NATIONAL TOXICOLOGY PROGRAM
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No. 312

TOXICOLOGY AND CARCINOGENESIS STUDIES OF *n*-BUTYL CHLORIDE

(CAS NO. 109-69-3)

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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IN F344/N RATS AND B6C3F$_1$ MICE

(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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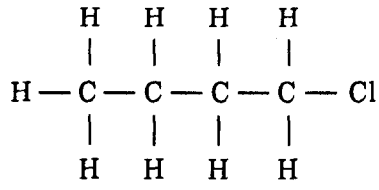


n-Butyl Chloride

(1-Chlorobutane; Butyl Chloride; *n*-Propylcarbinyl Chloride)

CAS No. 109-69-3

C_4H_9Cl Molecular weight 92.57

ABSTRACT

Toxicology and carcinogenesis studies of *n*-butyl chloride (greater than 99.5% pure), a solvent as well as an alkylating agent, were conducted by exposing groups of F344/N rats and $B6C3F_1$ mice to *n*-butyl chloride in corn oil by gavage for 14 days, 13 weeks, and 2 years. In the 14-day studies, no compound-related gross pathologic effects were observed in groups of five male or female rats or mice administered doses of up to 3,000 mg/kg body weight. However, deaths occurred in the groups administered 750, 1,500, or 3,000 mg/kg. Tremors and convulsions following gavage administration were observed.

In the 13-week studies, groups of 10 male and 10 female rats were administered up to 500 mg/kg *n*-butyl chloride, and similar groups of mice received up to 1,000 mg/kg. Three of 10 male rats in the 500 mg/kg dose group and one female mouse in the 120 mg/kg dose group died before the end of the studies. Mild to moderate extramedullary hematopoiesis was observed in 3/10 male rats receiving 500 mg/kg. Mean body weights of male and female rats receiving 250 or 500 mg/kg were lower than those of the vehicle controls. Convulsions were observed in male and female rats receiving 250 mg/kg or higher and in 2/10 female mice receiving 1,000 mg/kg. Based on these results, 2-year toxicology and carcinogenesis studies of *n*-butyl chloride were conducted by administering doses of 0, 60, or 120 mg/kg in corn oil by gavage to groups of 50 male and 50 female rats and doses of 0, 500, or 1,000 mg/kg to groups of 50 male and 50 female mice.

In the 2-year studies, survival relative to that of vehicle controls was significantly lower in high dose male rats (40/50 vs 17/50) and high dose female rats (35/50 vs 11/50) and in male mice receiving 1,000 mg/kg (33/50 vs 10/50). Due to excessive mortality in the 1,000 mg/kg female mice, the group was terminated in the 45th week and a second series of 2-year studies in mice of each sex was started at concentrations of 0 and 250 mg/kg. Male mice in the 1,000 mg/kg group had 10% lower mean body weights than the vehicle control group. No adverse effects on survival or body weights in other dosed groups of rats and mice were observed. Convulsions were observed before or after gavage administration on several occasions during the rat studies. These observations were noted primarily in the high dose groups (male: vehicle control, 1/50; low dose, 3/50; high dose, 27/50; female: vehicle control, 0/50; low dose, 7/50; high dose, 45/50). Hemorrhage of the brain and alveoli were observed primarily in high dose male and female rats dying from convulsions. Lymphoid depletion of the spleen and splenic hemosiderosis were also observed in these animals. In mice, convulsions were observed only in the first studies (in the high dose female mice that were terminated early and in 6/50 high dose male mice).

Pheochromocytomas of the adrenal gland occurred at a marginally increased incidence in low dose female rats (1/50; 6/50; 1/49). Hyperplasia was observed in 3/50 vehicle controls, 7/50 low dose females, and 4/49 high dose females. The incidence of pheochromocytomas was low, not dose related, and not seen in male rats, and thus it was not considered to be compound related. Cytoplasmic vacuolization of the adrenal cortex occurred at increased incidences in male (5/50; 10/50; 20/50) but not in female rats. Nephropathy of the kidney occurred at increased incidences in female rats (13/50; 25/50; 20/50) but not in male rats. Additional nonneoplastic lesions such as congestion, inflammation, or nephrosis were not present to any degree in either vehicle control or dosed female rats.

An increased incidence of alveolar/bronchiolar adenomas or carcinomas (combined) was observed in the 500 mg/kg group of female mice (3/50 vs 9/50), but little effect was seen in the 250 mg/kg group (6/50 vs 8/50). The incidences of adenomas or carcinomas (combined) in dosed female mice were not significantly different from that in the pooled vehicle control group from the first and second studies (pooled controls, 9/100; 250 mg/kg, 8/50; 500 mg/kg, 9/50). The lack of hyperplasia in female mice and the negative trend in male mice suggest that these marginal effects were probably not related to the administration of *n*-butyl chloride.

An increased incidence of hepatocellular adenomas or carcinomas (combined) was observed in the 500 mg/kg group of female mice (3/50 vs 8/50) but not in the 250 mg/kg group (9/50 vs 7/50). An increased incidence of hemangiosarcomas was observed in male mice in the first study (1/50; 3/50; 4/50) but not in the second study (4/50 vs 2/50). Neither of these marginal effects was regarded as compound related.

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

An audit of the experimental data was conducted for the 2-year studies of *n*-butyl chloride. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** of *n*-butyl chloride for male and female F344/N rats at daily doses of 60 or 120 mg/kg, for male B6C3F$_1$ mice at doses of 250, 500, or 1,000 mg/kg, or for female B6C3F$_1$ mice at doses of 250 or 500 mg/kg. Chemical-induced toxicity in high dose rats (primarily females) reduced the sensitivity of the study for determining carcinogenicity.

*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 *n*-Butyl Chloride is based on the 13-week studies that began in March 1979 and ended in June 1979, on the 2-year studies that began in February 1980 and ended in March 1982, and on the supplemental 2-year studies in mice that began in March 1981 and ended in March 1983 at EG&G Mason Research Institute.

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

Joseph H. Roycroft, Ph.D., Chemical Manager

Gary A. Boorman, D.V.M., Ph.D.
Bhola Gupta, B.V.Sc., Ph.D.
Joseph K. Haseman, Ph.D.
James Huff, Ph.D.
C.W. Jameson, Ph.D.
Jim Mason, 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 Studies in Rats and Mice, 2/24/83)

Robert Sauer, V.M.D. (Chair)
Clement Associates
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Scot Eustis, D.V.M., Ph.D. (NTP)
Charles Kircher, D.V.M., Ph.D.
McNeil Pharmaceutical
Henk Solleveld, D.V.M. (NTP)
Marilyn Wolfe, D.V.M., Ph.D. (NTP)

(Evaluated Slides and Prepared Pathology Report on the Second Studies in Mice, 8/29/84)

Katsuhiko Yoshitomi, D.V.M., Ph.D. (Chair, NTP)
Gary A. Boorman, D.V.M., Ph.D. (NTP)
Bhola Gupta, B.V.Sc., Ph.D. (NTP)
Henk Solleveld, D.V.M., Ph.D. (NTP)

Principal Contributors at EG&G Mason Research Institute
(Conducted Studies and Evaluated Tissues)

Herman S. Lilja, Ph.D.
Principal Investigator
Agnes Russfield, M.D., Ph.D.
Pathologist (rat studies)
Miasnig Hagopian, Ph.D.
Chemist
D. Stuart Wyand, D.V.M.
Pathologist (mouse studies)

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

Melvin Hamlin, D.V.M.
J. Gauchat, Pathology Coordinator

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 *n*-butyl chloride on August 14, 1985, 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

Frederica Perera, Dr.P.H.
Division of Environmental Sciences
School of Public Health, Columbia University
New York, New York

James Swenberg, D.V.M., Ph.D.
Head, Department of Biochemical Toxicology and Pathobiology
Chemical Industry Institute of Toxicology
Research Triangle Park, North Carolina

Ad Hoc Subcommittee Panel of Experts

John J. Crowley, Ph.D. (Principal Reviewer)
Division of Public Health Science
The Fred Hutchinson Cancer Research Center
Seattle, Washington

Kim Hooper, Ph.D.
Chief, Hazard Evaluation System and Information Services
Department of Health Services
State of California
Berkeley, California

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

Richard J. Kociba, D.V.M., Ph.D.
(Principal Reviewer)
Dow Chemical USA
Midland, Michigan

David Kotelchuck, Ph.D.
Environmental Health Science Program
Hunter School of Health Sciences
New York, New York

Franklin E. Mirer, Ph.D.*
Director, Health and Safety Department
International Union, United Auto Workers, Detroit, Michigan

I.F.H. Purchase, Ph.D.
Central Toxicology Laboratory
Imperial Chemical Industries, PLC
Alderley Park, England

Robert A. Scala, Ph.D.*
Senior Scientific Advisor, Medicine and Environmental Health Department
Research and Environmental Health Division, Exxon Corporation
East Millstone, New Jersey

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

*Unable to attend

SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF *n*-BUTYL CHLORIDE

On August 14, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of *n*-butyl chloride 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, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Crowley, a principal reviewer, agreed with the conclusions for male and female rats but suggested that the findings in male and female mice indicate an inadequate study of carcinogenicity because the the first study was terminated due to toxicity after 1 year and the incidences of tumors for vehicle control groups for the two studies varied. Dr. Turnbull and Dr. Kotelchuck agreed that the mice studies were inadequate. Dr. Kotelchuck questioned the combining of the vehicle control groups. Dr. J. Huff, NIEHS, reported that in only one site were there statistically significant differences between the two vehicle control groups (liver tumors in female mice) and thus it was considered proper to combine vehicle control groups for supplemental data comparisons.

As a second principal reviewer, Dr. Kociba agreed with the conclusions. He said that the rationale for dose selection should have included some parameters other than body weights (depression) and clinical observations (convulsions). In the absence of comparative absorption and metabolism data, inhalation exposure or skin application might have been a more appropriate route than corn oil gavage. Dr. J. Roycroft, NTP, said that the overt toxicity observed in the 2-year studies was not predictable from the short-term studies in that there were only minimal effects in mean body weights and convulsive episodes only in two high dose (1,000 mg/kg) female mice.

As a third principal reviewer, Dr. Jones agreed with the conclusions.

In further discussion on the appropriateness of combining the two concurrent vehicle control groups for the studies in mice, Dr. E. McConnell, NIEHS, said that a similar combination was done for the oral asbestos studies; the current studies were conducted in the same laboratory with similar environmental factors and with genetically similar animals. Dr. Swenberg proposed adding a footnote explaining that combining vehicle control groups is done infrequently and why this was considered appropriate for *n*-butyl chloride. [See pages 46-48.]

