

Norman Altman, D.V.M.
Principal Investigator
Fred Bock, Ph.D.
Principal Investigator
Fahzal Ahmed, Ph.D.
Chemist
John W. Sagartz, D.V.M.
Pathologist

Principal Contributors at Experimental Pathology Laboratory
(Provided Pathology Quality Assurance)

J. Hardisty, D.V.M.

Principal Contributors at Carltech Associates, Inc.
(Contractor for Technical Report Preparation)

William D. Theriault, Ph.D.
Project Manager
Abigail C. Jacobs, Ph.D.
Senior Scientist
John Warner, M.S.
Chemist/Statistician

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on November 2, 1984, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors
Technical Reports Review Subcommittee

Jerry B. Hook, Ph.D. (Chair)
Vice President, Preclinical Research and Development
Smith Kline & French Laboratories
Philadelphia, Pennsylvania

Curtis Harper, Ph.D.
Associate Professor of Pharmacology
School of Medicine
University of North Carolina
Chapel Hill, North Carolina

James Swenberg, D.V.M., Ph.D.
(Principal Reviewer)
Chief of Pathology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Ad Hoc Subcommittee Panel of Experts

Louis S. Beliczky, M.S., M.P.H.
Wickcliffe, Ohio

Devra L. Davis, Ph.D.*
Board on Toxicology and Environmental Health Hazards
National Academy of Sciences
Washington, D.C.

Seymour L. Friess, Ph.D.
Arlington, Virginia

Thomas C. Jones, D.V.M.
Professor, Comparative Pathology
New England Regional Primate Research Center
Harvard Medical School
Southborough, Massachusetts

Richard J. Kociba, D.V. M., Ph.D.
Dow Chemical USA
Midland, Michigan

David Kotelchuck, Ph.D. (Principal Reviewer)
Director, Environmental Health Sciences Program
Hunter School of Health Sciences
New York, New York

Tom Slaga, Ph.D. (Principal Reviewer)
Science Park, Research Division
University of Texas System Cancer Center
Smithville, Texas

Steven R. Tannenbaum, Ph.D.*
Professor, Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts

Bruce W. Turnbull, Ph.D.
Professor and Associate Director
College of Engineering
Cornell University
Ithaca, New York

John R. Van Ryzin, Ph.D.
Division of Biostatistics
School of Public Health
Columbia University
New York, New York

*Unable to attend meeting

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF ISOPHORONE

On November 2, 1984, the draft Technical Report on the toxicology and carcinogenesis studies of isophorone received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Swenberg, a principal reviewer, did not agree with the conclusions for male rats because the increased incidence of kidney tumors was not dose related, and he indicated that this response was typical in animals exposed to chemicals that cause nephrotoxicity and thus probably represents a secondary response. He suggested equivocal evidence of carcinogenicity, and Dr. Kociba agreed. More discussion of the observed nephrotoxicity would be useful. Regarding the preputial gland tumors, Dr. Swenberg said the variation in historical incidence made these lesions also equivocal evidence of carcinogenicity. Dr. J. Bucher, NTP, responded that the designation of some evidence of carcinogenicity for male rats was based on incidences of the uncommon neoplasms of the kidney and not on a perceived mechanism. Further, the incidence of nephropathy was high in vehicle control animals, but no neoplasms were observed. Dr. Swenberg agreed to some evidence of carcinogenicity but asked that the discussion section include a historical evaluation of renal tumors observed in other studies that also showed nephrotoxicity. [This evaluation is underway; see p. 50.]

As a second principal reviewer, Dr. Slaga agreed with the conclusion in male rats but felt the significant increase in mesenchymal tumors in the integumentary system called for a finding of some evidence of carcinogenicity rather than equivocal evidence of carcinogenicity in male mice. He noted that human exposure to isophorone usually occurs via the inhalation or dermal route and the use of one or both of those routes in these studies would have been desirable.

As a third principal reviewer, Dr. Kotelchuck agreed with the conclusions. He commented on the number of apparent gavage errors that resulted in the accidental killing of almost 10% of the test animals. Dr. Friess asked if there were guidelines for how much gavage error is permitted. Dr. E. McConnell, NTP, said that gavage error must be placed in the context of total accidental deaths and that 2% or lower is acceptable whereas 10% or greater is unacceptable. Dr. J. Huff, NTP, reminded the Panel that a 104-week gavage study using two species, both sexes, and four dose groups (vehicle control and three dose groups) requires 800 gavages to be done per day or 416,000 gavages over the course of the studies; thus, mistakes can occur. The NTP requires practical evidence of gavage proficiency before contract award.

Further discussion by the Panel members suggested agreement with the NTP selection of equivocal evidence of carcinogenicity for the various neoplasms cited as increased in male mice. Dr. Swenberg moved that the Technical Report on the Toxicology and Carcinogenesis Studies of Isophorone be accepted with the conclusions as stated and revisions discussed. Mr. Beliczky seconded the motion, and the report was approved unanimously by the Peer Review Panel.

I. INTRODUCTION

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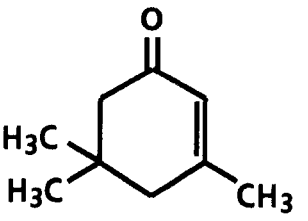

ISOPHORONE

(3,5,5-TRIMETHYL-2-CYCLOHEXEN-1-ONE)

CAS NO. 78-59-1

$C_9H_{14}O$ Molecular weight 138.2

Isophorone (3,5,5-trimethyl-2-cyclohexen-1-one) is a colorless liquid with an odor resembling peppermint. Some properties of isophorone are given in Table 1.

Isophorone is manufactured commercially by passing acetone over calcium oxide, hydroxide, or carbide at 350° C or by heating acetone at 200°-250° C under pressure. Both processes generate a mixture of isophorone and a large number of byproducts including mesitylene, mesityl oxide, phorone, and xylitone isomers. Isophorone is distilled from the mixture and is available commercially at a purity of 96%-98% (USEPA, 1980).

Production: Since only two companies manufacture isophorone, production figures are not published by the U.S. Tariff Commission. However, estimates of production have been made from available data on the consumption of acetone for isophorone manufacture. Assuming a 90% yield and a consumption of 35 million pounds of acetone (Blackford, 1975) in the manufacture of isophorone, the estimated production of isophorone in 1973 was 25 million pounds. More recent figures are not available.

Uses: Isophorone is used as a solvent or cosolvent for polyvinyl and nitrocellulose resins, lacquers, finishes, pesticides, herbicides, and a variety of fats, oils, and gums (Sittig, 1980). It is used primarily as a solvent for vinylic resins applied by roller coating (Blackford, 1975). Isophorone is also a chemical intermediate in the manufacture of 3,5-xylenol, 3,3,5-trimethylcyclohexanol, and certain plant growth retardants (Haruta et al., 1974). Isophorone has recently been patented for use as a woodpecker repellent for utility poles (Reese, 1984).

TABLE 1. PROPERTIES OF ISOPHORONE (a)

Empirical formula	$C_9H_{14}O$	Molecular weight	138.21
Freezing point	−8.1° C	Boiling point (760 mm Hg)	215.2° C
Specific gravity (20/20° C)	0.9229 g/ml	Refractive index n_D (20° C)	1.4781
Vapor pressure (25° C)	0.44 mm Hg	Air saturation	0.06%
Commercial purity (weight percent)	96%-98%	Water solubility	
Impurities:		(weight percent at 20° C)	1.2
β-isophorone	2%-4%		
Mesitylene (1,3,5-trimethylbenzene)	Trace		
Mesityl oxide (2-methyl-2-pentene-4-one)	Trace		
Phorone (2,6-dimethyl-2,5-heptadien-4-one)	Trace		
Isoxylitones	Trace		
Water	Trace		

(a) USEPA, 1979; Union Carbide, 1975; NIOSH, 1978

Environmental Occurrence and Human Exposure: Trace quantities (less than 0.01 ppb) of isophorone have been found in the Delaware River near a Philadelphia industrial area (Sheldon and Hites, 1978), and isophorone has been detected in the waste water from a tire manufacturing plant (Jungclaus et al., 1976) and in effluents from latex and chemical plants (Shackelford and Keith, 1976). Isophorone was found at concentrations of 1.5-2.9 µg/liter in finished drinking water in the New Orleans area and was also identified in Cincinnati drinking water at a concentration of 0.02 µg/liter. The highest concentration of isophorone found in a nationwide survey of finished drinking water was 9.5 µg/liter; using this figure, the Environmental Protection Agency (EPA) estimated the maximum daily intake of isophorone from ingestion of water and fish/shellfish taken from contaminated waters at 21.8 µg per day (USEPA, 1980).

Using existing toxicity data, the EPA has set an acceptable ambient water quality criteria level of 5.2 mg/liter (USEPA, 1980). In aqueous solutions, isophorone is converted by sunlight into three different tricyclic diketodimers (Jennings, 1965). The significance of this reaction in reducing the concentration of isophorone in surface water is unknown. Isophorone is degraded by microorganisms in both domestic waste water and in synthetic saltwater (Price, 1974).

The National Institute for Occupational Safety and Health (NIOSH) estimates that 1,507,000 workers are occupationally exposed to isophorone in the United States, principally through dermal contact and inhalation of vapors (NIOSH, 1978). The breathing zone of workers in a screen printing plant was shown to contain isophorone at time-weighted-average concentrations of 8.3-23 ppm (Samimi, 1982). These concentrations are within the range of concentrations found to cause irritation of mucosal membranes (USEPA, 1980).

In a sensory threshold study, Silverman et al. (1946) exposed humans to the vapors of several industrial solvents including isophorone. Twelve subjects exposed to vapors for 15-minute periods reported that exposure to isophorone at 23 ppm produced irritation of the eyes, nose, and throat and that isophorone was the most irritating of all the ketonic solvents tested. The highest tolerable level for an 8-hour exposure was judged to be 10 ppm. In a study by Union Carbide (1963), 1-minute exposures of humans to isophorone at 200 ppm were found intolerable, as were 4-minute exposures at 40 ppm. Isophorone did not cause allergic sensitization in the 10 volunteers in the Union Carbide study. Besides irritation of the eyes, nose, and throat, other symptoms produced by inhaled isophorone included nausea, headache, dizziness, faintness, inebriation, and a feeling of suffocation. Isophorone also has a narcotic action common to ketones (Smyth and Seaton, 1940).

The current 8-hour time-weighted-average threshold limit value established by the American Conference of Governmental and Industrial Hygienists for isophorone is 5 ppm in the workplace air (ACGIH, 1983). The current U.S. Federal standard is 25 ppm, but NIOSH recommends a permissible exposure limit of 4 ppm for a 40-hour workweek (Sittig, 1980).

The degree of absorption of isophorone by humans through dermal contact has not been determined; however, toxicity in animals has resulted from dermal exposures (Union Carbide, 1975). Isophorone is a primary skin irritant, and application to the eyes of rabbits caused opacity of the cornea, inflammation of the eyelids and conjunctiva, and a purulent discharge (Truhaut et al., 1972).

Absorption, Distribution, and Metabolism: No information was found on the absorption or distribution of isophorone by any route of administration, but Dutertre-Catella et al. (1978) investigated the metabolism of isophorone in New Zealand rabbits and Wistar rats receiving a single dose of 1 g/kg body weight by gavage in olive oil. Metabolites included 5,5-dimethyl-2-cyclohexen-1-one-3-carboxylic acid, thought to arise by methyloxidation; isophorol (3,5,5-trimethyl-2-cyclohexen-1-ol), found as the glucuronide conjugate and formed by reduction of the ketone; and dihydroisophorone (3,5,5-trimethylcyclohexanone) resulting from the hydrogenation of the cyclohexene double bond.

Isophorone is lipid soluble and would therefore be expected to accumulate to some degree in fat.

Concentrations of isophorone in bluegill sunfish have been found to be seven times greater than those in ambient water (Ray and Trieff, 1980).

Effects in Animals: The oral LD_{50} value for isophorone in rats and mice is approximately 2 g/kg (Smyth et al., 1970; Union Carbide, 1975). The dermal LD_{50} value after placement of a covered dose of isophorone on the skin of rabbits for 24 hours is 1.39 g/kg (Union Carbide, 1975).

Inhalation of air saturated with isophorone (approximately 580 ppm) for 8 hours caused the death of 1/6 rats (Union Carbide, 1975). Smyth and Seaton (1940) reported deaths of rats exposed to isophorone for 4 hours at a purported concentration of 1,840 ppm but not at lower concentrations. In these same studies, guinea pigs were found to survive an 8-hour exposure to air saturated with isophorone. Rats that died from inhalation of isophorone showed petechial and massive hemorrhage of the lungs, congestion of the stomach and liver, excess peritoneal fluid, a pale brownish color of the kidneys, and orange-tinted spleens. In animals killed 14 days after the exposure, rats showed frequent and more severe pathologic effects than did guinea pigs. Secretions, red cell leakage, and desquamated epithelial cells were frequently seen in alveoli and bronchioles of the lungs. Dilation of Bowman's capsule and general congestion were noted in kidneys along with cloudy swelling, dilation, granular detritis, and hyaline casts in the convoluted tubules; however, deaths were attributed to paralysis of the respiratory center by the narcotic action common to ketones.

The isophorone used by Smyth and Seaton (1940) was not pure and apparently contained several highly volatile components that may have contributed to the observed toxicity (Patty, 1963). This same applies to the repeated-exposure inhalation studies performed by Smyth et al. (1942) in which male Wistar rats and male and female guinea pigs were exposed to isophorone at concentrations from 25 to 500 ppm, 8 hours per day, 5 days per week, for 6 weeks. In these studies, about half of the guinea pigs exposed to isophorone at 500 ppm died before the 30th exposure, but none died from inhalation at 100 ppm or lower. Similarly, no rats died from exposure to isophorone at concentrations of 50 ppm or lower. Both species showed poor growth when exposed at 100 ppm or greater, and animals exposed at 500 ppm excreted albumin in their urine.

The principal pathologic findings in the repeated-exposure study (Smyth et al., 1942) were similar to those observed after 4- and 8-hour exposure by inhalation (Smyth and Seaton, 1940). Deaths appeared to result from a combination of kidney and lung injury in both species, and lesions were dose related. Kidneys were congested, with dilation of Bowman's capsule, granular secretions in the convoluted tubules, and cloudy swelling; toxic regeneration or necrosis of the tubular epithelium also was observed. Lungs were congested and showed red blood cells and increased secretions in the bronchioles and alveoli and desquamation of bronchiolar epithelium.

Ninety-day feeding studies were performed with isophorone in rats and dogs in 1972 by Parkin (USEPA, 1980). In the rat study, 20 weanling male and female CFE albino rats were fed isophorone in the diet at 0, 750, 1,500, or 3,000 ppm for 90 days. No compound-related deaths occurred during the study, and no effects on body weights or food consumption were noted. Similarly, no abnormalities were observed in hematologic or clinical chemistry determinations or in urinalyses. No pathologic lesions were observed by either gross or microscopic examination. In the dog study, four male and four female beagles were given isophorone for 90 days at doses of 0, 35, 75, or 150 mg/kg body weight per day in gelatin capsules. As in the rat study, isophorone administration was found to have no effect on mortality, weight gain, clinical chemical results, or results of urinalysis; and it did not cause gross or microscopic changes in any of the 28 selected tissues (USEPA, 1980).

Teratogenicity and Reproductive Effects: No information was found on the teratogenic or reproductive effects of exposure of mammals to isophorone, but an early life-stage toxicity test with the sheepshead minnow was reported (Ward et al., 1981). The hatching success of sheepshead minnows was markedly reduced when they were exposed to isophorone at a concentration of 287 mg/liter; over a 28-day

exposure period, mortality of exposed juveniles was 100% compared with 4% in the controls. Exposure at 156 mg/liter did not decrease hatching success or increase mortality, but growth was severely stunted. Two abnormal fish were observed--a two-headed embryo in the 100 embryos exposed at 18 mg/liter and a one-eyed fish in the 40 mg/liter group.

Mutagenicity: No information was found in the literature regarding the genetic toxicity of isophorone; however, the NTP has tested this compound in several genetic toxicity assays. Isophorone was tested for mutagenicity in the Salmonella/microsome assay and in the mouse lymphoma L5178Y/TK$^{+/-}$ assay (Appendix L, Tables L1 and L2). Isophorone was not mutagenic in strains TA100, TA1535, TA1537, or TA98 of *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced Sprague-Dawley male rat or male Syrian hamster liver S9. Isophorone was weakly mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the absence of S9; it was not tested in the presence of S9. Isophorone was also found to induce sister-chromatid exchanges in Chinese hamster ovary cells in the absence of S9, but this effect was eliminated in the presence of Aroclor 1254-induced male rat liver S9 (Appendix L, Table L3). In addition, isophorone did not induce chromosomal aberrations in the presence or absence of S9 in Chinese hamster ovary cells (Appendix L, Table L4).

Carcinogenicity: No animal or epidemiologic studies of the carcinogenic potential of isophorone were found in the literature.

Study Rationale: Isophorone was nominated for carcinogenicity and toxicity evaluation after the EPA reviewed chemicals found in drinking water. Isophorone was selected based on its presence in municipal water supplies, its potential for industrial exposure, and the lack of adequate epidemiologic or animal toxicity or carcinogenicity studies. The oral route of administration was chosen to mimic human exposure in drinking water; however, isophorone was administered by gavage in corn oil because the chemical was insoluble in water at the concentrations required to deliver the desired doses. It might have been possible to perform these studies using isophorone-dosed feed (the stability of the chemical in feed has not been determined by the NTP). Based on occupational exposures, administration of isophorone via dermal or inhalation exposures would also have been appropriate.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF ISOPHORONE

PREPARATION OF DOSE MIXTURES

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

PROCUREMENT AND CHARACTERIZATION OF ISOPHORONE

Isophorone was obtained from the Leidy Chemical Corporation (Danbury, CT) in two lots (Table 2). Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G).

The identity of isophorone was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance analyses. All spectroscopic data were in agreement with the literature or consistent with those expected for isophorone.

Cumulative analytical data indicated that lot no. 1204 was 97% pure and lot no. L052281 was 94% pure. Karl Fischer analyses indicated that lot no. 1204 contained 0.3% water and lot no. L052281 contained 1.4% water. Fourteen impurities constituting 2.8% of the total material (1 with an area of 1.9% that of the major peak) were detected in lot no. 1204 by gas chromatography. The 1.9% impurity could not be positively identified, but the fragmentation pattern obtained by mass spectroscopy suggested it was an isomer of isophorone. Ten impurities were detected in lot no. L052281 by one gas chromatographic system, and 8 impurities (1 with an area of 2.5% that of the major peak) were detected in lot no. L052281 in a second gas chromatographic system. Gas chromatography/mass spectroscopy indicated that the 2.5% impurity had a molecular ion (m/z = 152) which suggested an isophorone-type structure with an added methylene group. This impurity is probably the 3-ethyl-5,5-dimethyl- or the 2,3,5,5-tetramethyl- homolog of isophorone. These homologs could form during the synthesis of isophorone by the condensation of two molecules of acetone with methyl ethyl ketone, a common impurity in acetone.

Lot no. L052281 was similar in purity to lot no. 1204, although the water content was higher. The gas chromatographic profiles for the two lots were similar, but the total relative impurity area was slightly greater for lot no. L052281, and the areas of some of the individual impurities varied significantly from lot no. 1204.

The isophorone test material was stored at 4° C in the dark. Results of periodic reanalysis of the bulk chemical by gas chromatography and comparison with a reference sample of isophorone stored at −20° C indicated no notable change in isophorone throughout the studies.

TABLE 2. IDENTITY AND SOURCE OF LOTS USED IN THE GAVAGE STUDIES OF ISOPHORONE

	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers Used	1204	1204	1204 for the first 6 months, L052281 for the remainder of the studies
Supplier	Leidy Chem Corp., Manufacturer: Union Carbide (Danbury, CT)	Same as 16-d studies	Same as 16-d studies
Date of Initial Use of Each Lot	N/A	N/A	8/03/81

PREPARATION OF DOSE MIXTURES

Appropriate amounts of isophorone and corn oil were mixed to give the desired concentrations (Table 3 and Appendix H). Methods and results of periodic analyses of formulated isophorone/corn oil mixtures at the testing laboratory and of referee analyses at the analytical chemistry laboratory are given in Appendixes I and J. Because 70/73 mixtures analyzed had isophorone concentrations within 10% of target concentrations, it is estimated that dose mixtures were prepared within specifications more than 95% of the time (Table 4). Isophorone in corn oil was found to be stable for 7 days at room temperature. Formulated isophorone/corn oil mixtures were stored at 2°-8° C for no longer than 7 days except for the first 26 days of the 2-year studies when the formulated mixture was held for 2 weeks.

TABLE 3. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF ISOPHORONE

	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation	Isophorone was added to corn oil in a graduated cylinder. Dose mixtures were prepared by further diluting this stock solution with corn oil to the appropriate concentrations.	Same as 16-d studies	Same as 16-d studies
Maximum Storage Time	1 wk	1 wk	2 wk until 2/26/80; then 1 wk
Storage Conditions	2°-8° C	2°-8° C	2°-8° C

TABLE 4. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

	Target Concentration (percent)		
	2.50	5.00	10.00
Mean (percent)	2.59	5.09	9.86
Standard deviation	0.129	0.227	0.616
Coefficient of variation (percent)	5.0	4.5	6.2
Range (percent)	2.38-2.94	4.72-5.88	8.36-10.59
Number of samples	19	35	19

SIXTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 18 days before the study began. Groups of five rats and five mice of each sex were administered 0, 125, 250, 500, 1,000, or 2,000 mg/kg isophorone in corn oil by gavage, 5 days per week for 2 weeks (a total of 12 doses). Animals were housed five per cage and received water and feed ad libitum. Details of animal maintenance are presented in Table 5. The animals were observed twice daily and weighed on days 0 and 16.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of isophorone and to determine the doses to be used in the 2-year studies. Four-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries, observed for 18 days, and then assigned to test groups according to two tables of random numbers. Groups of 10 rats and 10 mice of each sex were administered 0, 62.5, 125, 250, 500, or 1,000 mg/kg isophorone in corn oil, 5 days per week for 13 weeks. Rats were housed 5 per cage, and mice were housed 10 per cage. Feed and water were available ad libitum. Further experimental details are summarized in Table 5. Animals were checked twice daily; moribund animals were killed. Individual animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats and 50 mice of each sex were administered 0, 250, or 500 mg/kg isophorone in corn oil by gavage, 5 days per week for 103 weeks.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female, × C3H/HeN MTV$^-$, male) mice used in this study were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding starts for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for testing were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the testing laboratory at 4-6 weeks of age. The animals were quarantined at the testing facility for 15 days. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 6-8 weeks of age. The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix K).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid B6C3F$_1$ test animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoretograms that demonstrate phenotype expressions of known genetic loci.

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid B6C3F$_1$ mice used in these studies. The influence of the potential genetic

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF ISOPHORONE

	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Testing Laboratory	Papanicolaou Cancer Research Institute	Same as 16-d studies	Same as 16-d studies
Size of Test Groups	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses	0, 125, 250, 500, 1,000, or 2,000 mg/kg isophorone in corn oil by gavage; dose vol: rats--1 ml; mice--0.5 ml	0, 62.5, 125, 250, 500, or 1,000 mg/kg isophorone in corn oil by gavage; dose vol: rats--1 ml; mice--0.5 ml	0, 250, or 500 mg/kg isophorone in corn oil by gavage; dose vol: rats--5 ml/kg; mice--10 ml/kg
Date of First Dose	2/19/79	5/7/79	1/31/80
Date of Last Dose	3/6/79	8/3/79	Rats--1/22/82; mice--1/20/82
Duration of Dosing	5 d/wk for 2 wk (12 doses over 16 d)	5 d/wk for 13 wk	5 d/wk for 103 wk
Type and Frequency of Observation	Observed 2 × d; weighed on d 0 and 16	Observed 2 × d; weighed 1 × wk for 13 wk	Observed 2 × d; weighed 1 × wk for 13 wk, 1 × mo thereafter
Necropsy and Histologic Examination	Necropsy performed on all animals; tissues examined: skin, mammary gland, mandibular lymph node, salivary gland, thigh muscle, sciatic nerve, vertebrae, femur (mice), costochondral junction (rib), thymus, larynx, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, eyes, ileum, colon, cecum, rectum, mesenteric lymph node, liver, gallbladder (mice), pancreas, spleen, kidney, adrenal glands, urinary bladder, seminal vesicles/prostate/ testes or ovaries/uterus, nasal cavity, brain, pituitary gland, spinal cord. Histopathologic examination performed on the following 10 animals: 2,000 mg/kg--3 male rats, 1 female rat; 1,000 mg/kg--2 female rats, 2 male mice, and 2 female mice; tissues examined microscopically are the same as those listed under 13-wk studies	Necropsy performed on all animals; histopathologic exam performed on the following tissues of vehicle control and high dose animals: skin, mammary gland, sciatic nerve, salivary gland, mandibular lymph node, thymus, heart, lungs, trachea, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, ileum, colon, rectum, mesenteric lymph node, pancreas, spleen, liver, gallbladder (mice), kidneys, adrenal glands, urinary bladder, seminal vesicles, prostate/testes or ovaries/uterus, brain, pituitary gland, bone marrow, spinal cord, and nasal cavity	Necropsy performed on all animals; the following tissues of all animals were microscopically examined: gross lesions and tissue masses, skin, mammary gland, thymus, heart, lungs and bronchi, trachea, thyroid gland, parathyroids, esophagus, stomach, colon, small intestine, mesenteric lymph node, pancreas, spleen, liver, gallbladder (mice), kidneys, adrenal glands, urinary bladder, prostate/ testes or ovaries/uterus, brain, pituitary gland, eyes (if grossly abnormal), thoracic vertebrae, including bone marrow and spinal cord

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF ISOPHORONE (Continued)

	Sixteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source	Charles River Breeding Laboratories (Portage, MI)	Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories (Portage, MI)
Time Held Before Test	18 d	18 d	15 d
Age When Placed on Study	Rats--47-54 d; mice--47-61 d	8 wk	Rats--6-7 wk; mice--6-8 wk
Age When Killed	Rats--9-10 wk; mice-- 9-11 wk	21 wk	Rats--111-112 wk; mice--110-113 wk
Necropsy Dates	3/7/79	8/6/79-8/8/79	Rats--2/2-2/4/82 ; mice--1/28/82, 1/29/82, 2/1/82
Method of Animal Distribution	According to weight class; then assigned to cages according to a table of random numbers; cages then assigned to groups according to another table of random numbers	Same as 16-d studies	Same as 16-d studies
Animal Identification	Ear tag, toe clip, and injection of india ink into the footpad on all animals for a 3-digit identification number	Same as 16-d studies	Same as 16-d studies
Feed	Purina Lab Chow® (Ralston Purina, St. Louis, MO); available ad libitum	Same as 16-d studies	NIH 07 pellets (Ziegler Bros, Inc. Gardners, PA); available ad libitum
Bedding	Semi-chip hardwood (Pinewood Products Co.,Miami, FL)	Same as 16-d studies	Beta Chip hardwood (Northeastern Products Corp., Warrensburg, NY)
Water	Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 16-d studies	Same as 16-d studies
Cages	Polycarbonate Lab Products (Rochelle Park, NJ)	Same as 16-d studies	Polycarbonate (Lab Products Garfield, NJ, or Hanford Metal Products, Aberdeen, MD)
Animal Room Environment	Temp--23°- 24° C (excursions in temp not reported); humidity--not monitored; fluorescent light 12 h/d; 18-20 room air changes/h	Temp--23° - 24° C (excursions in temp not reported); humidity--not monitored; fluorescent light 12 h/d; 18-20 room air changes/h	Temp--21° - 27° C (1 morning, temp was 32° C, but it was 26° C by noon); average 23° C; humidity--29% - 74%; average 56%; fluorescent light 12 h/d; 10-15 room air changes/h
Cage Filters	Cerex spun nylon (Monsanto, St. Louis, MO)	Same as 16-d studies	Same as 16-d studies
Animals per Cage	5	Rats--5; mice--10	5

nonuniformity in the hybrid mice on these results is not known, but the results of the studies are not affected because concurrent controls were included in the study.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 5.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the study. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 5.

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. Individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues (male rats--kidney, adrenal glands, pancreas, thyroid gland; female rats--kidney, adrenal glands, pancreas; male mice--liver; female mice--none), and all tissues from a randomly selected 10% of the animals were evaluated by a quality assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent evaluations, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1985).

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

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

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic

examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: Three statistical methods are used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. All reported P values for tumor analyses are one-sided.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the study were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of four time intervals: weeks 0-52, weeks 53-85, week 86 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals on which a necropsy was actually performed during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendix containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for decision-making, there are certain instances in which historical control data can be helpful in the overall evaluation of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984) are included for those tumors in these studies appearing to show compound-related effects.

III. RESULTS

RATS

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SIXTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SIXTEEN-DAY STUDIES

Four of five females and one of five males that received 2,000 mg/kg died before the end of the studies (Table 6). Final mean body weights relative to those of the vehicle controls were 13.9% and 6.7% lower for male and female rats that received 1,000 mg/kg and 25.2% and 11.4% lower for surviving male and female rats that received 2,000 mg/kg. All dosed rats were lethargic after dosing. No compound-related effects were observed at gross necropsy. No lesions were noted upon microscopic examination of the tissues from six selected rats from the two highest dose groups. Because deaths were observed in the 2,000 mg/kg groups, the high dose selected for the 13-week studies was 1,000 mg/kg.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF ISOPHORONE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	148	230	+82	--
125	5/5	142	224	+82	97.4
250	5/5	138	220	+82	95.7
500	5/5	148	219	+71	95.2
1,000	5/5	139	198	+59	86.1
2,000	(c) 4/5	136	172	+36	74.8
FEMALE					
0	5/5	111	149	+38	--
125	5/5	98	154	+56	103.4
250	5/5	112	153	+41	102.7
500	5/5	110	152	+42	102.0
1,000	5/5	110	139	+29	93.3
2,000	(d) 1/5	111	132	+21	88.6

(a) Number surviving/number initially in the group
(b) Mean body weight change of the survivors
(c) Day of death: 2
(d) Day of death: 2,2,3,3

THIRTEEN-WEEK STUDIES

One female rat that received 1,000 mg/kg died (Table 7). Final mean body weights for rats were not clearly related to dose. Rats that received 1,000 mg/kg were sluggish and lethargic after dosing. No compound-related gross or microscopic pathologic effects were observed. The kidneys of the high dose and vehicle control male and female rats were reviewed because of the reported nephrotoxicity of this compound; toxic changes were not found in the present studies.

Recuts and special stains on the kidneys of the high dose and vehicle control male rats were done to verify that subtle changes had not been missed in the original evaluation.

Dose Selection Rationale: Doses selected for rats for the 2-year studies were 250 and 500 mg/kg isophorone, to be administered in corn oil by gavage, 5 days per week for 103 weeks. The high dose of 500 mg/kg was based on the perceived potential of isophorone to produce cumulative toxicity during the 2-year studies. (Deaths were observed in the 2,000 mg/kg dose groups in the 16-day studies.)

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF ISOPHORONE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	107 ± 3	274 ± 4	+167 ± 6	--
62.5	10/10	103 ± 3	263 ± 9	+160 ± 8	96.0
125	10/10	105 ± 3	290 ± 9	+185 ± 9	105.8
250	10/10	110 ± 3	288 ± 9	+178 ± 6	105.1
500	10/10	101 ± 2	274 ± 11	+173 ± 10	100.0
1,000	10/10	108 ± 3	260 ± 7	+152 ± 7	94.9
FEMALE					
0	10/10	93 ± 2	174 ± 5	+81 ± 5	--
62.5	10/10	90 ± 2	174 ± 6	+84 ± 5	100.0
125	10/10	87 ± 2	174 ± 6	+87 ± 5	100.0
250	10/10	86 ± 2	168 ± 5	+82 ± 4	96.6
500	10/10	85 ± 2	160 ± 5	+75 ± 5	92.0
1,000	(d) 9/10	92 ± 3	172 ± 4	+82 ± 4	98.9

(a) Number surviving/number initially in the group
(b) Initial group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 5

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were approximately 5% lower than those of the vehicle controls after week 1 (Table 8 and Figure 1). Mean body weights of high dose female rats averaged about 8% lower than those of the vehicle controls after week 43. Deprivation of food or water and scale malfunction were discounted as causes for the markedly lower weights of high dose males at week 51 and the high dose females at weeks 47 and 51. No compound-related clinical signs were observed.

TABLE 8. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

Weeks on Study	Vehicle Control		250 mg/kg			500 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh controls)	No. of Survivors
MALE								
0	119	50	113	95	50	121	102	50
1	161	50	140	87	50	145	90	50
2	182	50	174	96	50	172	95	50
3	205	50	200	98	50	186	91	50
4	238	50	232	97	50	223	94	49
5	249	50	243	98	50	234	94	49
6	246	50	246	100	49	234	95	49
7	267	50	260	97	49	252	94	49
8	279	50	276	99	49	268	96	48
9	295	50	288	98	49	280	95	48
10	302	50	293	97	48	286	95	47
11	307	50	308	100	48	296	96	46
12	316	50	315	100	48	303	96	46
13	332	50	328	99	48	319	96	46
17	334	50	352	105	48	330	99	46
22	363	50	342	94	48	340	94	44
26	383	50	378	99	48	367	96	44
30	380	49	390	103	47	378	99	44
34	401	49	411	102	47	385	96	44
38	417	49	409	98	46	399	96	44
43	434	49	439	101	46	411	95	44
47	432	49	441	102	46	414	96	44
51	434	49	444	102	46	396	91	44
55	452	49	459	102	46	425	94	44
60	454	49	455	100	46	434	96	42
64	447	49	456	102	46	431	96	41
68	453	49	452	100	46	437	96	38
72	458	47	460	100	44	435	95	38
76	465	47	462	99	43	439	94	37
81	468	46	462	99	41	450	96	34
85	463	45	452	98	41	444	96	34
89	460	41	464	101	40	442	96	33
93	441	36	458	104	38	416	94	27
98	435	36	452	104	34	414	95	21
101	430	34	443	103	33	400	93	16
105	424	33	426	100	33	394	93	13
FEMALE								
0	101	50	100	99	50	100	99	50
1	126	50	119	94	50	118	94	50
2	136	50	134	99	50	133	98	50
3	144	50	142	99	50	140	97	50
4	155	50	156	101	50	156	101	49
5	163	50	164	101	49	161	99	49
6	166	50	167	101	49	164	99	48
7	173	50	172	99	48	172	99	48
8	178	50	178	100	48	177	99	47
9	181	50	180	99	47	178	98	47
10	186	50	183	98	47	183	98	46
11	189	50	189	100	47	186	98	46
12	193	50	191	99	47	189	98	46
13	198	50	196	99	47	193	97	46
17	205	49	206	100	47	198	97	45
22	213	49	208	98	47	208	98	39
26	221	49	221	100	46	214	97	36
30	224	49	223	100	46	218	97	36
34	232	49	230	99	46	223	96	36
38	234	48	228	97	46	225	96	36
43	246	48	240	98	46	232	94	36
47	247	47	238	96	46	223	90	36
51	250	47	245	98	46	220	88	35
55	259	47	252	97	46	241	93	35
60	263	46	251	95	45	244	93	35
64	263	46	263	100	42	247	94	34
68	271	46	267	99	42	246	91	34
72	280	46	277	99	41	252	90	34
76	291	46	282	97	40	263	90	34
81	291	42	285	98	38	259	89	34
85	293	41	290	99	38	264	90	33
89	297	39	298	100	38	274	92	32
93	284	39	297	105	37	273	96	29
98	279	34	292	105	27	266	95	25
101	278	32	295	106	24	267	96	23
105	282	30	300	106	22	263	93	20

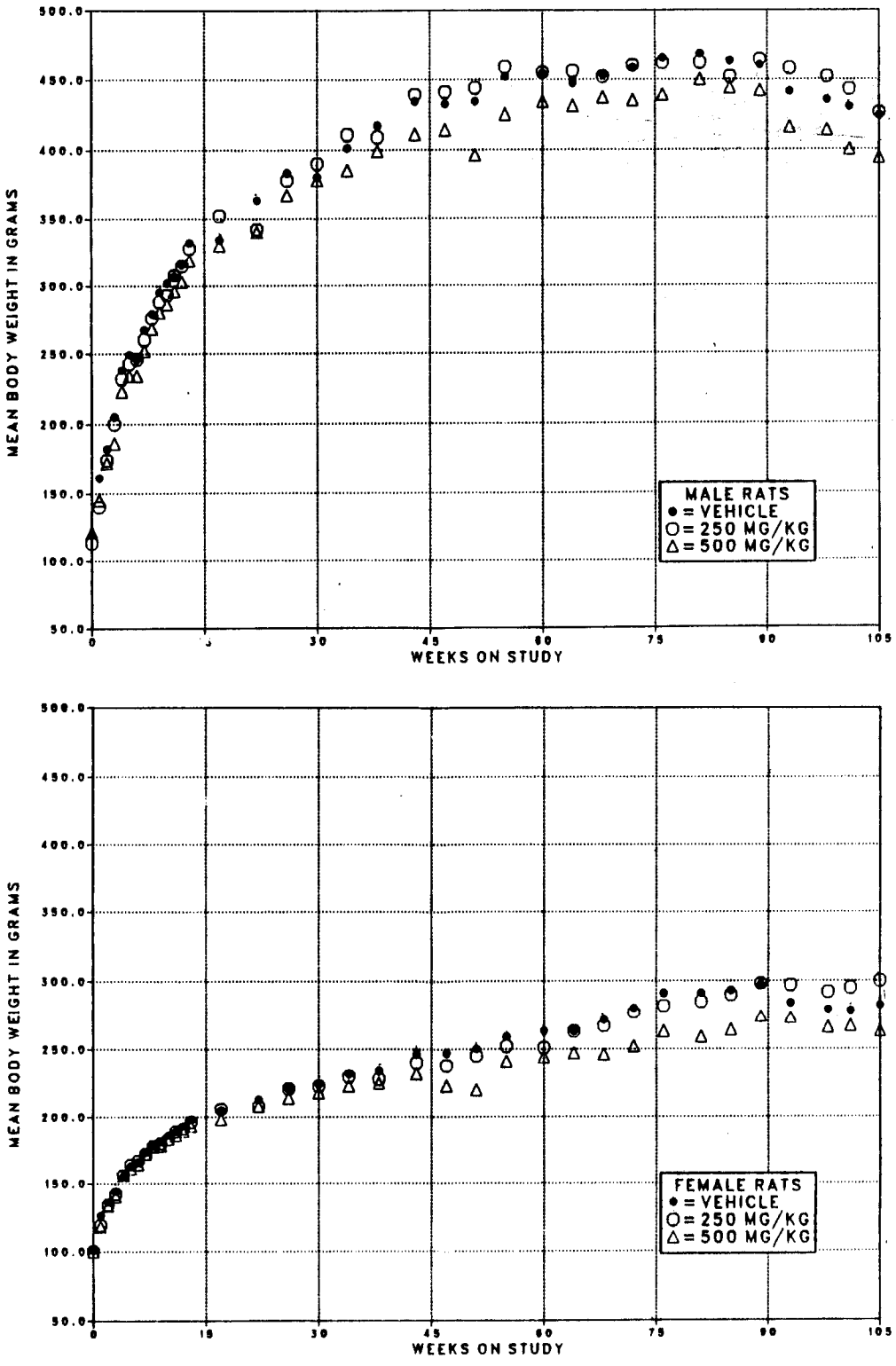

FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED ISOPHORONE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of the survival of male and female rats administered isophorone at the doses used in these studies and those of the vehicle controls are shown in the Kaplan and Meier curves in Figure 2. The survival of the high dose group of male rats was significantly lower than that of the vehicle control group after week 96 (Table 9). Gavage errors accounted for all of the 36 accidental deaths of male and female rats. Deaths related to gavage error increased with dose in females.