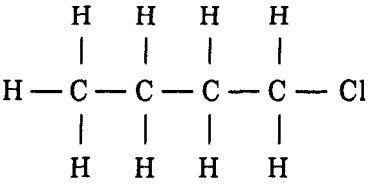
Dr. Hook said that the Panel needed to decide whether the mouse studies were adequate studies before the members could rule on the conclusions as written. Dr. Swenberg moved that these be considered adequate studies for at least one dose per sex and species. Dr. Kociba seconded the motion. There were four affirmative votes (Dr. Jones, Dr. Kociba, Dr. Kotelchuck, and Dr. Swenberg), four negative votes (Dr. Crowley, Dr. Hooper, Dr. Perera, and Dr. Turnbull), and one abstention (Dr. Purchase). As Chair, Dr. Hook cast the tie-breaking vote to approve the motion.

Dr. Kociba then moved that the conclusion as written for rats and mice of both sexes be accepted, including the last sentence, "Chemical-induced toxicity in high dose rats (primarily females) reduced the sensitivity of the study for determining carcinogenicity." Dr. Turnbull seconded the motion, and the Technical Report on *n*-butyl chloride was approved by six affirmative votes (Dr. Hooper, Dr. Jones, Dr. Kociba, Dr. Kotelchuck, Dr. Perera, and Dr. Turnbull); there was one negative vote (Dr. Swenberg) with two abstentions (Dr. Crowley and Dr. Purchase).

I. INTRODUCTION

Animal Toxicity Studies
Mutagenicity
Carcinogenicity
Human Exposure
Study Rationale

I. INTRODUCTION



n-Butyl Chloride

(1-Chlorobutane; Butyl Chloride; *n*-Propylcarbinyl Chloride)

CAS No. 109-69-3

C_4H_9Cl Molecular weight 92.57

n-Butyl chloride, a colorless, volatile liquid with a characteristic sweet odor, has a specific gravity of 0.878 (20° C/4° C), a boiling point of 78° C, a melting point of −123.1° C, and a vapor pressure of 80.1 mm Hg at 20° C. *n*-Butyl chloride is insoluble in water (0.066% at 12° C) and is miscible with alcohol and ether. It is flammable with a flash point of −7° C (closed cup). Flammable limits in air are between 1.8% and 10.1%. *n*-Butyl chloride is stable when stored in the dry state; however, it hydrolyzes in the presence of moisture, liberating hydrogen chloride. Thermal decomposition may produce phosgene. It can react vigorously with oxidizing materials (Merck, 1983; Sedivec and Flek, 1976; Oettingen, 1955; Sax, 1984).

n-Butyl chloride is used as a solvent as well as an alkylating agent in organic syntheses (e.g., in the manufacture of butyl cellulose) and in the production of tin stabilizers for vinyl chloride resins. It has also been used as an anthelmintic in veterinary medicine, primarily for removal of ascarids and hookworms in dogs (Wright and Schaffer, 1932). Although a weak central nervous system depressant, it has also been used as a veterinary anesthetic (Abreu et al., 1939).

n-Butyl chloride is prepared by heating *n*-butyl alcohol with hydrochloric acid and anhydrous zinc chloride. It is commercially available at greater than 99.5% purity. The production of *n*-butyl chloride in the United States was estimated to be greater than 2,300 kilograms in 1982 (USITC, 1983). More accurate production estimates, as well as import and export figures, are not available, since only one company reports production. Information on the incidence of environmental occurrence or human exposure was not available from the literature. No occupational standard for *n*-butyl chloride has been established by the Occupational Safety and Health Administration.

Animal Toxicity Studies

Smyth et al. (1954) determined the oral LD_{50} value for *n*-butyl chloride to be 2.67 g/kg in Carworth-Wistar rats. When rats were exposed by inhalation to *n*-butyl chloride at 8,000 ppm for 4 hours, deaths in two of six animals occurred over a 14-day period. *n*-Butyl chloride was readily absorbed through the skin of New Zealand albino rabbits (greater than 20 ml/kg) and produced a primary skin irritation (3 in the standard Draize irritation index). In addition, eye injury to rabbits administered 0.5 ml neat *n*-butyl chloride was determined to be minimal (small area of corneal necrosis). The LC_{50} value for 2- to 3-month-old fish (guppies) has been determined to be 3.02 µmol/liter (Konemann, 1981).

To determine the efficacy of *n*-butyl chloride as a canine anthelmintic, Wright and Schaffer (1932) administered a single dose of *n*-butyl chloride (0.1, 0.2, 0.3, 0.5, 3.0, or 10.0 ml/kg) to dogs fasted for 12 hours. The dogs were observed daily for up to 4 days before being killed. *n*-Butyl chloride was well tolerated by all experimental animals and was effective in the removal of ascarids and hookworms. No visible reaction or

macroscopic postmortem lesions were observed. Microscopic lesions of the liver were observed in animals dosed at 0.3 ml/kg and higher and consisted of cloudy swelling and passive congestion with deposits of bilirubin. In several animals, there was a slight fatty infiltration of the liver which may have been associated with the administration of *n*-butyl chloride. Since the compound was efficacious in removing canine internal parasites and well tolerated, it was recommended for veterinary use as an anthelmintic. However, its use has been reduced in the past 10 years due to the introduction of new, more efficacious drugs.

Female Wistar rats (180-200 g) were gavaged daily with *n*-butyl chloride at concentrations of 0.72, 110, or 733 mg/kg in sunflower oil during the first 19 days of pregnancy and were evaluated for embryotoxic and teratogenic effects (Leonskaya, 1980). An increase in embryo mortality was seen in the 733 mg/kg dose group; no effect was seen in the lower dose groups. There was an increase in the number of fetuses with internal organ hemorrhage in the 733 mg/kg dose group. Progeny of the dosed females were observed for 30 days following birth. No compound-related effects were observed in mortality, body weight change, time of appearance of body hair, or opening of eyes. The offspring were crossbred (within dose group) and subsequently evaluated. *n*-Butyl chloride at a dose of 733 mg/kg substantially increased embryo mortality in the second generation. The author concluded that *n*-butyl chloride induced a hazardous effect on embryogenesis only in large doses that had pronounced toxic effects.

Mutagenicity

n-Butyl chloride was not mutagenic in *Salmonella typhimurium* when tested in a modified liquid suspension assay instead of in a plate assay (Eder et al., 1980), according to the preincubation protocol (Appendix G), or when the cells were exposed to the vapors in a sealed container (Barber et al., 1981). However, Simmon (1981) reported that when the cells were exposed to vapors in a desiccator (a protocol similar to that of Barber et al., 1981), *n*-butyl chloride was mutagenic in strain TA100 of *S. typhimurium* in the absence of S9. The experiment was not performed in the presence of S9. *n*-Butyl chloride was mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the absence of S9; it was not tested in the presence of S9 (Appendix G). *n*-Butyl chloride did not induce sister-chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9. In summary, *n*-butyl chloride is mutagenic in *S. typhimurium* TA100 under certain conditions; it is mutagenic in mammalian cells but does not cause cytogenetic effects in mammalian cells in vitro.

Carcinogenicity

Poirier et al. (1975) evaluated pulmonary tumor response in A/Heston mice. Male and female mice were given *n*-butyl chloride (in tricaprylin) weekly by intraperitoneal injections for 24 weeks with a total dose of 1.2, 3.0, or 6.0 g/kg. No significant increase in lung tumor incidence was observed in strain A mice following the administration of *n*-butyl chloride; however, doses of 3.2 g/kg *sec*-butyl chloride and 1.2 g/kg *tert*-butyl chloride increased lung tumor incidence.

Human Exposure

Although there are no data on human exposure to *n*-butyl chloride, workers may be exposed to *n*-butyl chloride during its use. *n*-Butyl chloride is a potential eye, skin, lung, and mucous membrane irritant.

Study Rationale

n-Butyl chloride was nominated by the National Cancer Institute as a model alkyl chloride following an organohalide class study. It is of particular interest because of the lack of long-term toxicity and carcinogenicity information and its potential for human exposure. Although occupational exposure occurs largely by the dermal or inhalation routes, NTP made the decision to conduct these studies by the gavage route.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *n*-BUTYL CHLORIDE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

- Study Design
- Source and Specifications of Animals
- Animal Maintenance
- Clinical Examinations and Pathology
- Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF *n*-BUTYL CHLORIDE

n-Butyl chloride was obtained in one batch (lot no. 780135-3) from Publicker Industries, Inc. (Philadelphia, Pennsylvania), which was used for all the studies.

Purity and identity analyses conducted at Midwest Research Institute on lot no. 780135-3 of *n*-butyl chloride showed that in addition to *n*-butyl chloride, water and 25 ppm acid components were present. The identity of the *n*-butyl chloride was confirmed by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. All spectroscopic data were consistent with the structure of *n*-butyl chloride and with literature spectra. The cumulative data from elemental analyses, gas chromatography, and free acid titration indicated the purity of the *n*-butyl chloride test material to be greater than 99.5%.

n-Butyl chloride was found to be stable for 2 weeks at 60° C (Appendix H). *n*-Butyl chloride was stored at the testing laboratory in the dark at 0° C. Results of periodic analyses of the bulk test material at the testing laboratory by gas chromatography and titration for free acid indicated that *n*-butyl chloride remained stable during the course of the studies.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

The accurately weighed amounts of *n*-butyl chloride and corn oil were mixed to give the desired concentrations (Table 1). The analytical chemistry laboratory found dose mixtures of *n*-butyl chloride (6% in corn oil) to be stable for 7 days at room temperature (Appendix I). The testing laboratory did additional analyses during the 13-week studies which indicated that the *n*-butyl chloride dose mixtures were stable for up to 3 weeks. *n*-Butyl chloride/corn oil mixtures were stored at 0° C for no longer than 14 days.

Periodic analyses for *n*-butyl chloride in corn oil were performed by the testing and analytical chemistry laboratories to determine if the dose mixtures contained the correct concentrations of *n*-butyl chloride (Appendix J). Because 62/63 mixtures analyzed were within ± 10% of the target concentration, it is estimated that dosing solutions were prepared within specifications 98% of the time (Table 2; Appendix K).