Pathology and Statistical Analyses of Results

This section describes significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the kidney, preputial gland, lung, adrenal gland, pancreas, and pituitary gland. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1 and E2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 9. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	13	12	30
Accidentally killed	4	5	6
Killed at termination	33	33	14
Survival P values (c)	<0.001	0.917	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	19	21	16
Accidentally killed	1	6	14
Killed at termination	30	23	20
Survival P values (c)	0.748	0.537	0.886

(a) Terminal kill period: week 105
(b) Includes moribund animals that were killed
(c) The vehicle control column contains results of the life table trend test; the columns for dosed groups contain the life table pairwise comparisons with the vehicle controls.

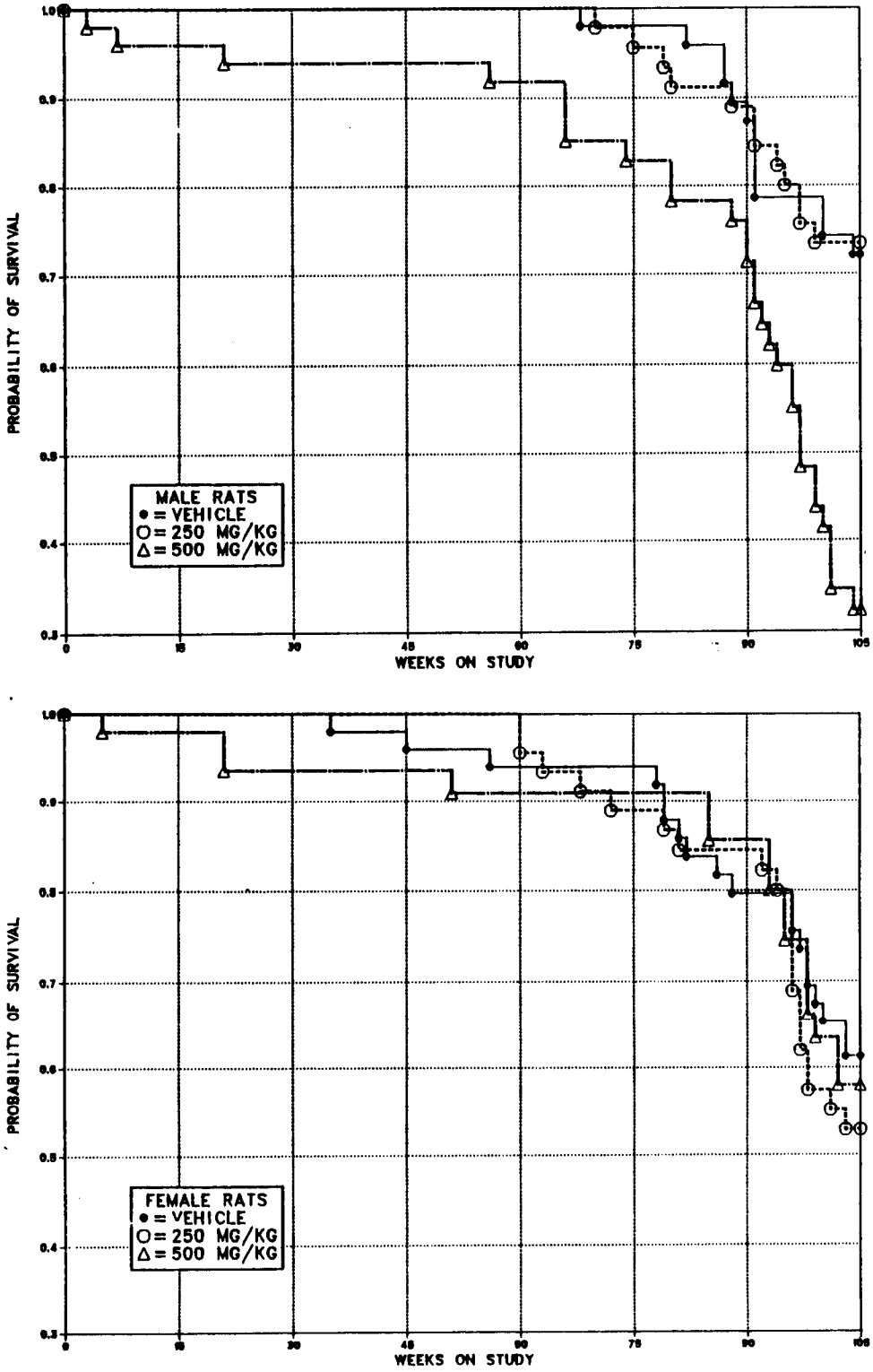

FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED ISOPHORONE IN CORN OIL BY GAVAGE FOR TWO YEARS

Kidney: Tubular cell hyperplasia was noted in one low dose and four high dose male rats (Table 10). Tubular cell lesions were termed hyperplastic when they were confined to one tubule but showed dilation and proliferation of the epithelial cell layer. The cells varied in size and showed nuclear pleomorphism. If more than one adjacent tubule was involved, the lesion was termed an adenoma. These lesions were generally well demarcated from the surrounding parenchyma, and tubular formation was still distinct. A lesion was termed an adenocarcinoma if evidence of infiltrative growth, cellular and nuclear pleomorphism, and indistinct tubular formation was present. Tubular cell adenomas and adenocarcinomas were observed in dosed male rats, and incidences were significantly increased from that in the vehicle controls (Appendix E, Table E1). No kidney tumors were observed in female rats.

Tubular cell mineralization was increased in dosed male rats but not in dosed female rats. This lesion was characterized by basophilic aggregates of mineral most often found in the medullary collecting ducts and occurred coincidentally with lesions of chronic nephropathy. The incidence of nephropathy was moderately increased in dosed female rats, and although the incidence of nephropathy was similar in dosed and vehicle control male rats, the severity was greater in low dose males. Hyperplasia of the renal pelvis was observed in five low dose and five high dose male rats but in no vehicle controls. Renal calculi were not observed in any group of male rats.

TABLE 10. NUMBER OF RATS WITH RENAL LESIONS IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
MALE			
Number of rats examined	50	50	50
Tubular cell hyperplasia	0	1	4
Tubular cell adenoma	0	0	2
Tubular cell adenocarcinoma	0	3	1
Tubular cell adenoma or adenocarcinoma (combined) (a)			
Overall rates	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted rates	0.0%	9.1%	12.0%
Terminal rates	0/33 (0%)	3/33 (9%)	1/14 (7%)
Life table tests	P=0.014	P=0.120	P=0.025
Incidental tumor tests	P=0.034	P=0.120	P=0.073
Epithelial hyperplasia of the renal pelvis	0	5	5
Tubule mineralization	1	31	20
Nephropathy	49	47	46
FEMALE			
Number of rats examined	50	50	50
Tubular cell hyperplasia	0	0	1
Epithelial hyperplasia of the renal pelvis	0	0	1
Tubule mineralization	10	4	2
Nephropathy	21	39	32

(a) Historical incidence in NTP studies of tubular cell adenoma or adenocarcinoma (combined): 4/1,091, 0.4%

Preputial Gland: The incidence of carcinomas in male rats occurred with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 11). These lesions were noted on gross necropsy and generally were greater than 1 cm in diameter. Microscopically, the cells had abundant eosinophilic cytoplasm with large anaplastic nuclei, grew in solid sheets or formed acini, and invaded adjacent adipose tissue.

Lung: Chronic interstitial pneumonia or chronic bronchopneumonia was observed in all groups of rats (male: 10/50, 20%; 8/50, 16%; 10/50, 20%; female: 12/50, 24%; 8/50, 16%; 8/50, 16%).

Adrenal Cortex: Fatty metamorphosis was observed at an increased incidence in dosed male rats but not in dosed female rats (male: 7/50, 14%; 21/50, 42%; 26/50, 52%; female: 13/50, 26%; 8/50, 16%; 5/50, 10%). The term "fatty metamorphosis" was used to indicate lesions in which adrenal cortical cells contained cytoplasmic vacuoles. Small vacuoles often contained eosinophilic fibrillar material. This lesion was most frequently seen in the zona fasciculata.

TABLE 11. ANALYSIS OF PREPUTIAL GLAND TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (a)

	Vehicle Control	250 mg/kg	500 mg/kg
Carcinoma (b)			
Overall Rates	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates	0.0%	0.0%	17.9%
Terminal Rates	0/33 (0%)	0/33 (0%)	1/14 (7%)
Life Table Tests	P=0.002	(c)	P=0.012
Incidental Tumor Tests	P=0.019	(c)	P=0.068

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence of adenomas or carcinomas (combined) in NTP studies: 38/1,094, 3%.
(c) No P value is reported because no tumors were observed in the 250 mg/kg and vehicle control groups.

Pancreas: The incidences of hyperplasia were similar in dosed and vehicle control groups. Results of statistical analysis of the incidence of male rats with hyperplasia or adenomas (combined) were similar to those of male rats with adenomas. Acinar cell adenomas occurred in male rats with a significant positive trend by the life table test. The incidence in the high dose group was significantly greater than that in the vehicle controls only by the life table test (Table 12).

Anterior Pituitary: Focal hyperplasia was observed at increased incidences in dosed female rats but not in dosed male rats (male: 8/48, 17%; 11/49, 22%; 8/47, 17%; female: 3/49, 6%; 6/48, 13%; 13/47, 28%). However, the incidence of adenomas occurred with a negative trend in female rats; the incidences were similar in dosed and vehicle control males (male: 10/48, 21%; 12/49, 41%; 8/47, 17%; female: 21/49, 43%; 17/48, 35%; 12/47, 25%).

TABLE 12. ANALYSIS OF PANCREATIC ACINAR CELL LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
MALE			
Hyperplasia			
Overall Rates	15/50 (30%)	17/50 (34%)	12/50 (24%)
Adenoma (a)			
Overall Rates	4/50 (8%)	9/50 (18%)	6/50 (12%)
Adjusted Rates	12.1%	26.3%	34.6%
Terminal Rates	4/33 (12%)	8/33 (24%)	4/14 (29%)
Life Table Tests	P=0.027	P=0.114	P=0.045
Incidental Tumor Tests	P=0.059	P=0.102	P=0.086
Adenoma or Hyperplasia			
Overall Rates	15/50 (30%)	20/50 (18%)	13/50 (24%)
Adjusted Rates	43.9%	57.1%	61.7%
Terminal Rates	14/33 (42%)	18/33 (55%)	7/14 (50%)
Life Table Tests	P=0.026	P=0.184	P=0.046
Incidental Tumor Tests	P=0.109	P=0.148	P=0.169
FEMALE			
Hyperplasia			
Overall Rates	4/50 (8%)	4/50 (8%)	3/50 (6%)
Adenoma			
Overall Rates	1/50 (2%)	0/50 (0%)	1/50 (2%)
Adenoma or Hyperplasia			
Overall Rates	5/50 (10%)	4/50 (8%)	4/50 (8%)

(a) Historical incidence in NTP studies (mean ± SD): 35/1,076, 3.3% ± 7.2%

SIXTEEN-DAY STUDIES

All mice administered 2,000 mg/kg isophorone died before the end of the studies (Table 13). Final mean body weights relative to those of the controls were 7.8% lower for males that received 1,000 mg/kg and 7.3%-9.3% lower for females that received 250, 500, or 1,000 mg/kg. Male mice lost weight during week 1, probably as a consequence of fighting. Male and female mice that received 1,000 mg/kg staggered after dosing. No compound-related effects were observed at gross necropsy, nor were lesions noted in tissues examined microscopically from two male and two female mice from the 1,000 mg/kg dose group.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF ISOPHORONE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	25.3	30.6	+5.3	--
125	5/5	25.8	33.3	+7.5	108.8
250	5/5	23.3	30.7	+7.4	100.3
500	5/5	24.1	30.0	+5.9	98.0
1,000	5/5	22.9	28.2	+5.3	92.2
2,000	0/5	19.0	(c)	(c)	(c)
FEMALE					
0	5/5	17.4	24.7	+7.3	--
125	5/5	18.9	24.4	+5.5	98.8
250	5/5	19.3	22.7	+3.4	91.9
500	5/5	18.7	22.9	+4.2	92.7
1,000	5/5	18.0	22.4	+4.4	90.7
2,000	0/5	18.7	(c)	(c)	(c)

(a) Number surviving/number initially in the group
(b) Mean body weight change of the survivors
(c) No data are reported due to the 100% mortality in this group.

THIRTEEN-WEEK STUDIES

Three of 10 females that received 1,000 mg/kg died before the end of the studies (Table 14). Final mean body weights for mice of each sex were not dose related. No compound-related gross or microscopic pathologic effects were observed. The kidneys of high dose and vehicle control male and female mice were reviewed on two separate occasions to confirm a lack of evidence of nephrotoxicity.

Dose Selection Rationale: Doses selected for mice for the 2-year studies were 250 and 500 mg/kg isophorone, to be administered in corn oil by gavage, 5 days per week for 103 weeks. The high dose of 500 mg/kg was chosen for female mice because deaths were observed in females given 1,000 mg/kg in the 13-week studies. The high dose of 500 mg/kg was also chosen for male mice based on a perceived potential for cumulative toxicity during the 2-year study. (Deaths were observed in the 2,000 mg/kg dose group in the 16-day study.)

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF IOSPHORONE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	25.1 ± 0.2	35.4 ± 0.7	+10.3 ± 0.8	--
62	(d) 9/10	25.5 ± 0.6	34.3 ± 0.8	+ 8.6 ± 0.8	96.9
125	9/10	24.7 ± 0.7	31.4 ± 1.0	+ 6.2 ± 0.9	88.7
250	10/10	25.1 ± 0.7	32.3 ± 1.1	+ 7.2 ± 1.6	91.2
500	10/10	26.6 ± 0.4	31.3 ± 0.5	+ 4.7 ± 0.5	88.4
1,000	(e) 9/10	27.1 ± 0.4	32.1 ± 1.0	+ 5.0 ± 1.0	90.7
FEMALE					
0	9/10	19.3 ± 0.3	24.4 ± 0.3	+ 5.1 ± 0.4	--
62	10/10	19.5 ± 0.2	24.3 ± 0.4	+ 4.8 ± 0.4	99.6
125	10/10	19.5 ± 0.3	24.7 ± 0.7	+ 5.2 ± 0.5	101.2
250	10/10	19.5 ± 0.3	23.9 ± 0.6	+ 4.4 ± 0.5	98.0
500	10/10	19.5 ± 0.2	24.4 ± 0.6	+ 4.9 ± 0.5	100.0
1,000	(f) 7/10	18.9 ± 0.4	24.0 ± 0.3	+ 5.5 ± 0.4	98.4

(a) Number surviving/number initially in the group
(b) Initial group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) One animal was found to be missing during week 6.
(e) Week of death: 1 (gavage accident)
(f) Week of death: 8,11,13 (deaths considered compound related)

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and vehicle control male mice were comparable throughout most of the study (Table 15 and Figure 3). The mean body weights of high dose and vehicle control female mice were comparable for the 1st year of the study. During the 2nd year of the study, mean body weights of high dose female mice averaged about 5% lower than those of the vehicle controls. No compound-related clinical signs were observed.

TABLE 15. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

Weeks on Study	Vehicle Control		250 mg/kg			500 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh controls)	No. of Survivors
MALE								
0	26.6	50	26.5	100	50	26.8	101	50
1	28.0	50	27.6	99	50	27.2	97	50
2	28.9	50	29.2	101	50	28.4	98	50
3	28.6	47	28.1	98	50	29.9	105	50
4	30.5	45	30.5	100	50	30.4	100	50
5	31.4	44	31.2	99	50	31.3	100	48
6	32.8	44	32.4	99	50	32.1	98	48
7	33.3	44	32.0	96	50	33.0	99	48
8	33.4	44	32.5	97	50	33.3	100	48
9	34.4	44	33.4	97	50	33.8	98	48
10	35.8	44	34.1	95	50	34.8	97	48
11	36.1	44	34.3	95	50	34.8	96	47
12	36.6	44	35.5	97	50	35.0	96	47
13	37.3	44	36.3	97	50	35.4	95	47
17	40.3	44	39.9	99	50	38.7	96	46
22	38.6	44	39.9	103	50	39.7	103	44
26	38.5	44	39.6	103	50	39.2	102	44
30	42.9	43	42.0	98	49	41.9	98	43
34	42.6	41	41.4	97	49	42.2	99	42
38	44.3	40	42.2	95	49	43.9	99	42
43	45.2	39	45.1	100	47	44.7	99	42
47	46.5	39	44.7	96	46	45.6	98	42
51	45.5	39	44.5	98	45	46.2	102	42
55	45.9	38	47.3	103	45	46.8	102	42
60	45.9	37	44.5	97	43	46.0	100	42
64	45.9	37	45.3	99	43	46.3	101	42
68	46.0	37	45.6	99	43	46.2	100	42
72	44.4	34	45.2	102	43	46.2	104	38
76	45.5	32	45.1	99	42	45.2	99	36
81	45.1	29	45.0	100	38	44.7	99	34
85	44.4	27	43.5	98	38	44.1	99	31
89	42.7	24	42.2	99	37	43.4	102	27
93	43.3	21	40.4	93	33	41.0	95	26
98	41.7	19	39.2	94	24	39.3	94	23
101	41.0	17	38.4	94	20	37.6	92	23
104	39.7	15	38.0	96	16	38.8	98	19
FEMALE								
0	20.3	50	24.3	120	50	20.4	100	50
1	19.9	50	22.8	115	50	23.3	117	50
2	20.5	50	21.3	104	50	21.3	104	50
3	22.5	50	22.2	99	50	21.7	96	49
4	23.3	50	22.9	98	48	22.4	96	46
5	23.8	50	23.3	98	48	23.0	97	46
6	24.1	50	23.7	98	48	22.6	94	45
7	23.7	50	23.8	100	48	23.6	100	45
8	24.1	50	24.3	101	48	23.8	99	45
9	24.6	50	24.6	100	48	24.0	98	45
10	25.5	50	24.9	98	47	25.1	98	45
11	25.6	50	24.9	97	47	24.6	96	45
12	25.7	50	25.6	100	47	24.8	96	45
13	26.3	50	25.4	97	47	25.2	96	39
17	29.3	50	28.4	97	47	28.0	96	39
22	29.4	50	30.1	102	47	29.2	99	39
26	27.0	50	29.7	110	47	28.4	105	39
30	31.8	50	33.5	105	47	30.9	97	39
34	32.2	50	32.4	101	47	31.4	98	39
38	34.6	50	34.3	99	47	33.7	97	39
43	36.1	50	37.6	104	47	35.7	99	39
47	37.6	50	39.1	104	47	37.8	101	39
51	36.5	50	38.1	104	46	36.1	99	39
55	38.9	50	38.2	98	46	37.6	97	39
60	38.9	50	38.9	100	46	37.0	95	39
64	40.0	50	39.7	99	46	37.9	95	37
68	41.3	50	41.1	100	46	40.0	97	37
72	41.3	50	41.7	101	45	40.2	97	37
76	43.2	50	42.8	99	45	41.8	97	37
81	44.5	48	43.5	98	45	42.1	95	37
85	42.8	45	43.7	102	44	40.4	94	37
89	43.4	40	43.4	100	44	41.7	96	37
93	41.9	34	42.6	102	42	40.4	96	37
98	40.5	29	41.5	102	39	38.4	95	35
101	41.0	28	40.2	98	37	38.7	94	34
104	40.2	26	40.2	100	33	37.2	93	34

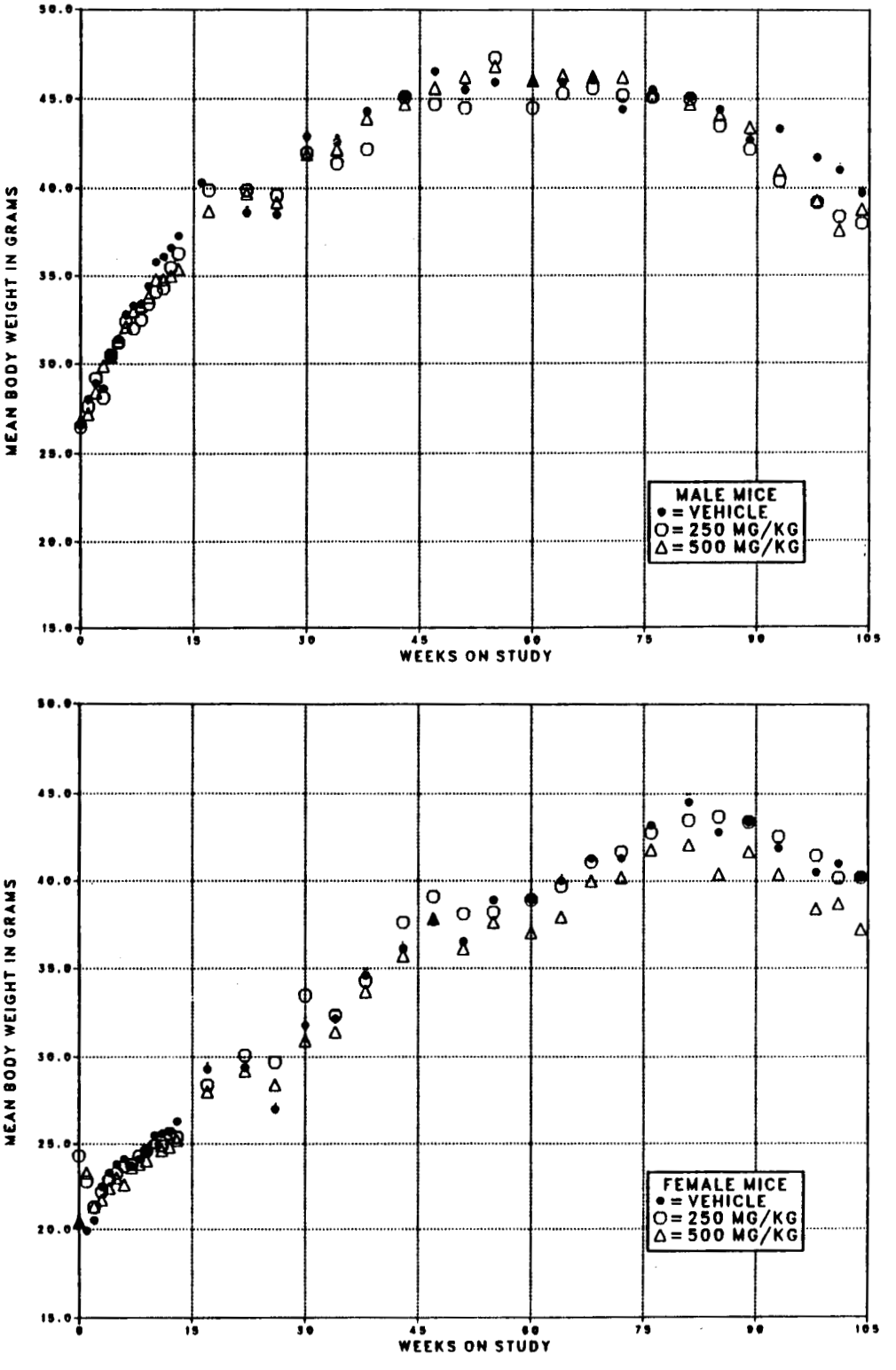

FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED ISOPHORONE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival of male and female mice administered isophorone at the doses used in these studies and those of the vehicle controls are shown in the Kaplan and Meier curves in Figure 4. There was a significant ($P<0.05$) trend toward improved survival in dosed female mice relative to that of vehicle controls (Table 16). No other significant differences in survival were observed between any groups of either sex.

The survival of male mice was adversely affected by fighting, which was considered a contributory cause of most natural deaths of dosed and vehicle control male mice during the study. Of the 14 deaths listed as accidental, 9 were due to gavage error and 1 animal drowned during a water nozzle failure. No cause was reported for the other four accidental deaths; these and some of the deaths in high dose female mice before week 15, recorded as "natural," may also have resulted from gavage accidents. However, no definite evidence, such as a record of oil in the lungs or a tear in the esophagus, exists to document this classification.

Pathology and Statistical Analyses of Results

This section describes significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the liver, integumentary system, hematopoietic system, forestomach, kidney, lung, reproductive system, and pituitary gland. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 16. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	28	34	29
Accidentally killed	5	0	2
Animals missing	1	0	0
Killed at termination	13	13	18
Died during termination period	3	3	1
Survival P values (c)	0.699	0.844	0.780
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	23	14	11
Accidentally killed	1	1	5
Killed at termination	24	33	34
Died during termination period	2	2	0
Survival P values (c)	0.045	0.086	0.077

(a) Terminal kill period: weeks 104-105
(b) Includes moribund animals that were killed
(c) The vehicle control column contains results of the life table trend test; the columns for dosed groups contain the life table pairwise comparisons with the vehicle controls.

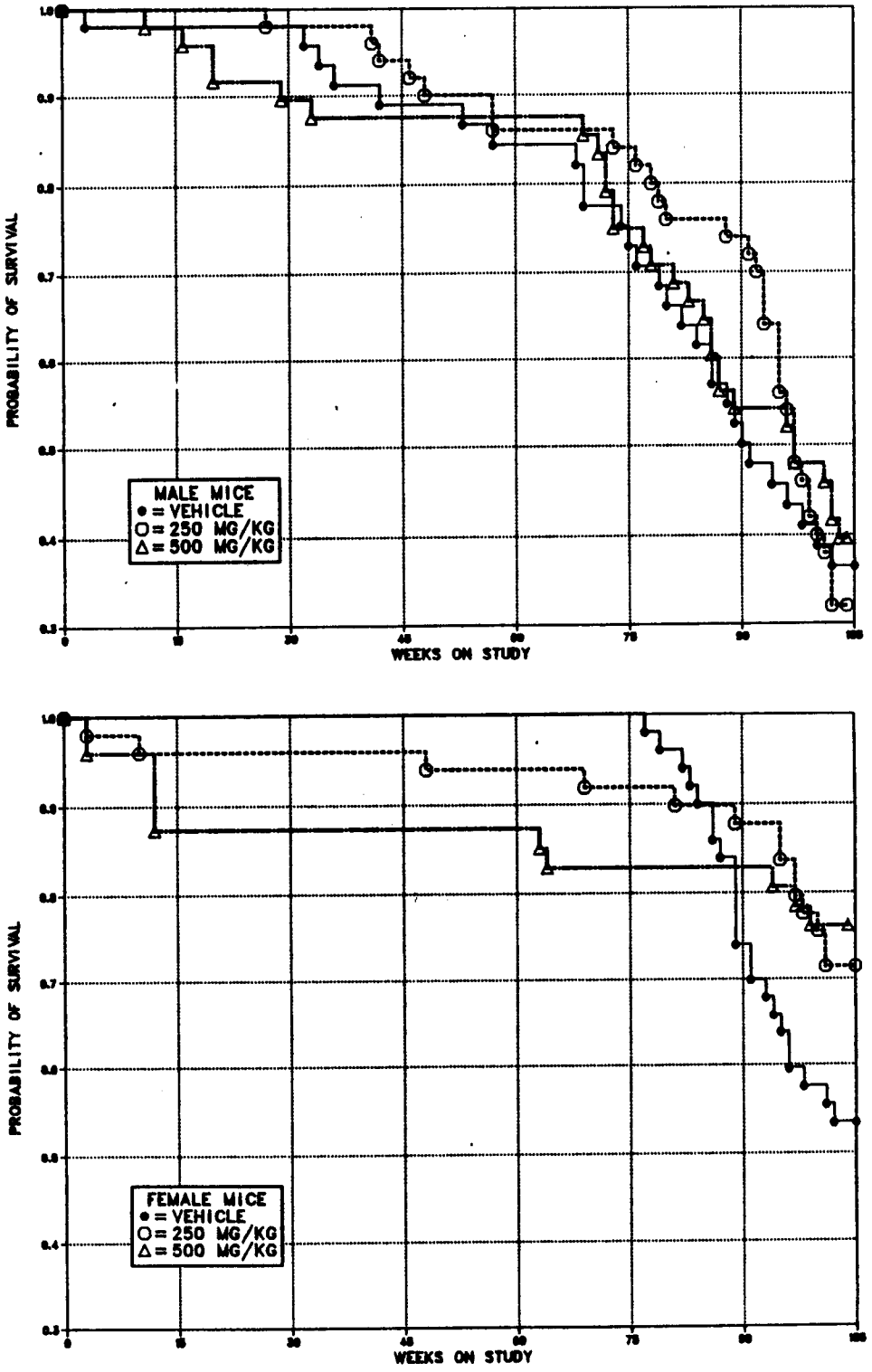

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED ISOPHORONE IN CORN OIL BY GAVAGE FOR TWO YEARS

Liver: Coagulative necrosis and hepatocytomegaly were observed at increased incidences in dosed male mice but at decreased incidences in dosed female mice (coagulative necrosis--male: 3/48, 6%; 10/50, 20%; 11/50, 22%; female: 6/50, 12%; 3/50, 6%; 2/50, 4%; hepatocytomegaly--male: 23/48, 48%; 39/50, 78%; 37/50, 74%; female: 32/50, 64%; 21/50, 42%; 9/50, 18%). The incidence of hepatocellular adenomas or carcinomas (combined) in male mice occurred with a significant positive trend by the incidental tumor test, and the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 17). The incidences of hepatocellular adenomas or hepatocellular carcinomas (combined) in dosed female mice were not significantly different from that in the vehicle controls (4/50, 8%; 6/50, 12%; 8/50, 16%).

Microscopically, hepatocellular adenomas appeared as sharply demarcated, expanding masses of hyperchromatic cells arranged in cords and sheets. Hepatocellular carcinomas had more anaplastic hepatocytes forming irregular cords or trabeculae.

TABLE 17. ANALYSIS OF LIVER TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (a)

	Vehicle Control	250 mg/kg	500 mg/kg
Hepatocellular Adenoma (b)			
Overall Rates	6/48 (13%)	7/50 (14%)	13/50 (26%)
Adjusted Rates	28.5%	43.7%	52.5%
Terminal Rates	3/16 (19%)	7/16 (44%)	8/19 (42%)
Life Table Tests	P=0.085	P=0.541	P=0.138
Incidental Tumor Tests	P=0.063	P=0.551	P=0.098
Hepatocellular Carcinoma (c)			
Overall Rates	14/48 (29%)	13/50 (26%)	22/50 (44%)
Adjusted Rates	45.1%	52.0%	71.9%
Terminal Rates	2/16 (13%)	6/16 (38%)	11/19 (58%)
Life Table Tests	P=0.177	P=0.290N	P=0.237
Incidental Tumor Tests	P=0.073	P=0.354N	P=0.094
Hepatocellular Adenoma or Carcinoma (d)			
Overall Rates	18/48 (38%)	18/50 (36%)	29/50 (58%)
Adjusted Rates	58.5%	76.0%	90.3%
Terminal Rates	5/16 (31%)	11/16 (69%)	16/19 (84%)
Life Table Tests	P=0.100	P=0.358N	P=0.150
Incidental Tumor Tests	P=0.027	P=0.420N	P=0.036

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence in NTP studies (mean ± SD): 132/1,034, 12.8% ± 6.5%
(c) Historical incidence in NTP studies (mean ± SD): 218/1,034, 21.1% ± 7.6%
(d) Historical incidence in NTP studies (mean ± SD): 335/1,034, 32.4% ± 9.4%

Integumentary System: The incidences of mice with fibromas, sarcomas, fibrosarcomas, or neurofibrosarcomas (combined) were observed with a significant positive trend; the incidence in the high dose male group was significantly greater than that in the vehicle controls (Table 18). A sarcoma was observed in one low dose female mouse, and a fibrosarcoma was observed in one high dose female mouse.

Hematopoietic System: The incidence of lymphomas or lymphomas or leukemia (combined) in low dose male mice was significantly greater than the incidence of lymphomas or lymphomas or leukemia (combined) in the vehicle controls by the Fisher exact test; the incidence of lymphomas in high dose male mice was similar to that in the vehicle controls (Table 19). The incidence of lymphomas or leukemia (combined) in dosed female mice was not significantly different from that in the vehicle controls.

TABLE 18. ANALYSIS OF INTEGUMENTARY SYSTEM TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma (a)			
Overall Rates	6/48 (13%)	8/50 (14%)	14/50 (28%)
Adjusted Rates	24.6%	31.3%	45.2%
Terminal Rates	2/16 (13%)	3/16 (19%)	5/19 (26%)
Life Table Tests	P=0.073	P=0.548	P=0.108
Incidental Tumor Tests	P=0.034	P=0.452	P=0.050

(a) Historical incidence in NTP studies (mean ± SD): 70/1,040, 7% ± 7%

TABLE 19. ANALYSIS OF HEMATOPOIETIC SYSTEM TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
Lymphoma, All Malignant (a)			
Overall Rates	7/48 (15%)	18/50 (36%)	5/50 (10%)
Adjusted Rates	35.4%	62.5%	18.2%
Terminal Rates	4/16 (25%)	7/16 (44%)	2/19 (11%)
Life Table Tests	P=0.206N	P=0.046	P=0.272N
Incidental Tumor Tests	P=0.253N	P=0.067	P=0.320N
Lymphoma or Leukemia			
Overall Rates	8/48 (17%)	18/50 (36%)	5/50 (10%)
Adjusted Rates	37.8%	62.5%	18.2%
Terminal Rates	4/16 (25%)	7/16 (44%)	2/19 (11%)
Life Table Tests	P=0.146N	P=0.081	P=0.187N
Incidental Tumor Tests	P=0.176N	P=0.124	P=0.223N

(a) Historical incidence in NTP studies (mean ± SD): 126/1,040, 12% ± 5%

Forestomach: Hyperkeratosis was observed at increased incidences in dosed male and high dose female mice (male: 0/47; 5/49, 10%; 4/49, 8%; female: 1/50, 2%; 0/50; 5/49, 10%).

Kidney: Chronic focal inflammation was observed at increased incidences in dosed male mice (male: 7/48, 15%; 18/50, 36%; 21/50, 42%; female: 17/50, 34%; 11/50, 22%; 16/50, 32%). The incidences of nephropathy in dosed mice of each sex were lower than those in the vehicle controls (male: 16/48, 33%; 15/50, 30%; 9/50, 18%; female: 13/50, 26%; 8/50, 16%; 2/50, 4%).

Lung: Alveolar/bronchiolar adenomas in male mice occurred with a significant negative trend (Table 20). The incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in low dose male mice was significantly lower than that in the vehicle controls.

TABLE 20. ANALYSIS OF LUNG LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
Alveolar Epithelium Hyperplasia			
Overall Rates	0/47 (0%)	1/50 (2%)	1/50 (2%)
Alveolar/Bronchiolar Adenoma (a)			
Overall Rates	6/47 (13%)	0/50 (0%)	0/50 (0%)
Adjusted Rates	25.7%	0.0%	0.0%
Terminal Rates	2/16 (13%)	0/16 (0%)	0/19 (0%)
Life Table Tests	P=0.001N	P=0.009N	P=0.011N
Incidental Tumor Tests	P=0.001N	P=0.007N	P=0.013N
Alveolar/Bronchiolar Carcinoma (b)			
Overall Rates	2/47 (4%)	1/50 (2%)	3/50 (6%)
Alveolar/Bronchiolar Adenoma or Carcinoma (c)			
Overall Rates	7/47 (15%)	1/50 (2%)	3/50 (6%)
Adjusted Rates	31.0%	2.6%	12.5%
Terminal Rates	3/16 (19%)	0/16 (0%)	1/19 (5%)
Life Table Tests	P=0.059N	P=0.018N	P=0.104N
Incidental Tumor Tests	P=0.074N	P=0.020N	P=0.126N

(a) Historical incidence in NTP studies (mean ± SD): 98/1,032, 9.5% ± 4.6%
(b) Historical incidence in NTP studies (mean ± SD): 58/1,032, 5.6% ± 4.1%
(c) Historical incidence in NTP studies (mean ± SD): 154/1,032, 14.9% ± 5.8%

Reproductive System: Acute inflammation or suppurative inflammation of the uterus or ovary or chronic ovarian abscess was observed in 14 vehicle control, 14 low dose, and 9 high dose female mice. These lesions were present in 7/15 vehicle control, 1/9 low dose, and 0/3 high dose female mice that died between week 89 and the terminal kill. No specific tests for Klebsiella were performed, although Klebsiella have been isolated from similar lesions in other NTP studies.