TABLE 1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation	Preparations were hand agitated for 10 sec and sealed in serum vials	Same as 14-d studies	Same as 14-d studies
Maximum Storage Time	7 d	10 d	14 d
Storage Conditions	4° C	4° C	0° ± 5° C

TABLE 2. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

	Concentration of *n*-Butyl Chloride in Corn Oil for Target Concentration (mg/ml)				
	12	24	50	100	200
Mean (mg/ml)	11.1	22.7	50.0	99.6	199.4
Standard deviation	1.06	0.63	0.95	3.46	5.33
Coefficient of variation (percent)	9.5	2.8	1.9	3.5	2.7
Range (mg/ml)	7.75-11.9	22.0-23.8	48.1-51.7	93.5-105.0	192.0-206.9
Number of samples	13	13	13	12	12

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 19 days before the studies began. The rats were approximately 7 weeks old and the mice 7-9 weeks old when placed on study.

Groups of five rats and five mice of each sex were administered 0, 190, 380, 750, 1,500, or 3,000 mg/kg *n*-butyl chloride in corn oil by gavage for 14 consecutive days. Animals were housed five per cage. Water and feed were freely available. The rats and mice were observed twice per day; the rats were weighed daily and the mice on days 1 and 14 and at the end of the studies. A necropsy was performed on all animals; however, histologic examinations were not performed. Details of animal maintenance are presented in Table 3.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of *n*-butyl chloride and to determine the doses to be used in the 2-year studies. Four-week-old male and female F344/N rats and 5- to 6-week-old B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 18 days (rats) or 16 days (mice), and assigned to test groups so that the average cage weights were approximately equal for all animals of the same sex and species.

Groups of 10 rats of each sex were administered 0, 30, 60, 120, 250, or 500 mg/kg *n*-butyl chloride in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex were administered 0, 60, 120, 250, 500, or 1,000 mg/kg *n*-butyl chloride on the same schedule. Rats and mice were housed five per cage in polycarbonate cages. Feed and water were available ad libitum.

Animals were checked two times per day; 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 3.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 60, or 120 mg/kg *n*-butyl chloride in corn oil by gavage, 5 days per week for 103 weeks. Groups of 50 mice of each sex were administered 0, 500, or 1,000 mg/kg, 5 days per week on the same schedule. All the female mice in the 1,000 mg/kg group were dead by week 52. Histologic examinations were performed on some of these animals that died early; the cause of death could not be established but was attributed to *n*-butyl chloride. Because of the large number of deaths in the 1,000 mg/kg mouse groups, another dose group (250 mg/kg) and matching vehicle controls were started for male and female mice approximately 13 months after initiation of the other studies.

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
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, 190, 380, 750, 1,500, or 3,000 mg/kg *n*-butyl chloride in corn oil by gavage; dose vol--5 ml/kg	Rats--0, 30, 60, 120, 250, or 500 mg/kg *n*-butyl chloride in corn oil by gavage; mice--0, 60, 120, 250, 500, or 1,000 mg/kg *n*-butyl chloride in corn oil by gavage; dose vol--5 ml/kg	Rats--0, 60, or 120 mg/kg *n*-butyl chloride in corn oil by gavage; mice (1st study)--0, 500, or 1,000 mg/kg *n*-butyl chloride in corn oil by gavage; mice (2nd study)--0 or 250 mg/kg *n*-butyl chloride in corn oil by gavage; dose vol--5 ml/kg
Date of First Dose	11/28/78	3/30/79	Rats--3/3/80; mice (1st study)--2/20/80; mice (2nd study)--3/17/81
Date of Last Dose	12/12/78	6/28/79	Rats--2/24/82; mice (1st study)--2/9/82; mice (2nd study)--3/7/83
Duration of Dosing	14 consecutive days	5d/wk for 13 wk	5d/wk for 103 wk
Type and Frequency Observation	Rats--observed 2 × d; weighed daily; mice--observed 2 × d; weighed on d 1, 14, and at the end of the studies	Observed 2 × d; weighed 1 × wk	Observed 2 × d; weighed initially, 1 × wk for 12 wk, then 1 × 4 wk
Necropsy and Histologic Examination	Necropsy performed on all animals; histologic examination not performed	Necropsy and histologic examination performed on all animals; the following tissues were examined: gross lesions and tissue masses, mandibular lymph node, mammary gland, skin, salivary gland, sternebrae, thyroid gland, small intestine, colon, liver, prostate/testes or ovaries/uterus, gallbladder (mice), lungs and bronchi, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, spinal cord (if neurologic signs present), and eyes (if grossly abnormal)	Necropsy and histologic examination performed on all animals; the following tissues were examined: tissue masses, abnormal regional lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, bone marrow, costochondral junction, thymus, larynx, trachea, lungs and bronchi, heart, thyroid gland, parathyroids, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder (mice), pancreas, spleen, kidneys, adrenal glands, seminal vesicles/prostate/testes or ovaries/uterus, brain, and pituitary gland
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species	F344/N rats; B6C3F$_1$ mice	Same as 14-d studies	Same as 14-d studies
Animal Source	Charles River Breeding Laboratories (Portage, MI)	Same as 14-d studies	Same as 14-d studies

TABLE 3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF *n*-BUTYL CHLORIDE (Continued)

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Testing Laboratory	EG&G Mason Research Institute	EG&G Mason Research Institute	EG&G Mason Research Institute
Method of Animal Identification	Ear punch	Ear punch	Ear punch
Time Held Before Test	19 d	Rats--18 d; mice--16 d	3 wk
Age When Placed on Study	Rats--7 wk; mice--7-9 wk	Rats--7 wk; mice--7-8 wk	1st study--7 wk; 2nd study (mice)--8 wk
Age When Killed	Rats--9-10 wk; mice--10-12 wk	Rats--21 wk; mice--21-22 wk	Rats--111-113 wk; mice (1st study)--111-112 wk; mice (2nd study)--112-113 wk
Necropsy Dates	Rats--12/15/78-12/18/78; mice--12/18/78-12/19/78	Rats--7/2/79-7/9/79; mice--7/2/79-7/5/79	Rats--3/4/82-3/13/82; mice (1st study)--2/17/82-2/24/82; mice (2nd study)--3/15/83-3/23/83
Method of Animal Distribution	Animals were assigned to test groups such that all cage weights were approximately equal	Assigned to test groups such that the average cage weights were approximately equal	Randomized to cages by one random numbers table, then to groups by another random numbers table
Feed	Wayne Lab Blox pellets (Allied Mills, Chicago, IL); available ad libitum	Same as 14-d studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum
Bedding	Aspen Bed (American Excelsior, Baltimore, MD)	Aspen Bed hardwood chips (American Excelsior, Co., Baltimore, MD) or Betta Chips hardwood chips (Agway, Inc., Syracuse, NY)	Aspen Bed hardwood chips (American Excelsior, Co., Baltimore, MD)
Water	Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as 14-d studies	Same as 14-d studies
Cages	Polycarbonate (Lab Products, Rochelle Park, NJ)	Same as 14-d studies	Same as 14-d studies
Cage Filters	Disposable nonwoven fiber filters (Lab Products, Rochelle Park, NJ)	Nonwoven fiber filters (Lab Products, Rochelle Park, NJ)	Same as 13-wk studies
Animals per Cage	5	5	5
Other Chemicals on Test in the Same Room	None	None	None
Animal Room Environment	Temperature--19.4°-26.1° C; humidity--<1%-50%; fluorescent light 12 h/d; 10 room air changes/h	Temperature--mean 21.8° C; humidity--5%-74% (av 40%); fluorescent light 12 h/d; 10 room air changes/h	Temperature--mean 23° C; 2nd study--mean 22.9° C; humidity--9%-78% (mean 41%); fluorescent light 12 h/d; 12 room air changes/h

II. MATERIALS AND METHODS

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 these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies 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. Rats were shipped to the testing laboratory at 4 weeks of age, mice for the first studies were shipped at 4 weeks of age, and mice for the second studies were shipped at 5 weeks of age. The animals were quarantined at the testing facility for 3 weeks. 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 7 weeks of age (rats and mice in first studies) or at 8 weeks (mice in second studies). The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

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

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 3.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12 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 studies. 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 3.

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, 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. (1986).

Nonneoplastic lesions are not examined routinely by the quality assurance pathologist or PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and PWG if they are considered part of the toxic response to a chemical or if they are deemed of special interest.

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 five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 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.) A recently developed method for the analysis of incidental tumors based on logistic regression (Dinse and Lagakos, 1983) was also employed as a supplemental test in some instances. This method has the advantage of not requiring time intervals in the statistical evaluation.

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 evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

III. RESULTS: RATS

FOURTEEN-DAY STUDIES

All the rats that received 1,500 or 3,000 mg/kg and 3/5 males and 1/5 females that received 750 mg/kg *n*-butyl chloride died before the end of the studies (Table 4). No gavage accidents were noted; therefore, all deaths were considered compound related. The final mean body weight of the male rats that received 750 mg/kg was 14% lower than that of the vehicle controls. The final mean body weight of the female rats that received 750 mg/kg was 6% lower than that of the vehicle controls. Convulsions were observed in males that received 750 mg/kg or more and in one female that received 1,500 mg/kg.

Aggressiveness and hyperactivity were observed in rats that received 750 mg/kg. A bloody discharge from the nose and mouth was observed in males that received 750 mg/kg or more and in females that received 1,500 mg/kg. At necropsy, blood was found in the cranial cavity of males that received 750 mg/kg or more and females that received 1,500 mg/kg or more. Histologic examinations were not performed. Doses selected for the 13-week studies were based on weight gain depression and clinical signs observed in the 14-day studies.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	164 ± 5	206 ± 3	+42 ± 3	--
190	5/5	164 ± 5	207 ± 4	+43 ± 3	100
380	5/5	164 ± 6	202 ± 6	+38 ± 2	98
750	(d) 2/5	165 ± 5	178 ± 8	+19 ± 1	86
1,500	(e) 0/5	165 ± 3	(f)	(f)	(f)
3,000	(g) 0/5	166 ± 3	(f)	(f)	(f)
FEMALE					
0	5/5	126 ± 3	154 ± 2	+28 ± 2	--
190	5/5	126 ± 3	154 ± 2	+28 ± 1	100
380	5/5	126 ± 3	156 ± 4	+30 ± 2	101
750	(h) 4/5	126 ± 3	144 ± 5	+16 ± 3	94
1,500	(i) 0/5	125 ± 3	(f)	(f)	(f)
3,000	(j) 0/5	126 ± 3	(f)	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial mean 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 of the group ± standard error of the mean
(d) Day of death: 6, 7, 7
(e) Day of death: 3, 3, 3, 3, 4
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: 2, 2, 2, 2, 3
(h) Day of death: 8
(i) Day of death: 3, 3, 4, 4, 5
(j) Day of death: all 3

THIRTEEN-WEEK STUDIES

Six of 10 male rats that received 500 mg/kg *n*-butyl chloride died before the end of the studies (Table 5). Because of the increased irritability of rats at the higher doses, dosing by gavage became extremely difficult; three deaths occurred in the 500 mg/kg group because of gavage accidents. The final mean body weights of males that received 250 or 500 mg/kg were 11% or 20% lower than that of the vehicle controls. Final mean body weights of females that received 250 or 500 mg/kg were 6% or 10% lower than that of the vehicle controls. Five of 10 males and 2/10 females that received 250 mg/kg and 9/10 males and 8/10 females that received 500 mg/kg had convulsions on one or more occasions. Extramedullary hematopoiesis of the spleen was observed in 3/10 males that received 500 mg/kg. The severity was mild in two rats and moderate in a third. This lesion was not observed in vehicle control animals.