Pituitary Gland: Focal hyperplasia occurred at increased incidences in dosed female mice (Table 21). Adenomas and adenomas or adenocarcinomas (combined) in female mice occurred with a significant negative trend. The incidence of adenomas or adenocarcinomas in high dose female mice was significantly lower than that in the vehicle controls.

TABLE 21. ANALYSIS OF PITUITARY GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
Hyperplasia			
Overall Rates	5/47 (11%)	7/41 (17%)	13/44 (30%)
Adenoma (a)			
Overall Rates	11/47 (23%)	10/41 (24%)	4/44 (9%)
Adjusted Rates	42.1%	31.3%	12.1%
Terminal Rates	10/25 (40%)	10/32 (31%)	4/33 (12%)
Life Table Tests	P=0.006N	P=0.245N	P=0.009N
Incidental Tumor Tests	P=0.009N	P=0.299N	P=0.015N
Adenocarcinoma (b)			
Overall Rates	5/47 (11%)	3/41 (7%)	1/44 (2%)
Adenoma or Adenocarcinoma (c)			
Overall Rates	16/47 (34%)	13/41 (32%)	4/44 (9%)
Adjusted Rates	59.1%	40.6%	12.1%
Terminal Rates	14/25 (56%)	13/32 (41%)	4/33 (12%)
Life Table Tests	P<0.001N	P=0.083N	P<0.001N
Incidental Tumor Tests	P<0.001N	P=0.138N	P<0.001N

(a) Historical incidence of all types of pituitary gland adenoma in NTP studies (mean ± SD): 113/905, 12.5% ± 6.1%
(b) Historical incidence of all types of pituitary gland carcinoma in NTP studies (mean ± SD): 10/905, 1.1% ± 2.4%
(c) Historical incidence of all types of pituitary gland adenoma or carcinoma in NTP studies (mean ± SD): 123/905, 13.6% ± 6.9%

IV. DISCUSSION AND CONCLUSIONS

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Two-year toxicology and carcinogenesis studies of isophorone were conducted on groups of 50 F344/N rats and 50 B6C3F$_1$ mice of each sex. Doses of 0, 250, or 500 mg/kg body weight per day were administered by gavage in corn oil to males and females of both species. The doses were selected based on 16-day studies in which rats and mice of each sex received doses of 0-2,000 mg/kg per day and on 13-week studies in which doses of 0-1,000 mg/kg per day were administered.

Despite the overall low survival of dosed and vehicle control male mice and dosed female rats, the NTP considers the present 2-year studies an acceptable assessment of the chronic toxicity and carcinogenicity of isophorone. Fighting apparently contributed to the low survival of the group-housed male mice, and low survival reduces the power of the study to detect changes in the tumor incidences; however, since fighting occurred in all groups, nearly equal numbers of vehicle control and high dose male mice remained at risk for development of neoplastic and nonneoplastic lesions throughout the study. The lower survival of dosed female rats was due in part to a greater incidence of gavage accidents in the dosed animals. Although 14 gavage-related deaths occurred in the high dose female rats, survival remained above 50% through week 98. The survival of high dose male rats was lower than that of the vehicle control and low dose animals after week 96. The reduced survival is most likely a chemically related effect; however, it probably had a minimal impact even on the incidence of late-developing neoplasms because the steep decline in survival occurred late in the study. In contrast, the survival of dosed female mice was notably greater than that of the vehicle controls. Of the 25 vehicle control female mice that died of natural causes before or during the terminal kill, 15 had at least one type of neoplasm, but no one cause could be identified to account for the accelerated mortality of this group after week 87.

The high dose of 500 mg/kg isophorone appeared appropriate for male rats and female mice. Although the survival of high dose male rats was significantly lower than that of the vehicle controls, the decline in survival occurred late in the study. The dose of 500 mg/kg did not cause neoplastic or significant nonneoplastic lesions in female mice, whereas a twofold greater dose caused deaths in the 13-week studies, and there was a small (5%) decrease in body weights of the high dose animals after week 55 of the study. Male mice and female rats might have tolerated a slightly higher dose; however, a marginal increase in neoplastic lesions was observed in the male mice, and a fourfold higher dose caused deaths of both male mice and female rats in the 16-day studies.

There were no chemically related clinical signs in either rats or mice during the 2-year studies. Certain organs or organ systems, however, showed histopathologic changes in response to isophorone exposure in both rats and mice.

The kidneys of isophorone-dosed male rats had increased incidences of proliferative lesions. Three low dose and one high dose male rats were found to have tubular cell adenocarcinomas; two adenomas were observed in high dose male rats. These incidences are low, but they are statistically significant relative to matched vehicle controls. In addition, kidney neoplasms of any type are rarely observed in corn oil vehicle control F344/N rats. A direct comparison of the rates observed in this study with the overall historical control rate of tubular cell tumors in male rats (4/1,091, 0.4%; Appendix F, Table F3) indicates that both the low dose and the high dose effects are statistically significant ($P<0.005$) by the Fisher exact test. Further support for the biologic significance of these proliferative lesions was provided by the presence of tubular cell hyperplasia in one low dose and four high dose male rats but not in vehicle controls. Thus, tubular cell hyperplasia, adenoma, or adenocarcinoma occurred in 0/50 vehicle control, 4/50 low dose, and 7/50 high dose male rats. A second type of proliferative lesion, epithelial hyperplasia of the renal pelvis, was seen in five low dose and five high dose male rats but not in vehicle controls. Kidney neoplasms have occasionally been noted in other NTP studies in which chemical nephrosis was present. The possible relationship between nephrosis and kidney neoplasia is currently under study by the NTP. Isophorone does not appear to be a potent nephrotoxicant; there was minimal nephrotoxicity in male rats in the 2-year studies and none in the 13-week studies.

Isophorone exposure resulted in mineralization of the renal tubules in male rats (vehicle control, 1/50; low dose, 31/50; high dose, 20/50). This lesion was frequently observed in the medullary collecting ducts and was coincident with chronic nephropathy. The overall incidence of nephropathy was similar in dosed and vehicle control male rats, but the severity of this lesion appeared most prominently in the low dose group. This suggests that nephropathy was probably not the cause of the increased late mortality of the high dose male rats. Isophorone may also have increased the incidence of nephropathy in female rats (vehicle control, 21/50; low dose, 39/50; high dose, 32/50); no increase in kidney lesions was observed in mice of either sex.

Preputial gland carcinomas were observed in five high dose male rats. The absence of this neoplasm in vehicle controls or in the low dose group and the low historical incidence (12/1,094, 1%) in corn oil vehicle controls in previous NTP 2-year studies suggest that this effect may be chemically related. No preputial gland tumors were observed in male mice, but two clitoral gland adenomas were seen in low dose female rats, providing further evidence for the association of isophorone exposure with this type of neoplasm. However, the prepuce and clitoris are among those tissues examined microscopically only when a neoplasm is visible to the prosector. Therefore, although the neoplasms observed in this study were rather large, the actual incidence of all types of proliferative lesions of the prepuce or clitoris is not known, since only seven animals were sampled for histopathologic examination (five high dose male rats and two low dose female rats). The diagnosis or the actual occurrence of preputial tumors has been sporadic in vehicle controls in previous NTP studies. The number of preputial gland adenomas or carcinomas (combined) in corn oil vehicle controls in previous studies has ranged from zero to seven; five were observed in the corn oil vehicle controls in the one previous comparable study performed at this laboratory (Appendix F, Table F1). These factors make it difficult to relate with certainty the occurrence of preputial gland carcinomas with exposure to isophorone. Nonetheless, this finding should not be discounted.

Isophorone exposure was associated with a marginal increase in the incidence of neoplastic lesions of the liver and the integumentary and lymphoreticular systems of male mice. Nonneoplastic lesions were also observed in the liver and adrenal cortex of dosed male mice.

The incidence of hepatocellular adenomas or carcinomas (combined) was greater in the high dose male mice than that in the vehicle controls (vehicle control, 18/48; low dose, 18/50; high dose, 29/50). Although the incidence in vehicle controls was similar to the historical average for adenomas and carcinomas in vehicle controls in previous NTP corn oil studies (32.4%), the incidence in the high dose group was nearly double this and also exceeded the greatest incidence ever observed in vehicle controls in previous NTP studies (Appendix F, Table F7). Isophorone-exposed male mice also had an increased incidence of heptocytomegaly and coagulative necrosis of the liver. Acute and/or chronic inflammation of the liver was also noted in 11 of the high dose male mice but in only 1 vehicle control. However, there was no evidence of chemically related nonneoplastic or neoplastic liver lesions in female mice, and hepatocytomegaly was observed less frequently in the dosed female animals (vehicle control, 32/50; low dose, 21/50; high dose, 9/50).

The incidence of mesenchymal tumors of the integumentary system was also significantly elevated in high dose male mice compared with that of vehicle controls by trend analyses and pairwise comparison (fibroma, fibrosarcoma, neurofibrosarcoma, or sarcoma: vehicle control, 6/48; low dose, 8/50; high dose, 14/50). The incidence of these neoplasms in high dose male mice exceeded the mean incidence in historical controls by over fivefold (Appendix F, Table F4) and is therefore regarded as a chemically related effect.

Lymphoreticular neoplasms were found at a greater incidence in low dose male mice (18/50) than in vehicle controls (8/48) or high dose males (5/50). The low incidence in high dose males argues against a chemically related effect, but the incidence in the vehicle controls is similar to

that seen in the vehicle controls in previous 2-year studies, and the incidence in the low dose group exceeds the upper range of observed lymphomas or leukemias (combined) in historical controls (Table 19; Appendix F, Table F6). Thus, there is equivocal evidence that exposure to isophorone causes lymphoreticular neoplasms in male mice. No increase in lymphoma or leukemia was observed in dosed female mice or in rats of either sex.

The incidence of fatty metamorphosis of the adrenal cortex was related to isophorone exposure in male rats (vehicle control, 7/50; low dose, 21/50; high dose, 26/50). Whether this change has any biologic significance remains to be established.

Pancreatic acinar cell tumors were found in both dosed and vehicle control male rats (vehicle control, 4/50; low dose, 9/50; high dose, 6/50). These tumors are rarely observed in controls in feed studies (0.5%), but they occasionally appear with a greater incidence in studies that employ corn oil as a gavage vehicle (3.3%; Appendix F, Table F2) (Boorman and Eustis, 1984). The borderline increased incidence of acinar cell tumors in the dosed animals in the present study suggests that there may be an effect of isophorone exposure ($P=0.059$, incidental tumor test), but any effect may be largely obscured by the higher than usual background rate demonstrated by the vehicle control group.

Focal hyperplasia of the anterior pituitary was observed at increased incidence in dosed female rats and mice but not in males; however, the incidence of pituitary adenoma showed a negative trend in the female rats and mice. Therefore, the overall incidence of proliferative lesions of the anterior pituitary was not affected by isophorone exposure.

Pulmonary congestion and hemorrhage were frequently noted in male and female rats in both dosed groups and in vehicle controls, but pulmonary alveolar emphysema was observed at a greater incidence in dosed male and female rats than in vehicle controls. Since single and repeated inhalation exposures to isophorone have been shown to irritate the lung (Smyth et al., 1942), the development of emphysematous changes could conceivably occur after long-term exposure to isophorone through aspiration of the chemical during gavage. However, in the present study, the emphysematous changes were determined to be an artifact of hyperinflation of the lung during fixation; thus, no pulmonary lesions were attributed to isophorone exposure.

The current study is the only assessment in rodents of the potential for carcinogenic or other chronic toxic effects of exposure to isophorone. A comparison of the results of these 2-year gavage studies with those of earlier single- or repeated-exposure inhalation studies that employed impure isophorone (Smyth and Seaton, 1940; Smyth et al., 1942) is of limited value because of the uncertainty of the agent responsible for the reported toxication in the studies reported by Smyth and coworkers. A more appropriate comparison can be made with the 90-day feeding studies of Parkin (USEPA, 1980). In those studies, no adverse effects were noted after exposure of weanling CFE albino rats at up to approximately 350 mg/kg per day or exposure of beagles at up to 150 mg/kg per day. These results are in agreement with the absence of significant findings in the lower dose groups in the present 16-day and 13-week studies with both rats and mice.

Although negative in the Salmonella/microsome assay with or without activation with S9, isophorone was found to be a weak direct-acting mutagen in the mouse lymphoma assay. Isophorone also induced sister-chromatid exchanges in Chinese hamster ovary cells in the absence of S9; however, this effect was not observed in the presence of S9. As an *alpha-*, *beta*-unsaturated ketone, isophorone should tend to undergo nucleophilic addition to its carbon-carbon double bond, and therefore it may behave as a direct-acting alkylating agent. However, it is not possible to ascribe any particular toxic or carcinogenic activity of isophorone to the parent compound without further characterization and study of its metabolites.

Conclusions: Under the conditions of these 2-year gavage studies, there was *some evidence of carcinogenicity** of isophorone in male F344/N rats as shown by the occurrence of renal tubular cell adenomas and adenocarcinomas in animals given 250 or 500 mg/kg per day; carcinomas of the preputial gland were also observed at increased incidence in male rats given 500 mg/kg. There was *no evidence of carcinogenicity* in female F344/N rats given 250 or 500 mg/kg per day. For male B6C3F$_1$ mice, there was *equivocal evidence of carcinogenicity* of isophorone as shown by an increased incidence of hepatocellular adenomas or carcinomas (combined) and of mesenchymal tumors in the integumentary system in animals given 500 mg/kg per day and by an increase in malignant lymphomas in animals given 250 mg/kg per day. There was *no evidence of carcinogenicity* of isophorone in female B6C3F$_1$ mice given 250 or 500 mg/kg per day.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2.

V. REFERENCES

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1. American Conference of Governmental and Industrial Hygienists, Inc. (ACGIH) (1983) Threshold Limit Values for Chemical Substances and Physical Agents in the Work Environment with Intended Changes for 1983-84. ACGIH, Cincinnati, OH, p. 23.

2. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons, Inc., pp. 362-365.

3. Berenblum, I., Ed. (1969) Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2. Geneva: International Union Against Cancer.

4. Blackford, J. (1975) Acetone. Chemical Economics Handbook. Stanford Research Institute, Menlo Park, CA.

5. Boorman, G.; Eustis, S. (1984) Proliferative lesions of the exocrine pancreas in male F344/N rats. Environ. Health Perspect. 56:213-217.

6. Boorman, G.; Montgomery, C., Jr.; Hardisty, J.; Eustis, S,; Wolfe, M.; McConnell, E. (1985) Quality assurance in pathology for rodent toxicology and carcinogenicity tests. Milman, H.; Weisburger, E., Eds.: Handbook of Carcinogen Testing. Park Ridge, NJ: Noyes Publications (in press).

7. Clive, D.; Johnson, K.; Spector, J.; Batson, A.; Brown, M. (1979) Validation and characterization of the L5178Y/TK$^{+/-}$ mouse lymphoma mutagen assay system. Mutat. Res. 59:61-108.

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

9. Dutertre-Catella, H.; Nguyen, P.; Dang, Q.; Truhaut, R. (1978) Metabolic transformation of the 3,5,5-trimethyl-2-cyclohexene-1-one (isophorone). Toxicol. Eur. Res. 1:209-216.

10. Eight Peak Index of Mass Spectra, First edition, Vol. I (1970) Mass Spectrometry Data Centre, AWRE, Aldermaston, RG7PR, United Kingdom, Spectrum No. W0093, p. 375.

11. Gart, J.; Chu, K.; Tarone, R. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62(4):957-974.

12. Goto, K.; Maeda, S; Kano, Y.; Sugimura, T. (1978) Factors involved in differential Giemsa-staining of sister chromatids. Chromosoma 66:351-359.

13. Haruta, H.; Yagi, H.; Iwata, T.; Tamura, S. (1974) New plant growth retardants. II. Syntheses and plant growth retardant activities of quaternary ammonium compounds derived from α-ionone and isophorone. Agric. Biol. Chem. 38:417-422.

14. Haseman, J. (1984) Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environ. Health Perspect. 58:385-392.

15. Haseman J.; Huff, J.; Boorman, G. (1984) Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol. 12:126-135.

16. Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W.; Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. Suppl. 1:3-142.

17. Jennings, P. (1965) Photochemistry of isophorone. 1. Diss. Abstr. 26:698.

18. Jungclaus, G.; Games, L.; Hites, R. (1976) Identification of trace organic compounds in tire manufacturing plant wastes. Anal. Chem. 48:1894-1896.

19. Kaplan, E.; Meier, P. (1958) Nonparametric estimation of incomplete observations. J. Am. Stat. Assoc. 53:457-481.

20. Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J. (1974) Carcinogenesis bioassay data system. Comp. Biomed. Res. 7:230-248.

21. Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

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

23. McConnell, E.; Solleveld, H.; Swenberg, J.; Boorman, G. (1985) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. (in press).

24. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassays in Small Rodents. NCI Carcinogenesis Technical Report Series No. 1.

25. National Institute for Occupational Safety and Health (NIOSH) (1978) Criteria for a recommended standard....Occupational exposure to ketones. Publication No. 78-173, Department of Health, Education, and Welfare, NIOSH.

26. National Institutes of Health (NIH), NIH Specification NIH-11-133f, November 1, 1978.

27. Patty, F.A., Ed. (1963) Industrial Hygiene and Toxicology, 2nd ed., Vol. 2. New York: Interscience Publishers, pp. 1722-1724, 1763-1765.

28. Perry, P.; Wolff, S. (1974) New Giemsa method for the differential staining of sister chromatids. Nature (London) 251:156-158.

29. Price, K.; Waggy, G.; Conway, R. (1974) Brine shrimp bioassay and BOD of petrochemicals. J. Water Pollut. Control Fed. 46:63-77.

30. Ray, S.; Trieff, N. (1980) Bioaccumulation of anthropogenic toxins in the ecosystem. Trieff, N., Ed.: Environment and Health. Ann Arbor, MI: Ann Arbor Science Pub., Inc., pp. 93-120.

31. Reese, K. (1984) How to repel woodpeckers. Chem. Eng. News 62:132.

32. Sadtler Standard Spectra, Sadtler Research Laboratories, Philadelphia, PA, IR No. 122 (Midget ed.); UV No. 44; NMR No. 7311 M.

33. Samimi, B. (1982) Exposure to isophorone and other organic solvents in a screen plant. Am. Ind. Hyg. Assoc. J. 43:43-48.

34. Shackelford, W.; Keith, L. (1976) Frequency of organic compounds identified in water. U.S. Environmental Protection Agency 600/4-76-062. Athens, GA, p. 626.

35. Sheldon, L.; Hites, R. (1978) Organic compounds in the Delaware River. Environ. Sci. Technol. 12:1188-1194.

36. Silverman, L.; Schulte, H.; First, M. (1946) Further studies on sensory response to certain industrial solvent vapors. J. Ind. Hyg. Toxicol. 28:262-266.

37. Sittig, M., Ed. (1980) Priority Toxic Pollutants Health Impact and Allowable Limits. Park Ridge, NJ: Noyes Data Corp., pp. 255-259.

38. Smyth, H.; Seaton, J. (1940) Acute response of guinea pigs and rats to inhalation of the vapors of isophorone. J. Ind. Hyg. Toxicol. 22:477-483.

39. Smyth, H., Jr.; Seaton, J.; Fischer, L. (1942) Response of guinea pigs and rats to repeated inhalation of vapor of mesityl oxide and isophorone. J. Ind. Hyg. Toxicol. 24:46-50.

40. Smyth, H., Jr.; Weil, C.; West, J.; Carpenter, C. (1970) An exploration of joint toxic action. II. Equitoxic versus equivolume mixtures. Toxicol. Appl. Pharmacol. 17:498-503.

41. Stahl, E., Ed. (1969) Thin Layer Chromatography. New York: Springer-Verlag. p. 871.

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

43. Truhaut, R.; Dutertre-Catella, H.; Nguyen, P. (1972) Study of the toxicity of an industrial solvent, isophorone. Irritating capacity with regard to the skin and the mucosae. J. Eur. Toxicol. 5:31-37.

44. Union Carbide Corporation (1963) Toxicology Studies--Isophorone Summary Data Sheet. New York: Ind. Med. Toxicol. Dept.

45. Union Carbide Corporation (1975) Ketones Technical Booklet (F-41971A). New York: Chemical Plastics Division.

46. U.S. Environmental Protection Agency (USEPA) (1979).

47. U.S. Environmental Protection Agency (USEPA) (1980) Ambient Water Quality Criteria for Isophorone. EPA 440/5-80-056.

48. Ward, G.; Parrish, P.; Rigby, R. (1981) Early life stage toxicity tests with a saltwater fish: Effects of eight chemicals on survival, growth, and development of sheepshead minnows (*Cyprinodon variegatus*). J. Toxicol. Environ. Health 8:225-240.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
SQUAMOUS CELL CARCINOMA		1 (2%)	
LIPOMA	1 (2%)		
NEUROFIBROMA		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROMA	4 (8%)	6 (12%)	1 (2%)
FIBROSARCOMA		1 (2%)	1 (2%)
LIPOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (8%)	2 (4%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
TUBULAR CELL ADENOCARCINOMA, MET		1 (2%)	
C-CELL CARCINOMA, METASTATIC	1 (2%)		
OSTEOSARCOMA, UNC PRIM OR META			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA, MONONUCLEAR CELL	6 (12%)	10 (20%)	8 (16%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	2 (4%)
#SALIVARY GLAND	(48)	(49)	(49)
FIBROSARCOMA, INVASIVE		1 (2%)	
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	4 (8%)	9 (18%)	2 (4%)
HEPATOCELLULAR CARCINOMA	1 (2%)		
#PANCREAS	(50)	(50)	(50)
ACINAR CELLADENOMA	4 (8%)	9 (18%)	6 (12%)
#FORESTOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#DUODENUM	(50)	(50)	(50)
LEIOMYOMA			1 (2%)
#JEJUNUM	(50)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR CELL ADENOMA			2 (4%)
TUBULAR CELL ADENOCARCINOMA		3 (6%)	1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY INTERMEDIA	(48)	(49)	(47)
ADENOMA, NOS		1 (2%)	
#ANTERIOR PITUITARY	(48)	(49)	(47)
ADENOMA, NOS	10 (21%)	12 (24%)	8 (17%)
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	1 (2%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	1 (2%)	2 (4%)	1 (2%)
CORTICAL CARCINOMA	1 (2%)		
#ADRENAL CORTEX	(50)	(50)	(50)
OSTEOSARCOMA, UNC PRIM OR META			1 (2%)
#ADRENAL MEDULLA	(50)	(50)	(50)
PHEOCHROMOCYTOMA	16 (32%)	13 (26%)	15 (30%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	
#THYROID	(49)	(50)	(49)
FOLLCULAR CELL ADENOMA			2 (4%)
FOLLCULAR CELL CARCINOMA	1 (2%)	1 (2%)	
C-CELL ADENOMA	6 (12%)	5 (10%)	2 (4%)
C-CELL CARCINOMA	2 (4%)	1 (2%)	
#PANCREATIC ISLETS	(50)	(50)	(50)
ISLET CELL ADENOMA	5 (10%)	5 (10%)	4 (8%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA		1 (2%)	
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS			5 (10%)
*SEMINAL VESICLE	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)		
#TESTIS	(48)	(50)	(50)
INTERSTITIAL CELL TUMOR	43 (90%)	41 (82%)	38 (76%)
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
GRANULAR CELL TUMOR, NOS		1 (2%)	
ASTROCYTOMA		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*ZYMBAL GLAND	(50)	(50)	(50)
SEBACEOUS ADENOCARCINOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*PELVIC BONES	(50)	(50)	(50)
OSTEOSARCOMA	1 (2%)		
BODY CAVITIES			
*MESENTERY	(50)	(50)	(50)
MESOTHELIOMA, INVASIVE		1 (2%)	
*TUNICA VAGINALIS	(50)	(50)	(50)
MESOTHELIOMA, NOS	3 (6%)		2 (4%)
MESOTHELIOMA, MALIGNANT		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MESOTHELIOMA, NOS	1 (2%)	1 (2%)	
MESOTHELIOMA, MALIGNANT			1 (2%)
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	5	5	11
MORIBUND SACRIFICE	8	7	19
TERMINAL SACRIFICE	33	33	14
DOSING ACCIDENT	3	3	3
ACCIDENTALLY KILLED, NOS	1	2	3
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	47	45	39
TOTAL PRIMARY TUMORS	120	132	107
TOTAL ANIMALS WITH BENIGN TUMORS	45	44	39
TOTAL BENIGN TUMORS	96	99	83
TOTAL ANIMALS WITH MALIGNANT TUMORS	12	20	16
TOTAL MALIGNANT TUMORS	15	22	18
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	3	
TOTAL SECONDARY TUMORS	1	3	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-- BENIGN OR MALIGNANT	8	10	3
TOTAL UNCERTAIN TUMORS	9	11	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-- PRIMARY OR METASTATIC			1
TOTAL UNCERTAIN TUMORS			2

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA		1 (2%)	
KERATOACANTHOMA		1 (2%)	1 (2%)
FIBROMA			1 (2%)
RESPIRATORY SYSTEM			
*NARES	(50)	(50)	(50)
SARCOMA, NOS			1 (2%)
#LUNG	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA	1 (2%)		
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA		1 (2%)	
SARCOMA, NOS, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
LEUKEMIA, MONONUCLEAR CELL	9 (18%)	5 (10%)	5 (10%)
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(50)
HEMANGIOSARCOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	3 (6%)	1 (2%)	1 (2%)
#PANCREAS	(50)	(50)	(50)
ACINAR CELL ADENOMA	1 (2%)		1 (2%)
#ESOPHAGUS	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
#FORESTOMACH	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA			2 (4%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#ANTERIOR PITUITARY	(49)	(48)	(47)
ADENOMA, NOS	21 (43%)	17 (35%)	12 (26%)
ADENOCARCINOMA, NOS	4 (8%)	2 (4%)	
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	4 (8%)	3 (6%)	2 (4%)
#ADRENAL CORTEX	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#ADRENAL MEDULLA	(50)	(50)	(50)
PHEOCHROMOCYTOMA	6 (12%)	3 (6%)	6 (12%)
PHEOCHROMOCYTOMA, MALIGNANT		1 (2%)	
#THYROID	(50)	(50)	(48)
C-CELL ADENOMA		1 (2%)	1 (2%)
#PANCREATIC ISLETS	(50)	(50)	(50)
ISLET CELL ADENOMA	1 (2%)	2 (4%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)		1 (2%)
FIBROADENOMA	7 (14%)	8 (16%)	4 (8%)
*CLITORAL GLAND	(50)	(50)	(50)
ADENOMA, NOS		2 (4%)	
#UTERUS	(49)	(50)	(49)
ADENOMA, NOS	2 (4%)		
ADENOCARCINOMA, NOS			1 (2%)
ENDOMETRIAL STROMAL POLYP	10 (20%)	11 (22%)	5 (10%)
ENDOMETRIAL STROMAL SARCOMA	3 (6%)	1 (2%)	1 (2%)
#OVARY	(49)	(50)	(49)
ADENOCARCINOMA, NOS, INVASIVE			1 (2%)
CYSTADENOMA, NOS			1 (2%)
GRANULOSA CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(49)	(49)
ASTROCYTOMA			1 (2%)
SPECIAL SENSE ORGANS			
*ZYMBAL GLAND	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
ADENOMA, NOS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	7	11	10
MORIBUND SACRIFICE	12	10	6
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	30	23	20
DOSING ACCIDENT	1	5	11
ACCIDENTALLY KILLED, NOS		1	3
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	43	36	30
TOTAL PRIMARY TUMORS	73	63	50
TOTAL ANIMALS WITH BENIGN TUMORS	34	28	25
TOTAL BENIGN TUMORS	52	49	37
TOTAL ANIMALS WITH MALIGNANT TUMORS	14	11	12
TOTAL MALIGNANT TUMORS	18	12	12
TOTAL ANIMALS WITH SECONDARY TUMORS##	2		2
TOTAL SECONDARY TUMORS	2		2
TOTAL ANIMALS WITH TUMORS UNCERTAIN--			
BENIGN OR MALIGNANT	3	2	1
TOTAL UNCERTAIN TUMORS	3	2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN--			
PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	105	105	105	105	105	105	105	105	105	105	105	091	105	068	087	082	105	105	090	105	080	091	091	
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma																								X	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma			X										X			X		X							
Lipoma	X																								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma						X			X		X														
C-cell carcinoma, metastatic				X																					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule											X							X							
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar-cell adenoma								X																	
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma		X																							
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS							X																		
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Adenoma, NOS								X			X		X	X						X					
Adenocarcinoma, NOS				X																					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Cortical carcinoma																									
Pheochromocytoma	X	X	X				X		X	X		X	X						X	X					
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell carcinoma																								X	
C-cell adenoma		X												X						X					
C-cell carcinoma				X			X																		
Parathyroid	–	–	+	–	+	+	+	+	–	+	+	+	+	+	–	+	–	+	–	+	+	+	+	–	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma											X									X					
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	N	N	N	+	+	+	+	+	+	+	+	N	+	N	N	N	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–
Interstitial-cell tumor	X	X	X	X	X	X	X		X	X	X	X	X	X		X	X	X	X	X		X	X	X	
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	+	N	+	N
Mesothelioma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sebaceous adenocarcinoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																								X	
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
Leukemia, mononuclear cell	X										X										X				X

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	088	090	105	088	105	070	105	105	105	091	029	105	100	105	105	087	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Lipoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										4
Lipoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X														4
C-cell carcinoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule											X					X										4
Hepatocellular carcinoma															X											1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar-cell adenoma	X					X				X																4
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS										X	X	X	X										X			10
Adenocarcinoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																		X								1
Cortical carcinoma			X																							1
Pheochromocytoma					X										X	X					X		X	X		16
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	49
Follicular-cell carcinoma																										1
C-cell adenoma		X									X		X													6
C-cell carcinoma																										2
Parathyroid	+	+	+	–	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	38
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma	X									X											X					5
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	N	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Interstitial-cell tumor	X	X	X	X	X	X	X	X		X	X	X			X	X	X	X	X	X	X	X	X	X	X	43
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS												X														1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sebaceous adenocarcinoma				X																						1
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS										X		X												X		3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS																				N						1
Leukemia, mononuclear cell					X											X										6

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	072	105	105	105	105	105	070	105	105	105	105	105	105	105	105	105	105	105	097	095	099	097	091	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																		X							
Neurofibroma												X													
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma	X			X										X					X						
Fibrosarcoma																								X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma					X																				
Alveolar/bronchiolar carcinoma																									
Tubular-cell adenocarcinoma, metas												X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	+	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, invasive																								X	
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule								X	X												X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar-cell adenoma			X		X				X			X	X							X					
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular-cell adenocarcinoma												X													
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X							X			X@						X		X	X		
Adenocarcinoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																	X								
Pheochromocytoma			X		X						X											X			X
Pheochromocytoma, malignant	X																								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell carcinoma													X												
C-cell adenoma										X				X											
C-cell carcinoma															X										
Parathyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																	X		X						X
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	+	N	N	+	+	N	N	N	+	N	+	+	N	+	+	N	+	N	N	N	N	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor	X	X	X	X	X	X	X	X	X	X		X	X	X	X		X	X	X	X	X		X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular-cell tumor, NOS																									
Astrocytoma																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, malignant									X																
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, invasive									X																
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
Leukemia, mononuclear cell							X	X												X	X			X	

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
@ : Multiple Occurrence of Morphology
: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	028	105	105	006	105	105	080	105	091	088	034	105	105	094	105	105	105	105	105	105	105	079	075	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Neurofibroma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma				X			X																			6
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																				X						2
Alveolar/bronchiolar carcinoma																					X					1
Tubular-cell adenocarcinoma, metas																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	+	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−	6
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma															X											1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Fibrosarcoma, invasive																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule	X									X			X	X					X			X				9
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar-cell adenoma	X															X						X				9
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular-cell adenocarcinoma																			X			X				3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X				X				X			X	X							X				12
Adenocarcinoma, NOS																									X	1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma			X																							2
Pheochromocytoma							X				X			X		X	X	X	X	X						13
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell carcinoma																										1
C-cell adenoma							X		X																X	5
C-cell carcinoma																										1
Parathyroid	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	44
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma			X				X																			5
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	N	N	N	+	+	+	+	N	N	N	N	+	N	+	+	N	+	N	+	N	N	+	N	*50
Fibroadenoma						X																				1
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial-cell tumor	X		X	X		X	X	X	X	X			X	X	X	X	X	X	X	X	X	X			X	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular-cell tumor, NOS														X												1
Astrocytoma																								X		1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, malignant																										1
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS								X																		1
Leukemia, mononuclear cell										X				X	X	X			X							10

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	101	021	033	061	100	105	077	105	105	056	104	105	105	092	088	097	091	021	097	105	101	107
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma											X														
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																							X		
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+
Osteosarcoma, unc prim or metas																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Thymus	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma								X																	
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule			X					X																	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar-cell adenoma	X															X								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma			X																						
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular-cell adenoma								X																	
Tubular-cell adenocarcinoma	X																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–
Adenoma, NOS		X													X				X						
Adenocarcinoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma	X		X								X	X			X				X			X	X	X	
Osteosarcoma, unc prim or metas																						X			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Follicular-cell adenoma	X																								
C-cell adenoma		X		X																					
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	–	+	–	+	+	+	+	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma			X								X														
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	+	N	+	N	N	+	+	+	+	+	N	+	+	+	+	+	N	N	
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor	X	X	X	X				X	X	X	X	X	X	X	X	X	X		X		X	X	X		
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS											X		X					X							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS	X							X																	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant																									
Leukemia, mononuclear cell			X																				X		

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	0262	0272	0289	0290	0301	0312	0323	0334	0345	0356	0367	0378	0389	0400	0411	0422	0433	0444	0455	0466	0477	0488	0499	0500	TOTAL
WEEKS ON STUDY	0666	1056	0666	1051	0110	0996	1055	0994	0999	1001	0009	0801	1055	0596	0666	0990	0991	0990	0774	0997	0996	0809	0993	1015	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																									1
Fibrosarcoma																			X						1
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Osteosarcoma, unc prim or metas																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	–	–	–	–	+	–	–	+	–	–	+	–	–	–	–	–	–	–	–	–	–	+	–	–	8
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma															X										2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																									2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar-cell adenoma							X			X			X		X										6
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																									1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular-cell adenoma		X																							2
Tubular-cell adenocarcinoma																									1
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	48
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma, NOS		X							X		X					X								X	8
Adenocarcinoma, NOS									X																1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma											X														1
Pheochromocytoma								X	X								X		X	X			X		15
Osteosarcoma, unc prim or metas																									1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular-cell adenoma		X																							2
C-cell adenoma																									2
Parathyroid	+	+	+	+	–	+	+	–	+	+	+	+	+	–	–	+	+	+	+	–	+	+	+	+	39
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma				X			X																		4
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	N	+	N	+	+	+	N	N	+	+	N	+	+	+	+	N	N	N	+	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial-cell tumor		X		X		X	X	X	X		X	X			X	X	X	X	X	X	X	X	X	X	38
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																			X		X				5
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																								X	1
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																									2
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																				X					1
Leukemia, mononuclear cell						X			X									X	X			X	X		8

*Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	098	099	105	105	098	079	105	045	055	053	055	055	081	050	055	050	052	085	055	088	095	100
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Adenocarcinoma, NOS, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule			X				X																X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar-cell adenoma																									X
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS			X				X		X	X		X	X	X		X		X	X			X			
Adenocarcinoma, NOS						X																	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma	X					X									X										
Pheochromocytoma					X									X		X								X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma								X	X													X	X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS						X																			
Endometrial stromal polyp								X		X						X				X					X
Endometrial stromal sarcoma															X								X		
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell				X									X		X						X	X			

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL
WEEKS ON STUDY	1105	0996	1095	0935	0977	1055	0787	1055	1055	1055	0117	0886	0996	1055	0556	1105	1105	1105	1105	1105	0779	1105	1105	1103	1105	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic															X											1
Adenocarcinoma, NOS, metastatic				X																						1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	2
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar-cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X		X			X	X	X				X		X		X		X					X	21
Adenocarcinoma, NOS		X								X																4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																				X						4
Pheochromocytoma														X								X				6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid	+	+	–	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	+	–	+	+	+	+	44
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma	X																									1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS				X																						1
Fibroadenoma	X							X					X													7
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
Adenoma, NOS																							X			2
Endometrial stromal polyp				X	X															X			X		X	10
Endometrial stromal sarcoma												X														3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma															X											1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell							X			X									X					X		9

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: LOW DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	005	105	105	105	101	105	096	105	079	098	103	105	068	105	105	105	096	105	077	022	097	092	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Keratoacanthoma												X													
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																							X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	+	+	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule														X											
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS							X																		
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X			X				X		X		X		X		X		X							X
Adenocarcinoma, NOS										X															
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Cortical adenoma										X															
Pheochromocytoma						X																			
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																								X	
Parathyroid	+	+	+	+	+	–	–	+	+	+	–	+	+	+	–	+	+	+	–	+	+	–	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma		X						X		X		X											X		
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp						X	X						X			X				X				
Endometrial stromal sarcoma															X										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa-cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell	X										X		X												

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0262	0271	0282	0299	0301	0311	0321	0333	0344	0355	0366	0377	0388	0399	0400	0411	0422	0433	0444	0455	0466	0477	0488	0499	0500	TOTAL
WEEKS ON STUDY	1005	1005	1005	0997	0996	1005	0881	0996	1005	1005	1005	0600	1005	0605	1005	0008	0963	0998	0996	0972	0994	1005	0996	0559	0997	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma							X																			1
Keratoacanthoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
Thymus	–	–	–	–	+	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	–	–	–	–	6
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	48
Adenoma, NOS	X						X	X		X		X			X			X			X	X				17
Adenocarcinoma, NOS																										2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																								X		1
Cortical adenoma	X											X														3
Pheochromocytoma								X	X																	3
Pheochromocytoma, malignant				X																						1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell adenoma																										1
Parathyroid	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	40
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell adenoma	X								X																	2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*50
Fibroadenoma	X								X												X					8
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS	X																	X								2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp								X	X			X	X			X		X								11
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa-cell tumor						X																				1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell					X																			X		5