Dose Selection Rationale: Because of weight gain depression and convulsions observed at 250 mg/kg, doses selected for rats in the 2-year studies were 60 and 120 mg/kg *n*-butyl chloride administered in corn oil by gavage, 5 days per week.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The initial mean body weights of the dosed male rats were lower than that of the vehicle controls, and the mean body weights of the high dose group remained slightly lower throughout the studies (Table 6 and Figure 1). Mean body weights of dosed and vehicle control female rats were comparable throughout the studies. Many dosed rats had tremors and convulsions after being gavaged. Antibodies to Sendai virus and RC virus were detected in sentinel animals throughout the studies (Appendix L, Table L1).

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

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	131 ± 2	299 ± 4	+168 ± 3	--
30	10/10	131 ± 2	300 ± 5	+169 ± 5	100
60	10/10	130 ± 2	290 ± 4	+160 ± 3	97
120	10/10	131 ± 2	285 ± 3	+154 ± 4	95
250	10/10	131 ± 2	265 ± 4	+134 ± 3	89
500	(d) 4/10	131 ± 2	240 ±10	+113 ± 9	80
FEMALE					
0	10/10	103 ± 1	181 ± 8	+ 78 ± 6	--
30	10/10	102 ± 1	177 ± 3	+ 75 ± 2	98
60	10/10	103 ± 1	176 ± 2	+ 73 ± 1	97
120	10/10	103 ± 2	174 ± 1	+ 71 ± 1	96
250	10/10	103 ± 1	171 ± 2	+ 68 ± 2	94
500	10/10	103 ± 1	163 ± 2	+ 60 ± 2	90

(a) Number surviving/number initially in the group
(b) Initial mean 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 of the group ± standard error of the mean. Final body weights were taken during week 12 of the study.
(d) Day of death: 7, 10, 11, 11, 12, 12. Three of these deaths were accidental.

TABLE 6. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

Weeks on Study	Vehicle Control Av Wt (grams)	Vehicle Control No. of Survivors	60 mg/kg Av Wt (grams)	60 mg/kg Wt (percent of veh controls)	60 mg/kg No. of Survivors	120 mg/kg Av Wt (grams)	120 mg/kg Wt (percent of veh controls)	120 mg/kg No. of Survivors
MALE								
0	167	50	159	95	50	160	96	50
1	190	50	181	95	50	180	95	50
2	216	50	211	98	50	205	95	50
3	236	50	251	106	50	235	100	50
4	250	50	240	96	50	244	98	50
5	272	50	261	96	50	261	96	50
6	285	50	276	97	50	272	95	50
7	296	50	284	96	50	281	95	50
8	316	50	299	95	50	295	93	50
9	322	50	310	96	50	305	95	50
10	332	50	320	96	50	311	94	50
11	339	50	326	96	50	320	94	50
12	345	50	336	97	50	327	95	50
16	376	50	372	99	50	357	95	50
20	388	50	377	97	50	360	93	50
24	414	50	401	97	50	377	91	50
28	425	50	412	97	50	392	92	50
32	439	50	434	99	50	405	92	49
36	450	50	436	97	50	418	93	49
40	470	50	454	97	49	434	92	48
44	484	50	473	98	49	452	93	47
48	490	49	481	98	49	459	94	45
52	494	49	485	98	48	469	95	44
56	499	49	496	99	48	471	94	43
60	497	49	492	99	48	472	95	41
64	502	49	501	100	47	477	95	39
68	512	48	511	100	47	481	94	39
72	505	48	510	101	47	479	95	35
76	521	48	510	98	47	483	93	34
80	500	48	508	102	47	481	96	31
84	500	47	505	101	44	479	96	31
88	496	46	504	101	42	472	95	29
92	516	45	507	98	39	479	93	23
96	496	45	508	102	38	476	96	22
100	497	42	509	102	34	479	96	19
104	482	40	501	104	32	468	97	17
FEMALE								
0	121	50	124	102	50	120	99	50
1	138	50	140	101	50	136	99	50
2	150	50	151	101	50	147	98	50
3	163	50	163	100	50	160	98	50
4	166	50	165	99	50	160	96	50
5	175	50	174	99	50	169	97	50
6	181	50	178	98	50	173	96	50
7	181	50	185	102	50	181	100	50
8	189	50	191	101	50	186	98	50
9	192	50	195	102	50	190	99	50
10	195	50	198	102	50	192	98	50
11	198	50	200	101	50	194	98	50
12	202	50	202	100	50	198	98	50
16	212	50	213	100	50	214	101	50
20	218	50	219	100	50	215	99	50
24	226	50	228	101	50	224	99	50
28	226	50	228	101	50	227	100	50
32	240	50	242	101	50	242	101	50
36	249	50	251	101	50	245	98	50
40	259	50	259	100	50	254	98	45
44	264	50	268	102	50	261	99	43
48	270	50	274	101	50	262	97	38
52	276	50	281	102	50	272	99	35
54	--	--	--	--	--	276	--	33
56	287	50	292	102	50	284	99	32
58	--	--	--	--	--	292	--	30
60	291	50	297	102	49	293	101	28
62	--	--	--	--	--	300	--	25
64	302	50	308	102	48	305	101	25
66	--	--	--	--	--	311	--	25
68	314	50	322	103	48	316	101	24
70	--	--	--	--	--	317	--	24
72	323	50	330	102	48	326	101	24
76	326	50	335	103	48	332	102	23
80	324	47	332	102	47	330	102	21
84	331	45	338	102	47	334	101	18
88	346	42	341	99	46	333	96	18
92	336	38	345	103	45	338	101	16
96	343	37	348	101	44	341	99	16
100	345	36	355	103	40	341	99	15
104	335	35	359	107	38	331	99	12

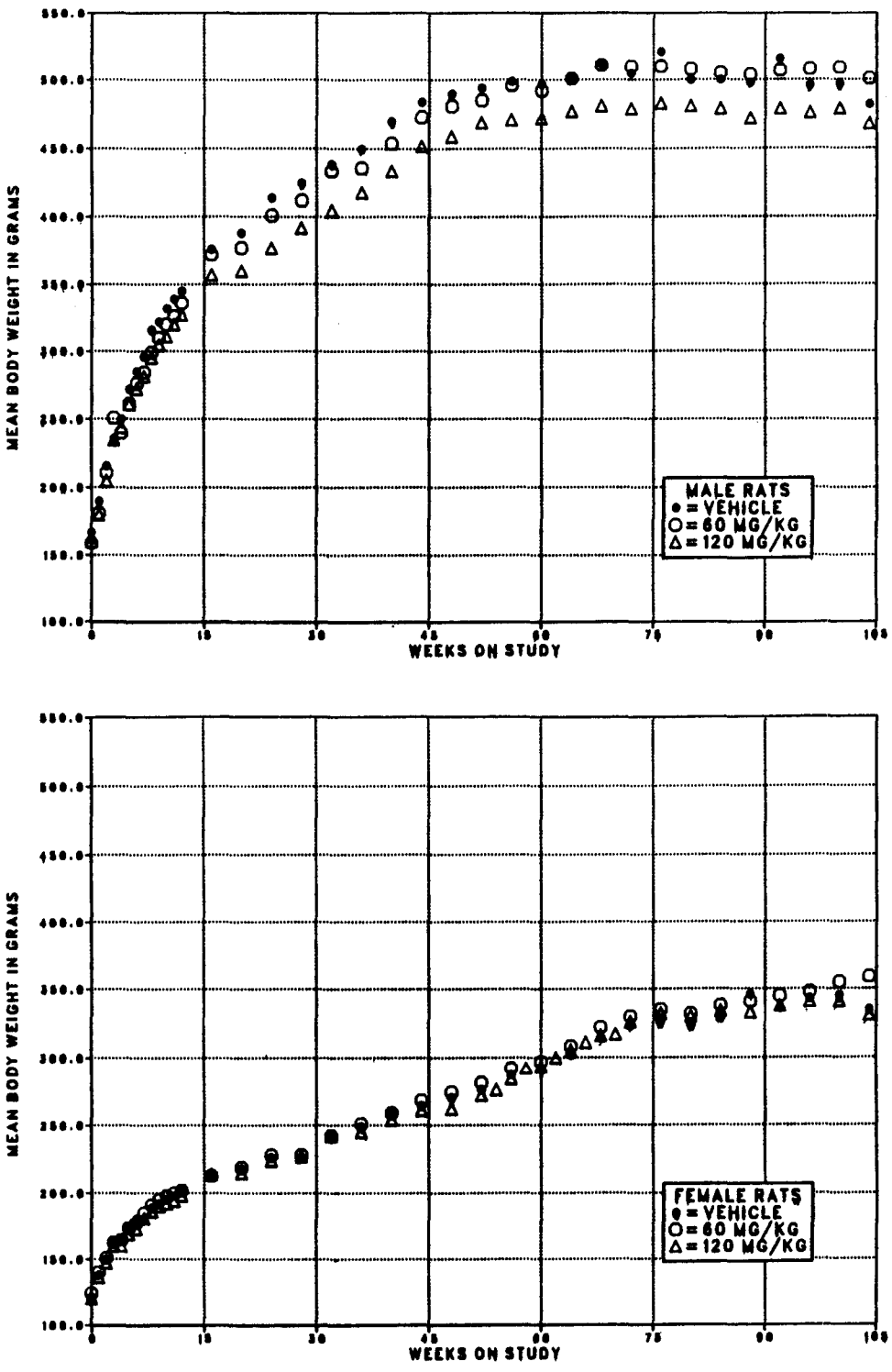


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED *n*-BUTYL CHLORIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered *n*-butyl chloride at the doses used in these studies and for the vehicle controls are shown in the Kaplan and Meier curves in Figure 2. The survival of both the male (after week 59) and female (after week 41) high dose groups was significantly lower than that of the vehicle control groups (Table 7). Based on the survival in the 13-week studies, the high mortality in both the 60 and 120 mg/kg groups was unexpected.