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: HIGH DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	105	085	021	105	063	021	105	093	021	105	102	105	023	090	105	105	105	026	105	105	095	003	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma							X																		
Fibroma		X																							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																				X					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N
Sarcoma, NOS																				X					
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Lymph nodes	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	+	–	+	+	–	–	+	–	–	–	+	–	–	–	+	+	–	+	–	+	–	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar-cell adenoma															X										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma											X														
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X	X		X			X			X	X			X		X					X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																							X		
Pheochromocytoma														X		X							X		
Thyroid	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																									
Parathyroid	+	–	–	+	+	–	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Fibroadenoma		X															X			X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Endometrial stromal polyp	X															X	X								
Endometrial stromal sarcoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive																									
Cystadenoma, NOS																							X		
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																									X
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, histiocytic type																									
Leukemia, mononuclear cell								X									X						X		

+ : Tissue Examined Microscopically
– : Required Tissue Not Examined Microscopically
X : Tumor Incidence
N : Necropsy, No Autolysis, No Microscopic Examination
S : Animal Missexed
: : No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL
WEEKS ON STUDY	0933	1002	0551	1005	1002	0995	0998	0922	0909	0998	0221	1051	0221	1050	1050	0209	0858	0999	0997	0998	1005	0007	1005	1005	0005	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																										1
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Sarcoma, NOS																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	–	–	–	–	–	–	–	+	–	–	+	–	–	–	–	+	–	–	+	–	–	+	–	–	+	16
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																								X		1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar-cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma						X																				2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	47
Adenoma, NOS	X				X																X					12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																				X						2
Pheochromocytoma					X										X								X			6
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	48
C-cell adenoma														X												1
Parathyroid	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	–	+	–	+	+	–	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	N	+	+	+	N	+	+	+	+	N	+	N	+	+	+	+	+	*50
Adenocarcinoma, NOS																							X			1
Fibroadenoma																	X									4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	49
Adenocarcinoma, NOS															X											1
Endometrial stromal polyp									X														X			5
Endometrial stromal sarcoma				X																						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	49
Adenocarcinoma, NOS, invasive															X											1
Cystadenoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	49
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS				X																						1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, histiocytic type					X																					1
Leukemia, mononuclear cell												X						X								5

*Animals Necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	48	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(50)	(50)
BASAL CELL TUMOR		1 (2%)	
FIBROMA	2 (4%)	1 (2%)	
NEUROFIBROSARCOMA		1 (2%)	
*SUBCUT TISSUE	(48)	(50)	(50)
SARCOMA, NOS			1 (2%)
FIBROMA		2 (4%)	3 (6%)
FIBROSARCOMA	3 (6%)	4 (8%)	10 (20%)
LEIOMYOSARCOMA		1 (2%)	
OSTEOSARCOMA		1 (2%)	
NEUROFIBROSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(47)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)	3 (6%)	2 (4%)
ALVEOLAR/BRONCHIOLAR ADENOMA	6 (13%)		
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	3 (6%)
FIBROSARCOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(48)	(50)	(50)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE	7 (15%)	7 (14%)	1 (2%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE		9 (18%)	4 (8%)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
LEUKEMIA, NOS	1 (2%)		
#SPLEEN	(44)	(50)	(47)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
#INGUINAL LYMPH NODE	(41)	(50)	(48)
FIBROSARCOMA, METASTATIC	1 (2%)		
#SMALL INTESTINE	(45)	(48)	(44)
MALIGNANT LYMPHOMA, MIXED TYPE		1 (2%)	
CIRCULATORY SYSTEM			
#SPLEEN	(44)	(50)	(47)
HEMANGIOSARCOMA	1 (2%)	1 (2%)	
#MESENTERIC LYMPH NODE	(41)	(50)	(48)
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
#HEART	(47)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
#LIVER	(48)	(50)	(50)
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(48)	(50)	(50)
BILE DUCT CARCINOMA	1 (2%)		
HEPATOCELLULAR ADENOMA	6 (13%)	7 (14%)	13 (26%)
HEPATOCELLULAR CARCINOMA	14 (29%)	13 (26%)	22 (44%)
PHEOCHROMOCYTOMA, METASTATIC		1 (2%)	
HEPATOBLASTOMA			1 (2%)
#PANCREAS	(46)	(50)	(49)
ACINAR CELL CARCINOMA			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#FORESTOMACH	(47)	(49)	(49)
PAPILLOMA, NOS			2 (4%)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
SQUAMOUS CELL CARCINOMA	1 (2%)		
#ILEUM	(45)	(48)	(44)
ADENOCARCINOMA, NOS	1 (2%)		
*RECTUM	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(48)	(50)	(50)
TUBULAR CELL ADENOCARCINOMA			1 (2%)
#KIDNEY/CAPSULE	(48)	(50)	(50)
FIBROSARCOMA, METASTATIC			1 (2%)
ENDOCRINE SYSTEM			
#ANTERIOR PITUITARY	(38)	(43)	(45)
ADENOCARCINOMA, NOS	1 (3%)		
#ADRENAL	(46)	(49)	(47)
CORTICAL ADENOMA	3 (7%)	2 (4%)	
#ADRENAL/CAPSULE	(46)	(49)	(47)
FIBROSARCOMA, METASTATIC			1 (2%)
#ADRENAL MEDULLA	(46)	(49)	(47)
PHEOCHROMOCYTOMA	3 (7%)	5 (10%)	2 (4%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)	1 (2%)	
#THYROID	(41)	(47)	(48)
FOLLCULAR CELL ADENOMA	4 (10%)	1 (2%)	2 (4%)
#PANCREATIC ISLETS	(46)	(50)	(49)
ISLET CELL ADENOMA	2 (4%)		
REPRODUCTIVE SYSTEM			
#PROSTATE	(47)	(49)	(49)
OSTEOSARCOMA, INVASIVE		1 (2%)	
*SEMINAL VESICLE	(48)	(50)	(50)
OSTEOSARCOMA, INVASIVE		1 (2%)	
#TESTIS	(48)	(50)	(50)
INTERSTITIAL CELL TUMOR		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(48)	(50)	(50)
ADENOMA, NOS		1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
NONE			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*PELVIS	(48)	(50)	(50)
OSTEOSARCOMA		1 (2%)	
*PLEURA	(48)	(50)	(50)
BILE DUCT CARCINOMA, METASTATIC	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(48)	(50)	(50)
ACINAR CELL CARCINOMA, METASTATIC			1 (2%)
SARCOMA, NOS, UNC PRIM OR META	1 (2%)		
MESOTHELIOMA, MALIGNANT		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	15	17	19
MORIBUND SACRIFICE	16	20	11
TERMINAL SACRIFICE	13	13	18
DOSING ACCIDENT	2		2
ACCIDENTALLY KILLED, NDA	3		
ANIMAL MISSING	1		
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	35	40	40
TOTAL PRIMARY TUMORS	61	67	68
TOTAL ANIMALS WITH BENIGN TUMORS	19	14	20
TOTAL BENIGN TUMORS	26	22	24
TOTAL ANIMALS WITH MALIGNANT TUMORS	25	35	33
TOTAL MALIGNANT TUMORS	34	45	44
TOTAL ANIMALS WITH SECONDARY TUMORS##	4	6	4
TOTAL SECONDARY TUMORS	6	7	6
TOTAL ANIMALS WITH TUMORS UNCERTAIN-- BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-- PRIMARY OR METASTATIC	1		
TOTAL UNCERTAIN TUMORS	1		

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
SARCOMA, NOS		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
FIBROSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)	1 (2%)	2 (4%)
SARCOMA, NOS, METASTATIC		1 (2%)	
MESOTHELIOMA, METASTATIC			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE	9 (18%)	9 (18%)	11 (22%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	9 (18%)	10 (20%)	3 (6%)
MALIGNANT LYMPHOMA, MIXED TYPE	2 (4%)	3 (6%)	3 (6%)
#SPLEEN	(50)	(50)	(50)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#MESENTERIC LYMPH NODE	(47)	(49)	(43)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE		1 (2%)	1 (2%)
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(50)	(50)
HEMANGIOSARCOMA	1 (2%)		
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	2 (4%)	4 (8%)	6 (12%)
HEPATOCELLULAR CARCINOMA	2 (4%)	2 (4%)	2 (4%)
#PANCREAS	(50)	(50)	(49)
ACINAR CELLADENOMA			1 (2%)
#FORESTOMACH	(50)	(50)	(49)
PAPILLOMA, NOS	1 (2%)		1 (2%)
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM			
#PITUITARY INTERMEDIA	(47)	(41)	(44)
ADENOMA, NOS			1 (2%)
#ANTERIOR PITUITARY	(47)	(41)	(44)
ADENOMA, NOS	11 (23%)	10 (24%)	4 (9%)
ADENOCARCINOMA, NOS	5 (11%)	3 (7%)	1 (2%)
#ADRENAL	(48)	(50)	(50)
CORTICAL ADENOMA	1 (2%)		1 (2%)
#ADRENAL/CAPSULE	(48)	(50)	(50)
ADENOMA, NOS	1 (2%)		
#ADRENAL MEDULLA	(48)	(50)	(50)
PHEOCHROMOCYTOMA		3 (6%)	1 (2%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#THYROID	(49)	(49)	(46)
FOLLCULAR CELL ADENOMA	2 (4%)	2 (4%)	
FOLLCULAR CELL CARCINOMA	1 (2%)	2 (4%)	
C-CELL CARCINOMA	1 (2%)		
#PANCREATIC ISLETS	(50)	(50)	(49)
ISLET CELL ADENOMA			1 (2%)
ISLET CELL CARCINOMA	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS		1 (2%)	
#UTERUS	(50)	(49)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
ENDOMETRIAL STROMAL POLYP	3 (6%)	5 (10%)	
#OVARY	(49)	(45)	(47)
CYSTADENOMA, NOS		2 (4%)	
TERATOMA, BENIGN		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(49)	(50)
ADENOCARCINOMA, NOS, INVASIVE	1 (2%)		
*SPINAL CORD	(50)	(50)	(50)
OSTEOSARCOMA		1 (2%)	
*SPINAL GANGLION	(50)	(50)	(50)
NEURILEMOMA, MALIGNANT			1 (2%)
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
ADENOMA, NOS	2 (4%)	3 (6%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*PLEURA	(50)	(50)	(50)
MESOTHELIOMA, MALIGNANT			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
OSTEOSARCOMA, METASTATIC		1 (2%)	

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	16	7	9
MORIBUND SACRIFICE	9	9	2
TERMINAL SACRIFICE	24	33	34
DOSING ACCIDENT	1	1	4
ACCIDENTALLY KILLED, NOS			1
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	16	41	28
TOTAL PRIMARY TUMORS	60	65	43
TOTAL ANIMALS WITH BENIGN TUMORS	17	23	17
TOTAL BENIGN TUMORS	26	31	19
TOTAL ANIMALS WITH MALIGNANT TUMORS	26	29	20
TOTAL MALIGNANT TUMORS	34	34	24
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	2	1
TOTAL SECONDARY TUMORS	1	2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN--BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN--PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* NUMBER OF ANIMALS NECROPSIED
** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: VEHICLE CONTROL

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	0032	0074	1005	0088	0069	1005	1005	0075	1005	1005	0884	1004	0557	0794	0944	0966	1005	1076	0768	0990	0800	1004	1004	1004	1005
INTEGUMENTARY SYSTEM																									
Skin	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma						X																			
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma		X													X							X			
Neurofibrosarcoma											X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic				X				X																	
Alveolar/bronchiolar adenoma					X					X						X								X	
Alveolar/bronchiolar carcinoma					X																				
Trachea	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma						X																			
Lymph nodes	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, metastatic																					X				
Hemangiosarcoma, metastatic						X																			
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma, metastatic						X																			
DIGESTIVE SYSTEM																									
Salivary gland	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct carcinoma				X																					
Hepatocellular adenoma		X										X												X	
Hepatocellular carcinoma		X		X	X	X	X	X			X		X	X							X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+		+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	N	+	+	N	+	N	+	+	N	+	+	N	+	+	+	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									X
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+
Adenocarcinoma, NOS																								X	
Adrenal	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																		X	X						
Pheochromocytoma, malignant																									
Thyroid	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma							X																		
Parathyroid	–	–	+	–	+	+	+	+	+	+	–	+	–	+	+	–	+	+	–	–	+	–	–	+	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell adenoma																								X	
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Bile duct carcinoma, metastatic				X																					
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, unc prim or meta														X											
Malig. lymphoma, lymphocytic type			X									X					X		X				X	X	
Leukemia, NOS																									

+	Tissue Examined Microscopically		No Tissue Information Submitted
–	Required Tissue Not Examined Microscopically	C	Necropsy, No Histology Due To Protocol
X	Tumor Incidence	A	Autolysis
N	Necropsy, No Autolysis, No Microscopic Examination	M	Animal Missing
S	Animal Missexed	B	No Necropsy Performed

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	02 68	02 77	02 88	02 99	03 30	03 11	03 22	03 33	03 44	03 55	03 66	03 77	03 88	03 99	04 00	04 11	04 22	04 33	04 44	04 55	04 66	04 77	04 88	04 99	05 00	TOTAL
WEEKS ON STUDY	08 22	09 88	10 22	10 04	10 55	10 30	10 55	10 55	06 99	03 66	00 33	00 33	09 11	08 66	00 33	08 99	10 44	04 22	05 33	03 34	00 33	00 33	10 55	10 55	08 66	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	M	+	+	+	+	+	A	+	+	N	+	+	+	+	+	+	+	+	+	+	*48
Fibroma							X																			2
Subcutaneous tissue	+	+	+	+	+	M	+	+	+	+	+	A	+	+	N	+	+	+	+	+	+	+	+	+	+	*48
Fibrosarcoma																										3
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	M	+	+	+	+	+	A	+	+	–	+	+	+	+	+	+	+	+	+	+	47
Hepatocellular carcinoma, metastatic																										2
Alveolar/bronchiolar adenoma													X												X	6
Alveolar/bronchiolar carcinoma								X																		2
Trachea	+	+	+	+	+	M	+	+	+	+	–	A	+	+	–	+	+	–	+	+	A	+	+	+	+	43
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	–	+	+	A	A	–	+	+	+	44
Hemangiosarcoma																										1
Lymph nodes	+	+	+	+	+	M	+	+	+	+	+	A	–	+	–	+	+	–	+	A	A	–	+	+	+	41
Fibrosarcoma, metastatic																										1
Hemangiosarcoma, metastatic																										1
Thymus	+	–	–	–	–	M	–	–	–	–	–	A	–	+	–	–	–	–	+	A	A	–	–	–	–	5
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	M	+	+	+	+	+	A	+	+	–	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	M	+	+	+	–	+	A	+	+	–	+	+	–	+	+	A	–	+	+	+	42
Liver	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bile duct carcinoma																										1
Hepatocellular adenoma			X		X									X												6
Hepatocellular carcinoma	X	X	X										X													14
Bile duct	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	N	+	+	+	+	M	+	+	+	+	+	A	+	N	+	N	+	N	N	N	+	+	+	+	N	*48
Pancreas	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	46
Esophagus	+	+	+	+	+	M	+	+	+	+	+	A	+	+	–	+	+	–	+	+	A	+	+	+	+	44
Stomach	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	47
Squamous cell carcinoma																									X	1
Small intestine	+	–	+	+	+	M	+	+	+	–	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	45
Adenocarcinoma, NOS																										1
Large intestine	+	+	+	+	+	M	+	+	+	+	+	A	–	+	+	+	+	+	+	A	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	M	+	+	+	+	–	A	+	+	–	+	+	+	+	A	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	M	+	+	+	+	–	A	+	+	–	+	+	+	–	A	A	+	+	+	–	38
Adenocarcinoma, NOS																										1
Adrenal	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	46
Cortical adenoma													X				X						X			3
Pheochromocytoma									X																	3
Pheochromocytoma, malignant		X																								1
Thyroid	+	+	+	+	+	M	+	+	+	+	+	A	+	+	–	+	+	–	+	A	A	–	+	+	+	41
Follicular-cell adenoma													X			X							X			4
Parathyroid	–	–	–	–	+	M	+	+	+	–	–	A	+	+	–	–	–	–	–	A	A	–	+	+	+	23
Pancreatic islets	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	46
Islet-cell adenoma			X																							2
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	M	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Testis	+	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Prostate	–	+	+	+	+	M	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	M	+	+	+	+	+	A	+	+	–	+	+	+	+	+	+	+	+	+	+	46
BODY CAVITIES																										
Pleura	N	N	N	N	N	M	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Bile duct carcinoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	M	N	N	N	N	N	A	N	N	N	N	N	N	N	N	N	N	N	N	N	*48
Sarcoma, NOS, unc prim or meta																										1
Malig. lymphoma, lymphocytic type			X																							7
Leukemia, NOS																									X	1

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: LOW DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	091	104	092	093	104	101	104	088	097	104	027	057	104	104	057	104	098	104	104	080	095	102	099	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal-cell tumor																		X							
Fibroma			X																						
Neurofibrosarcoma																					X				
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma													X					X							
Fibrosarcoma																									
Leiomyosarcoma									X																
Osteosarcoma																	X								
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic	X																X								
Alveolar/bronchiolar carcinoma																				X					
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																	X								
Malignant lymphoma, mixed type																									X
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	–	+	–	–	–	–	–	–	–	–	–	–	–	+	+	+	–	+	–	–	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma		X			X								X			X		X	X					X	
Hepatocellular carcinoma	X	X					X	X					X	X			X					X				
Pheochromocytoma, metastatic				X																					
Hemangiosarcoma, metastatic																	X								
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	+	+	N	+	+	N	N	+	+	N	N	+	+	+	N	N	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																			X						
Small intestine	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Malignant lymphoma, mixed type														X											
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma													X												
Pheochromocytoma														X				X			X				
Pheochromocytoma, malignant				X																					
Thyroid	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma																									
Parathyroid	+	–	+	+	–	–	+	–	–	–	–	–	–	–	+	–	+	+	+	+	–	–	–	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial-cell tumor																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Osteosarcoma, invasive																									
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Osteosarcoma, invasive																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant	X																								
Malig. lymphoma, lymphocytic type		X				X		X													X				
Malig. lymphoma, histiocytic type																			X					X	
Malignant lymphoma, mixed type																						X			

+ Tissue Examined Microscopically
– Required Tissue Not Examined Microscopically
X Tumor Incidence
N Necropsy, No Autolysis, No Microscopic Examination
S Animal Missexed
No Tissue Information Submitted
C Necropsy, No Histology Due To Protocol
A Autolysis
M Animal Missing
B No Necropsy Performed

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	076	104	073	095	100	078	104	099	097	079	102	046	097	104	095	041	093	042	096	048	104	047	104	093	102	095	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*50
Basal-cell tumor																										1
Fibroma																										1
Neurofibrosarcoma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*50
Fibroma																										2
Fibrosarcoma					X				X			X										X				4
Leiomyosarcoma																										1
Osteosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic						X																				3
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	–	–	+	–	–	–	–	–	–	–	–	–	+	+	–	–	–	+	–	–	–	–	–	+	12
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										7
Hepatocellular carcinoma		X				X	X				X														X	13
Pheochromocytoma, metastatic																										1
Hemangiosarcoma, metastatic																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	N	N	+	+	+	N	+	N	N	N	+	+	N	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, mixed type																										1
Large intestine	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	47
Rectum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	*50
Adenocarcinoma, NOS																	X									1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	43
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma													X													2
Pheochromocytoma							X			X																5
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular-cell adenoma							X																			1
Parathyroid	+	+	+	+	–	–	–	+	+	–	–	–	–	–	+	–	+	+	+	–	–	–	–	–	+	22
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	+	N	+	N	+	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial-cell tumor															X											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma, invasive															X											1
Seminal vesicle	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Osteosarcoma, invasive															X											1
NERVOUS SYSTEM																										
Brain	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS															X											1
BODY CAVITIES																										
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma															X											1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																										1
Malig lymphoma, lymphocytic type				X																				X	X	7
Malig lymphoma, histiocytic type		X					X								X		X		X		X		X			9
Malignant lymphoma, mixed type																										1

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: HIGH DOSE

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	104	104	073	089	073	081	087	104	083	085	040	104	104	086	101	097	069	104	104	097	104	104	104	071	033
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Sarcoma, NOS														X											
Fibroma	X											X													
Fibrosarcoma					X		X			X						X								X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																	X								
Alveolar/bronchiolar carcinoma								X																	
Fibrosarcoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Thymus	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–	+	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma		X							X			X					X			X	X			
Hepatocellular carcinoma				X		X		X	X				X		X	X	X			X	X	X	X	X	
Hepatoblastoma																								X	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell carcinoma																	X								
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS								X																	
Small intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–
Large intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma																									
Fibrosarcoma, metastatic										X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Adrenal	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																X									
Fibrosarcoma, metastatic										X															
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Follicular cell adenoma		X				X																			
Parathyroid	+	+	+	–	+	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	–	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS		X													X										
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Acinar-cell carcinoma, metastatic																	X								
Malig lymphoma, lymphocytic type			X																						
Malig lymphoma, histiocytic type				X																			X		

+ Tissue Examined Microscopically
– Required Tissue Not Examined Microscopically
X Tumor Incidence
N Necropsy, No Autolysis, No Microscopic Examination
S Animal Missexed
No Tissue Information Submitted
C Necropsy, No Histology Due To Protocol
A Autolysis
M Animal Missing
B No Necropsy Performed

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	022 026	022 027	022 028	022 029	033 030	033 031	033 032	033 033	033 034	033 035	033 036	033 037	033 038	033 039	044 040	044 041	044 042	044 043	044 044	044 045	044 046	044 047	044 048	044 049	055 050	TOTAL
WEEKS ON STUDY	104	102	096	104	077	087	072	104	104	078	102	104	086	104	104	200	201	101	104	044	093	104	072	116	029	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
Fibroma																						X				3
Fibrosarcoma			X	X		X						X											X			10
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic					X																					2
Alveolar/bronchiolar carcinoma					X																X					3
Fibrosarcoma, metastatic			X																							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	47
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	48
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	+	+	–	–	–	–	–	–	+	–	6
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma	X			X				X				X	X							X	X					13
Hepatocellular carcinoma	X	X		X	X				X	X	X				X							X				22
Hepatoblastoma																										1
Bile duct	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	+	+	N	+	+	+	+	+	h	+	N	+	N	+	+	+	+	+	+	+	+	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Acinar cell carcinoma																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	h	h	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	h	+	+	–	+	+	+	+	+	+	+	49
Papilloma, NOS			X																							2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	–	44
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular-cell adenocarcinoma					X																					1
Fibrosarcoma, metastatic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
ENDOCRINE SYSTEM																										
Pituitary	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	45
Adrenal	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	47
Pheochromocytoma		X																								2
Fibrosarcoma, metastatic																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	48
Follicular-cell adenoma																										2
Parathyroid	+	+	+	+	+	–	+	+	–	–	–	–	–	+	–	+	+	–	+	+	+	+	–	–	–	20
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Acinar-cell carcinoma, metastatic																										1
Malig. lymphoma, lymphocytic type																										1
Malig. lymphoma, histiocytic type							X															X				4

*Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: VEHICLE CONTROL

ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	101	105	105	105	105	105	089	105	105	091	105	098	093	089	089	104	077	105	091	105	096
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma			X					X															X		
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Malig. lymphoma, histiocytic type																							X		
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	–	–	–	–	–	–	–	+	–	–	–	+	–	–	+	–	–	–	+	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X				X																	
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	N	+	N	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X			X				X			X	X													
Adenocarcinoma, NOS						X							X										X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Cortical adenoma											X														
Thyroid	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma											X														
Follicular-cell carcinoma													X												
C-cell carcinoma																							X		
Parathyroid	–	+	+	–	+	+	+	+	+	–	–	+	–	+	+	+	+	–	–	–	–	+	–	–	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell carcinoma															X										
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma				X																					
Endometrial stromal polyp	X										X	X													
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive													X												
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS									X																
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type						X				X				X											X
Malig. lymphoma, histiocytic type															X	X						X			
Malignant lymphoma, mixed type																				X					

+ Tissue Examined Microscopically
– Required Tissue Not Examined Microscopically
X Tumor Incidence
N Necropsy, No Autolysis, No Microscopic Examination
S Animal Missexed
: No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	090	086	105	102	089	096	105	094	105	079	105	105	105	089	095	083	084	105	105	086	087	104	082	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma															X											1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
Malig. lymphoma, histiocytic type																										1
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	47
Thymus	–	–	+	–	–	+	–	+	+	–	–	+	+	–	+	–	–	–	–	–	–	–	–	+	–	12
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																										2
Hepatocellular carcinoma																			X					X		2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	N	+	+	N	+	+	+	+	+	N	N	+	N	+	+	+	N	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma, NOS																X										1
Small intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47
Adenoma, NOS									X			X	X						X			X		X		11
Adenocarcinoma, NOS				X																					X	5
Adrenal	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	48
Adenoma, NOS											X															1
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular-cell adenoma												X														2
Follicular-cell carcinoma																										1
C-cell carcinoma																										1
Parathyroid	+	–	+	–	–	+	+	+	+	+	+	+	+	–	+	–	–	–	–	–	–	–	+	+		26
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Endometrial stromal polyp																										3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, invasive																										1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																	X									2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, lymphocytic type			X						X									X					X	X		9
Malig. lymphoma, histiocytic type				X		X		X			X				X							X				9
Malignant lymphoma, mixed type										X																2

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: LOW DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	105	010	105	105	104	105	105	105	105	105	081	004	105	003	105	097	105	105	048	105	105	097	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Sarcoma, NOS, metastatic											X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Malig. lymphoma, lymphocytic type																									
Thymus	–	+	–	–	–	–	–	+	–	–	–	+	–	–	+	–	–	+	–	+	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X																	
Hepatocellular carcinoma																								X	X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	–	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	+	–	+	–	+	+	+	+	–	+	–	–	+	–	+
Adenoma, NOS				X					X				X				X	X							X
Adenocarcinoma, NOS															X										
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma	X												X			X									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma								X					X												
Follicular-cell carcinoma															X										
Parathyroid	–	–	+	+	+	+	+	–	–	+	–	–	+	+	–	–	–	–	–	+	–	–	–	–	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet-cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	N	+	+	N	N	+	N	N	N	+
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp								X		X															
Ovary	+	+	+	+	–	+	–	+	+	+	+	–	+	–	+	+	+	+	+	+	+	–	+	+	+
Cystadenoma, NOS																									X
Teratoma, benign		X																							
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS					X																				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma, metastatic																									
Malig lymphoma, lymphocytic type					X					X															
Malig lymphoma, histiocytic type															X	X	X	X	X	X					
Malignant lymphoma, mixed type																							X		

+ Tissue Examined Microscopically
– Required Tissue Not Examined Microscopically
X Tumor Incidence
N Necropsy, No Autolysis, No Microscopic Examination
S Animal Missexed
No Tissue Information Submitted
C Necropsy, No Histology Due To Protocol
A Autolysis
M Animal Missing
B No Necropsy Performed

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	02 26	02 27	02 28	02 29	03 30	03 31	03 32	03 33	03 34	03 35	03 36	03 37	03 38	03 39	04 40	04 41	04 42	04 43	04 44	04 45	04 46	04 47	04 48	04 49	05 50	TOTAL
WEEKS ON STUDY	09 05	10 05	10 05	10 05	10 01	10 04	10 05	10 05	10 05	09 01	08 09	10 05	10 05	10 05	10 05	10 05	10 00	06 09	10 05	09 05	10 05	10 05	09 08	10 05	10 05	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																									X	1
Sarcoma, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malig. lymphoma, lymphocytic type																				X						1
Thymus	–	–	+	–	+	+	–	+	–	–	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	12
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X			X			X													4
Hepatocellular carcinoma																										2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	41
Adenoma, NOS				X				X											X		X					10
Adenocarcinoma, NOS							X					X														3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular-cell adenoma																										2
Follicular-cell carcinoma																			X							2
Parathyroid	–	–	+	–	+	+	–	–	–	–	–	–	–	+	–	+	–	+	–	–	–	+	+	+	+	19
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet-cell carcinoma																							X			1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS	X																									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp		X											X	X												5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Cystadenoma, NOS													X													2
Teratoma, benign																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	49
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Osteosarcoma																		X								1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS		X											X													3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma, metastatic																		X								1
Malig. lymphoma, lymphocytic type					X		X		X	X	X	X													X	9
Malig. lymphoma, histiocytic type			X													X							X	X		10
Malignant lymphoma, mixed type						X								X												3

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE: HIGH DOSE

ANIMAL NUMBER	0001	0002	0003	0004	0005	0006	0007	0008	0009	0010	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025
WEEKS ON STUDY	097	104	099	104	104	094	104	104	104	104	104	104	104	064	104	104	012	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma	X								X																
Mesothelioma, metastatic														X											
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Malig. lymphoma, lymphocytic type																									
Thymus	+	–	–	+	–	+	–	+	–	–	–	–	–	+	–	+	+	–	+	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X		X																	X	
Hepatocellular carcinoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar-cell adenoma													X												
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Adenoma, NOS				X												X					X	X			
Adenocarcinoma, NOS																						X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																								X	
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	–	–	+	–	–	+	–	+	–	–	–	+	–	–	–	–	+	–	+	+	–	–	–	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma	X																								
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spinal cord	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																									
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenoma, NOS																								X	
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant														X											
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type							X			X	X					X		X	X			X		X	
Malig. lymphoma, histiocytic type		X		X																					
Malignant lymphoma, mixed type						X		X															X		

+ Tissue Examined Microscopically
– Required Tissue Not Examined Microscopically
X Tumor Incidence
N Necropsy, No Autolysis, No Microscopic Examination
S Animal Missexed
. No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	012	005	003	012	021	041	042	012	041	041	041	033	041	041	041	041	042	033	012	033	012	041	041	063	041	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Mesothelioma, metastatic																										1
Trachea	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	–	+	43
Malig. lymphoma, lymphocytic type																X										1
Thymus	+	+	+	+	+	–	+	+	+	–	–	–	+	–	+	–	–	–	–	+	–	+	–	–	–	20
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X		X														X	6
Hepatocellular carcinoma							X											X								2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	N	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Acinar-cell adenoma																										1
Esophagus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Papilloma, NOS																					X					1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	–	–	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	–	+	44
Adenoma, NOS							X																			5
Adenocarcinoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma										X																1
Pheochromocytoma																										1
Thyroid	+	+	+	+	–	+	+	–	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	46
Parathyroid	–	+	+	+	–	+	–	–	–	+	+	+	–	–	–	+	–	–	–	+	–	+	–	+	+	19
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spinal cord	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurilemoma, malignant									X																	1
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Adenoma, NOS																										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig. lymphoma, lymphocytic type							X		X							X										11
Malig. lymphoma, histiocytic type										X																3
Malignant lymphoma, mixed type																										3

* Animals Necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)	
HYPERPLASIA, BASAL CELL	1 (2%)		
HYPERKERATOSIS	1 (2%)	1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
ABSCESS, CHRONIC			1 (2%)
GRANULOMA, FOREIGN BODY			3 (6%)
RESPIRATORY SYSTEM			
#TRACHEA	(49)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
#LUNG	(50)	(50)	(50)
VEGETABLE FOREIGN BODY		1 (2%)	
EMPHYSEMA, ALVEOLAR	(a) 1 (2%)	(a) 4 (8%)	(a) 12 (24%)
CONGESTION, NOS	6 (12%)	6 (12%)	15 (30%)
EDEMA, NOS	1 (2%)	2 (4%)	2 (4%)
HEMORRHAGE	22 (44%)	10 (20%)	5 (10%)
BRONCHOPNEUMONIA, ACUTE		1 (2%)	1 (2%)
PNEUMONIA INTERSTITIAL CHRONIC	9 (18%)	8 (16%)	10 (20%)
BRONCHOPNEUMONIA, CHRONIC	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
HISTIOCYTOSIS	11 (22%)	2 (4%)	5 (10%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(50)	(50)
HYPERPLASIA, HEMATOPOIETIC			1 (2%)
#SPLEEN	(50)	(50)	(50)
GRANULOMA, NOS	1 (2%)		
FIBROSIS, FOCAL	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
INFARCT, HEALED	1 (2%)		
PIGMENTATION, NOS	36 (72%)	28 (56%)	33 (66%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	2 (4%)
HEMATOPOIESIS	33 (66%)	30 (60%)	32 (64%)
#SPLENIC CAPSULE	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
FIBROSIS, FOCAL		1 (2%)	
#SPLENIC FOLLICLES	(50)	(50)	(50)
ATROPHY, DIFFUSE		1 (2%)	
#MANDIBULAR LYMPH NODE	(50)	(50)	(48)
CYST, NOS		1 (2%)	
#MESENTERIC LYMPH NODE	(50)	(50)	(48)
CONGESTION, NOS		1 (2%)	3 (6%)
EDEMA, NOS	1 (2%)	1 (2%)	3 (6%)
HEMOSIDEROSIS		1 (2%)	1 (2%)
MASTOCYTOSIS			1 (2%)

(a) The NTP has reexamined these tissues and determined that emphysematous changes were related to hyperinflation of the lungs during fixation and did not result from isophorone exposure.