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the adrenal gland, pancreas, urinary bladder, lung, brain, spleen, kidney, prostate, or multiple organs. 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 7. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

	Vehicle Control	60 mg/kg	120 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	10	18	33
Killed at termination	40	32	17
Survival P values (c)	<0.001	0.107	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	15	12	39
Killed at termination	34	38	11
Died during termination period	1	0	0
Survival P values (c)	<0.001	0.561	<0.001

(a) Terminal kill period: male--weeks 104-106; female--weeks 105-106
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

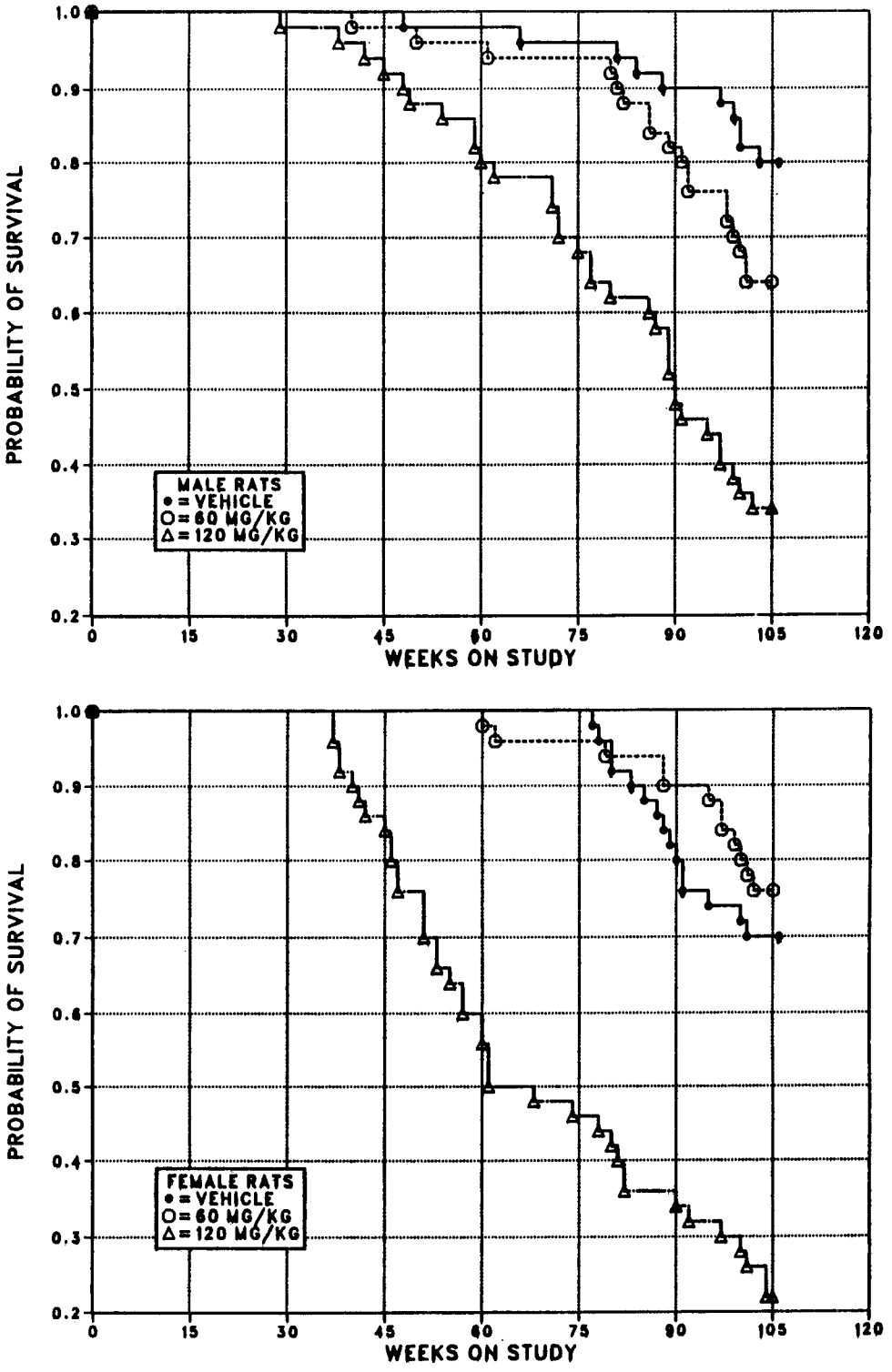


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED *n*-BUTYL CHLORIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

Adrenal Gland: Cytoplasmic vacuolization of the adrenal cortex was observed at increased incidences in dosed male rats (vehicle control, 5/50, 10%; low dose, 10/50, 20%; high dose, 20/50, 40%) but not in the dosed female rats (vehicle control, 4/50, 8%; low dose, 5/50, 10%; high dose, 3/49, 6%). The incidence of pheochromocytomas in low dose female rats was significantly greater than that in the vehicle controls (Table 8). The incidences of pheochromocytomas in dosed male rats were lower than that in the vehicle controls (vehicle control, 15/50, 30%; low dose, 11/50, 22%; high dose, 4/50, 8%). Malignant pheochromocytomas were observed in one male and one female vehicle control animal.

Pancreas: Acinar cell adenomas in male rats occurred with a significant positive trend by the life table test; the incidences in the dosed groups were not significantly greater than that in the vehicle controls (Table 9).

TABLE 8. ANALYSIS OF ADRENAL GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (a)

	Vehicle Control	60 mg/kg	120 mg/kg
Medullary Hyperplasia			
Overall Rates	3/50 (6%)	7/50 (14%)	4/49 (8%)
Pheochromocytoma (b)			
Overall Rates	0/50 (0%)	6/50 (12%)	1/49 (2%)
Adjusted Rates	0.0%	15.0%	6.7%
Terminal Rates	0/35 (0%)	5/38 (13%)	0/11 (0%)
Week of First Observation		88	100
Life Table Tests	P=0.091	P=0.023	P=0.320
Incidental Tumor Tests	P=0.143	P=0.011	P=0.602
Malignant Pheochromocytoma			
Overall Rates	1/50 (2%)	0/50 (0%)	0/49 (0%)
Adjusted Rates	2.9%	15.0%	6.7%
Terminal Rates	1/35 (3%)	5/38 (13%)	0/11 (0%)
Week of First Observation	105	88	100
Life Table Tests	P=0.189	P=0.074	P=0.518
Incidental Tumor Tests	P=0.258	P=0.043	P=0.714

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence of pheochromocytomas (all types) at testing laboratory (mean ± SD): 13/199 (7% ± 2%); historical incidence in NTP studies: 65/1,093 (6% ± 3%)

TABLE 9. ANALYSIS OF PANCREATIC ACINAR CELL ADENOMAS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (a)

	Vehicle Control	60 mg/kg	120 mg/kg
Overall Rates	4/50 (8%)	9/50 (18%)	5/48 (10%)
Adjusted Rates	10.0%	27.1%	29.4%
Terminal Rates	4/40 (10%)	8/32 (25%)	5/17 (29%)
Week of First Observation	104	99	104
Life Table Tests	P=0.040	P=0.050	P=0.076
Incidental Tumor Tests	P=0.050	P=0.054	P=0.076

(a) Historical incidence at testing laboratory (mean ± SD): 5/196 (3% ± 1%); historical incidence in NTP studies: 47/1,086 (4% ± 8%)

Urinary Bladder: Transitional cell papillomas were observed in one low dose male rat and in one high dose female rat.

Lung: Hemorrhage of the alveoli was observed at increased incidences in high dose male and female rats (Table 10).

Brain: Hemorrhage of the brain was observed at increased incidences in high dose male and female rats (Table 10).

Spleen: Lymphoid depletion and hemosiderosis were observed at increased incidences in high dose male and female rats (Table 10).

Kidney: Nephropathy was observed at increased incidences in dosed female rats (vehicle control, 13/50, 26%; low dose, 25/50, 50%; high dose, 20/50, 40%).

Prostate: Focal hyperplasia was observed in 5/42 (12%) low dose male rats but not in the other groups. In addition, 1/42 (2%) low dose male rats had a prostate adenoma.

Multiple Organs: Congestion of multiple organs was observed at increased incidences in high dose rats (male: vehicle control, 2/50, 4%; low dose, 6/50, 12%; high dose, 15/50, 30%; female: vehicle control, 0/50; low dose, 1/50, 2%; high dose, 28/50, 56%).

TABLE 10. INCIDENCES OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE (a)

	Male			Female		
Lesion/Site	Vehicle Control	60 mg/kg	120 mg/kg	Vehicle Control	60 mg/kg	120 mg/kg
Hemorrhage						
Brain	2/49	4/50	18/49	1/50	1/50	25/50
Lung	0/50	2/50	19/50	0/50	1/50	26/50
Lymphoid depletion						
Spleen	1/50	1/50	15/50	1/50	1/50	24/50
Hemosiderosis						
Spleen	6/50	3/50	16/50	3/50	3/50	27/50

FOURTEEN-DAY STUDIES

All the mice that received 3,000 mg/kg and 3/5 males and 2/5 females that received 1,500 mg/kg died before the end of the studies (Table 11). No gavage accidents occurred; therefore, the deaths were attributed to dosing. The final mean body weight of males that received 750 mg/kg was 7% lower than that of the vehicle controls; the final mean body weight of the survivors of the 1,500 mg/kg group was greater than that of the vehicle controls. Final mean body weights of dosed and vehicle control female mice were comparable. Mice that received 1,500 or 3,000 mg/kg were hyperactive. Two of 10 males that received 3,000 mg/kg had convulsions. No compound-related gross pathologic effects were observed in animals that lived to the end of the studies. Histologic evaluation was not required. Doses for the 13-week studies were based on survival and weight gain depression in the 14-day studies.