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#THYMUS	(0)	(6)	(8)
CONGESTION, NOS		1 (17%)	
HEMORRHAGE			1 (13%)
CIRCULATORY SYSTEM			
*THORACIC CAVITY	(50)	(50)	(50)
PERIARTERITIS			1 (2%)
#HEART	(50)	(50)	(50)
THROMBOSIS, NOS	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC FOCAL	43 (86%)	41 (82%)	39 (78%)
#HEART/ATRIUM	(50)	(50)	(50)
THROMBUS, ORGANIZED		1 (2%)	1 (2%)
#ENDOCARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
*MESENTERIC ARTERY	(50)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
PERIARTERITIS	1 (2%)	1 (2%)	
*MESENTERY	(50)	(50)	(50)
PERIARTERITIS			2 (4%)
DIGESTIVE SYSTEM			
*TONGUE	(50)	(50)	(50)
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)
#SALIVARY GLAND	(48)	(49)	(49)
INFLAMMATION, CHRONIC FOCAL	1 (2%)	3 (6%)	2 (4%)
#LIVER	(50)	(50)	(50)
CONGENITAL MALFORMATION, NOS	2 (4%)	2 (4%)	1 (2%)
CYST, NOS			1 (2%)
CONGESTION, NOS	5 (10%)	2 (4%)	3 (6%)
GRANULOMA, NOS	1 (2%)		2 (4%)
NECROSIS, COAGULATIVE	4 (8%)	5 (10%)	7 (14%)
INFARCT, ACUTE	1 (2%)		
METAMORPHOSIS FATTY	9 (18%)	2 (4%)	5 (10%)
CYTOPLASMIC VACUOLIZATION	3 (6%)	4 (8%)	9 (18%)
BASOPHILIC CYTO CHANGE	1 (2%)		
FOCAL CELLULAR CHANGE	41 (82%)	35 (70%)	22 (44%)
CLEAR CELL CHANGE	1 (2%)	1 (2%)	1 (2%)
HEPATOCYTOMEGALY		2 (4%)	2 (4%)
ANGIECTASIS			1 (2%)
#LIVER/PERIPORTAL	(50)	(50)	(50)
INFLAMMATION, MULTIFOCAL		3 (6%)	
INFLAMMATION, CHRONIC FOCAL	27 (54%)	24 (48%)	15 (30%)
METAMORPHOSIS FATTY			1 (2%)
#BILE DUCT	(50)	(50)	(50)
MULTILOCULAR CYST		1 (2%)	
FIBROSIS, FOCAL	1 (2%)		
HYPERPLASIA, FOCAL	46 (92%)	44 (88%)	41 (82%)
#PANCREAS	(50)	(50)	(50)
HEMORRHAGE	2 (4%)		1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	18 (36%)	22 (44%)	15 (30%)
ATROPHY, NOS			1 (2%)
#PANCREATIC ACINUS	(50)	(50)	(50)
ATROPHY, NOS		3 (6%)	5 (10%)
ATROPHY, FOCAL	1 (2%)		1 (2%)
HYPERPLASIA, NOS	2 (4%)		2 (4%)
HYPERPLASIA, FOCAL	13 (26%)	17 (34%)	10 (20%)
#ESOPHAGUS	(50)	(50)	(50)
DILATATION, NOS			1 (2%)
HEMORRHAGE	2 (4%)	1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#GLANDULAR STOMACH	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTRA		3 (6%)	
INFLAMMATION, CHRONIC	1 (2%)		
DEGENERATION, NOS		1 (2%)	
DEGENERATION, CYSTIC	15 (30%)	9 (18%)	28 (56%)
#FORESTOMACH	(50)	(50)	(50)
ULCER, NOS	1 (2%)	1 (2%)	4 (8%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
INFLAMMATION ACTIVE CHRONIC			3 (6%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
EROSION		1 (2%)	
HYPERPLASIA, EPITHELIAL	2 (4%)	1 (2%)	
HYPERKERATOSIS	7 (14%)	1 (2%)	5 (10%)
#DUODENUM	(50)	(50)	(50)
ULCER, ACUTE			1 (2%)
#COLON	(49)	(50)	(50)
CYST, NOS	1 (2%)		
PARASITISM	3 (6%)	14 (28%)	8 (16%)
#CECUM	(49)	(50)	(50)
HEMATOMA, NOS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS		2 (4%)	
CONGESTION, NOS	2 (4%)	3 (6%)	3 (6%)
NEPHROPATHY	49 (98%)	47 (94%)	46 (92%)
PIGMENTATION, NOS		1 (2%)	1 (2%)
HYPERPLASIA, TUBULAR CELL		1 (2%)	4 (8%)
#KIDNEY/CORTEX	(50)	(50)	(50)
CYST, NOS	2 (4%)		1 (2%)
MULTIPLE CYSTS			1 (2%)
HEMORRHAGE	1 (2%)		
#KIDNEY/TUBULE	(50)	(50)	(50)
MINERALIZATION	1 (2%)	31 (62%)	20 (40%)
PIGMENTATION, NOS	39 (78%)	39 (78%)	27 (54%)
REGENERATION, NOS		1 (2%)	
#KIDNEY/PELVIS	(50)	(50)	(50)
HEMORRHAGE		3 (6%)	5 (10%)
HYPERPLASIA, EPITHELIAL		5 (10%)	5 (10%)
#URINARY BLADDER	(49)	(49)	(48)
CALCULUS, GROSS OBSERVATION ONLY		1 (2%)	
CALCULUS, MICROSCOPIC EXAMINATION	1 (2%)	2 (4%)	2 (4%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION, ACUTE DIFFUSE		1 (2%)	
*URETHRA	(50)	(50)	(50)
CALCULUS, MICROSCOPIC EXAMINATION	6 (12%)	6 (12%)	7 (14%)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
ENDOCRINE SYSTEM			
#ANTERIOR PITUITARY	(48)	(49)	(47)
EMBRYONAL DUCT CYST			1 (2%)
CYST, NOS	1 (2%)	2 (4%)	1 (2%)
MULTIPLE CYSTS	2 (4%)	1 (2%)	2 (4%)
CONGESTION, NOS		1 (2%)	
HEMORRHAGE	1 (2%)		
HEMORRHAGIC CYST	2 (4%)		1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#ANTERIOR PITUITARY (Continued)	(48)	(49)	(47)
GRANULOMA, NOS		1 (2%)	
CHOLESTEROL DEPOSIT	1 (2%)		
HYPERPLASIA, FOCAL	8 (17%)	11 (22%)	8 (17%)
ANGIECTASIS	1 (2%)		
#ADRENAL	(50)	(50)	(50)
ANGIECTASIS	32 (64%)	30 (60%)	27 (54%)
#ADRENAL CORTEX	(50)	(50)	(50)
ACCESSORY STRUCTURE		2 (4%)	
CYST, NOS		1 (2%)	
CONGESTION, NOS	1 (2%)		
HEMORRHAGE			1 (2%)
METAMORPHOSIS FATTY	7 (14%)	21 (42%)	26 (52%)
PIGMENTATION, NOS		1 (2%)	2 (4%)
HYPERPLASIA, FOCAL	8 (16%)	15 (30%)	6 (12%)
#ADRENAL MEDULLA	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	2 (4%)
HYPERPLASIA, FOCAL	9 (18%)	10 (20%)	7 (14%)
#THYROID	(49)	(50)	(49)
EMBRYONAL DUCT CYST	3 (6%)	4 (8%)	4 (8%)
FOLLICULAR CYST, NOS	2 (4%)	3 (6%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
PIGMENTATION, NOS	6 (12%)	8 (16%)	
HYPERPLASIA, C-CELL	5 (10%)	8 (16%)	11 (22%)
HYPERPLASIA, FOLLICULAR CELL	1 (2%)	1 (2%)	1 (2%)
#THYROID FOLLICLE	(49)	(50)	(49)
MULTIPLE CYSTS	2 (4%)	1 (2%)	5 (10%)
#PANCREATIC ISLETS	(50)	(50)	(50)
HYPERPLASIA, FOCAL			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
CYSTIC DUCTS	1 (2%)		
HYPERPLASIA, CYSTIC	3 (6%)	1 (2%)	4 (8%)
*PREPUCE	(50)	(50)	(50)
ULCER, ACUTE			1 (2%)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
ABSCESS, CHRONIC			2 (4%)
#PROSTATE	(49)	(50)	(49)
INFLAMMATION, ACUTE FOCAL	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE DIFFUSE		1 (2%)	
INFLAMMATION ACTIVE CHRONIC	12 (24%)	7 (14%)	4 (8%)
INFLAMMATION, CHRONIC FOCAL	2 (4%)	2 (4%)	3 (6%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL		2 (4%)	1 (2%)
*SEMINAL VESICLE	(50)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE		1 (2%)	
INFLAMMATION ACTIVE CHRONIC	11 (22%)	6 (12%)	6 (12%)
INFLAMMATION, CHRONIC FOCAL	3 (6%)	3 (6%)	4 (8%)
ATROPHY, DIFFUSE		1 (2%)	
HYPERPLASIA, EPITHELIAL		2 (4%)	3 (6%)
METAPLASIA, NOS			1 (2%)
#TESTIS	(48)	(50)	(50)
DEGENERATION, NOS			1 (2%)
ATROPHY, DIFFUSE	1 (2%)		
OLIGOSPERMIA		1 (2%)	1 (2%)
HYPERPLASIA, INTERSTITIAL CELL	36 (75%)	36 (72%)	40 (80%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#TESTIS/TUBULE	(48)	(50)	(50)
MINERALIZATION	6 (13%)	8 (16%)	1 (2%)
DEGENERATION, NOS	35 (73%)	35 (70%)	30 (60%)
ATROPHY, DIFFUSE	1 (2%)	1 (2%)	1 (2%)
*SCROTUM	(50)	(50)	(50)
STEATITIS		2 (4%)	
NERVOUS SYSTEM			
#CEREBRAL VENTRICLE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
#BRAIN	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	2 (4%)
HEMORRHAGE	2 (4%)	2 (4%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
INFARCT, FOCAL			1 (2%)
INFARCT, ACUTE	2 (4%)	1 (2%)	
ATROPHY, PRESSURE	2 (4%)	1 (2%)	
*SPINAL CORD	(50)	(50)	(50)
CONGESTION, NOS	34 (68%)	30 (60%)	27 (54%)
HEMORRHAGE			2 (4%)
INFARCT, ACUTE		1 (2%)	
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
HEMORRHAGE		2 (4%)	1 (2%)
HEMATOMA, ORGANIZED			1 (2%)
STEATITIS	1 (2%)		
*PERICARDIUM	(50)	(50)	(50)
STEATITIS		1 (2%)	
INFLAMMATION, ACUTE			1 (2%)
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
*MESENTERY	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
STEATITIS	4 (8%)		1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS			4 (8%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	4 (8%)	5 (10%)	4 (8%)
PIGMENTATION, NOS		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
ADIPOSE TISSUE			
INFLAMMATION, CHRONIC FOCAL			1
SPECIAL MORPHOLOGY SUMMARY			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)
HYPERKERATOSIS		2 (4%)	
*SUBCUT TISSUE	(50)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)	
INFLAMMATION ACTIVE CHRONIC			1 (2%)
GRANULOMA, FOREIGN BODY			1 (2%)
GRANULOMA, PYOGENIC	1 (2%)		
RESPIRATORY SYSTEM			
*LARYNX	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
#TRACHEA	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
#PERITRACHEAL TISSUE	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
#LUNG/BRONCHIOLE	(50)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)	1 (2%)
FOREIGN MATERIAL, NOS	1 (2%)		
#LUNG	(50)	(50)	(50)
EMPHYSEMA, ALVEOLAR	(a) 2 (4%)	(a) 4 (8%)	(a) 12 (24%)
CONGESTION, NOS	10 (20%)	12 (24%)	10 (20%)
EDEMA, NOS		3 (6%)	2 (4%)
HEMORRHAGE	10 (20%)	17 (34%)	10 (20%)
BRONCHOPNEUMONIA, ACUTE	2 (4%)		
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
PNEUMONIA INTERSTITIAL CHRONIC	10 (20%)	7 (14%)	6 (12%)
BRONCHOPNEUMONIA, CHRONIC	2 (4%)	1 (2%)	2 (4%)
FOREIGN MATERIAL, NOS		2 (4%)	
HYPERPLASIA, ALVEOLAR EPITHELIUM	2 (4%)		1 (2%)
HISTIOCYTOSIS	13 (26%)	5 (10%)	5 (10%)
#LUNG/ALVEOLI	(50)	(50)	(50)
SCLEROSIS		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(50)	(50)
FIBROSIS, FOCAL	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
INFARCT, NOS	1 (2%)		
PIGMENTATION, NOS	39 (78%)	45 (90%)	42 (84%)
METAPLASIA, OSSEOUS	1 (2%)		
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID		2 (4%)	1 (2%)
HEMATOPOIESIS	38 (76%)	34 (68%)	36 (72%)
#SPLENIC FOLLICLES	(50)	(50)	(50)
ATROPHY, DIFFUSE	1 (2%)		

(a) The NTP has reexamined these tissues and determined that emphysematus changes were related to hyperinflation of the lungs during fixation and did not result from isophorone exposure.

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#MESENTERIC LYMPH NODE	(50)	(49)	(48)
CONGESTION, NOS	1 (2%)		2 (4%)
EDEMA, NOS	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
PIGMENTATION, NOS	1 (2%)		
HYPERPLASIA, RETICULUM CELL	2 (4%)		1 (2%)
#MESENTERIC LYMPH NODE	(50)	(49)	(48)
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	1 (2%)
MASTOCYTOSIS		1 (2%)	1 (2%)
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)		
#ADRENAL CORTEX	(50)	(50)	(50)
LYMPHOCYTOSIS	1 (2%)		
#THYMUS	(2)	(6)	(16)
CONGESTION, NOS		1 (17%)	
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	38 (76%)	41 (82%)	29 (58%)
*MESENTERIC ARTERY	(50)	(50)	(50)
PERIARTERITIS		1 (2%)	
*PULMONARY VEIN	(50)	(50)	(50)
INFLAMMATION, ACUTE NECROTIZING	1 (2%)		
*PORTAL VEIN	(50)	(50)	(50)
DILATATION, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
ATROPHY, FOCAL			1 (2%)
#LIVER	(50)	(50)	(50)
CONGENITAL MALFORMATION, NOS	3 (6%)	1 (2%)	
CYST, NOS	1 (2%)		
CONGESTION, NOS	1 (2%)	3 (6%)	2 (4%)
ABSCESS, NOS			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
GRANULOMA, NOS	5 (10%)		
PELIOSIS HEPATIS		1 (2%)	
NECROSIS, COAGULATIVE	1 (2%)	3 (6%)	1 (2%)
INFARCT, ACUTE		1 (2%)	
METAMORPHOSIS FATTY	6 (12%)	1 (2%)	1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
BASOPHILIC CYTO CHANGE	8 (16%)	5 (10%)	
FOCAL CELLULAR CHANGE	42 (84%)	35 (70%)	22 (44%)
CLEAR CELL CHANGE	2 (4%)		1 (2%)
HEPATOCYTOMEGALY	1 (2%)	2 (4%)	5 (10%)
HYPERTROPHY, NOS	2 (4%)		
HYPERTROPHY, FOCAL	1 (2%)		
ANGIECTASIS	1 (2%)	1 (2%)	
REGENERATION, NOS			1 (2%)
#LIVER/PERIPORTAL	(50)	(50)	(50)
INFLAMMATION, MULTIFOCAL	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	33 (66%)	26 (52%)	14 (28%)
METAMORPHOSIS FATTY		2 (4%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, FOCAL	40 (80%)	37 (74%)	34 (68%)
#PANCREAS	(50)	(50)	(50)
CYSTIC DUCTS			1 (2%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	22 (44%)	20 (40%)	9 (18%)
FIBROSIS, FOCAL		1 (2%)	
#PANCREATIC ACINUS	(50)	(50)	(50)
ATROPHY, NOS	3 (6%)	5 (10%)	3 (6%)
ATROPHY, FOCAL		1 (2%)	
HYPERPLASIA, FOCAL	4 (8%)	4 (8%)	3 (6%)
#ESOPHAGUS	(50)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)	4 (8%)
#GLANDULAR STOMACH	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
EROSION		2 (4%)	
DEGENERATION, NOS		1 (2%)	
DEGENERATION, CYSTIC	27 (54%)	19 (38%)	23 (46%)
HYPERPLASIA, EPITHELIAL		1 (2%)	
#FORESTOMACH	(50)	(50)	(50)
ULCER, ACUTE		1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)
ULCER, CHRONIC	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)	
HYPERKERATOSIS		5 (10%)	
#COLON	(50)	(50)	(48)
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)	
PARASITISM	5 (10%)	2 (4%)	6 (13%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
HYDRONEPHROSIS	1 (2%)		
CYST, NOS			1 (2%)
CONGESTION, NOS	1 (2%)	4 (8%)	4 (8%)
HEMORRHAGE		1 (2%)	1 (2%)
NEPHROPATHY	21 (42%)	39 (78%)	32 (64%)
INFARCT, NOS		1 (2%)	
PIGMENTATION, NOS		1 (2%)	
CYTOPLASMIC VACUOLIZATION			1 (2%)
HYPERPLASIA, TUBULAR CELL			1 (2%)
#PERIRENAL TISSUE	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
#KIDNEY/TUBULE	(50)	(50)	(50)
MINERALIZATION	10 (20%)	4 (8%)	2 (4%)
CYST, NOS		1 (2%)	
METAMORPHOSIS FATTY	1 (2%)		
PIGMENTATION, NOS	39 (78%)	37 (74%)	28 (56%)
CYTOPLASMIC VACUOLIZATION		1 (2%)	1 (2%)
#KIDNEY/PELVIS	(50)	(50)	(50)
CALCULUS, MICROSCOPIC EXAMINATION	1 (2%)		
HEMORRHAGE	2 (4%)	1 (2%)	2 (4%)
HYPERPLASIA, EPITHELIAL			1 (2%)
#URINARY BLADDER	(46)	(47)	(47)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#URINARY BLADDER/SEROSA	(46)	(47)	(47)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#ANTERIOR PITUITARY	(49)	(48)	(47)
EMBRYONAL DUCT CYST	1 (2%)		
CYST, NOS	2 (4%)	3 (6%)	1 (2%)
MULTIPLE CYSTS	23 (47%)	10 (21%)	8 (17%)
CONGESTION, NOS		1 (2%)	
HEMORRHAGE		1 (2%)	1 (2%)
PIGMENTATION, NOS			1 (2%)
HYPERPLASIA, FOCAL	3 (6%)	6 (13%)	13 (28%)
ANGIECTASIS	1 (2%)		1 (2%)
#ADRENAL	(50)	(50)	(50)
MINERALIZATION		1 (2%)	
ANGIECTASIS	32 (64%)	41 (82%)	32 (64%)
#ADRENAL/CAPSULE	(50)	(50)	(50)
FIBROSIS, MULTIFOCAL	1 (2%)		
#ADRENAL CORTEX	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)		
NECROSIS, FOCAL	2 (4%)		
METAMORPHOSIS FATTY	13 (26%)	8 (16%)	5 (10%)
PIGMENTATION, NOS	1 (2%)		1 (2%)
HYPERPLASIA, FOCAL	15 (30%)	8 (16%)	6 (12%)
#ADRENAL MEDULLA	(50)	(50)	(50)
MINERALIZATION	1 (2%)		
HYPERPLASIA, FOCAL	6 (12%)	4 (8%)	6 (12%)
#THYROID	(50)	(50)	(48)
EMBRYONAL DUCT CYST	2 (4%)	1 (2%)	
FOLLICULAR CYST, NOS	1 (2%)	1 (2%)	
HEMORRHAGE		1 (2%)	
PIGMENTATION, NOS		1 (2%)	
HYPERPLASIA, C-CELL	11 (22%)	16 (32%)	11 (23%)
HYPERPLASIA, FOLLICULAR CELL			1 (2%)
#THYROID FOLLICLE	(50)	(50)	(48)
MULTIPLE CYSTS	1 (2%)	1 (2%)	1 (2%)
#PARATHYROID	(44)	(40)	(38)
HYPERPLASIA, FOCAL			2 (5%)
#PANCREATIC ISLETS	(50)	(50)	(50)
HYPERPLASIA, FOCAL			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
HYPERPLASIA, CYSTIC	12 (24%)	16 (32%)	10 (20%)
*CLITORAL GLAND	(50)	(50)	(50)
ABSCESS, CHRONIC		1 (2%)	
#UTERUS	(49)	(50)	(49)
HYDROMETRA	8 (16%)	5 (10%)	3 (6%)
CONGESTION, NOS			1 (2%)
INFLAMMATION, ACUTE FOCAL	3 (6%)	2 (4%)	5 (10%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)	
FIBROSIS, FOCAL	1 (2%)		
METAPLASIA, SQUAMOUS	1 (2%)		1 (2%)
#CERVIX UTERI	(49)	(50)	(49)
POLYP	1 (2%)		
#UTERUS/ENDOMETRIUM	(49)	(50)	(49)
CYST, NOS	1 (2%)		
FIBROSIS, FOCAL	1 (2%)		
HYPERPLASIA, CYSTIC	14 (29%)	14 (28%)	11 (22%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH
REPRODUCTIVE SYSTEM (Continued)			
#OVARY/PAROVARIAN	(49)	(50)	(49)
HEMORRHAGE			1 (2%)
STEATITIS	2 (4%)	2 (4%)	
#OVARY	(49)	(50)	(49)
PAROVARIAN CYST	2 (4%)		2 (4%)
CONGESTION, NOS		2 (4%)	
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(49)	(49)
CONGESTION, NOS			1 (2%)
#CEREBRAL VENTRICLE	(50)	(49)	(49)
HEMORRHAGE			1 (2%)
#BRAIN	(50)	(49)	(49)
HYDROCEPHALUS, INTERNAL		1 (2%)	
HEMORRHAGE	1 (2%)	3 (6%)	
INFARCT, ACUTE		1 (2%)	
ATROPHY, PRESSURE	3 (6%)	2 (4%)	1 (2%(
NERVOUS SYSTEM (Continued)			
*SPINAL CORD	(50)	(50)	(50)
CONGESTION, NOS	31 (62%)	32 (64%)	17 (34%)
HEMORRHAGE		2 (4%)	
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
ATROPHY, FOCAL			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*THORACIC CAVITY	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
*MEDIASTINUM	(50)	(50)	(50)
HEMORRHAGE			6 (12%)
STEATITIS		1 (2%)	
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
*PLEURA	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
*PERICARDIUM	(50)	(50)	(50)
STEATITIS			2 (4%)
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
*MESENTERY	(50)	(50)	(50)
HEMORRHAGE	1 (2%)		
STEATITIS		1 (2%)	1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS	1 (2%)	3 (6%)	13 (26%)
HEMORRHAGE			2 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)	9 (18%)
ADIPOSE TISSUE			
HEMORRHAGE			1
SPECIAL MORPHOLOGY SUMMARY			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING	1		
ANIMALS NECROPSIED	48	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
ULCER, NOS		1 (2%)	1 (2%)
ULCER, ACUTE			1 (2%)
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
ULCER, CHRONIC	1 (2%)	4 (8%)	2 (4%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)	2 (4%)	
GRANULATION, TISSUE	1 (2%)	2 (4%)	
PARASITISM	1 (2%)	7 (14%)	7 (14%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
HYPERKERATOSIS	13 (27%)	13 (26%)	15 (30%)
*SUBCUT TISSUE	(48)	(50)	(50)
HEMORRHAGE	1 (2%)		
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
GRANULATION, TISSUE		2 (4%)	
RESPIRATORY SYSTEM			
*TRACHEAL LUMEN	(48)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)	
#TRACHEA	(43)	(48)	(47)
HEMORRHAGE	1 (2%)		2 (4%)
#LUNG	(47)	(50)	(50)
EMPHYSEMA, ALVEOLAR	1 (2%)	5 (10%)	2 (4%)
CONGESTION, NOS	20 (43%)	21 (42%)	22 (44%)
EDEMA, NOS	4 (9%)	2 (4%)	2 (4%)
HEMORRHAGE	13 (28%)	16 (32%)	10 (20%)
INFLAMMATION, INTERSTITIAL		2 (4%)	
ABSCESS, NOS	1 (2%)		
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	1 (2%)		
PNEUMONIA INTERSTITIAL CHRONIC	4 (9%)	9 (18%)	2 (4%)
BRONCHOPNEUMONIA, CHRONIC	2 (4%)	2 (4%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	1 (2%)
HISTIOCYTOSIS	5 (11%)		3 (6%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(48)	(50)	(50)
LEUKEMOID REACTION			1 (2%)
#BONE MARROW	(47)	(50)	(50)
NECROSIS, FOCAL		2 (4%)	
HYPERPLASIA, GRANULOCYTIC	15 (32%)	15 (30%)	18 (36%)
#SPLEEN	(44)	(50)	(47)
INFLAMMATION, ACUTE DIFFUSE		1 (2%)	
PIGMENTATION, NOS	12 (27%)	27 (54%)	24 (51%)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
HYPERPLASIA, LYMPHOID	4 (9%)	4 (8%)	3 (6%)
HEMATOPOIESIS	32 (73%)	38 (76%)	38 (81%)
#SPLENIC CAPSULE	(44)	(50)	(47)
FIBROSIS, FOCAL	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#SPLENIC FOLLICLES	(44)	(50)	(47)
NECROSIS, DIFFUSE		1 (2%)	1 (2%)
#MANDIBULAR LYMPH NODE	(41)	(50)	(48)
PIGMENTATION, NOS		1 (2%)	
ERYTHROPHAGOCYTOSIS			1 (2%)
#MESENTERIC LYMPH NODE	(41)	(50)	(48)
CYST, NOS			1 (2%)
CONGESTION, NOS	12 (29%)	13 (26%)	15 (31%)
EDEMA, NOS		1 (2%)	
HEMORRHAGE		3 (6%)	
INFLAMMATION, ACUTE FOCAL		1 (2%)	
INFLAMMATION, ACUTE DIFFUSE		3 (6%)	5 (10%)
PIGMENTATION, NOS	1 (2%)	2 (4%)	1 (2%)
CYTOMEGALY		1 (2%)	
HISTIOCYTOSIS			1 (2%)
PLASMACYTOSIS			1 (2%)
ERYTHROPHAGOCYTOSIS	4 (10%)	7 (14%)	3 (6%)
HYPERPLASIA, RETICULUM CELL	3 (7%)	1 (2%)	1 (2%)
HYPERPLASIA, LYMPHOID	6 (15%)	6 (12%)	4 (8%)
HEMATOPOIESIS	1 (2%)		
#LIVER	(48)	(50)	(50)
HEMATOPOIESIS	2 (4%)	1 (2%)	2 (4%)
#KIDNEY	(48)	(50)	(50)
LYMPHOCYTOSIS	1 (2%)	1 (2%)	1 (2%)
#ADRENAL CORTEX	(46)	(49)	(47)
LYMPHOCYTOSIS		1 (2%)	
#THYMUS	(5)	(12)	(6)
EMBRYONAL DUCT CYST	1 (20%)		
CONGESTION, NOS	1 (20%)		2 (33%)
INFLAMMATION, ACUTE DIFFUSE			1 (17%)
CIRCULATORY SYSTEM			
#HEART	(47)	(50)	(50)
THROMBUS, ORGANIZED		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	13 (28%)	13 (26%)	14 (28%)
ENDOCARDIOSIS			1 (2%)
CYTOMEGALY	1 (2%)		
*PULMONARY ARTERY	(48)	(50)	(50)
THROMBUS, ORGANIZED			1 (2%)
*PULMONARY VEIN	(48)	(50)	(50)
THROMBOSIS, NOS		1 (2%)	
*MESENTERY	(48)	(50)	(50)
PERIARTERITIS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(42)	(49)	(48)
INFLAMMATION, FOCAL		1 (2%)	
INFLAMMATION, MULTIFOCAL		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	17 (40%)	12 (24%)	13 (27%)
#LIVER	(48)	(50)	(50)
CYST, NOS		1 (2%)	
CONGESTION, NOS	4 (8%)	6 (12%)	6 (12%)
INFLAMMATION, ACUTE FOCAL		1 (2%)	4 (8%)
INFLAMMATION, ACUTE/CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)	2 (4%)	4 (8%)
NECROSIS, COAGULATIVE	3 (6%)	10 (20%)	10 (20%)
NECROSIS, CASEOUS			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#LIVER (Continued)	(48)	(50)	(50)
INFARCT, NOS			1 (2%)
METAMORPHOSIS FATTY		1 (2%)	1 (2%)
PIGMENTATION, NOS		1 (2%)	1 (2%)
CYTOPLASMIC VACUOLIZATION	1 (2%)	3 (6%)	1 (2%)
FOCAL CELLULAR CHANGE	2 (4%)	4 (8%)	6 (12%)
HEPATOCYTOMEGALY	23 (48%)	39 (78%)	37 (74%)
REGENERATION, NOS		1 (2%)	
#LIVER/CENTRILOBULAR	(48)	(50)	(50)
NECROSIS, COAGULATIVE			1 (2%)
HYPERTROPHY, NOS			1 (2%)
#LIVER/PERIPORTAL	(48)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	2 (4%)
#PANCREAS	(46)	(50)	(49)
CYSTIC DUCTS	1 (2%)		
CONGESTION, NOS			1 (2%)
HEMORRHAGE			2 (4%)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	7 (15%)	5 (10%)	4 (8%)
INFLAMMATION, CHRONIC DIFFUSE	1 (2%)	1 (2%)	
ATROPHY, FOCAL		1 (2%)	
ATROPHY, DIFFUSE			1 (2%)
#PANCREATIC DUCT	(46)	(50)	(49)
MULTIPLE CYSTS			1 (2%)
#PANCREATIC ACINUS	(46)	(50)	(49)
CYTOPLASMIC VACUOLIZATION	5 (11%)	1 (2%)	4 (8%)
ATROPHY, FOCAL	1 (2%)	1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
*ESOPHAGEAL LUMEN	(48)	(50)	(50)
HEMORRHAGE		1 (2%)	1 (2%)
#ESOPHAGUS	(44)	(50)	(50)
HEMORRHAGE	1 (2%)		
#GLANDULAR STOMACH	(47)	(49)	(49)
MINERALIZATION		1 (2%)	1 (2%)
CYST, NOS	2 (4%)		2 (4%)
ULCER, ACUTE	1 (2%)		
ULCER, CHRONIC	1 (2%)		
EROSION		1 (2%)	
#FORESTOMACH	(47)	(49)	(49)
CYST, NOS		1 (2%)	
INFLAMMATION, NOS		1 (2%)	
INFLAMMATION, FOCAL		1 (2%)	
ULCER, ACUTE			1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	4 (8%)
HYPERKERATOSIS		5 (10%)	4 (8%)
#DUODENUM	(45)	(48)	(44)
HEMORRHAGE		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(48)	(50)	(50)
HYDRONEPHROSIS	1 (2%)	1 (2%)	
CYST, NOS			1 (2%)
CONGESTION, NOS	2 (4%)	2 (4%)	2 (4%)
HEMORRHAGE	1 (2%)	1 (2%)	
LYMPHOCYTIC INFLAMMATORY INFILTRA		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		
PYELONEPHRITIS, ACUTE/CHRONIC		1 (2%)	
PYELONEPHRITIS, CHRONIC	2 (4%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#KIDNEY			
INFLAMMATION, CHRONIC FOCAL	7 (15%)	18 (36%)	21 (42%)
NEPHROPATHY	16 (33%)	15 (30%)	9 (18%)
INFARCT, FOCAL	1 (2%)		1 (2%)
INFARCT, HEALED			1 (2%)
METAMORPHOSIS FATTY		1 (2%)	
METAPLASIA, OSSEOUS		1 (2%)	1 (2%)
#KIDNEY/CORTEX	(48)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
NECROSIS, COAGULATIVE	1 (2%)		
#KIDNEY/TUBULE	(48)	(50)	(50)
MINERALIZATION	3 (6%)	2 (4%)	1 (2%)
METAMORPHOSIS FATTY	19 (40%)	25 (50%)	21 (42%)
CYTOPLASMIC VACUOLIZATION	2 (4%)	4 (8%)	3 (6%)
HYPERPLASIA, EPITHELIAL	1 (2%)		
#URINARY BLADDER	(45)	(48)	(49)
CALCULUS, MICROSCOPIC EXAMINATION	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)	3 (6%)	1 (2%)
INFLAMMATION, CHRONIC DIFFUSE	2 (4%)		
HYPERPLASIA, EPITHELIAL		2 (4%)	1 (2%)
*URETHRA	(48)	(50)	(50)
CALCULUS, MICROSCOPIC EXAMINATION	5 (10%)	5 (10%)	2 (4%)
ENDOCRINE SYSTEM			
#PITUITARY	(38)	(43)	(45)
EMBRYONAL DUCT CYST	2 (5%)	1 (2%)	1 (2%)
CYST, NOS			2 (4%)
CONGESTION, NOS			1 (2%)
INFLAMMATION, CHRONIC DIFFUSE	1 (3%)		
#ANTERIOR PITUITARY	(38)	(43)	(45)
HYPERPLASIA, NOS	1 (3%)		
HYPERPLASIA, FOCAL	2 (5%)	2 (5%)	
#ADRENAL	(46)	(49)	(47)
CONGESTION, NOS		1 (2%)	
ANGIECTASIS	9 (20%)	8 (16%)	13 (28%)
#ADRENAL/CAPSULE	(46)	(49)	(47)
HYPERPLASIA, FOCAL	32 (70%)	40 (82%)	37 (79%)
#ADRENAL CORTEX	(46)	(49)	(47)
HYPERTROPHY, FOCAL			1 (2%)
HYPERPLASIA, FOCAL	8 (17%)	1 (2%)	7 (15%)
#ADRENAL MEDULLA	(46)	(49)	(47)
NECROSIS, FOCAL			1 (2%)
HYPERPLASIA, FOCAL	6 (13%)	14 (29%)	7 (15%)
ANGIECTASIS			1 (2%)
#THYROID	(41)	(47)	(48)
EMBRYONAL DUCT CYST	2 (5%)		2 (4%)
FOLLICULAR CYST, NOS	4 (10%)	3 (6%)	3 (6%)
GRANULOMA, NOS			1 (2%)
HYPERPLASIA, C-CELL	2 (5%)	6 (13%)	
HYPERPLASIA, FOLLICULAR CELL	1 (2%)	3 (6%)	1 (2%)
#THYROID FOLLICLE	(41)	(47)	(48)
MULTIPLE CYSTS	5 (12%)	5 (11%)	3 (6%)
#PANCREATIC ISLETS	(46)	(50)	(49)
HYPERPLASIA, FOCAL	7 (15%)	2 (4%)	3 (6%)
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(48)	(50)	(50)
CYSTIC DUCTS		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#PROSTATE	(47)	(49)	(49)
HEMORRHAGE		1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE	3 (6%)	2 (4%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)
*SEMINAL VESICLE	(48)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		3 (6%)
#TESTIS	(48)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
OLIGOSPERMIA	2 (4%)		1 (2%)
HYPERPLASIA, INTERSTITIAL CELL	13 (27%)	12 (24%)	11 (22%)
#TESTIS/TUBULE	(48)	(50)	(50)
MINERALIZATION	2 (4%)	3 (6%)	1 (2%)
DEGENERATION, NOS	5 (10%)	3 (6%)	2 (4%)
#TESTIS/INTERSTITIAL	(48)	(50)	(50)
MINERALIZATION		1 (2%)	
*EPIDIDYMIS	(48)	(50)	(50)
GRANULOMA, SPERMATIC			1 (2%)
*VAS DEFERENS	(48)	(50)	(50)
INFLAMMATION, CHRONIC DIFFUSE		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(46)	(49)	(50)
CONGESTION, NOS	3 (7%)	1 (2%)	4 (8%)
HEMORRHAGE	3 (7%)	5 (10%)	4 (8%)
CORPORA AMYLACEA	24 (52%)	28 (57%)	22 (44%)
*SPINAL CORD	(48)	(50)	(50)
CONGESTION, NOS	8 (17%)	1 (2%)	4 (8%)
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(48)	(50)	(50)
INFLAMMATION ACTIVE CHRONIC			1 (2%)
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)
*EYE/LACRIMAL GLAND	(48)	(50)	(50)
ATROPHY, FOCAL			1 (2%)
MUSCULOSKELETAL SYSTEM			
*VERTEBRA	(48)	(50)	(50)
HERNIATED NUCLEUS PULPOSUS		1 (2%)	1 (2%)
*SKELETAL MUSCLE	(48)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
*MUSCLE OF NECK	(48)	(50)	(50)
FOREIGN BODY, NOS	1 (2%)		
ABSCESS, NOS	1 (2%)		
BODY CAVITIES			
*THORACIC CAVITY	(48)	(50)	(50)
VEGETABLE FOREIGN BODY	1 (2%)		
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
*MEDIASTINUM	(48)	(50)	(50)
HEMORRHAGE	1 (2%)		1 (2%)
*PLEURA	(48)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES (Continued)			
*EPICARDIUM	(48)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
*MESENTERY	(48)	(50)	(50)
HEMORRHAGE		1 (2%)	
HEMATOMA, ORGANIZED		1 (2%)	
STEATITIS		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(48)	(50)	(50)
CONGESTION, NOS	3 (6%)	4 (8%)	3 (6%)
HEMORRHAGE	1 (2%)		
LYMPHOCYTIC INFLAMMATORY INFILTRA	1 (2%)		3 (6%)
INFLAMMATION, CHRONIC FOCAL	2 (4%)	4 (8%)	4 (8%)
AMYLOIDOSIS	1 (2%)		1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
ANIMAL MISSING/NO NECROPSY	1		
AUTO/NECROPSY/HISTO PERF	2		
AUTOLYSIS/NO NECROPSY	1		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
ULCER, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	2 (4%)	1 (2%)	2 (4%)
INFLAMMATION, CHRONIC DIFFUSE	1 (2%)	2 (4%)	
PARASITISM	4 (8%)	4 (8%)	2 (4%)
ALOPECIA	1 (2%)		
HYPERKERATOSIS	27 (54%)	22 (44%)	12 (24%)
*SUBCUT TISSUE	(50)	(50)	(50)
EDEMA, NOS	1 (2%)		
HEMORRHAGE			1 (2%)
ABSCESS, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(50)	(48)	(48)
MULTIPLE CYSTS		1 (2%)	
INFLAMMATION, CHRONIC DIFFUSE	3 (6%)		
#LUNG/BRONCHIOLE	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
#LUNG	(50)	(50)	(50)
CONGESTION, NOS	15 (30%)	7 (14%)	17 (34%)
EDEMA, NOS	3 (6%)	1 (2%)	2 (4%)
HEMORRHAGE	15 (30%)	21 (42%)	15 (30%)
LYMPHOCYTIC INFLAMMATORY INFILTRA	1 (2%)		
INFLAMMATION, INTERSTITIAL		1 (2%)	
BRONCHOPNEUMONIA, ACUTE	2 (4%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
PNEUMONIA INTERSTITIAL CHRONIC	7 (14%)	8 (16%)	4 (8%)
BRONCHOPNEUMONIA, CHRONIC		1 (2%)	
INFECTION, PROTOZOAN		1 (2%)	
FOREIGN MATERIAL, NOS			1 (2%)
HEMATOIDIN	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
HISTIOCYTOSIS	3 (6%)	10 (20%)	3 (6%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(50)	(50)
PIGMENTATION, NOS			4 (8%)
MYELOFIBROSIS			2 (4%)
HYPERPLASIA, GRANULOCYTIC	22 (44%)	19 (38%)	16 (32%)
#SPLEEN	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
HEMORRHAGE	1 (2%)		
HEMATOMA, NOS		1 (2%)	
INFLAMMATION, ACUTE DIFFUSE	1 (2%)		
NECROSIS, DIFFUSE	1 (2%)		
NECROSIS, COAGULATIVE		1 (2%)	
PIGMENTATION, NOS	30 (60%)	35 (70%)	34 (68%)
HYPERPLASIA, RETICULUM CELL			1 (2%)
HYPERPLASIA, LYMPHOID	4 (8%)	8 (16%)	9 (18%)
HEMATOPOIESIS	42 (84%)	44 (88%)	38 (76%)
#LYMPH NODE	(47)	(49)	(43)
CONGESTION, NOS		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#MANDIBULAR LYMPH NODE	(47)	(49)	(43)
PIGMENTATION, NOS		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)		
#MESENTERIC LYMPH NODE	(47)	(49)	(43)
CONGESTION, NOS	2 (4%)	3 (6%)	1 (2%)
EDEMA, NOS		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
INFLAMMATION, CHRONIC DIFFUSE	2 (4%)		
ANGIECTASIS			1 (2%)
HISTIOCYTOSIS			1 (2%)
ERYTHROPHAGOCYTOSIS		1 (2%)	
HYPERPLASIA, RETICULUM CELL		2 (4%)	
HYPERPLASIA, LYMPHOID	2 (4%)	5 (10%)	3 (7%)
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS	7 (14%)	3 (6%)	14 (28%)
#KIDNEY	(50)	(50)	(50)
LYMPHOCYTOSIS	1 (2%)		
#THYMUS	(12)	(12)	(20)
INFLAMMATION, ACUTE DIFFUSE			1 (5%)
NECROSIS, DIFFUSE		1 (8%)	
CIRCULATORY SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
PERIARTERITIS	1 (2%)		
#HEART	(50)	(50)	(50)
MINERALIZATION		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	10 (20%)	7 (14%)	10 (20%)
ENDOCARDIOSIS	1 (2%)	1 (2%)	
NECROSIS, FOCAL	1 (2%)		
#HEART/ATRIUM	(50)	(50)	(50)
THROMBUS, ORGANIZED		2 (4%)	
#CARDIAC VALVE	(50)	(50)	(50)
ENDOCARDIOSIS		1 (2%)	
#ADRENAL	(48)	(50)	(50)
THROMBOSIS, NOS			1 (2%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(47)	(48)	(45)
INFLAMMATION, CHRONIC FOCAL	15 (32%)	12 (25%)	6 (13%)
#LIVER	(50)	(50)	(50)
CONGESTION, NOS	2 (4%)	1 (2%)	2 (4%)
INFLAMMATION, MULTIFOCAL		1 (2%)	
INFLAMMATION, ACUTE FOCAL	4 (8%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE DIFFUSE	2 (4%)		
INFLAMMATION ACTIVE CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL	4 (8%)	6 (12%)	4 (8%)
NECROSIS, FOCAL	1 (2%)		
NECROSIS, COAGULATIVE	6 (12%)	3 (6%)	2 (4%)
METAMORPHOSIS FATTY	1 (2%)	3 (6%)	2 (4%)
CYTOPLASMIC VACUOLIZATION	6 (12%)	4 (8%)	5 (10%)
FOCAL CELLULAR CHANGE	1 (2%)	3 (6%)	4 (8%)
HEPATOCYTOMEGALY	32 (64%)	21 (42%)	9 (18%)
REGENERATION, NOS		1 (2%)	
#LIVER/PERIPORTAL	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
METAMORPHOSIS FATTY	1 (2%)		
*GALLBLADDER	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#PANCREAS	(50)	(50)	(49)
CYSTIC DUCTS	1 (2%)	1 (2%)	2 (4%)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	2 (4%)		
INFLAMMATION, CHRONIC FOCAL	10 (20%)	8 (16%)	12 (24%)
NECROSIS, FOCAL			1 (2%)
ATROPHY, FOCAL	1 (2%)	1 (2%)	
#PANCREATIC ACINUS	(50)	(50)	(49)
CYTOPLASMIC CHANGE, NOS	1 (2%)		
CYTOPLASMIC VACUOLIZATION	7 (14%)	9 (18%)	
ATROPHY, FOCAL		1 (2%)	
HYPERPLASIA, FOCAL	1 (2%)		2 (4%)
#ESOPHAGUS	(50)	(50)	(48)
HEMORRHAGE	1 (2%)		
INFLAMMATION, ACUTE FOCAL			1 (2%)
#GLANDULAR STOMACH	(50)	(50)	(49)
CYST, NOS		1 (2%)	
ULCER, NOS			1 (2%)
EROSION	1 (2%)		
DEGENERATION, CYSTIC		1 (2%)	
#FORESTOMACH	(50)	(50)	(49)
ULCER, ACUTE		1 (2%)	1 (2%)
INFLAMMATION, ACUTE FOCAL			1 (2%)
HYPERPLASIA, EPITHELIAL		1 (2%)	1 (2%)
HYPERKERATOSIS	1 (2%)		5 (10%)
#DUODENUM	(48)	(48)	(49)
INFLAMMATION, CHRONIC DIFFUSE			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CYST, NOS		1 (2%)	
CONGESTION, NOS		2 (4%)	4 (8%)
HEMORRHAGE			2 (4%)
PYELONEPHRITIS, ACUTE		1 (2%)	
INFLAMMATION, ACUTE FOCAL	2 (4%)		
INFLAMMATION ACTIVE CHRONIC		1 (2%)	
PYELONEPHRITIS, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	17 (34%)	11 (22%)	16 (32%)
NEPHROPATHY	13 (26%)	8 (16%)	2 (4%)
INFARCT, HEALED		1 (2%)	
#KIDNEY/CORTEX	(50)	(50)	(50)
METAPLASIA, OSSEOUS	1 (2%)		
#KIDNEY/GLOMERULUS	(50)	(50)	(50)
CYTOPLASMIC VACUOLIZATION			1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)
CYST, NOS		2 (4%)	1 (2%)
MULTIPLE CYSTS			3 (6%)
METAMORPHOSIS FATTY	1 (2%)		
CYTOPLASMIC VACUOLIZATION		1 (2%)	
#KIDNEY/PELVIS	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
#URINARY BLADDER	(48)	(48)	(48)
INFLAMMATION, MULTIFOCAL		1 (2%)	
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	6 (13%)	4 (8%)	5 (10%)
INFLAMMATION, CHRONIC DIFFUSE	1 (2%)		
HYPERPLASIA, EPITHELIAL			2 (4%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#ANTERIOR PITUITARY	(47)	(41)	(44)
CYST, NOS			1 (2%)
HYPERPLASIA, NOS			1 (2%)
HYPERPLASIA, FOCAL	5 (11%)	7 (17%)	12 (27%)
ANGIECTASIS	1 (2%)		1 (2%)
#ADRENAL	(48)	(50)	(50)
CONGESTION, NOS	1 (2%)		4 (8%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
AMYLOID,	1 (2%)		1 (2%)
ANGIECTASIS	8 (17%)	13 (26%)	17 (34%)
#ADRENAL/CAPSULE	(48)	(50)	(50)
HYPERPLASIA, FOCAL	46 (96%)	43 (86%)	44 (88%)
#ADRENAL CORTEX	(48)	(50)	(50)
CYST, NOS		1 (2%)	
DEGENERATION, NOS	1 (2%)		
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY		1 (2%)	
HYPERPLASIA, FOCAL	6 (13%)	5 (10%)	7 (14%)
#ADRENAL MEDULLA	(48)	(50)	(50)
CONGESTION, NOS			1 (2%)
HYPERPLASIA, FOCAL	4 (8%)	3 (6%)	1 (2%)
#THYROID	(49)	(49)	(46)
EMBRYONAL DUCT CYST	2 (4%)	1 (2%)	1 (2%)
FOLLICULAR CYST, NOS	5 (10%)	1 (2%)	7 (15%)
HEMORRHAGE			1 (2%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
HYPERPLASIA, C-CELL	4 (8%)	8 (16%)	
HYPERPLASIA, FOLLICULAR CELL	3 (6%)	3 (6%)	2 (4%)
#THYROID FOLLICLE	(49)	(49)	(46)
MULTIPLE CYSTS	9 (18%)	6 (12%)	9 (20%)
#PANCREATIC ISLETS	(50)	(50)	(49)
HYPERPLASIA, FOCAL	3 (6%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
HYPERPLASIA, CYSTIC	4 (8%)	2 (4%)	1 (2%)
#UTERUS	(50)	(49)	(50)
HYDROMETRA	1 (2%)	1 (2%)	
CONGESTION, NOS		1 (2%)	
HEMORRHAGE		5 (10%)	2 (4%)
INFLAMMATION, SUPPURATIVE	2 (4%)		
INFLAMMATION, ACUTE FOCAL	8 (16%)	14 (29%)	9 (18%)
INFLAMMATION, ACUTE DIFFUSE	2 (4%)		2 (4%)
INFLAMMATION ACTIVE CHRONIC	1 (2%)		
METAPLASIA, SQUAMOUS		1 (2%)	
#UTERUS/ENDOMETRIUM	(50)	(49)	(50)
HYPERPLASIA, CYSTIC	42 (84%)	48 (98%)	40 (80%)
#FALLOPIAN TUBE	(50)	(49)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#OVARY/PAROVARIAN	(49)	(45)	(47)
MULTILOCULAR CYST		1 (2%)	
STEATITIS	1 (2%)	1 (2%)	
ABSCESS, CHRONIC	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#OVARY	(49)	(45)	(47)
CYST, NOS		1 (2%)	1 (2%)
FOLLICULAR CYST, NOS	7 (14%)	2 (4%)	2 (4%)
PAROVARIAN CYST		2 (4%)	5 (11%)
HEMORRHAGIC CYST	1 (2%)		
INFLAMMATION, SUPPURATIVE	3 (6%)		
INFLAMMATION, ACUTE	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
ABSCESS, CHRONIC	1 (2%)		
#MESOVARIUM	(49)	(45)	(47)
ABSCESS, NOS			1 (2%)
#OVARY/FOLLICLE	(49)	(45)	(47)
MULTIPLE CYSTS	1 (2%)		1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(49)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
#BRAIN	(50)	(49)	(50)
CONGESTION, NOS	5 (10%)	2 (4%)	2 (4%)
HEMORRHAGE		1 (2%)	
STATUS SPONGIOSUS		1 (2%)	
CORPORA AMYLACEA	17 (34%)	21 (43%)	12 (24%)
ATROPHY, PRESSURE	2 (4%)	1 (2%)	
*SPINAL CORD	(50)	(50)	(50)
CONGESTION, NOS	8 (16%)		2 (4%)
HEMORRHAGE	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
RETINOPATHY		1 (2%)	
CATARACT		1 (2%)	
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, CHRONIC DIFFUSE		2 (4%)	
*EYE/CRYSTALLINE LENS	(50)	(50)	(50)
CATARACT		1 (2%)	
*HARDERIAN GLAND	(50)	(50)	(50)
ATROPHY, FOCAL	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*VERTEBRA	(50)	(50)	(50)
HERNIATED NUCLEUS PULPOSUS			1 (2%)
BODY CAVITIES			
*THORACIC CAVITY	(50)	(50)	(50)
HEMORRHAGE		1 (2%)	
*MEDIASTINUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE DIFFUSE			1 (2%)
*PERITONEUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)
*PERICARDIUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	2 (4%)		
*EPICARDIUM	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL			1 (2%)
INFLAMMATION, CHRONIC FOCAL			2 (4%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES (Continued)			
*MESENTERY	(50)	(50)	(50)
HEMORRHAGE	1 (2%)	1 (2%)	
STEATITIS		4 (8%)	1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC DIFFUSE	1 (2%)		
ABSCESS, CHRONIC	1 (2%)		
NECROSIS, FAT	1 (2%)	1 (2%)	
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
CONGESTION, NOS			1 (2%)
LYMPHOCYTIC INFLAMMATORY INFILTR	3 (6%)	3 (6%)	5 (10%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, ACUTE FOCAL	1 (2%)		
INFLAMMATION, ACUTE/CHRONIC	2 (4%)		
INFLAMMATION, CHRONIC FOCAL	9 (18%)	13 (26%)	3 (6%)
AMYLOIDOSIS	1 (2%)		
ADIPOSE TISSUE			
NECROSIS, FAT			1
BROAD LIGAMENT			
INFLAMMATION, ACUTE/CHRONIC	1		
SPECIAL MORPHOLOGY SUMMARY			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	10.4%	18.2%	7.1%
Terminal Rates (c)	2/33 (6%)	6/33 (18%)	1/14 (7%)
Life Table Tests (d)	P=0.468N	P=0.365	P=0.401N
Incidental Tumor Tests (d)	P=0.376N	P=0.320	P=0.265N
Cochran-Armitage Trend Test (d)	P=0.169N		
Fisher Exact Test		P=0.370	P=0.181N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	7/50 (14%)	2/50 (4%)
Adjusted Rates (b)	10.4%	20.2%	9.6%
Terminal Rates (c)	2/33 (6%)	6/33 (18%)	1/14 (7%)
Life Table Tests (d)	P=0.506	P=0.260	P=0.600N
Incidental Tumor Tests (d)	P=0.458N	P=0.202	P=0.375N
Cochran-Armitage Trend Test (d)	P=0.297N		
Fisher Exact Test		P=0.262	P=0.339N
Integumentary System: Fibroma or Neurofibroma			
Overall Rates (a)	4/50 (8%)	7/50 (14%)	1/50 (2%)
Adjusted Rates (b)	10.4%	21.2%	7.1%
Terminal Rates (c)	2/33 (6%)	7/33 (21%)	1/14 (7%)
Life Table Tests (d)	P=0.508N	P=0.258	P=0.401N
Incidental Tumor Tests (d)	P=0.416N	P=0.221	P=0.265N
Cochran-Armitage Trend Test (d)	P=0.178N		
Fisher Exact Test		P=0.262	P=0.181N
Integumentary System: Fibroma, Neurofibroma, or Fibrosarcoma			
Overall Rates (a)	4/50 (8%)	8/50 (16%)	2/50 (4%)
Adjusted Rates (b)	10.4%	23.2%	9.6%
Terminal Rates (c)	2/33 (6%)	7/33 (21%)	1/14 (7%)
Life Table Tests (d)	P=0.471	P=0.178	P=0.600N
Incidental Tumor Tests (d)	P=0.494N	P=0.133	P=0.375N
Cochran-Armitage Trend Test (d)	P=0.303N		
Fisher Exact Test		P=0.178	P=0.339N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	12.1%	6.1%	0.0%
Terminal Rates (c)	4/33 (12%)	2/33 (6%)	0/14 (0%)
Life Table Tests (d)	P=0.115N	P=0.335N	P=0.217N
Incidental Tumor Tests (d)	P=0.115N	P=0.335N	P=0.217N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test		P=0.339N	P=0.059N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	12.1%	9.1%	0.0%
Terminal Rates (c)	4/33 (12%)	3/33 (9%)	0/14 (0%)
Life Table Tests (d)	P=0.161N	P=0.500N	P=0.217N
Incidental Tumor Tests (d)	P=0.161N	P=0.500N	P=0.217N
Cochran-Armitage Trend Test (d)	P=0.049N		
Fisher Exact Test		P=0.500N	P=0.059N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	6/50 (12%)	10/50 (20%)	8/50 (16%)
Adjusted Rates (b)	15.4%	24.8%	35.3%
Terminal Rates (c)	1/33 (3%)	4/33 (12%)	3/14 (21%)
Life Table Tests (d)	P=0.077	P=0.217	P=0.092
Incidental Tumor Tests (d)	P=0.504	P=0.068	P=0.508
Cochran-Armitage Trend Test (d)	P=0.341		
Fisher Exact Test		P=0.207	P=0.387