THIRTEEN-WEEK STUDIES

The incidences of deaths in the various groups are given in Table 12. A number of gavage accidents occurred during the studies (two vehicle control females, a male and female in the 60 mg/kg groups, a female in the 120 mg/kg group, and two females in the 1,000 mg/kg group) and were attributed to handling and dosing of the animals by several different technicians during the studies. The final mean body weights of dosed and vehicle control mice were comparable. Two female mice in the 1,000 mg/kg group convulsed during the course of the study. No other compound-related clinical signs were observed for male and female mice. No compound-related histopathologic effects were observed.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	24.5 ± 0.8	26.2 ± 1.0	+1.7 ± 0.4	--
190	5/5	24.3 ± 0.9	27.6 ± 1.1	+3.3 ± 0.4	105.3
380	5/5	24.7 ± 0.8	27.8 ± 0.9	+3.1 ± 0.4	106.1
750	5/5	24.3 ± 0.9	24.4 ± 1.2	+0.1 ± 0.6	93.1
1,500	(d) 2/5	24.5 ± 0.8	27.0 ± 2.0	+1.2 ± 0.4	103.1
3,000	(e) 0/5	24.1 ± 0.8	(f)	(f)	(f)
FEMALE					
0	5/5	19.9 ± 0.3	21.4 ± 0.5	+1.5 ± 0.2	--
190	5/5	19.9 ± 0.4	21.4 ± 0.4	+1.5 ± 0.2	100.0
380	5/5	19.8 ± 0.3	21.6 ± 0.4	+1.8 ± 0.7	100.9
750	5/5	19.5 ± 0.5	21.6 ± 0.7	+2.1 ± 0.5	100.9
1,500	(g) 3/5	19.8 ± 0.5	22.0 ± 0.6	+1.4 ± 0.4	102.8
3,000	(h) 0/5	19.7 ± 0.7	(f)	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial group mean 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 weight change of the survivors of the group ± standard error of the mean
(d) Day of death: 15, 17, 18 while awaiting necropsy
(e) Day of death: 3, 6, 8, 9, 10
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: 11, 14
(h) Day of death: 3, 6, 6, 7, 8

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(d) 9/10	23.2 ± 0.5	31.5 ± 0.8	+8.2 ± 0.6	--
60	(e) 9/10	23.3 ± 0.5	32.3 ± 0.9	+8.8 ± 0.5	102.5
120	10/10	23.2 ± 0.5	31.9 ± 0.9	+8.7 ± 0.6	101.3
250	10/10	23.3 ± 0.5	30.6 ± 0.6	+7.3 ± 0.4	97.1
500	10/10	23.1 ± 0.4	32.3 ± 0.5	+9.2 ± 0.2	102.5
1,000	10/10	23.3 ± 0.4	32.3 ± 0.5	+9.0 ± 0.4	102.5
FEMALE					
0	(f) 8/10	18.6 ± 0.4	24.4 ± 0.5	+5.7 ± 0.3	--
60	(e) 9/10	19.0 ± 0.4	24.9 ± 0.5	+5.9 ± 0.2	102.0
120	(g) 9/10	19.0 ± 0.4	24.6 ± 0.6	+5.9 ± 0.5	100.8
250	10/10	18.3 ± 0.3	24.6 ± 0.5	+6.3 ± 0.3	100.8
500	10/10	18.5 ± 0.3	25.0 ± 0.3	+6.5 ± 0.2	102.5
1,000	(h) 7/10	18.6 ± 0.3	25.4 ± 0.5	+6.6 ± 0.3	104.1

(a) Number surviving/number in group
(b) Initial group mean 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. Final body weights were taken during week 12 of the study.
(d) Day of death: 12
(e) Day of death: 6, gavage accident
(f) Day of death: 1, 9, gavage accidents
(g) Day of death: 12, gavage accident
(h) Day of death: 7, 8, 12, two were gavage accidents

Dose Selection Rationale: The doses selected for mice in the 2-year studies were 500 and 1,000 mg/kg *n*-butyl chloride administered in corn oil by gavage, 5 days per week. The dose selection was based on the absence of reduction in body weight in males and females and on the absence of dose-related clinical signs in male mice and minimal clinical signs in female mice at the 1,000 mg/kg dose in the 13-week studies.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

In the first study, the mean body weights of the male mice that received 1,000 mg/kg were lower than those of the vehicle controls after week 36; the mean body weights of the female mice that received 500 mg/kg were greater than those of the vehicle controls throughout most of the study (Table 13 and Figure 3). Compound-related clinical signs included convulsions, primarily in high dose male mice. Because of the large number of deaths in the 1,000 mg/kg mouse groups, another dose group (250 mg/kg) and matching vehicle controls were started for male and female mice approximately 13 months after initiation of the other studies.

Sendai virus was present in female sentinel mice in the first study but not in the second study. Mouse hepatitis virus (MHV) was detected in vehicle controls at the end of both the first and second studies.

In the second studies, the mean body weights of the 250 mg/kg groups of male and female mice were greater than those of the vehicle controls throughout most of the studies (Table 14 and Figure 4).

TABLE 13. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE FIRST TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

Weeks on Study	Vehicle Control Av Wt (grams)	Vehicle Control No. of Survivors	500 mg/kg Av Wt (grams)	500 mg/kg Wt (percent of veh controls)	500 mg/kg No. of Survivors	1,000 mg/kg Av Wt (grams)	1,000 mg/kg Wt (percent of veh controls)	1,000 mg/kg No. of Survivors
MALE								
0	24.3	50	24.2	100	50	25.4	105	50
1	26.4	50	26.7	101	50	27.5	104	50
2	27.7	50	27.1	98	50	27.1	98	50
3	28.4	50	28.0	99	50	27.7	98	50
4	29.1	50	28.2	97	50	28.4	98	49
5	30.2	49	29.3	97	50	28.8	95	49
6	30.7	49	30.3	99	50	30.5	99	49
7	30.6	49	30.1	98	50	30.1	98	49
8	31.7	49	31.2	98	50	31.6	100	49
9	32.4	49	31.5	97	50	32.1	99	49
10	33.3	49	32.3	97	50	32.4	97	49
11	32.9	49	32.9	100	50	32.1	98	49
12	34.0	48	33.1	97	50	33.0	97	49
16	34.3	48	34.5	101	50	33.8	99	49
20	36.2	48	36.2	100	50	35.4	98	49
24	37.3	47	36.5	98	49	35.6	95	45
28	38.3	47	37.7	98	49	36.8	96	45
32	39.1	47	38.8	99	48	37.9	97	45
36	40.2	47	38.6	96	48	37.9	94	45
40	42.0	47	40.4	96	48	39.0	93	44
44	42.3	46	40.8	96	48	39.1	92	44
48	42.7	46	41.6	97	48	39.4	92	44
52	42.3	46	41.3	98	48	39.3	93	43
56	43.2	45	43.0	100	48	39.4	91	42
60	42.4	45	42.4	100	47	39.1	92	42
64	41.8	44	41.4	99	47	38.0	91	42
68	40.6	43	40.9	101	47	38.5	95	40
72	40.7	43	39.7	98	47	38.7	95	39
76	41.0	41	40.8	100	47	38.3	93	39
80	40.5	41	39.9	99	46	38.1	94	34
84	39.7	40	40.3	102	44	37.9	95	32
88	39.1	37	39.4	101	41	36.7	94	28
92	39.1	36	40.4	103	36	37.4	96	24
96	38.3	36	40.6	106	34	37.1	97	18
100	38.1	35	39.7	104	28	37.1	97	13
104	37.7	33	38.3	102	27	33.8	90	10
104								
FEMALE								
0	19.6	50	20.2	103	50	19.7	101	50
1	20.9	50	22.1	106	48	22.5	108	50
2	22.0	50	22.4	102	48	22.5	102	50
3	22.5	50	23.0	102	48	23.4	104	50
4	23.6	50	24.1	102	48	23.7	100	50
5	23.9	50	24.0	100	48	23.7	99	50
6	24.7	50	25.1	102	48	25.5	103	50
7	23.7	50	24.4	103	48	23.8	100	50
8	24.6	50	25.5	104	48	24.8	101	50
9	24.9	50	26.1	105	48	24.8	100	50
10	25.6	50	26.6	104	48	25.3	99	50
11	25.9	50	27.2	105	48	24.5	95	50
12	27.0	50	28.0	104	48	26.3	97	50
16	28.0	50	28.6	102	48	26.6	95	49
20	29.9	50	30.8	103	48	27.9	93	46
24	30.5	50	31.4	103	48	26.9	88	28
28	32.5	50	34.4	106	48	31.8	98	24
32	33.1	50	34.5	104	48	31.0	94	22
36	34.8	50	37.7	108	48	32.7	94	18
40	37.3	50	40.2	108	48	33.6	90	14
44	38.4	50	41.3	108	48	34.5	90	11
45	--	--	--	--	--	35.4	--	10
48	40.2	49	42.0	104	47	--	--	--
52	41.7	49	44.4	106	47	--	--	--
56	44.3	49	46.7	105	47	--	--	--
60	43.4	49	45.0	104	46	--	--	--
64	42.4	49	44.4	105	46	--	--	--
68	41.8	49	44.7	107	46	--	--	--
72	42.5	47	45.2	106	46	--	--	--
76	42.0	47	45.6	109	44	--	--	--
80	41.5	46	46.1	111	40	--	--	--
84	41.8	45	44.6	107	38	--	--	--
88	40.5	44	44.9	111	35	--	--	--
92	40.6	40	46.4	114	32	--	--	--
96	39.8	39	43.9	110	32	--	--	--
100	38.8	36	44.8	115	32	--	--	--
104	38.8	30	44.6	115	31	--	--	--

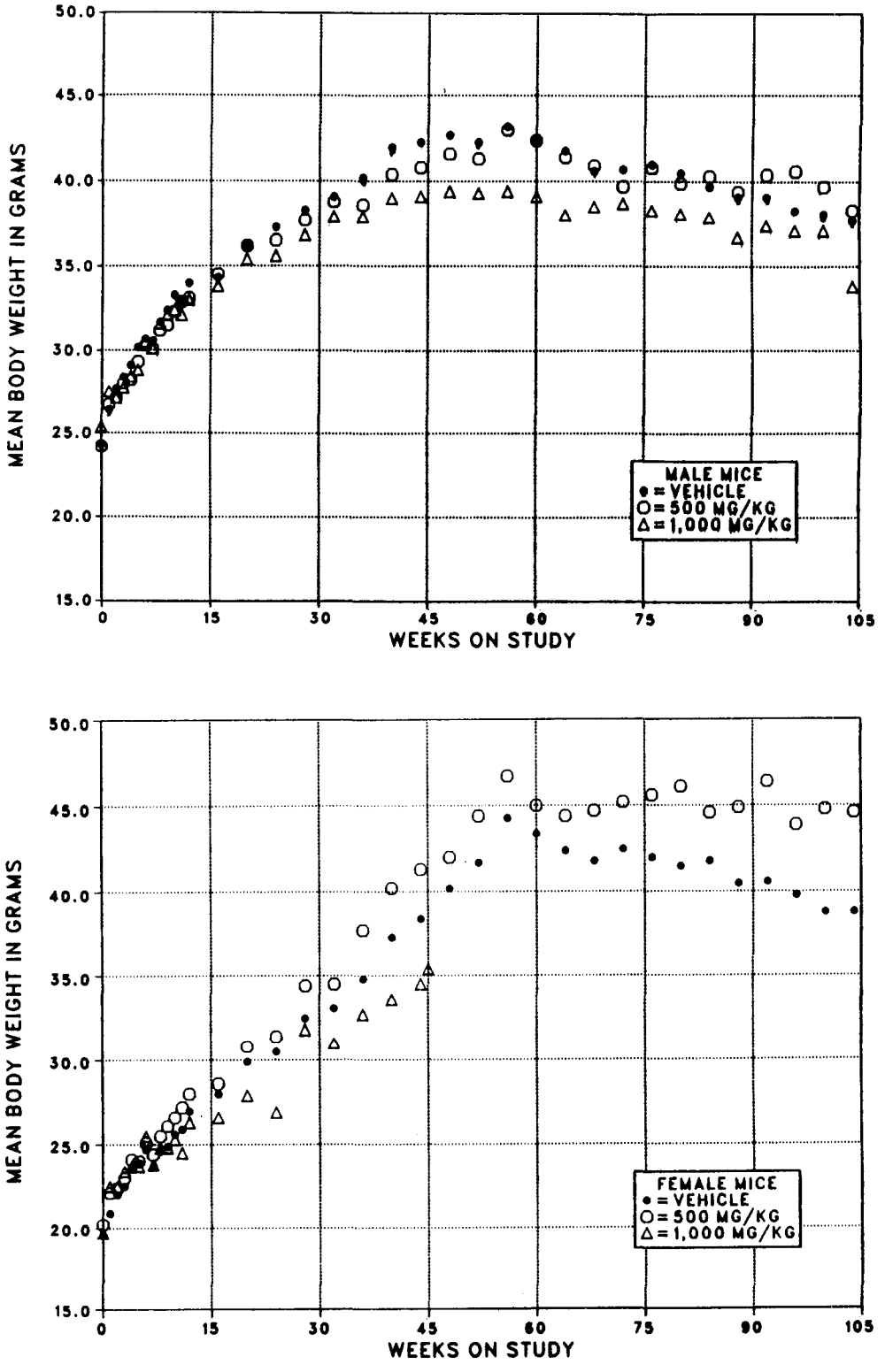


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED *n*-BUYTL CHLORIDE IN CORN OIL BY GAVAGE FOR TWO YEARS (FIRST STUDY)

TABLE 14. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE SECOND TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

Weeks on Study	Vehicle Control Av Wt (grams)	Vehicle Control No. of Survivors	250 mg/kg Av Wt (grams)	250 mg/kg Wt (percent of veh controls)	250 mg/kg No. of Survivors
MALE					
0	24.8	50	24.2	98	50
1	25.7	50	25.4	99	50
2	27.0	50	26.6	99	50
3	28.3	50	27.8	98	50
4	28.5	50	28.6	100	50
5	29.6	50	29.1	98	50
6	30.2	50	30.1	100	50
7	31.3	50	30.2	96	50
8	31.5	50	32.1	102	50
9	30.8	50	30.8	100	50
10	30.8	50	32.7	106	50
11	31.6	50	32.7	103	50
12	31.9	50	32.6	102	50
16	33.1	50	33.6	102	50
20	33.9	50	34.2	101	50
24	35.7	50	37.1	104	50
28	36.0	50	38.0	106	50
32	37.2	50	38.9	105	50
36	38.2	50	40.3	105	50
40	39.0	50	41.1	105	50
44	39.0	50	41.2	106	50
48	40.1	50	42.4	106	50
52	40.7	50	42.8	105	50
56	41.3	50	42.6	103	50
60	40.1	50	43.4	108	50
64	40.0	50	42.7	107	50
68	38.3	50	42.0	110	50
72	39.2	50	43.1	110	50
76	39.6	50	43.3	109	49
80	39.0	50	43.0	110	47
84	38.8	46	43.1	111	47
88	39.1	44	43.2	110	46
92	38.7	43	42.0	109	45
96	38.6	42	41.4	107	43
100	39.3	41	42.3	108	39
103	38.2	38	41.4	108	35
FEMALE					
0	19.6	50	19.6	100	50
1	20.5	50	20.6	100	50
2	21.4	50	21.2	99	50
3	21.9	50	22.0	100	50
4	22.5	50	22.4	100	50
5	23.5	50	23.4	100	50
6	24.7	50	24.1	98	50
7	24.7	50	24.5	99	50
8	25.8	50	25.9	100	50
9	25.0	50	25.2	101	50
10	26.7	50	26.9	101	50
11	25.7	50	26.0	101	50
12	26.6	50	26.6	100	50
16	27.5	49	27.2	99	50
20	29.8	49	29.4	99	50
24	30.3	49	31.7	105	50
28	31.8	49	32.8	103	50
32	32.7	49	34.4	105	50
36	34.6	49	36.2	105	50
40	35.7	49	37.3	104	50
44	35.9	49	37.9	106	50
48	36.7	49	39.9	109	50
52	39.0	49	40.8	105	50
56	38.8	49	41.6	107	50
60	40.2	49	43.3	108	50
64	40.3	48	43.3	107	50
68	38.4	47	41.9	109	50
72	39.7	46	42.8	108	50
76	40.2	45	43.8	109	48
80	39.8	45	44.1	111	48
84	39.7	43	43.7	110	46
88	41.2	40	46.3	112	43
92	41.4	32	44.7	108	40
96	39.1	31	43.5	111	39
100	39.4	28	43.4	110	38
103	41.8	26	41.9	100	36

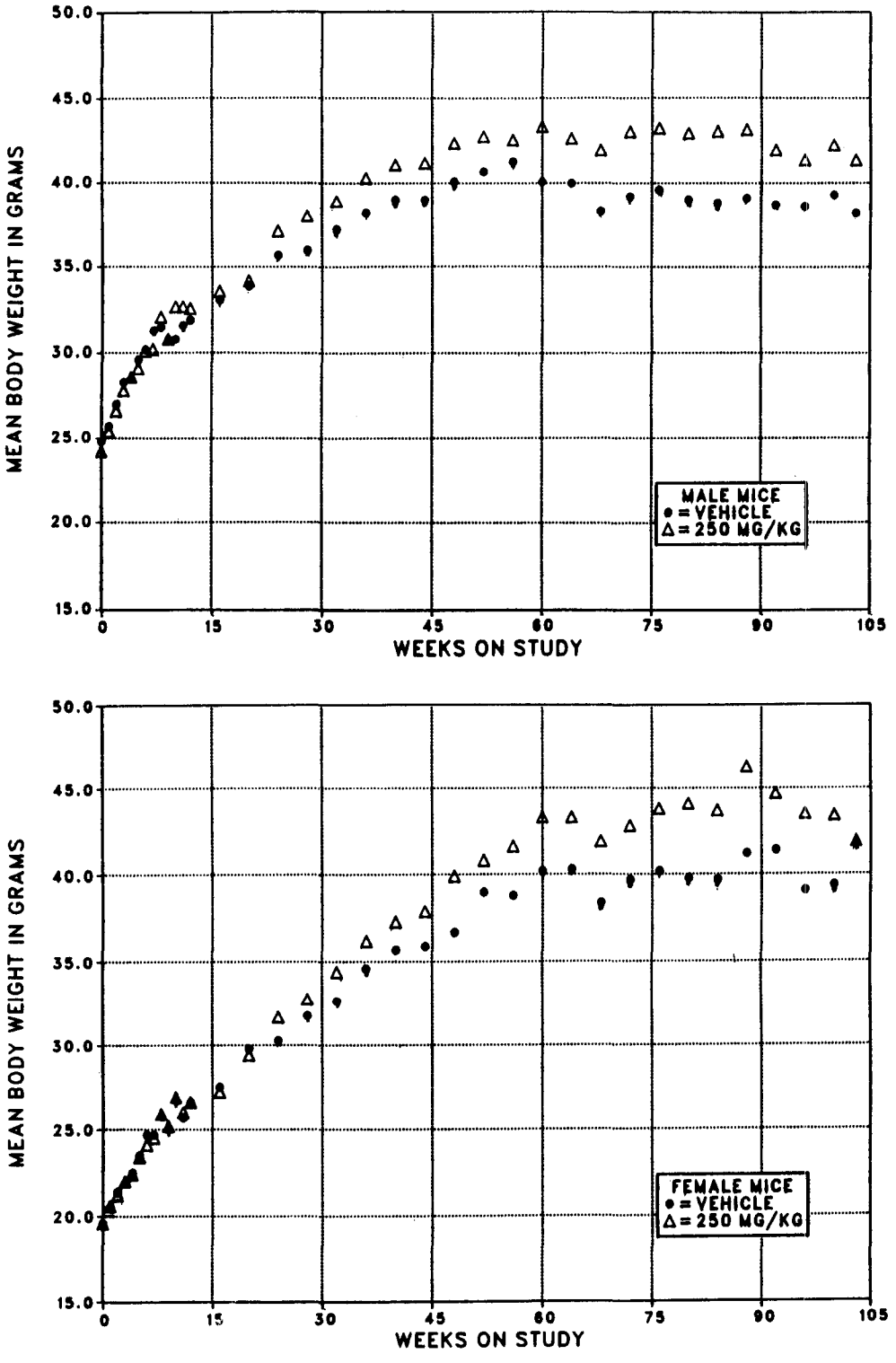


FIGURE 4. GROWTH CURVES FOR MICE ADMINISTERED *n*-BUYTL CHLORIDE IN CORN OIL BY GAVAGE FOR TWO YEARS (SECOND STUDY)

III. RESULTS: MICE

Survival

Estimates of the probabilities of survival for male and female mice administered *n*-butyl chloride at the doses used in these studies and for the vehicle controls are shown in the Kaplan and Meier curves in Figures 5 and 6. Because of the large number of deaths in the 1,000 mg/kg mouse groups, another dose group (250 mg/kg) and matching vehicle controls were started for male and female mice approximately 13 months after initiation of the other studies. The survival of the 1,000 mg/kg male group in the first study was significantly lower than that of the vehicle control group after week 89 (Table 15). No significant differences in survival were observed between the vehicle control and the 500 mg/kg groups in the first studies or the 250 mg/kg groups in the second studies (Tables 15 and 16).