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Liver: Neoplastic Nodule			
Overall Rates (a)	4/50 (8%)	9/50 (18%)	2/50 (4%)
Adjusted Rates (b)	11.6%	25.3%	12.0%
Terminal Rates (c)	3/33 (9%)	7/33 (21%)	1/14 (7%)
Life Table Tests (d)	P=0.402	P=0.119	P=0.635
Incidental Tumor Tests (d)	P=0.544N	P=0.085	P=0.521N
Cochran-Armitage Trend Test (d)	P=0.309N		
Fisher Exact Test		P=0.117	P=0.339N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	5/50 (10%)	9/50 (18%)	2/50 (4%)
Adjusted Rates (b)	14.6%	25.3%	12.0%
Terminal Rates (c)	4/33 (12%)	7/33 (21%)	1/14 (7%)
Life Table Tests (d)	P=0.512	P=0.194	P=0.607N
Incidental Tumor Tests (d)	P=0.438N	P=0.148	P=0.420N
Cochran-Armitage Trend Test (d)	P=0.209N		
Fisher Exact Test		P=0.194	P=0.218N
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	4/50 (8%)	9/50 (18%)	6/50 (12%)
Adjusted Rates (b)	12.1%	26.3%	34.6%
Terminal Rates (c)	4/33 (12%)	8/33 (24%)	4/14 (29%)
Life Table Tests (d)	P=0.027	P=0.114	P=0.045
Incidental Tumor Tests (d)	P=0.059	P=0.102	P=0.086
Cochran-Armitage Trend Test (d)	P=0.326		
Fisher Exact Test		P=0.117	P=0.370
Kidney: Tubular Cell Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	9.1%	7.1%
Terminal Rates (c)	0/33 (0%)	3/33 (9%)	1/14 (7%)
Life Table Tests (d)	P=0.155	P=0.120	P=0.329
Incidental Tumor Tests (d)	P=0.155	P=0.120	P=0.329
Cochran-Armitage Trend Test (d)	P=0.378		
Fisher Exact Test		P=0.121	P=0.500
Kidney: Tubular Cell Adenoma or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	0.0%	9.1%	12.0%
Terminal Rates (c)	0/33 (0%)	3/33 (9%)	1/14 (7%)
Life Table Tests (d)	P=0.014	P=0.120	P=0.025
Incidental Tumor Tests (d)	P=0.034	P=0.120	P=0.073
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test		P=0.121	P=0.121
Pituitary: Adenoma			
Overall Rates (a)	10/48 (21%)	12/49 (24%)	8/47 (17%)
Adjusted Rates (b)	28.0%	32.0%	36.3%
Terminal Rates (c)	8/33 (24%)	8/33 (24%)	3/14 (21%)
Life Table Tests (d)	P=0.195	P=0.406	P=0.228
Incidental Tumor Tests (d)	P=0.532N	P=0.341	P=0.589
Cochran-Armitage Trend Test (d)	P=0.372N		
Fisher Exact Test		P=0.426	P=0.416N
Pituitary: Adenoma or Adenocarcinoma			
Overall Rates (a)	11/48 (23%)	13/49 (27%)	8/47 (17%)
Adjusted Rates (b)	30.9%	34.8%	36.3%
Terminal Rates (c)	9/33 (27%)	9/33 (27%)	3/14 (21%)
Life Table Tests (d)	P=0.239	P=0.409	P=0.282
Incidental Tumor Tests (d)	P=0.477N	P=0.345	P=0.567N
Cochran-Armitage Trend Test (d)	P=0.287N		
Fisher Exact Test		P=0.430	P=0.323N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Adrenal: Pheochromocytoma			
Overall Rates (a)	16/50 (32%)	13/50 (26%)	15/50 (30%)
Adjusted Rates (b)	42.9%	36.9%	65.5%
Terminal Rates (c)	12/33 (36%)	11/33 (33%)	7/14 (50%)
Life Table Tests (d)	P=0.040	P=0.342N	P=0.033
Incidental Tumor Tests (d)	P=0.248	P=0.428N	P=0.257
Cochran-Armitage Trend Test (d)	P=0.456N		
Fisher Exact Test		P=0.330N	P=0.500N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	16/50 (32%)	14/50 (28%)	15/50 (30%)
Adjusted Rates (b)	42.9%	39.7%	65.5%
Terminal Rates (c)	12/33 (36%)	12/33 (36%)	7/14 (50%)
Life Table Tests (d)	P=0.036	P=0.425N	P=0.033
Incidental Tumor Tests (d)	P=0.231	P=0.518N	P=0.257
Cochran-Armitage Trend Test (d)	P=0.457N		
Fisher Exact Test		P=0.414N	P=0.500N
Thyroid: C-Cell Adenoma			
Overall Rates (a)	6/49 (12%)	5/50 (10%)	2/49 (4%)
Adjusted Rates (b)	17.3%	15.2%	12.3%
Terminal Rates (c)	5/33 (15%)	5/33 (15%)	1/14 (7%)
Life Table Tests (d)	P=0.404N	P=0.500N	P=0.480N
Incidental Tumor Tests (d)	P=0.314N	P=0.526N	P=0.341N
Cochran-Armitage Trend Test (d)	P=0.106N		
Fisher Exact Test		P=0.486N	P=0.134N
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	8/49 (16%)	6/50 (12%)	2/49 (4%)
Adjusted Rates (b)	23.2%	18.2%	12.3%
Terminal Rates (c)	7/33 (21%)	6/33 (18%)	1/14 (7%)
Life Table Tests (d)	P=0.243N	P=0.385N	P=0.316N
Incidental Tumor Tests (d)	P=0.181N	P=0.407N	P=0.209N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test		P=0.371N	P=0.046N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	5/50 (10%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	15.2%	15.2%	28.6%
Terminal Rates (c)	5/33 (15%)	5/33 (15%)	4/14 (29%)
Life Table Tests (d)	P=0.232	P=0.633	P=0.256
Incidental Tumor Tests (d)	P=0.232	P=0.633	P=0.256
Cochran-Armitage Trend Test (d)	P=0.432N		
Fisher Exact Test		P=0.630	P=0.500N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	43/48 (90%)	41/50 (82%)	38/50 (76%)
Adjusted Rates (b)	97.7%	97.6%	100.0%
Terminal Rates (c)	32/33 (97%)	32/33 (97%)	14/14 (100%)
Life Table Tests (d)	P<0.001	P=0.442N	P<0.001
Incidental Tumor Tests (d)	P=0.363	P=0.517N	P=0.456
Cochran-Armitage Trend Test (d)	P=0.051N		
Fisher Exact Test		P=0.218N	P=0.065N
Preputial Gland: Carcinoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	5/50 (10%)
Adjusted Rates (b)	0.0%	0.0%	17.9%
Terminal Rates (c)	0/33 (0%)	0/33 (0%)	1/14 (7%)
Life Table Tests (d)	P=0.002	(e)	P=0.012
Incidental Tumor Tests (d)	P=0.019	(e)	P=0.068
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test		(e)	P=0.028

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Tunica Vaginalis: Mesothelioma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	9.1%	3.0%	12.0%
Terminal Rates (c)	3/33 (9%)	1/33 (3%)	1/14 (7%)
Life Table Tests (d)	P=0.527	P=0.304N	P=0.515
Incidental Tumor Tests (d)	P=0.606N	P=0.304N	P=0.623
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test		P=0.309N	P=0.500N
All Sites: Mesothelioma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	12.1%	5.3%	15.4%
Terminal Rates (c)	4/33 (12%)	1/33 (3%)	1/14 (7%)
Life Table Tests (d)	P=0.444	P=0.346N	P=0.418
Incidental Tumor Tests (d)	P=0.537N	P=0.321N	P=0.580
Cochran-Armitage Trend Test (d)	P=0.417N		
Fisher Exact Test		P=0.339N	P=0.500N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 250 mg/kg and vehicle control groups.

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	9/50 (18%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (b)	25.1%	15.6%	21.2%
Terminal Rates (c)	5/30 (17%)	1/23 (4%)	3/20 (15%)
Life Table Tests (d)	P=0.369N	P=0.335N	P=0.446N
Incidental Tumor Tests (d)	P=0.253N	P=0.160N	P=0.353N
Cochran-Armitage Trend Test (d)	P=0.146N		
Fisher Exact Test		P=0.194N	P=0.194N
Liver: Neoplastic Nodule			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	9.0%	4.3%	5.0%
Terminal Rates (c)	2/30 (7%)	1/23 (4%)	1/20 (5%)
Life Table Tests (d)	P=0.312N	P=0.384N	P=0.441N
Incidental Tumor Tests (d)	P=0.291N	P=0.349N	P=0.410N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test		P=0.309N	P=0.309N
Pituitary: Adenoma			
Overall Rates (a)	21/49 (43%)	17/48 (35%)	12/47 (26%)
Adjusted Rates (b)	61.3%	61.9%	43.8%
Terminal Rates (c)	17/30 (57%)	13/23 (57%)	6/20 (30%)
Life Table Tests (d)	P=0.322N	P=0.524	P=0.338N
Incidental Tumor Tests (d)	P=0.226N	P=0.474N	P=0.264N
Cochran-Armitage Trend Test (d)	P=0.047N		
Fisher Exact Test		P=0.294N	P=0.058N
Pituitary: Adencarcinoma			
Overall Rates (a)	4/49 (8%)	2/48 (4%)	0/47 (0%)
Adjusted Rates (b)	11.3%	8.7%	0.0%
Terminal Rates (c)	2/30 (7%)	2/23 (9%)	0/20 (0%)
Life Table Tests (d)	P=0.080N	P=0.435N	P=0.119N
Incidental Tumor Tests (d)	P=0.062N	P=0.366N	P=0.090N
Cochran-Armitage Trend Test (d)	P=0.040N		
Fisher Exact Test		P=0.349N	P=0.064N
Pituitary: Adenoma or Adenocarcinoma			
Overall Rates (a)	24/49 (49%)	18/48 (38%)	12/47 (26%)
Adjusted Rates (b)	66.0%	65.8%	43.8%
Terminal Rates (c)	18/30 (60%)	14/23 (61%)	6/20 (30%)
Life Table Tests (d)	P=0.163N	P=0.506N	P=0.181N
Incidental Tumor Tests (d)	P=0.083N	P=0.297N	P=0.102N
Cochran-Armitage Trend Test (d)	P=0.012N		
Fisher Exact Test		P=0.175N	P=0.015N
Adrenal: Pheochromocytoma			
Overall Rates (a)	6/50 (12%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	17.3%	13.0%	25.9%
Terminal Rates (c)	3/30 (10%)	3/23 (13%)	4/20 (20%)
Life Table Tests (d)	P=0.321	P=0.382N	P=0.359
Incidental Tumor Tests (d)	P=0.374	P=0.281N	P=0.431
Cochran-Armitage Trend Test (d)	P=0.566		
Fisher Exact Test		P=0.244N	P=0.620N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	6/50 (12%)	4/50 (8%)	6/50 (12%)
Adjusted Rates (b)	17.3%	15.9%	25.9%
Terminal Rates (c)	3/30 (10%)	3/23 (13%)	4/20 (20%)
Life Table Tests (d)	P=0.315	P=0.532N	P=0.359
Incidental Tumor Tests (d)	P=0.380	P=0.393N	P=0.431
Cochran-Armitage Trend Test (d)	P=0.564		
Fisher Exact Test		P=0.371N	P=0.620N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Adrenal Cortex: Cortical Adenoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	13.3%	13.0%	8.5%
Terminal Rates (c)	4/30 (13%)	3/23 (13%)	1/20 (5%)
Life Table Tests (d)	P=0.448N	P=0.646N	P=0.525N
Incidental Tumor Tests (d)	P=0.427N	P=0.646N	P=0.493N
Cochran-Armitage Trend Test (d)	P=0.264N		
Fisher Exact Test		P=0.500N	P=0.339N
Adrenal Cortex: Cortical Adenoma or Adenocarcinoma, NOS			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	13.3%	15.5%	8.5%
Terminal Rates (c)	4/30 (13%)	3/23 (13%)	1/20 (5%)
Life Table Tests (d)	P=0.470N	P=0.505	P=0.525N
Incidental Tumor Tests (d)	P=0.426N	P=0.534	P=0.493N
Cochran-Armitage Trend Test (d)	P=0.274N		
Fisher Exact Test		P=0.643	P=0.339N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	7/50 (14%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	18.7%	29.1%	15.3%
Terminal Rates (c)	3/30 (10%)	5/23 (22%)	2/20 (10%)
Life Table Tests (d)	P=0.463N	P=0.333	P=0.470N
Incidental Tumor Tests (d)	P=0.406N	P=0.501	P=0.483N
Cochran-Armitage Trend Test (d)	P=0.226N		
Fisher Exact Test		P=0.500	P=0.263N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	10/49 (20%)	11/50 (22%)	5/49 (10%)
Adjusted Rates (b)	27.6%	36.9%	23.0%
Terminal Rates (c)	5/29 (17%)	6/23 (26%)	4/20 (20%)
Life Table Tests (d)	P=0.352N	P=0.313	P=0.339N
Incidental Tumor Tests (d)	P=0.281N	P=0.522	P=0.298N
Cochran-Armitage Trend Test (d)	P=0.116N		
Fisher Exact Test		P=0.521	P=0.131N
Uterus: Endometrial Stromal Sarcoma			
Overall Rates (a)	3/49 (6%)	1/50 (2%)	1/49 (2%)
Adjusted Rates (b)	8.2%	2.4%	5.0%
Terminal Rates (c)	1/29 (3%)	0/23 (0%)	1/20 (5%)
Life Table Tests (d)	P=0.290N	P=0.349N	P=0.420N
Incidental Tumor Tests (d)	P=0.257N	P=0.248N	P=0.356N
Cochran-Armitage Trend Test (d)	P=0.201N		
Fisher Exact Test		P=0.301N	P=0.309N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (c)	0/48 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (d)	0.0%	12.5%	15.8%
Terminal Rates (e)	0/16 (0%)	2/16 (13%)	3/19 (16%)
Life Table Tests (d)	P=0.107	P=0.236	P=0.149
Incidental Tumor Tests (d)	P=0.107	P=0.236	P=0.149
Cochran-Armitage Trend Test (d)	P=0.087		
Fisher Exact Test		P=0.258	P=0.129
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (c)	3/48 (6%)	4/50 (8%)	10/50 (20%)
Adjusted Rates (d)	10.6%	15.9%	31.3%
Terminal Rates (e)	0/16 (0%)	1/16 (6%)	2/19 (11%)
Life Table Tests (d)	P=0.044	P=0.618	P=0.086
Incidental Tumor Tests (d)	P=0.019	P=0.530	P=0.036
Cochran-Armitage Trend Test (d)	P=0.023		
Fisher Exact Test		P=0.523	P=0.042
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (c)	3/48 (6%)	6/50 (12%)	13/50 (26%)
Adjusted Rates (d)	10.6%	27.1%	43.4%
Terminal Rates (e)	0/16 (0%)	3/16 (19%)	5/19 (26%)
Life Table Tests (d)	P=0.012	P=0.340	P=0.025
Incidental Tumor Tests (d)	P=0.005	P=0.261	P=0.009
Cochran-Armitage Trend Test (d)	P=0.004		
Fisher Exact Test		P=0.264	P=0.008
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (c)	4/48 (8%)	4/50 (8%)	11/50 (22%)
Adjusted Rates (d)	13.8%	15.9%	33.5%
Terminal Rates (e)	0/16 (0%)	1/16 (6%)	2/19 (11%)
Life Table Tests (d)	P=0.056	P=0.509N	P=0.108
Incidental Tumor Tests (d)	P=0.023	P=0.638	P=0.043
Cochran-Armitage Trend Test (d)	P=0.030		
Fisher Exact Test		P=0.619N	P=0.054
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (c)	4/48 (8%)	6/50 (12%)	14/50 (28%)
Adjusted Rates (d)	13.8%	27.1%	45.2%
Terminal Rates (e)	0/16 (0%)	3/16 (19%)	5/19 (26%)
Life Table Tests (d)	P=0.016	P=0.492	P=0.036
Incidental Tumor Tests (d)	P=0.006	P=0.358	P=0.011
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test		P=0.397	P=0.011
Integumentary System: Fibroma			
Overall Rates (c)	2/48 (4%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (d)	12.5%	14.9%	15.8%
Terminal Rates (e)	2/16 (13%)	2/16 (13%)	3/19 (16%)
Life Table Tests (d)	P=0.495	P=0.549	P=0.581
Incidental Tumor Tests (d)	P=0.488	P=0.562	P=0.581
Cochran-Armitage Trend Test (d)	P=0.431		
Fisher Exact Test		P=0.520	P=0.520
Integumentary System: Fibroma or Fibrosarcoma			
Overall Rates (c)	5/48 (10%)	7/50 (14%)	13/50 (26%)
Adjusted Rates (d)	21.8%	29.1%	43.4%
Terminal Rates (e)	2/16 (13%)	3/16 (19%)	5/19 (26%)
Life Table Tests (d)	P=0.057	P=0.506	P=0.090
Incidental Tumor Tests (d)	P=0.029	P=0.441	P=0.045
Cochran-Armitage Trend Test (d)	P=0.027		
Fisher Exact Test		P=0.409	P=0.041

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Integumentary System: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (c)	4/48 (8%)	5/50 (10%)	11/50 (22%)
Adjusted Rates (d)	13.8%	18.5%	33.5%
Terminal Rates (e)	0/16 (0%)	1/16 (6%)	2/19 (11%)
Life Table Tests (d)	P=0.063	P=0.610N	P=0.108
Incidental Tumor Tests (d)	P=0.025	P=0.537	P=0.043
Cochran-Armitage Trend Test (d)	P=0.033		
Fisher Exact Test		P=0.526	P=0.054
Integumentary System: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (c)	6/48 (13%)	8/50 (16%)	14/50 (28%)
Adjusted Rates (d)	24.6%	31.3%	45.2%
Terminal Rates (e)	2/16 (13%)	3/16 (19%)	5/19 (26%)
Life Table Tests (d)	P=0.073	P=0.548	P=0.108
Incidental Tumor Tests (d)	P=0.034	P=0.452	P=0.050
Cochran-Armitage Trend Test (d)	P=0.033		
Fisher Exact Test		P=0.419	P=0.048
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	6/47 (13%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	25.7%	0.0%	0.0%
Terminal Rates (c)	2/16 (13%)	0/16 (0%)	0/19 (0%)
Life Table Tests (d)	P=0.001N	P=0.009N	P=0.011N
Incidental Tumor Tests (d)	P=0.001N	P=0.007N	P=0.013N
Cochran-Armitage Trend Test (d)	P=0.002N		
Fisher Exact Test		P=0.011N	P=0.011N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	2/47 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	8.9%	2.6%	12.5%
Terminal Rates (c)	1/16 (6%)	0/16 (0%)	1/19 (5%)
Life Table Tests (d)	P=0.466	P=0.449N	P=0.578
Incidental Tumor Tests (d)	P=0.409	P=0.624N	P=0.523
Cochran-Armitage Trend Test (d)	P=0.423		
Fisher Exact Test		P=0.477N	P=0.530
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	7/47 (15%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	31.0%	2.6%	12.5%
Terminal Rates (c)	3/16 (19%)	0/16 (0%)	1/19 (5%)
Life Table Tests (d)	P=0.059N	P=0.018N	P=0.104N
Incidental Tumor Tests (d)	P=0.074N	P=0.020N	P=0.126N
Cochran-Armitage Trend Test (d)	P=0.075N		
Fisher Exact Test		P=0.024N	P=0.134N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	7/48 (15%)	7/50 (14%)	1/50 (2%)
Adjusted Rates (b)	35.4%	25.5%	2.6%
Terminal Rates (c)	4/16 (25%)	1/16 (6%)	0/19 (0%)
Life Table Tests (d)	P=0.017N	P=0.466N	P=0.019N
Incidental Tumor Tests (d)	P=0.019N	P=0.335N	P=0.025N
Cochran-Armitage Trend Test (d)	P=0.028N		
Fisher Exact Test		P=0.581N	P=0.026N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	0/48 (0%)	9/50 (18%)	4/50 (8%)
Adjusted Rates (b)	0.0%	39.4%	16.0%
Terminal Rates (c)	0/16 (0%)	5/16 (31%)	2/19 (11%)
Life Table Tests (d)	P=0.164	P=0.006	P=0.087
Incidental Tumor Tests (d)	P=0.132	P=0.008	P=0.077
Cochran-Armitage Trend Test (d)	P=0.118		
Fisher Exact Test		P=0.002	P=0.064

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	7/48 (15%)	18/50 (36%)	5/50 (10%)
Adjusted Rates (b)	35.4%	62.5%	18.2%
Terminal Rates (c)	4/16 (25%)	7/16 (44%)	2/19 (11%)
Life Table Tests (d)	P=0.206N	P=0.046	P=0.272N
Incidental Tumor Tests (d)	P=0.253N	P=0.067	P=0.320N
Cochran-Armitage Trend Test (d)	P=0.316N		
Fisher Exact Test		P=0.013	P=0.351N
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	8/48 (17%)	18/50 (36%)	5/50 (10%)
Adjusted Rates (b)	37.8%	62.5%	18.2%
Terminal Rates (c)	4/16 (25%)	7/16 (44%)	2/19 (11%)
Life Table Tests (d)	P=0.146N	P=0.081	P=0.187N
Incidental Tumor Tests (d)	P=0.176N	P=0.124	P=0.223N
Cochran-Armitage Trend Test (d)	P=0.234N		
Fisher Exact Test		P=0.026	P=0.250N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	6/48 (13%)	7/50 (14%)	13/50 (26%)
Adjusted Rates (b)	28.5%	43.8%	52.5%
Terminal Rates (c)	3/16 (19%)	7/16 (44%)	8/19 (42%)
Life Table Tests (d)	P=0.085	P=0.541	P=0.138
Incidental Tumor Tests (d)	P=0.063	P=0.551	P=0.098
Cochran-Armitage Trend Test (d)	P=0.051		
Fisher Exact Test		P=0.532	P=0.075
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	14/48 (29%)	13/50 (26%)	22/50 (44%)
Adjusted Rates (b)	45.1%	52.0%	71.9%
Terminal Rates (c)	2/16 (13%)	6/16 (38%)	11/19 (58%)
Life Table Tests (d)	P=0.177	P=0.290N	P=0.237
Incidental Tumor Tests (d)	P=0.073	P=0.354N	P=0.094
Cochran-Armitage Trend Test (d)	P=0.071		
Fisher Exact Test		P=0.450N	P=0.094
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	18/48 (38%)	18/50 (36%)	29/50 (58%)
Adjusted Rates (b)	58.5%	76.0%	90.3%
Terminal Rates (c)	5/16 (31%)	11/16 (69%)	16/19 (84%)
Life Table Tests (d)	P=0.100	P=0.358N	P=0.150
Incidental Tumor Tests (d)	P=0.027	P=0.420N	P=0.036
Cochran-Armitage Trend Test (d)	P=0.025		
Fisher Exact Test		P=0.522N	P=0.033
Adrenal: Cortical Adenoma			
Overall Rates (a)	3/46 (7%)	2/49 (4%)	0/47 (0%)
Adjusted Rates (b)	16.5%	9.9%	0.0%
Terminal Rates (c)	2/16 (13%)	1/16 (6%)	0/19 (0%)
Life Table Tests (d)	P=0.057N	P=0.425N	P=0.093N
Incidental Tumor Tests (d)	P=0.058N	P=0.385N	P=0.098N
Cochran-Armitage Trend Test (d)	P=0.077N		
Fisher Exact Test		P=0.470N	P=0.117N
Adrenal: Pheochromocytoma			
Overall Rates (a)	3/46 (7%)	5/49 (10%)	2/47 (4%)
Adjusted Rates (b)	11.7%	25.0%	8.4%
Terminal Rates (c)	1/16 (6%)	3/16 (19%)	0/19 (0%)
Life Table Tests (d)	P=0.330N	P=0.415	P=0.414N
Incidental Tumor Tests (d)	P=0.405N	P=0.288	P=0.502N
Cochran-Armitage Trend Test (d)	P=0.409N		
Fisher Exact Test		P=0.393	P=0.490N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	4/46 (9%)	6/49 (12%)	2/47 (4%)
Adjusted Rates (b)	16.3%	27.1%	8.4%
Terminal Rates (c)	1/16 (6%)	3/16 (19%)	0/19 (0%)
Life Table Tests (d)	P=0.209N	P=0.471	P=0.258N
Incidental Tumor Tests (d)	P=0.268N	P=0.386	P=0.331N
Cochran-Armitage Trend Test (d)	P=0.277N		
Fisher Exact Test		P=0.411	P=0.328N
Thyroid: Follicular Cell Adenoma			
Overall Rates (a)	4/41 (10%)	1/47 (2%)	2/48 (4%)
Adjusted Rates (b)	20.0%	6.3%	8.0%
Terminal Rates (c)	2/16 (13%)	1/16 (6%)	1/19 (5%)
Life Table Tests (d)	P=0.185N	P=0.127N	P=0.269N
Incidental Tumor Tests (d)	P=0.203N	P=0.109N	P=0.294N
Cochran-Armitage Trend Test (d)	P=0.186N		
Fisher Exact Test		P=0.141N	P=0.266N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE

	Vehicle Control	250 mg/kg	500 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (b)	11.5%	2.9%	5.6%
Terminal Rates (c)	3/26 (12%)	1/35 (3%)	1/34 (3%)
Life Table Tests (d)	P=0.301N	P=0.205N	P=0.384N
Incidental Tumor Tests (d)	P=0.414N	P=0.205N	P=0.538N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test		P=0.309N	P=0.500N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	9/50 (18%)	10/50 (20%)	12/50 (24%)
Adjusted Rates (b)	27.4%	25.2%	35.3%
Terminal Rates (c)	5/26 (19%)	6/35 (17%)	12/34 (35%)
Life Table Tests (d)	P=0.449	P=0.473N	P=0.516
Incidental Tumor Tests (d)	P=0.115	P=0.366	P=0.267
Cochran-Armitage Trend Test (d)	P=0.268		
Fisher Exact Test		P=0.500	P=0.312
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	10/50 (20%)	10/50 (20%)	3/50 (6%)
Adjusted Rates (b)	31.7%	25.6%	8.8%
Terminal Rates (c)	5/26 (19%)	7/35 (20%)	3/34 (9%)
Life Table Tests (d)	P=0.013N	P=0.337N	P=0.015N
Incidental Tumor Tests (d)	P=0.067N	P=0.576N	P=0.124N
Cochran-Armitage Trend Test (d)	P=0.036N		
Fisher Exact Test		P=0.598	P=0.036N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	5.8%	8.6%	8.4%
Terminal Rates (c)	1/26 (4%)	3/35 (9%)	2/34 (6%)
Life Table Tests (d)	P=0.491	P=0.600	P=0.557
Incidental Tumor Tests (d)	P=0.348	P=0.530	P=0.355
Cochran-Armitage Trend Test (d)	P=0.412		
Fisher Exact Test		P=0.500	P=0.500
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	21/50 (42%)	23/50 (46%)	18/50 (36%)
Adjusted Rates (b)	57.1%	54.4%	51.4%
Terminal Rates (c)	11/26 (42%)	16/35 (46%)	17/34 (50%)
Life Table Tests (d)	P=0.102N	P=0.323N	P=0.121N
Incidental Tumor Tests (d)	P=0.458	P=0.347	P=0.530
Cochran-Armitage Trend Test (d)	P=0.306N		
Fisher Exact Test		P=0.420	P=0.341N
Liver: Hepatocellular Adenoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	6/50 (12%)
Adjusted Rates (b)	7.3%	11%	17.6%
Terminal Rates (c)	1/26 (4%)	3/35 (9%)	6/34 (18%)
Life Table Tests (d)	P=0.167	P=0.478	P=0.231
Incidental Tumor Tests (d)	P=0.108	P=0.431	P=0.139
Cochran-Armitage Trend Test (d)	P=0.099		
Fisher Exact Test		P=0.339	P=0.134
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	8/50 (16%)
Adjusted Rates (b)	14.7%	16.6%	23.5%
Terminal Rates (c)	3/26 (12%)	5/35 (14%)	8/34 (24%)
Life Table Tests (d)	P=0.256	P=0.561	P=0.325
Incidental Tumor Tests (d)	P=0.191	P=0.524	P=0.231
Cochran-Armitage Trend Test (d)	P=0.141		
Fisher Exact Test		P=0.370	P=0.178

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

	Vehicle Control	250 mg/kg	500 mg/kg
Pituitary: Adenoma			
Overall Rates (a)	11/47 (23%)	10/41 (24%)	4/44 (9%)
Adjusted Rates (b)	42.1%	31.3%	12.1%
Terminal Rates (c)	10/25 (40%)	10/32 (31%)	4/33 (12%)
Life Table Tests (d)	P=0.006N	P=0.245N	P=0.009N
Incidental Tumor Tests (d)	P=0.009N	P=0.299N	P=0.015N
Cochran-Armitage Trend Test (d)	P=0.056N		
Fisher Exact Test		P=0.555	P=0.058N
Pituitary: Adenocarcinoma			
Overall Rates (a)	5/47 (11%)	3/41 (7%)	1/44 (2%)
Adjusted Rates (b)	19.1%	9.4%	3.0%
Terminal Rates (c)	4/25 (16%)	3/32 (9%)	1/33 (3%)
Life Table Tests (d)	P=0.032N	P=0.228N	P=0.053N
Incidental Tumor Tests (d)	P=0.054N	P=0.302N	P=0.093N
Cochran-Armitage Trend Test (d)	P=0.085N		
Fisher Exact Test		P=0.436N	P=0.117N
Pituitary: Adenoma or Adenocarcinoma			
Overall Rates (a)	16/47 (34%)	13/41 (32%)	4/44 (9%)
Adjusted Rates (b)	59.1%	40.6%	12.1%
Terminal Rates (c)	14/25 (56%)	13/32 (41%)	4/33 (12%)
Life Table Tests (d)	P<0.001N	P=0.083N	P<0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.138N	P<0.001N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test		P=0.499N	P=0.004N
Adrenal: Pheochromocytoma			
Overall Rates (a)	0/48 (0%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	8.0%	2.9%
Terminal Rates (c)	0/26 (0%)	2/35 (6%)	1/34 (3%)
Life Table Tests (d)	P=0.454	P=0.184	P=0.554
Incidental Tumor Tests (d)	P=0.310	P=0.112	P=0.554
Cochran-Armitage Trend Test (d)	P=0.391		
Fisher Exact Test		P=0.129	P=0.510
Thyroid: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	4/49 (8%)	0/46 (0%)
Adjusted Rates (b)	11.5%	11.4%	0.0%
Terminal Rates (c)	3/26 (12%)	4/35 (11%)	0/34 (0%)
Life Table Tests (d)	P=0.063N	P=0.652N	P=0.077N
Incidental Tumor Tests (d)	P=0.063N	P=0.652N	P=0.077N
Cochran-Armitage Trend Test (d)	P=0.131N		
Fisher Exact Test		P=0.500	P=0.133N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	3/50 (6%)	5/49 (10%)	0/50 (0%)
Adjusted Rates (b)	11.5%	14.3%	0.0%
Terminal Rates (c)	3/26 (12%)	5/35 (14%)	0/34 (0%)
Life Table Tests (d)	P=0.070N	P=0.527	P=0.077N
Incidental Tumor Tests (d)	P=0.070N	P=0.527	P=0.077N
Cochran-Armitage Trend Test (d)	P=0.134N		
Fisher Exact Test		P=0.346	P=0.121N
Harderian Gland: Adenoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	5.9%	8.6%	2.9%
Terminal Rates (c)	1/26 (4%)	3/35 (9%)	1/34 (3%)
Life Table Tests (d)	P=0.328N	P=0.603	P=0.463N
Incidental Tumor Tests (d)	P=0.379N	P=0.530	P=0.539N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test		P=0.500	P=0.500N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF ISOPHORONE (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE

TABLE F1. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Number of Animals Examined	Number of Tumors	Diagnosis
Incidence at Papanicolaou Cancer Research Institute			
Trichloroethylene	50	4 (8%)	Adenoma, NOS
		1 (2%)	Adenocarcinoma, NOS
TOTAL		5 (10%)	
Overall Historical Incidence			
	1,094	19	Adenoma, NOS
		12	Carcinoma, NOS
		2	Squamous cell carcinoma
		5	Adenocarcinoma, NOS
TOTAL		38 (3.5%)	
Range			
Low		0/50	
High		7/50	

(a) Data as of March 16, 1983, for NTP carcinogenesis studies of at least 104 weeks

TABLE F2. HISTORICAL INCIDENCE OF PANCREATIC TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls	
	Acinar Cell Adenoma	Acinar Cell Carcinoma
Historical Incidence at Papanicolaou Cancer Research Institute		
Trichloroethylene	0/47	0/47
Overall Historical Incidence (b)		
TOTAL	35/1,076 (3.3%)	2/1,076 (0.2%)
SD (b)	7.18%	0.59%
Range (c)		
High	14/50	1/49
Low	0/50	0/50

(a) Data as of March 16, 1983, for NTP carcinogenesis studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F3. HISTORICAL INCIDENCE OF KIDNEY TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Historical Incidence at Papanicolaou Cancer Research Institute				
Trichloroethylene	0/48			
Overall Historical Incidence (b)				
Number of Animals Examined	Number of Tumors		Diagnosis	Site
1,091	1		Transitional cell papilloma	Kidney, NOS
	2		Adenocarcinoma, NOS	Kidney, NOS
	2		Tubular cell carcinoma	Kidney, NOS
TOTAL	1 (<0.1%)		Transitional cell tumors	
	4 (0.4%)		Tubular cell tumors	

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) No more than one kidney neoplasm was observed in any group.

TABLE F4. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence in Vehicle Controls			
Study	Fibroma	Fibrosarcoma	Sarcoma, Fibrosarcoma, or Neurofibrosarcoma	Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma
Historical Incidence at Papanicolaou Cancer Research Institute				
Trichloroethylene	0/49	0/49	0/49	0/49
Overall Historical Incidence				
TOTAL	16/1,040 (1.5%)	28/1,040 (2.7%)	54/1,040 (5.2%)	70/1,040 (6.7%)
SD (b)	2.44%	4.03%	5.14%	6.56%
Range (c)				
High	4/50	8/48	9/48	11/50
Low	0/50	0/50	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F5. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Papanicolaou Cancer Research Institute			
Trichloroethylene	4/49	3/49	7/49
Overall Historical Incidence			
TOTAL	98/1,032 (9.5%)	58/1,032 (5.6%) (b)	154/1,032 (14.9%) (b)
SD (c)	4.60%	4.05%	5.82%
Range (d)			
High	10/50	7/50	13/50
Low	0/47	0/50	2/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Includes one adenocarcinoma, unclear primary or metastatic
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F6. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Lymphoma	Leukemia	Lymphoma or Leukemia
Historical Incidence at Papanicolaou Cancer Research Institute			
Trichloroethylene	11/50	0/50	11/50
Overall Historical Incidence			
TOTAL	126/1,040 (12.1%)	6/1,040 (0.6%)	132/1,040 (12.7%)
SD (b)	5.13%	2.30%	5.89%
Range (c)			
High	11/50	5/48	13/48
Low	1/48	0/50	1/48

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F7. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Papanicolaou Cancer Research Institute			
Trichloroethylene	3/48	8/48	11/48
Overall Historical Incidence			
TOTAL	132/1,034 (12.8%)	218/1,034 (21.1%)	335/1,034 (32.4%)
SD (b)	6.45%	7.57%	9.35%
Range (c)			
High	13/50	18/50	25/50
Low	0/50	4/48	7/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F8. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	All Adenoma (b)	All Carcinoma (c)	All Adenoma or Carcinoma
Historical Incidence at Papanicolaou Cancer Research Institute			
Trichloroethylene	3/27	0/27	3/27
Overall Historical Incidence			
TOTAL	113/905 (12.5%)	10/905 (1.1%)	123/905 (13.6%)
SD (d)	6.07%	2.42%	6.93%
Range (e)			
High	11/43	4/47	14/49
Low	2/44	0/48	2/44

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Includes adenoma, NOS, and seven chromophobe adenomas. No adenomas of other descriptions were diagnosed.
(c) Includes carcinoma, NOS, and one acidophil carcinoma. No other malignant tumors were diagnosed.
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

APPENDIX G

CHEMICAL CHARACTERIZATION OF ISOPHORONE

I. Identity and Purity Determinations of Isophorone Performed by the Analytical Chemistry Laboratory

A. Lot no. 1204

1. Physical properties	Determined	Literature Values
a. Boiling point:	215°-216° C (visual, micro, Büchi mp/bp apparatus) Endotherm from 216°-220° C (Dupont 900 DTA)	215° C (Patty, 1963)
b. Density:	d_{22}^{22}: 0.9199 ±0.004 (s)	d_{20}^{20}: 0.9229 (Patty, 1963)
c. Appearance:	Clear, colorless liquid	

2. Spectral data

a. Infrared

Instrument:	Beckman IR-12	
Cell:	Thin film between silver	chloride plates
Results:	See Figure 5	Consistent with literature spectrum (Sadtler Standard Spectra)

b. Ultraviolet/visible

Instrument:	Cary 118			
Solvent:	Methanol		Cyclohexane	
Results:	λ_{max}	$\varepsilon_{max} \times 10^{-3}$	λ_{max}	$\varepsilon_{max} \times 10^{-3}$
	307	0.0576 ± 0.0001	335	0.0332
	236	12.8912 ± 0.1000	226	14.4570
			(Calculated from literature spectrum: Sadtler Standard Spectra)	

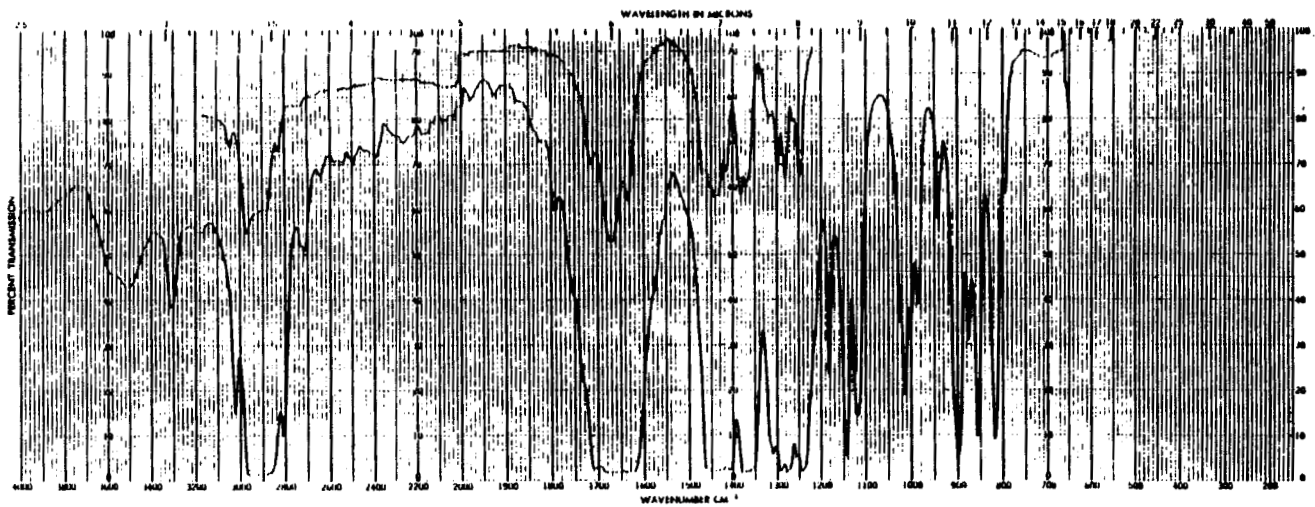

FIGURE 5. INFRARED ABSORPTION SPECTRUM OF ISOPHORONE (LOT NO. 1204)

c. Nuclear magnetic resonance	Determined	Literature Values
Instrument:	Varian EM-360-A	
Solvent:	Deuterated chloroform with internal tetramethylsilane standard	
Assignments:	See Figure 6	Consistent with literature spectrum (Sadtler Standard Spectra). On literature spectrum done in carbon tetrachloride, the (c) protons are partially resolved into two peaks.
Chemical shift (δ):	a s, 1.03 ppm b s, 1.95 ppm c s, 2.15 ppm (broad and unresolved) d m, 5.84 ppm	
Integration ratios:	a 6.12 b 2.71 c 4.16 d 1.00	

3. **Water analysis (Karl Fischer):** 0.28% ± 0.01 (δ)%

4. **Elemental analysis**

Element	C	H
Theory	78.21	10.21
Determined	78.59 78.30	10.43 10.48

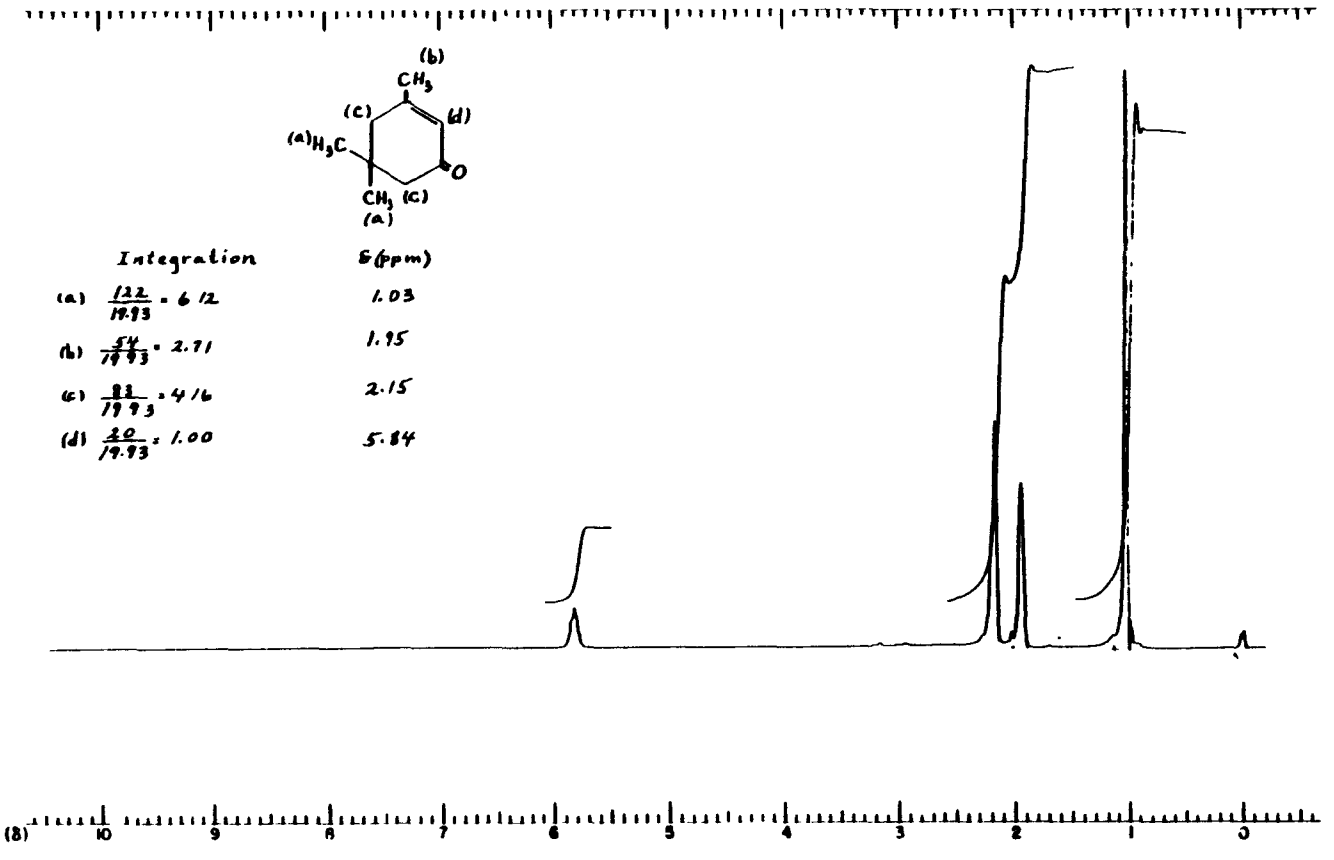

FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF ISOPHORONE (LOT NO. 1204)

5. **Chromatographic analyses**

a. **Thin-layer chromatography**

Plates: Silica Gel 60, F-254, 0.25 mm layer
Ref. standard: Ninhydrin, 10 µg (1 µg of a 10 µg/µl solution in methanol)
Amount spotted: 100 and 300 µg (10 and 30 µl of a 10 µg/µl solution of isophorone in methanol) and 1 µl of neat liquid. Chromatography was run in unsaturated tanks.
Visualization: Ultraviolet light (254 nm) and spray of 0.4% 2,4-dinitrophenylhydrazine in 2N hydrochloric acid (Stahl, 1969)

System 1: Hexanes:ethyl acetate (75:25)

Spot Intensity	R_f	R_{st}
Slight trace	0.89	13.75
Slight trace	0.79	12.15
Minor	0.73	11.31
Slight trace	0.67	10.26
Major	0.47	7.26
Trace	0.20	3.14

System 2: Chloroform (100%)

Spot Intensity	R_f	R_{st}
Slight trace	0.92	16.67
Trace	0.48	8.64
Trace	0.38	6.96
Major	0.27	4.96
Slight trace	0.08	1.47

b. **Gas chromatography**

Instrument: Varian 3700
Detector: Flame ionization
Inlet temperature: 200°C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min

System 1

Column: 10% SP-2100 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Detector temperature: 270° C
Oven temperature program: 50° C for 5 min, 50-250° C at 10° C/min
Sample injected: Neat liquid (4 µl) and 4 µl 1.0% and 0.5% isophorone in chloroform to quantitate the major peak and check for detector overload

Results: Major peak and 14 impurities, 1 before and 13 after the major peak. The peak before the major peak had an area of 1.9% of the major peak area. The combined area of all 13 impurity peaks after the major peak was 0.86% that of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major peak		Area (percent of major peak)
1	12.0	0.90		1.9
2	13.3	1.00		100.
3	14.7	1.11		0.03
4	14.9	1.12		0.10
5	15.3	1.15		0.06
6	15.4	1.16	Unresolved	0.05
7	15.6	1.17	group of	0.21
8	15.9	1.19	peaks	0.12
9	16.0	1.20		0.05
10	16.2	1.22		0.03
11	17.0	1.28		0.04
12	17.8	1.34		0.13
13	18.5	1.39		0.01
14	18.8	1.41		0.01
15	19.3	1.45		0.02

System 2

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m × 4 mm ID, glass
Detector temperature: 250° C
Oven temperature program: 60° C for 5 min, 60°-200° C at 10° C/min
Sample injected: Neat liquid (4 µl) and 4 µl of 1.0% and 0.5% isophorone in chloroform to quantitate the major peak and check for detector overload

Results: Major peak and seven impurities, three before and four after the major peak. One impurity before the major peak had an area of 1.5% of the major peak area. Three other impurities after the major peak had areas of 0.23% (two unresolved peaks) and 0.52% of the major peak area. The remaining three impurities had areas totaling 0.07% that of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major peak		Area (percent of major peak)
1	12.4	0.82		1.5
2	13.7	0.91	Unresolved	0.23
3	13.9	0.92		
4	15.0	1.00		100.00
5	16.4	1.09		0.52
6	18.0	1.20	Unresolved	0.06
7	18.2	1.21		
8	24.1	1.60		0.01

6. Identification of a 1.9% impurity (gas chromatography, system 1, peak 1) by gas chromatography/mass spectrometry

a. System

Instrument: Varian MAT 311-A mass spectrometer interfaced via a Watson-Biemann helium separator to a Varian 2700 gas chromatograph. Data processed by a Varian 620/i computer.
Chromatographic column: 10% SP-2100 on 100/120 Supelcoport; 1.8 m × 2 mm ID, glass
Carrier gas: Helium, 30 ml/min
Oven temperature program: 5 min at 50° C, then 50°-250° C at 10° C/min
Inlet temperature: 200° C
Transfer temperature: 285° C
Electron energy: 70 ev
Sample injected: 2 µl of a 200 ng/µl solution of isophorone in chloroform

b. Chromatographic results by ion current detection

Peak No.	Retention Time (min)	Retention Time Relative to Isophorone
1	14.2	0.92
2	15.4	1.00

c. Fragmentation pattern of the impurity peak (peak no. 1 above)

Fragmentation Pattern of Peak No. 1		Literature Spectrum of Isophorone (Eight Peak Index)	
m/e	Percent of Base Peak	m/e	Percent of Base Peak
82	100	82	100
138	26	39	28
69	20	138	17
54	13	27	17
83	13	41	13
55	12	54	13
81	9	53	9
91	6	29	7

Peak no. 1 could not be positively identified by comparison with literature spectra; however, the type of fragmentation obtained indicates that it is probably an isomer of isophorone.

7. **Conclusions:** Results of elemental analysis for carbon and hydrogen were in agreement with the theoretical values. Karl Fischer analysis indicated 0.28% ± 0.01(s)% water. Thin-layer chromatography by one system indicated three slight trace impurities, one trace impurity, and one minor impurity. A second thin-layer system indicated two slight trace impurities and two trace impurities. Gas chromatography with a 10% SP-2100 column indicated a major peak and 14 impurities, one before and 13 after the major peak. The peak before the major peak had an area of 1.9% of the major peak area and could be an isomer of isophorone. The remaining 13 impurities had peak areas totaling 0.86% of the major peak. A second gas chromatography system (10% Carbowax 20M-TPA) indicated seven impurities, three before and four after the major peak. One peak before the major peak had an area of 1.5% of the major peak area. Two unresolved peaks before the major peak had a combined area of 0.23% of the major peak, and one peak after the major peak had a relative area of 0.52%. The other three impurities had a combined relative area of 0.07%. The infrared and nuclear magnetic resonance spectra were consistent with the structure of isophorone. The ultraviolet/visible spectrum was consistent with the structure, but differed from the literature spectrum somewhat in λ_{max} and ε_{max}. The literature spectrum was run in a different solvent.

B. Lot no. L052281

1. Physical appearance: Clear, yellow, nonviscous liquid

2. Spectral data

	Determined	Literature Values
a. Infrared		
Instrument:	Perkin-Elmer 283	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 7	Consistent with literature spectrum (Sadtler Standard Spectra)

b. Ultraviolet/visible

	Determined		Literature Values	
Instrument:	Cary 219			
Solvent:	Methanol		Cyclohexane	
	No absorbance maxima from 800 to 350 nm, but an increase in absorbance toward 350 nm was noted.			
Results:	λ_{max} 10^{-3}	$\varepsilon_{max} \times 10^{-3}$	λ_{max}	$\varepsilon_{max} \times$
	308	0.0516 ± 0.0002(s)	335	0.0332
	235	12.7 ± 0.2(s)	226	14.4
			(Calculated from literature spectrum: Sadtler Standard Spectra)	

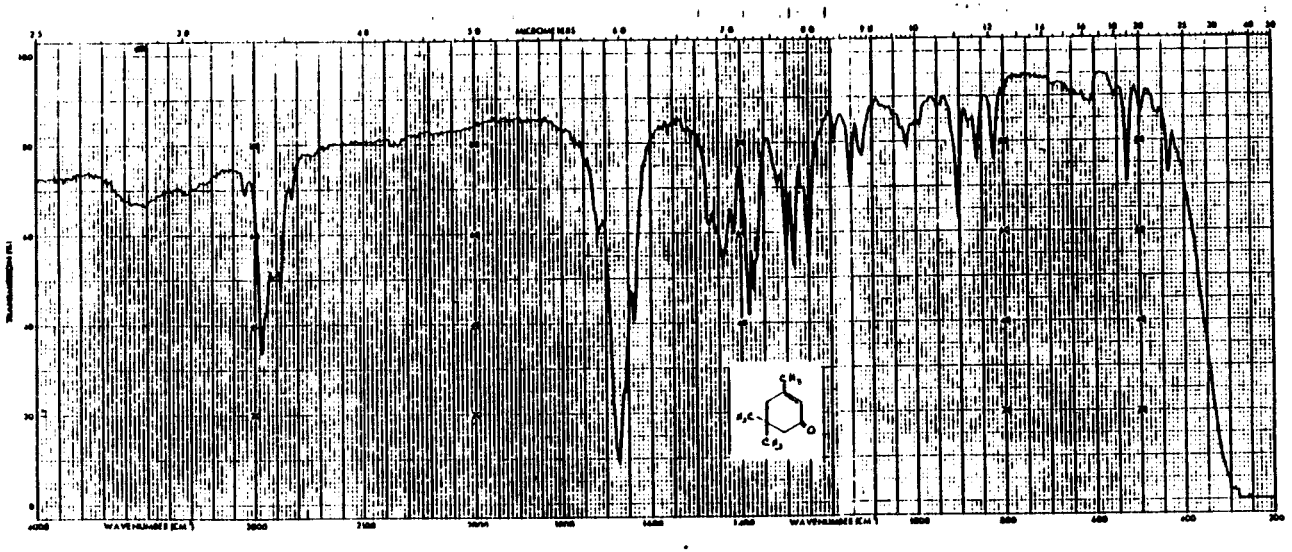

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF ISOPHORONE
(LOT NO. L052281)

c. Nuclear magnetic resonance	Determined	Literature Values
Instrument:	Varian EM-360-A	
Solvent:	Deuterated chloroform with tetramethylsilane internal standard	
Assignments:	See Figure 8	Consistent with literature spectrum (Sadtler Standard Spectra). On literature spectrum done in carbon tetrachloride, the (c) protons are partially resolved into two peaks.
Chemical shift (δ):	a s, 1.03 ppm b s, 1.93 ppm c s, 2.17 ppm d m, 5.82 ppm e impurity, 1.20 ppm f impurity, 3.35 ppm	
Integration ratios:	a 6.03 b 3.00 c 3.98 d 1.00 e impurity, 0.26 f impurity, 0.26	

3. **Water analysis (Karl Fischer):** 0.38% ± 0.01 (s)%

4. **Elemental analysis**

Element	C	H
Theory	78.21	10.21
Determined	78.61 78.49	10.44 10.55

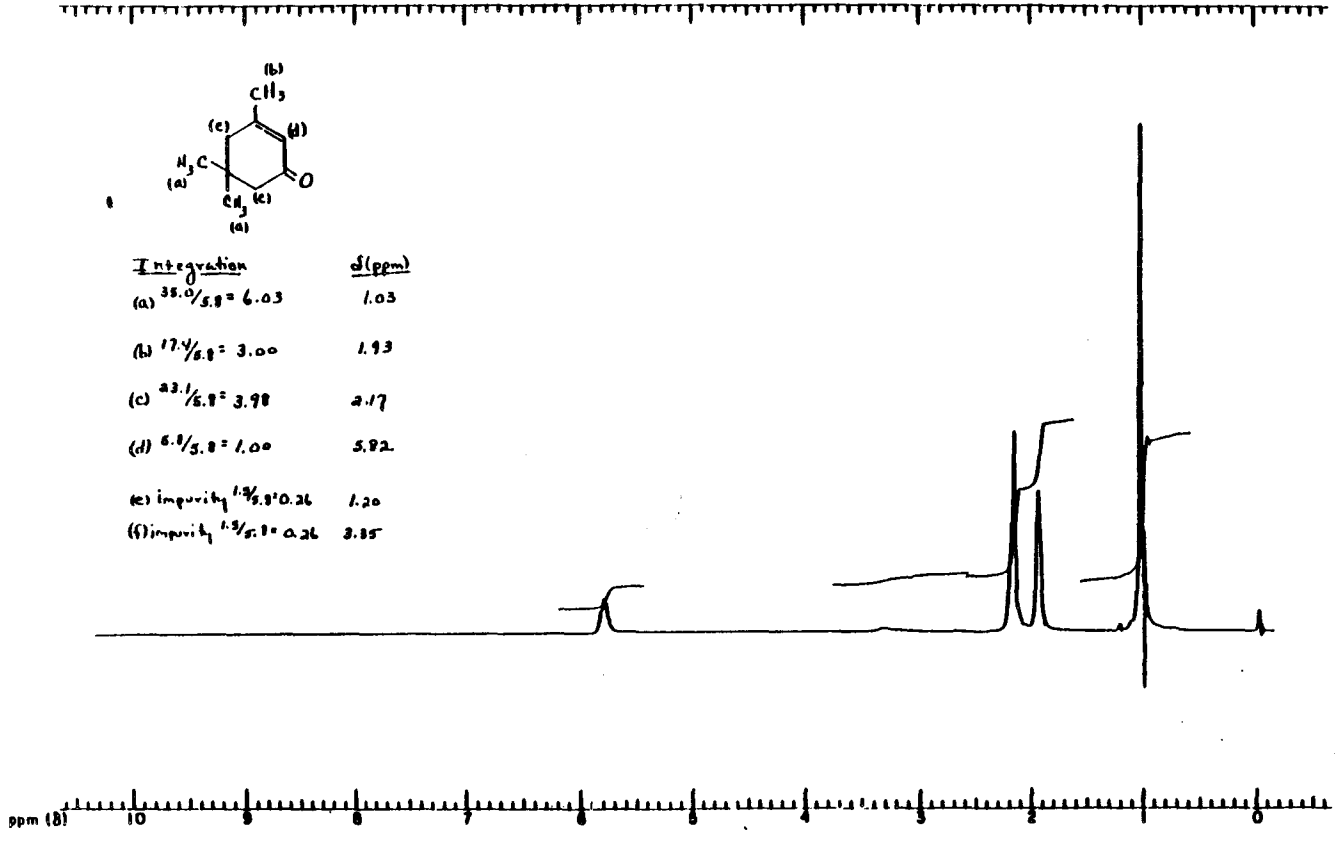

FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF ISOPHORONE (LOT NO. 052281)

5. **Chromatographic analysis**

a. **Thin-layer chromatography**

Plates: Silica Gel 60, F-254, 0.25 mm layer
Ref. standard: Ninhydrin, 10 µg (1 µg of a 10 µg/µl solution in methanol)
Amount spotted: 100 and 300 µg (10 and 30 µl of a 10 µg/µl solution of isophorone in methanol) and 1 µl of neat liquid. Chromatography was run in unsaturated tanks.
Visualization: Ultraviolet light (254 nm) and spray of 0.4% 2,4-dinitrophenylhydrazine in 2N hydrochloric acid (Stahl, 1969)

System 1: Hexanes:ethyl acetate (75:25)

Spot Intensity	R_f	R_{st}
Major	0.67	3.94
Minor	0.37	2.18
Slight trace	0.33	1.94
Slight trace	0.25	1.47
Slight trace	0.06	0.35
Slight trace	0.01	0.06
Reference	0.17	--

System 2: Chloroform (100%)

Spot Intensity	R_f	R_{st}
Minor	0.51	10.20
Major	0.36	7.20
Minor	0.08	1.60
Slight trace	0.02	0.40
Reference	0.05	--

b. **Gas Chromatography**

Instrument: Varian 3700
Detector: Flame ionization
Inlet temperature: 200°C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min

System 1

Column: 10% SP-2100 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Detector temperature: 270° C
Oven temperature program: 50° C for 5 min, then 50°-250° C at 10° C/min
Sample injected: Neat liquid (4 µl) and 1.0% and 0.5% solutions of isophorone in methylene chloride to quantitate the major peak and check for detector overload

Results: Major peak and 10 impurities, 1 before and 9 after the major peak. Peaks 3 through 9 were only partially resolved. The impurity before the major peak had an area of 0.46% relative to the major peak area. The nine impurities following the major peak had a combined relative area of 1.54%.

Peak No.	Retention Time (min)	Retention Time Relative to Major peak		Area (percent of major peak)
1	12.4	0.89		0.46
2	13.9	1.00		100
3	15.1	1.08	Unresolved	0.25
4	15.2	1.09		
5	15.4	1.11		0.11
6	15.8	1.13	Unresolved	0.14
7	15.9	1.14		
8	16.1	1.16		0.04
9	16.6	1.19		0.58
10	17.9	1.29		0.09
11	18.4	1.32		0.33

System 2

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m × 4 mm ID, glass
Detector temperature: 250° C
Oven temperature program: 60° C for 5 min, then 60°-200° C at 10° C/min
Sample injected: Neat liquid (4 µl) and 1.0% and 0.5% solutions of isophorone in methylene chloride to quantitate the major peak and check for detector overload

Results: Major peak and eight impurities, four before and four after the major peak. Peak no. 1, which occurred before the major peak and had a relative area of 0.45%, was actually a group of unresolved impurities. Peak no. 6, which was observed after the major peak, had an area of 2.5% relative to the major peak area. The remaining six impurities had a combined relative area of 1.32%.

Peak No.		Retention Time (min)	Retention Time Relative to Major peak	Area (percent of major peak)
1	Group of unresolved impurities	11.7-13.0	0.79-0.88	0.45
2	Unresolved	13.5	0.91	0.18
3	Unresolved	13.7	0.92	
4		14.3		0.06
5		14.8	0.97	
6		16.0	1.00	100
7	Unresolved	17.8	1.08	2.5
8	Unresolved	18.2		
9		23.6	1.20	0.28
			1.23	
			1.59	0.33

6. Identification of major component and a 2.5% impurity (gas chromatography, system 2, peak 6) by gas chromatography/mass spectrometry

a. Experimental conditions

Instrument: Finnigan 4000 mass spectrometer interfaced via a single stage glass jet separator to a Finnigan 9610 gas chromatograph. Data handled by an Incos 2300 data system.
Gas chromatographic column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW); 1.8 m × 2 mm ID; glass
Carrier gas: Helium
Carrier gas flow rate: 25 ml/min
Column oven temperature program: 135°C for 3 min, then 135°-155°C at 5° C/min
Heated zone temperatures

Inlet: 150°
Separator: 230°C
Transfer: 275°C
Ion source: 270°C

Electron energy: 70 eV
Electron multiplier voltage: −1,750 V
Pre-amplifier sensitivity: 10^{-7}
Emission current: 200 μA
Resolution: 1,000
Scan range: 38 to 475 amu
Scan times (sec): Up--2.90; Top--0.00; Down--0.00; Bottom--0.10
Sample injected: 2 μl of a 0.2% (v/v) solution of isophorone in hexanes

b. Results

Reconstructed ion chromatogram

The reconstructed ion chromatogram indicated that the major component eluted in 5.2 minutes and the impurity in 7.0 minutes on this system.

Spectra obtained

Major component (Figure 9)

The spectrum obtained from the major component is given below. Ions with abundances >5% of the base peak abundance are listed.

Spectrum Obtained from the Major Component

m/z	Relative Abundance (percent of m/z 82)
82	100
73	21
138	18
54	16
43	9
53	7
55	7
83	6
95	6
67	5

This spectrum is consistent with the fragmentation expected of isophorone. A fairly abundant molecular ion (m/z 138) was seen. The base peak in the spectrum (m/z 82) was provided by expulsion of 2-methyl-propene from the molecular ion via a Retro-Diels-Alder fragmentation mechanism. High mass range peaks, representing loss of a methyl group (m/z 123), carbon monoxide (m/z 110), and the combination of a methyl group and carbon monoxide (m/z 95) were observed. The ion at m/z 54 is thought to have arisen through loss of carbon monoxide from the base peak.

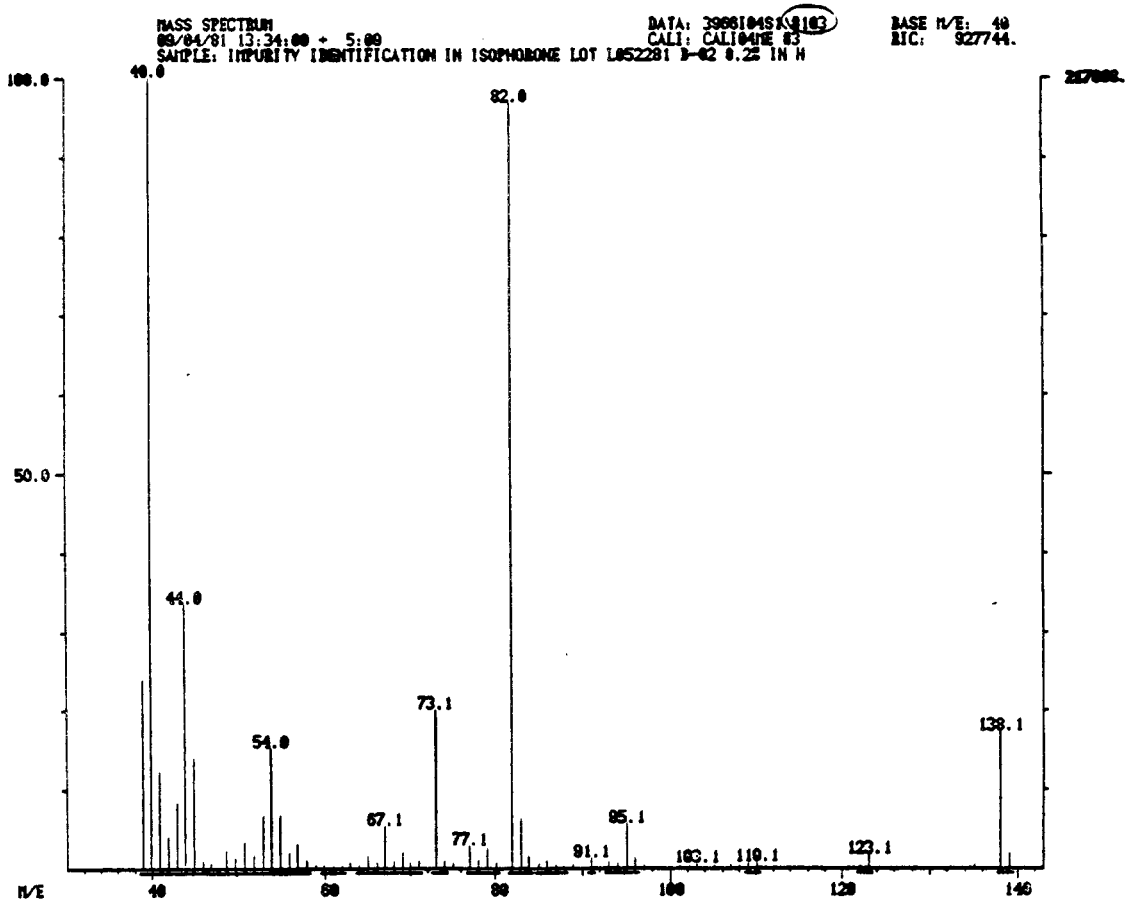

FIGURE 9. MASS SPECTRUM OF THE MAJOR COMPONENT OF ISOPHORONE (LOT NO. L052281)

Impurity (Figure 10)

A spectrum obtained from the impurity peak is given below. Ions with abundances >5% of the base peak abundance are listed.

Spectrum Obtained from the Impurity

m/z	Relative Abundance (percent of m/z 68)
68	100
96	64
39	54
40	35
41	23
152M$^+$	20
69	8
109	7
55	6
53	5
67	5

The molecular ion obtained (m/z 152) suggests an isophorone type structure with an added methylene group or replacement of a ring H by a methyl group.

Isophorone is synthesized by condensation of three molecules of acetone. In order to insert an extra methylene group into the molecule, condensation of two molecules of acetone and a four-carbon ketone or aldehyde is necessary. Condensation of two molecules of acetone and one molecule of methylethyl ketone, a likely impurity in acetone, could give 3,4,5,5-tetramethyl-2-cyclohexene-1-one, 2,3,5,5-tetramethyl-2-cyclohexene-1-one or 3-ethyl-5,5-dimethyl-2-cyclohexene-1-one. The spectrum is not consistent with the fragmentation expected of 3,4,5,5-tetramethyl-2-cyclohexene-1-one; however, it is consistent with the fragmentation expected of either 3-ethyl-5,5-dimethyl-2-cyclohexene-1-one or 2,3,5,5-tetramethyl-2-cyclohexene-1-one.

The fragmentation pattern for the impurity parallels that obtained for isophorone itself, i.e., loss of 2-methyl-propene (m/z 96), a methyl group (m/z 137), carbon monoxide (m/z 124), and a methyl group and carbon monoxide (m/z 109). The base peak in the impurity profile is, however, m/z 68, corresponding to loss of 84 from the molecular ion. The parallel peak in the isophorone spectrum is the m/z 54, a major fragmentation peak but not the base peak. Both the tetramethyl or ethyl dimethyl isomeric structures could theoretically fragment to give the m/z 68 base peak, the tetramethyl isomer by loss of 2-methylpropene and carbon monoxide, and the ethyldimethyl isomer by expulsion of ethylene and 2-methylpropene. The ethylene loss could take place through a six-membered ring transition state with hydrogen transfer to the carbonyl oxygen atom.

The spectrum obtained is consistent with the fragmentation expected of either 3-ethyl-5,5-dimethyl-2-cyclohexene-1-one or 2,3,5,5-tetramethyl-2-cyclohexene-1-one.

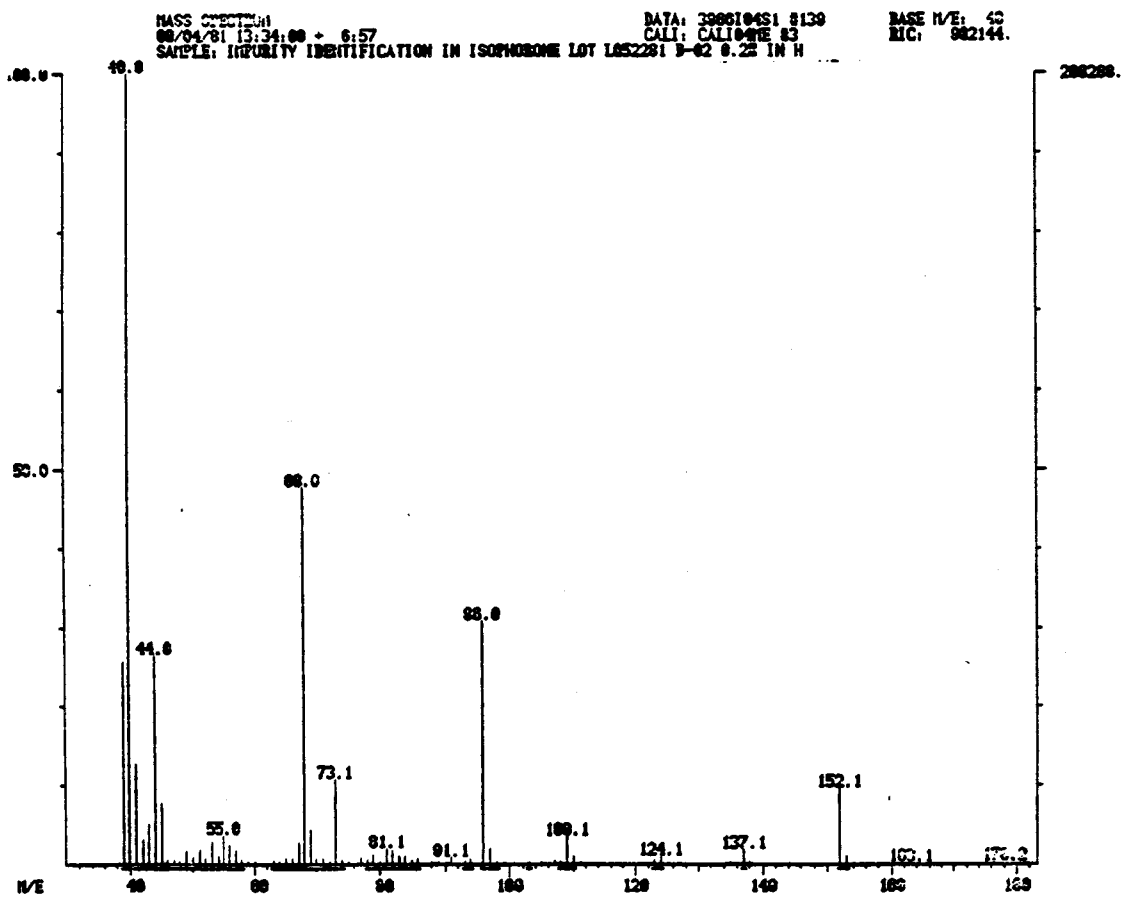

FIGURE 10. MASS SPECTRUM OF A 2.5% IMPURITY OF ISOPHORONE (LOT NO. L052281)

7. **Conclusions:** The result of the elemental analysis for hydrogen was in agreement with the theoretical value; the analysis for carbon was slightly high. Karl Fischer analysis indicated 1.38% ± 0.01(s)% water. Thin-layer chromatography by one system indicated a major spot with one minor and four slight trace impurities. A second thin-layer chromatographic system indicated a major spot with two minor impurities and a slight trace impurity. Gas chromatography with a 10% SP-2100 column indicated a major peak and 10 impurities, 1 before and 9 after the major peak, with a combined relative area of 2.00%. A second gas chromatographic system with a 10% Carbowax 20M-TPA column indicated a major peak and eight impurities, four before and four after the major peak. One impurity, observed after the major peak, had an area of 2.5% relative to the major peak area; the remaining seven impurities had a combined relative area of 1.77%. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of isophorone and with the spectra obtained for lot no. 1204.

   Lot no. L052281 was similar in purity to lot no. 1204 although the water content was higher. The basic gas chromatographic profiles for the two lots were similar, but the total relative impurity area was slightly greater for lot no. L052281 and the areas of some of the individual impurities varied significantly from those for lot no. 1204.

II. Test Chemical Stability Study of Lot No. 1204 Performed by the Analytical Chemistry Laboratory

A. Sample storage: Samples of isophorone were stored at – 20, 5, 25 and 60° C in glass tubes with Teflon-lined lids for two weeks.

B. Analytical method: Gas chromatography

Instrument: Varian 3700 with auto-injector
Detector: Flame ionization
Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m × 4 mm ID, glass
Inlet temperature: 200° C
Detector temperature: 350° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/min
Oven temperature program: 160° C isothermal
Samples injected Solutions of isophorone (0.5%) from each storage temperature in chloroform containing 0.4% pentadecane internal standard
Retention times: Pentadecane--1.8 min; Isophorone--2.8 min

The concentration of compound in the sample peaks was obtained by comparison of the peak areas of the standard of known concentration to the sample using a previously determined relative response ratio for compound and standard. Sample concentrations were then normalized to the – 20° C storage sample concentration.

C. Results

Storage Temperature (degrees centigrade)	Isophorone (percent of – 20° sample)
–20	100.0 ± 0.4
5	99.9 ± 0.4
25	99.6 ± 0.4
60	89.0 ± 0.4

Note: There is a small peak approximately 1.5% of the sample peak which decreases in size in the 60° C sample (retention time 1.6 min) and a peak in the 60° C sample not present in the other storage temperatures (retention time 3.9 min) with an area of about 1.0% of the major peak.

D. Conclusion: Isophorone is stable as the bulk chemical at temperatures up to 25° C. Between 25° and 60° C, some decomposition is evident.

III. Test Chemical Stability Studies Performed by the Testing Laboratory

A. Storage conditions: 0°-8° C

B. Analytical methods

1. Gas-liquid chromatography

Analyses performed on 12/12/79, 5/23/80, 7/24/80, 12/1/80, 3/11/81, 6/23/81, 8/7/81, 10/7/81 and 2/24/82

Instrument: Varian 3700 with CDS-111 integrator system
Column: 3% OV-17 on 80/100 Supelcoport
Detector: Flame ionization
Detector temperature: 170° C
Injector temperature: 140° C
Oven temperature program: 105° C isothermal
Carrier gas: Nitrogen
Sample size: 1-2 µl neat liquid

Analyses performed on 3/13/81, 6/18/81 and 8/5/81

Instrument: Varian 3700 with CDS-111 data system
Column: 10% Carbowax 20 M on 80/100 Chromosorb WAW
Detector: Flame ionization
Detector temperature: 250° C
Injector temperature: 200° C
Oven temperature program: 60° C for 5 min, then 60° to 180° C at 10° C/min
Carrier gas: Nitrogen
Sample size: 1-3 µl neat liquid

Analyses performed on 10/1/81 and 2/19/82

Same as **b.**, above, except:

Column: 10% Carbowax 20 M-TPA on 80/100 Chromosorb WAW

Results

Date	Percent Purity Lot No.	Bulk	Reference
12/12/79	1204	96.9	95.3
05/23/80		97.4	97.4
07/24/80		98.0	97.9
12/01/80		95.5	95.7
03/11/81		96.2	96.3
03/13/81		97.4	97.0
06/18/81		96.5	96.6
06/23/81		96.1	96.2
08/05/81	L052281	92.5	92.5
	92.6		
08/07/81		94.1	94.1
	93.9		
10/01/81		92.8	93.0
10/07/81		93.9	94.3
02/19/82		93.2	93.3
02/24/82		94.0	94.2

2. **Ultraviolet/visible spectroscopy** (Lot no. 1204 analysis performed on 2/11/81)

   Instrument: Zeiss DMP 21 Recording Spectrophotometer
   Concentration: 21.7 mM (0.3 g%) and 0.108 mM (1.5 mg%)
   Solvent: Methanol
   Spectrum consistent with that obtained by the analytical chemistry laboratory (Midwest Research Institute).

D. **Conclusion:** No notable degradation occurred during the studies.

APPENDIX H

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX H. PREPARATION AND CHARACTERIZATION

I. Studies Conducted at the Analytical Chemistry Laboratory

A. Sample preparation and storage: A 1.0939 ± 0.0001-g sample of isophorone was weighed into a 50-ml volumetric flask and diluted to volume with corn oil, mixing frequently during the addition. Total weight of the mixture was 46.1845 g, making the isophorone concentration 21.9 mg/ml (2.19% w/v) or 23.7 mg/g (2.37% w/w). From this freshly prepared solution, 10 approximately 1.51-g aliquots were weighed to the nearest 0.1 mg into separate 60-ml septum vials and immediately sealed (vial seals were Microsep F-138 gas chromatography septa with Teflon® film facing, from Canton Biomedical Products, Inc.). Duplicate vials were set aside for analysis at 0, 1, 3, 4, and 7 days.

B. Sample extraction and analysis: Storage samples were extracted by pipetting 20 ml of reagent grade anhydrous methanol into each septum vial, shaking vigorously by hand for 30 seconds and then sonicating in an ultrasonic bath for an additional 30 seconds. About 10 ml of each corn oil suspension was transferred to 12-ml centrifuge tubes and clarified by centrifuging for 5 minutes. Exactly 3 ml of the clear, upper methanolic extract layer was pipetted into 8.5-ml septum vials and mixed with exactly 3 ml of internal standard solutions, prepared by dissolving 0.1508 g of *n*-decyl alcohol in methanol and diluting to 50 ml. After internal standard was added, each vial was sealed and mixed thoroughly, and the isophorone content was determined by the gas chromatographic system described below.

Instrument: Bendix 2500 gas chromatograph with Heath recorder
Column: 3% OV-17 on 80/100 mesh Supelcoport, 1.8 m × 2 mm ID, glass, silanized
Detection: Flame ionization
Temperatures:
Inlet, 175°C
Oven, 90°C
Detector, 250°C
Carrier gas: Nitrogen, 30 ml/min
Volume injected: 4 µl
Retention times:
Test chemical, 3.0 min
Reference standard, 6.5 min

C. Quality control protocols: Analyses were carried out by making duplicate injections of duplicate extractions on all sample and recovery determinations. Results were related to an internal standard incorporated in each extract. Recovery studies were conducted with test material at the same concentrations as samples. Gas chromatographic linearity was determined with standard solutions of isophorone in methanol at 0.71, 0.89, and 1.06 mg/ml concentrations and with *n*-decyl alcohol as internal standard at levels of 1.21, 1.51, and 1.81 mg/ml.

D. Results

Storage Time (days)	Average Percent (w/w) Chemical Found in Chemical/Vehicle Mixture (a,b)
0	(c) 2.37 ± 0.03
1	2.37 ± 0.03
3	2.36 ± 0.03
4	2.35 ± 0.03
7	2.34 ± 0.03

(a) Corrected for zero-time recovery yield of 95% ± 1%.
(b) Target concentration of chemical in corn oil, 2.3685% ± 0.0002% (w/w)
(c) The error values in this table are average deviations obtained in the analytical measurements of the test solutions.

E. Conclusion: Isophorone is stable when dissolved in corn oil at a dose level of 2.37% and stored at room temperature for 7 days.

II. Preparation of Dose Mixtures at the Testing Laboratory

Procedure: Dose solutions were prepared in a ground glass-stoppered graduated cylinder by mixing the appropriate weight of isophorone, determined from the specific gravity of 0.923, with sufficient corn oil to make the desired volume of solution. The solutions were mixed for 2-3 minutes, producing a clear, homogeneous solution. Low dose solutions were prepared by diluting the high dose preparation. Dosing solutions were prepared every 2 weeks during the first 4 weeks of the 2-year studies and weekly thereafter.

APPENDIX I

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX I. METHODS OF ANALYSIS

I. Testing Laboratory Procedure

All chemical/vehicle analyses were performed by gas chromatography.

A. 5/13/80 through 9/2/80: A sample weighing 1.5 g was added to a vial. Twenty milliliters of reagent grade anhydrous methanol was added to the sample. The contents were shaken vigorously by hand for 30 seconds, followed by sonication in an ultrasonic bath for an additional 30 seconds. Approximately 10 ml of the suspension was transferred to a 12-ml centrifuge tube and clarified by centrifugation for 5 minutes. Exactly 3 ml of the clear upper methanolic layer was pipetted into a septum vial and mixed with 3 ml of internal standard solution, prepared by dissolving 0.1508 g of *n*-decyl alcohol in 50 ml of methanol.

B. 9/12/80 through 5/7/81: The samples were extracted by adding 2-25 ml of extracting solution (1.5 mg/ml *n*-decyl alcohol in methanol). The contents were mixed by hand for 30 seconds and sonicated for 30 seconds. Ten milliliters were transferred to a centrifuge tube and clarified by centrifugation for 5 minutes. The supernatant was transferred to serum vials and sealed with a Teflon® septum.

C. 6/1/81 through 1/6/82: The procedure was identical as described in **B.** except that the mixture was shaken for 30 minutes on an Eberbach® shaker and then centrifuged.

Instrument: Varian 3700 gas chromatograph with a CDS III Data System
Column: 3% OV-17 on 80/100 Supelcoport
Detector: Flame ionization
Detector temperature: 250° C
Injector temperature: 180° C
Oven temperature program: 90° C, isothermal
Carrier gas: Nitrogen

II. Analytical Chemistry Laboratory Procedure

Immediately before sampling for analysis, the referee corn oil sample and the undosed corn oil were allowed to equilibrate to room temperature and were homogenized by mixing on a vortex mixer.

A. Preparation of standard spiked corn oil: Two standard solutions of isophorone were prepared independently in methanol at concentrations of 5.10 and 4.08 mg/ml. These solutions were diluted with methanol to make four additional standards at concentrations of 2.55, 2.04, 1.28, and 1.02 mg/ml. Aliquots (20 ml) of the six standard solutions were pipetted into individual 35-ml septum vials containing 2 g of undosed corn oil to make spiked corn oil standards bracketing the specified dose range of the referee sample. One 35-ml septum vial containing 2 g of undosed corn oil was treated with 20 ml of methanol for use as a blank. After the vials were sealed with Teflon®-lined septa, the spiked corn oils and the corn oil blank were used in the analysis procedure described below.

B. Preparation of referee sample: Three portions (~2 g each) of the referee corn oil sample were transferred to individually tared 35-ml septum vials and weighed to the nearest 0.001 g. Methanol (20 ml) was pipetted into each vial; the vials were sealed and the samples analyzed immediately by the following procedure.

C. **Analysis:** Vials containing the samples, standards, and the blank were agitated for 10 seconds on a vortex mixer and then shaken for 15 minutes at maximum stroke on a Burrell, Model 75, Wrist-Action® shaker. After the extraction mixtures were centrifuged for 3 minutes, a 5-ml aliquot of the methanol layer from each vial was combined with 5 ml of internal standard solution (*n*-decyl alcohol in methanol, 3 mg/ml). The solutions were thoroughly mixed, and the isophorone content of each solution was determined by the gas chromatography system below.

Instrument: Varian 3700 Gas Chromatograph with Autosampler and Varian CDS 111-C integrator
Column: 3% OV-17 on 100/120 mesh Supelcoport, 1.8 m × 2 mm ID, glass, silanized
Detection: Flame ionization
Detector temperature: 250° C
Inlet temperature: 200° C
Temperature program: 100° C, isothermal
Carrier gas: Nitrogen, 30 ml/min
Volume of solution injected: 3 µl
Retention times
Isophorone: 3.8 - 5.8 min
n-Decyl alcohol internal standard: 6.0 - 9.5 min

D. **Quality assurance measures:** The referee corn oil sample was analyzed in triplicate, and the control corn oil sample was analyzed once. Individually spiked portions of control corn oil (six concentrations bracketing the specified dose range of the referee sample) were prepared from two independently weighed standards and were used for obtaining standard data. Triplicate injections of each standard and sample were introduced into the gas chromatograph in a randomized order. All determinations were related to an internal standard incorporated into the sample solutions.

The total amount of isophorone in the referee corn oil samples was computed from the linear regression equation obtained from the standard data, relating the ratio obtained by dividing the peak area of each spiked corn oil sample by the peak area of the internal standard, to the amount of chemical in the respective spiked corn oil sample.

APPENDIX J

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE J1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

Date Mixed	Concentration (a) of Isophorone in Corn Oil for Target Concentration (percent)		
	2.50	5.00	10.00
1/31/80		4.97	9.05
2/14/80		5.06	(b) 8.36
3/6/80	2.52	5.41	
3/13/80		5.00	9.25
3/20/80	2.61	4.89	
3/20/80		5.16	
3/27/80	(b) 2.94	5.12	
4/2/80		4.80	10.18
4/10/80			10.57
4/16/80	2.38	(b) 5.88	
4/16/80		5.21	
5/1/80	2.44		10.10
5/14/80		4.86	
5/14/80		5.29	
6/5/80	2.43	4.85	
6/13/80		5.23	
6/13/80		5.37	
7/3/80		5.15	9.78
8/13/80	2.66		
8/28/80	2.52	4.95	
9/4/80	2.50		10.59
9/4/80	2.53		
10/2/80	2.56	5.18	9.55
10/9/80		5.48	10.29
12/4/80	2.61	5.06	10.59
12/4/80		5.03	
1/7/81		5.06	10.59
2/3/81	2.66	5.34	10.31
3/3/81		4.95	9.06
3/31/81	2.71	4.95	
4/28/81		5.01	9.62
5/26/81	2.67	5.15	
6/23/81		5.01	9.78
7/20/81	2.58	4.95	
8/18/81		4.72	10.10
9/14/81	2.72	5.10	
10/13/81		5.25	9.71
11/10/81	2.60	4.90	
12/8/81		4.81	9.79
1/5/82	2.48	5.15	
Mean (percent)	2.59	5.09	9.86
Standard deviation	0.129	0.227	0.616
Coefficient of variation (percent)	5.0	4.5	6.2
Range (percent)	2.38-2.94	4.72-5.88	8.36-10.59
Number of samples	19	35	19

(a) Results of duplicate analysis
(b) More than 10% different from target concentration

TABLE J2. RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE

Date Mixed	Lot Number	Target Concentration (percent)	Determined Concentration (a)	
			Testing Laboratory	Referee Laboratory
3/27/80	1204	5.0	5.12	5.14
10/2/80	1204	10.0	9.55	9.78
3/31/81	1204	2.5	2.71	2.42
8/18/81	L052281	5.0	4.72	5.06
11/10/81	L052281	2.5	2.61	2.52
1/5/82	L052281	2.5	2.48	2.50

(a) Results of duplicate analysis

APPENDIX K

SENTINEL ANIMAL PROGRAM

APPENDIX K. SENTINEL ANIMAL PROGRAM

I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program were produced in optimally clean facilities to eliminate potential pathogens that may affect test 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 viral serology on sera from extra (sentinel) animals in the test rooms. These animals were untreated, and these animals and the test animals were both subject to identical environmental conditions. The sentinel animals came from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen B6C3F$_1$ mice and 15 F344/N rats of each sex were selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group were killed at 6, 12, and 18 months on study. Data from rats surviving 24 months were collected from 5/50 randomly selected control animals of each sex. The blood from each animal was collected and clotted, and the serum was separated. The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests were performed:

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

II. Results

Results are presented in Table K1.

TABLE K1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF ISOPHORONE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	10/10	RCV
12	8/9	RCV
18	10/10	RCV
24	2/10	RCV
MICE		
6	---	None positive
12	---	None positive
18	1/8	MHV
24	Not sampled	Not sampled

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control rats just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX L

GENETIC TOXICOLOGY OF ISOPHORONE

I. Mutagenicity

Results: Isophorone was not mutagenic in strains TA100, TA1535, TA1537, or TA98 of Salmonella in the presence or absence of Aroclor 1254-induced rat or hamster liver S9 (Table L1).

Isophorone was mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the absence of S9 (Table L2).

II. Cytogenetic Effects

Results: Isophorone induced sister-chromatid exchanges (SCE's) in the absence of Aroclor 1254-induced rat liver S9 in Chinese hamster ovary (CHO) cells (Table L3); it did not induce SCE's in the presence of S9 (Table L3), and it did not induce chromosomal aberrations in CHO cells in the presence or absence of S9 (Table L4).

TABLE L1. MUTAGENICITY OF ISOPHORONE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	82 ± 4.7	92 ± 7.5	79 ± 2.2
	100	74 ± 6.6	90 ± 2.2	88 ± 8.1
	333	88 ± 7.4	85 ± 9.4	117 ± 2.9
	1,000	Toxic	82 ± 4.2	99 ± 4.8
	3,333	---	68 ± 20.2	65 ± 3.3
	10,000	---	48 ± 7.2	80 ± 9.5
TA1535	0	6 ± 2.5	7 ± 0.9	7 ± 1.2
	33	---	5 ± 1.0	---
	100	4 ± 0.9	6 ± 1.0	6 ± 1.0
	333	2 ± 0.6	9 ± 2.8	6 ± 1.2
	1,000	Toxic	5 ± 0.3	4 ± 1.5
	3,333	---	5 ± 1.2	6 ± 1.2
	10,000	---	---	Toxic
TA1537	0	2 ± 0.3	3 ± 1.5	4 ± 0.7
	33	---	5 ± 1.5	4 ± 1.2
	100	1 ± 0.7	5 ± 1.0	5 ± 0.0
	333	2 ± 1.5	4 ± 0.6	4 ± 2.4
	1,000	4 ± 0.7	3 ± 0.7	6 ± 2.0
	3,333	Toxic	4 ± 0.9	4 ± 0.3
TA98	0	10 ± 2.0	11 ± 2.9	17 ± 1.0
	33	---	15 ± 0.9	13 ± 2.1
	100	12 ± 2.3	17 ± 1.3	13 ± 2.3
	333	9 ± 0.9	14 ± 0.9	15 ± 0.9
	1,000	Toxic	17 ± 2.0	12 ± 2.6
	3,333	---	16 ± 1.8	15 ± 0.9

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and test compound or solvent (water) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The analysis was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.

TABLE L2. MUTAGENICITY OF ISOPHORONE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9

Compound	Dose (μg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells) (a)
DMSO (1%)		79	52.7	6.8	50
		74	46.3	6.6	53
		80	50.3	6.9	53
		65	40.2	6.9	54
Ethyl methane-sulfonate	15	128	15.2	22.3	281
		69	12.2	13.4	189
Isophorone					
	400	139	74.2	118.3	62
		79	55.5	112.4	47
	600	175	77.2	74.8	76
		161	72.5	92.4	74
	800	188	68.2	62.8	92
		152	58.0	50.5	87
	1,000	328	74.3	18.9	147
		307	61.3	26.7	167
	1,200	344	41.8	7.2	274
		322	59.7	14.3	180

(a) Experiments were performed twice, and all doses were tested in duplicate, except the solvent control (DMSO), which was tested in quintuplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

TABLE L3. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY ISOPHORONE

−S9 (a)		+S9 (b)	
Dose (μg/ml)	SCE/Cell	Dose (μg/ml)	SCE/Cell
DMSO (10 μl)	9.12	DMSO (10 μl)	8.82
Isophorone		Isophorone	
250	9.58	160	9.26
500	11.20	500	9.10
750	12.64	1,000	9.22
1,000	13.24		
Mitomycin C		Cyclophosphamide	
0.001	26.04	0.3	12.48
0.01	74.90	2.0	34.00

(a) In the absence of S9, CHO cells were incubated with test compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation continued for 27-35 hours. Cells were washed, fresh medium containing BrdU (10 μM) and colcemid (0.1 μg/ml) was added, and incubation was continued for 2-3 hours. Cells were then collected by mitotic shake-off, treated for 3 minutes with potassium chloride (75 mM), washed twice with fixative, and dropped onto slides and air-dried. Staining was by a modified technique (after Perry and Wolff, 1974; Goto et al., 1978).
(b) In the presence of S9, cells were incubated with test compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 μM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 μg/ml) present for the final 2-3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

TABLE L4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY ISOPHORONE

−S9 (a)		+S9 (b)	
Dose (μg/ml)	Abs/100 Cells (percent cells w/abs)	Dose (μg/ml)	Abs/100 Cells (percent cells w/abs)
DMSO (10 μl)	2 (2)	DMSO (10 μl)	0 (0)
Isophorone		Isophorone	
250	5 (5)	750	0 (0)
500	3 (3)	1,000	1 (1)
1,000	3 (3)	1,250	1 (1)
1,600	3 (3)	1,500	2 (2)
Mitomycin C		Cyclophosphamide	
0.25	41 (35)	15	60 (43)
1.00	92 (50)	50	162 (74)

(a) In the absence of S9, CHO cells were incubated with test compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 μg/ml) was added. After a further 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the presence of S9, cells were incubated with test compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation continued for 8-10 hours. Colcemid (0.1 μg/ml) was added for the last 2-3 hours of incubation; then cells were harvested and fixed as above. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats.

APPENDIX M

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS OF THE NIH 07 DIET

Pelleted Diet: December 1979 to January 1982

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

TABLE M1. INGREDIENTS OF THE NIH 07 DIET (a)

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

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

TABLE M2. VITAMINS AND MINERALS IN THE NIH 07 DIET (a)

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

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

TABLE M3. NUTRIENT COMPOSITION OF THE NIH 07 DIET (a)

Nutrient	Mean	Range	Number of Samples
Crude protein (percent by weight)	24.29 ± 0.81	22.7-26.1	24
Crude fat (percent by weight)	4.81 ± 0.38	4.1-5.5	24
Crude fiber (percent by weight)	3.31 ± 0.50	1.4-4.3	24
Ash (percent by weight)	6.76 ± 0.44	5.83-7.43	24
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.840-0.827	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins (b)			
Vitamin A (IU/kg)	10,192 ± 2,534	6,700-17,000	24
Vitamin D (IU/kg)	6,300		1
A-tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	16.2 ± 4.5	7.4-27.0	24
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.34 ± 0.20	0.81-1.69	24
Phosphorous (percent)	1.01 ± 0.08	0.82-1.10	24
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) not analyzed for thiamine

TABLE M4. CONTAMINANT LEVELS OF THE NIH 07 DIET

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.39 ± 0.23	<0.05-1.06	24
Cadmium (ppm) (a)	0.11 ± 0.07	<0.05-0.40	24
Lead (ppm)	0.91 ± 0.51	0.50-2.65	24
Mercury (ppm) (b)	0.05		
Selenium (ppm)	0.29 ± 0.09	0.10-0.52	24
Aflatoxins (ppb) (b,c)	<10		24
Nitrate nitrogen (ppm) (d,e)	7.00 ± 3.70	<0.1-13.0	24
Nitrite nitrogen (ppm) (d,e)	1.45 ± 1.02	<0.1-4.0	24
BHA (ppm) (f,g)	3.83 ± 3.88	<0.2-13.0	24
BHT (ppm) (f)	2.97 ± 1.74	0.8-7.6	24
Aerobic plate count (CFU/g) (h)	48,786 ± 32,701	5,500-120,000	22
Aerobic plate count (CFU/g) (i)	70,970 ± 81,410	5,500-320,000	24
Coliform (MPN/g) (j)	39 ± 57	<3-240	20
Coliform (MPN/g) (k)	270 ± 580	<3-2,400	24
E. coli (MPN/g) (l)	<3		24
Total nitrosamines (ppb) (m,n)	7.63 ± 6.67	2.2-24.5	21
Total nitrosamines (ppb) (m,o)	29.77 ± 64.59	2.2-273	24
N-Nitrosodimethylamine (ppb) (m,n)	5.81 ± 6.30	1.1-20.0	21
N-Nitrosodimethylamine (ppb) (m,o)	27.79 ± 64.31	1.1-272	24
N-Nitrosopyrrolidine (ppb)	1.44 ± 0.89	0.5-3.5	24
Pesticides (ppm)			
Alpha BHC (b,p)	<0.01		24
Beta BHC (b)	<0.02		24
Gamma BHC-lindane (b)	<0.01		24
Delta BHC (b)	<0.01		24
Heptachlor (b)	<0.01		24
Aldrin (b)	<0.01		24
Heptachlor epoxide (b)	<0.01		24
DDE (b,q)	<0.01		24
DDD (b)	<0.01		24
DDT (b)	<0.01		24
HCB (b)	<0.01		24
Mirex (b)	<0.01		24
Methoxychlor (b,q)	<0.05	0.09 (8/26/81)	24
Dieldrin (b)	<0.01		24
Endrin (b)	<0.01		24
Telodrin (b)	<0.01		24
Chlordane (b)	<0.05		24
Toxaphene (b)	<0.1		24
Estimated PCB's (b)	<0.2		24
Ronnel (b)	<0.01		24
Ethion (b)	<0.02		24
Trithion (b)	<0.05		24
Diazinon (b,q)	<0.1	0.02 (4/27/81)	24
Methyl parathion (b)	<0.02		24
Ethyl parathion (b)	<0.02		24
Malathion (r)	0.10 ± 0.07	<0.05-0.27	24
Endosulfan I (b)	<0.01		24
Endosulfan II (b)	<0.01		24
Endosulfan sulfate (b)	<0.03		24

TABLE M4. CONTAMINANT LEVELS OF THE NIH 07 DIET (Continued)

(a) Three batches contained more than 0.1 ppm.
(b) All values were less than the detection limit, given in the table as the mean.
(c) Detection limit reduced from 10 ppb to 5 ppb after 7/81
(d) Source of contamination: Alfalfa, grains, and fish meal
(e) Two batches contained less than 0.1 ppm.
(f) Source of contamination: Soy oil and fish meal
(g) Six batches contained less than 0.5 ppm.
(h) Mean, standard deviation, and range exclude two extreme values (300,000 and 320,000) obtained in batches produced on 12/21/79 and 2/26/80. CFU = colony-forming units.
(i) Mean, standard deviation, and range include the two extreme values given in footnote h.
(j) Excludes four very high values in the range 1,100-2,400 obtained in batches produced on 2/4/80, 2/26/80, 5/29/80 and 12/16/80
(k) Includes the high values listed in footnote j
(l) All values were less than 3 MPN/g. MPN = most probable number.
(m) All values were corrected for percent recovery.
(n) Mean, standard deviation, and range exclude three very high values in the range of 115-280 ppb in batches produced on 1/26/81, 2/23/81, and 4/27/81.
(o) Mean, standard deviation, and range include the very high values given in footnote n.
(p) BHC = hexachlorocyclohexane or benzene hexachloride
(q) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(r) Nine batches contained more than 0.05 ppm.

APPENDIX N

DATA AUDIT SUMMARY

APPENDIX N. DATA AUDIT SUMMARY

The experimental data and tables of the draft NTP Technical Report on the Toxicology and Carcinogenesis Studies of Isophorone in F344/N rats and B6C3F$_1$ mice were audited for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The 2-year studies on isophorone were initiated at Papanicolaou Cancer Research Institute in January 1980 and completed in February 1982. The studies were started before the October 1981 NTP requirement for full compliance with good Laboratory Practices regulations. The data audit was conducted by the Dynamac Corporation in May/June of 1984. Audit team members were Dr. R. Schueler, Dr. F. Garner, Dr. K. Whitkin, Ms. C. Sexsmith, Mr. C. Dippel, Mr. J. Konz, and Mr. J. Plautz.

The full report of the audit of these studies is on file at the National Toxicology Program, NIEHS. The audit consisted of a review of the records for the in-life portion of the studies, including clinical observations and body weight data for 10% of the animals, and all of the environmental and mortality records; a review of all chemistry data, including chemical characterization, bulk chemical analysis, and characterization of dose mixtures; and a review of pathology data. All Individual Animal Pathology Data Records for rats and mice were reviewed for correlation of gross lesions and microscopic diagnoses. Ten percent of wet tissues were reviewed for animal identification and untrimmed lesions, and a complete slide/block match for both sexes of rats and mice was performed on the high dose and control groups.

The review of the toxicology data found minor discrepancies in the documentation of the randomization procedure and in clinical observations. A review of the available chemistry data found no discrepancies. Review of the pathology data found that positive animal identification was not possible because foot markings were not required to be retained with the wet tissues. No observations were made that would suggest that animal identification was a problem at any point in the studies. Wet tissue bags were missing for three mice (vehicle control males #31 and #37; high dose female #3), but all rat tissues were present. Discrepancies in gross and microscopic correlations of lesions were distributed as follows: rats, vehicle control male (2), low dose male (7), high dose male (3), vehicle control female (1), low dose female (4), high dose female (6); mice, vehicle control male (2), low dose male (7), high dose male (3), vehicle control female (1), low dose female (4), high dose female (6). These findings were determined to have no impact on the final interpretation of the studies and were therefore not pursued. However, three untrimmed liver lesions were noted in female vehicle control rats; these lesions were examined and the results incorporated in this Technical Report.

In conclusion, no discrepancies found during the audit which were not corrected before the completion of this report were considered of sufficient importance to influence the interpretation of the studies.

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