TABLE 15. SURVIVAL OF MICE IN THE FIRST TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

	Vehicle Control	500 mg/kg	1,000 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	17	23	40
Killed at termination	32	27	10
Died during termination period	1	0	0
Survival P values (c)	<0.001	0.456	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	21	18	40
Accidental deaths	0	2	0
Killed at termination	28	30	(d) 10
Died during termination period	1	0	
Survival P value		0.926	

(a) Terminal kill period: male--week 104; female--week 105
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.
(d) Survivors killed at week 45

TABLE 16. SURVIVAL OF MICE IN THE SECOND TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

	Vehicle Control	250 mg/kg
MALE (a)		
Animals initially in study	50	50
Nonaccidental deaths before termination (b)	13	15
Killed at termination	35	35
Died during termination period	2	0
Survival P value (c)		0.825
FEMALE (a)		
Animals initially in study	50	50
Nonaccidental deaths before termination (b)	24	14
Killed at termination	25	36
Died during termination period	1	0
Survival P value (c)		0.060

(a) Terminal kill period: weeks 104-105
(b) Includes animals killed in a moribund condition
(c) The result of the life table pairwise comparison with the vehicle controls is in the dosed column.

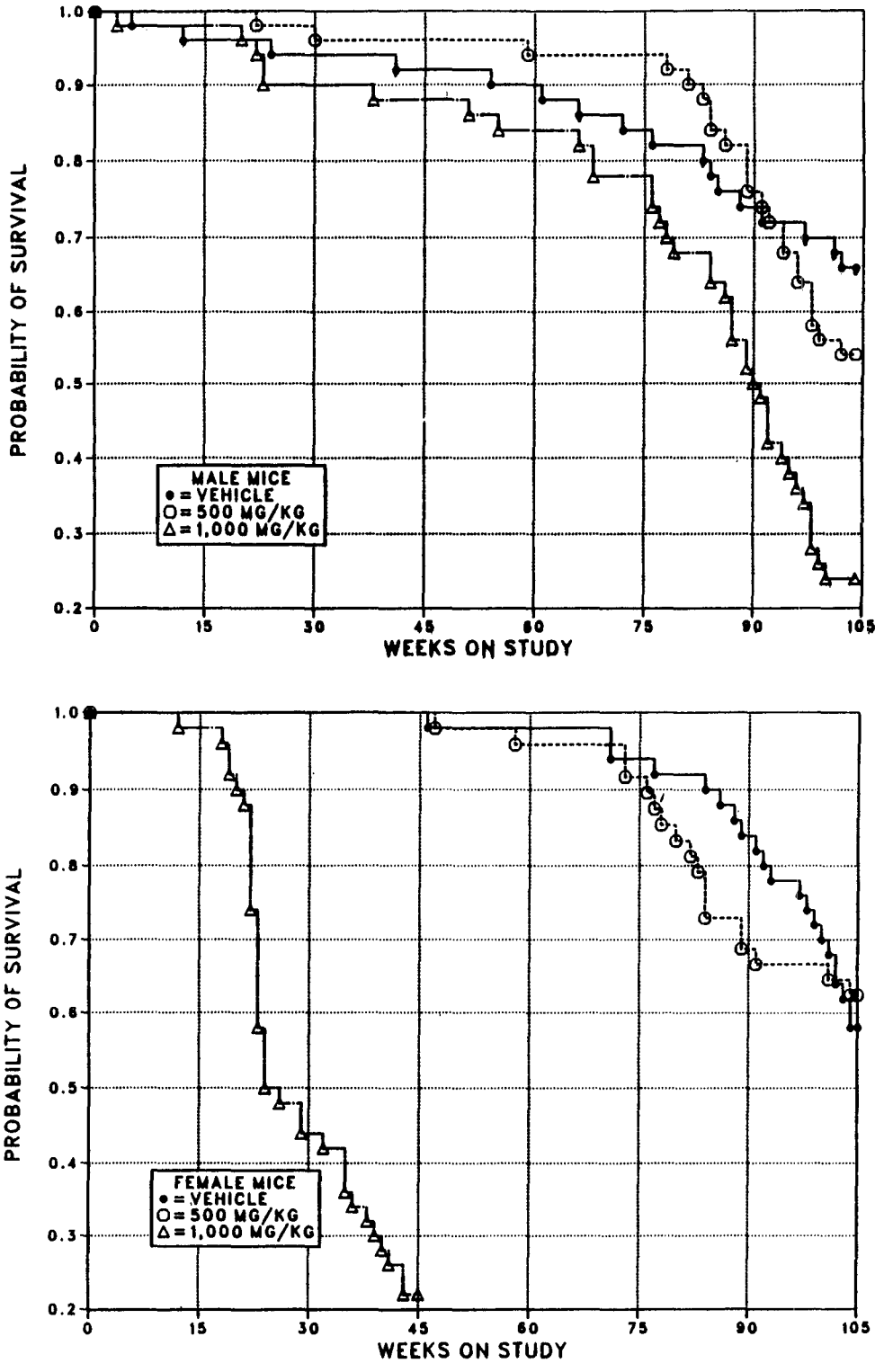


FIGURE 5. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED *n*-BUTYL CHLORIDE IN CORN OIL BY GAVAGE FOR TWO YEARS (FIRST STUDY)

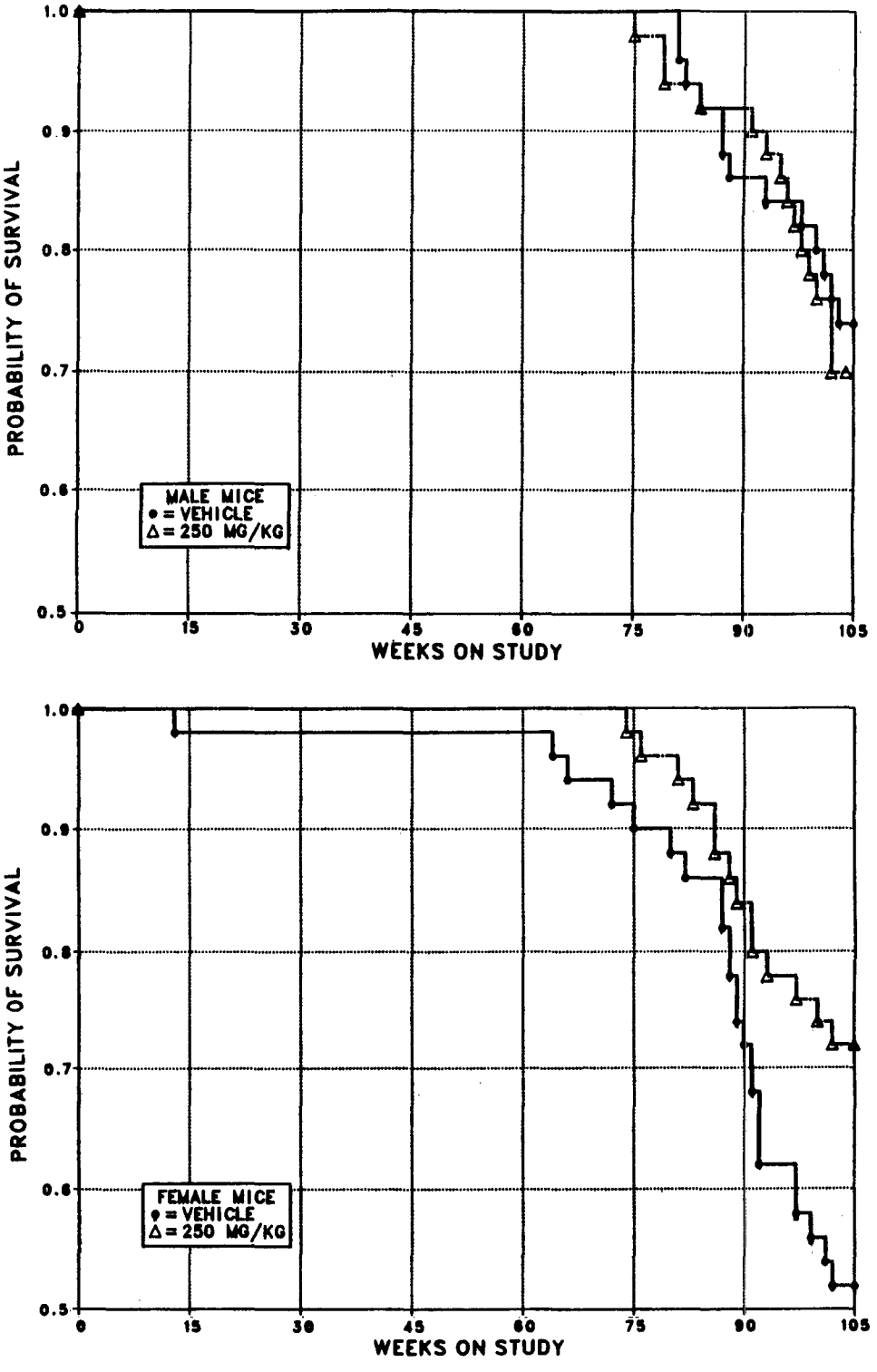


FIGURE 6. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED *n*-BUTYL CHLORIDE IN CORN OIL BY GAVAGE FOR TWO YEARS (SECOND STUDY)

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the lung, liver, circulatory system, ovary, or uterus. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1-B4); Appendix B (Tables B5-B8) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1-D4). Appendix E (Tables E3-E6) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the two or 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. A comparison of the vehicle control groups used in the first and second studies suggested that certain differences in survival and/or tumor incidence may have been present between the two groups. Consequently, these vehicle control groups were not combined routinely in the statistical analyses. Nevertheless, as a supplemental analysis the groups were pooled for those specific tumors showing some suggestion of a compound-related effect relative to the concurrent vehicle control.

Lung: The incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in the 500 mg/kg group in the first study of female mice was significantly greater ($P = 0.028$) than that in the vehicle controls by the incidental tumor test (Table 17). The use of logistic regression, an alternative test procedure for incidental tumors (Chapter II), had little effect on the P value ($P = 0.04$). However, this increased incidence was not significant relative to the pooled vehicle control group.

Liver: The incidence of hepatocellular adenomas or carcinomas (combined) in female mice that received 500 mg/kg in the first study was significantly greater ($P = 0.04$) than that in the vehicle controls by the incidental tumor test; however, it was not significant by logistic regression analysis ($P = 0.08$). In addition, this increased Incidence was not significant relative to the pooled vehicle control group. Moreover, the incidence of hepatocellular adenomas or carcinomas (combined) in the female vehicle controls in the second study was greater than that in the 500 mg/kg group in the first study (Table 18).

Circulatory System: The incidence of hemangiosarcomas in the male mice that received 1,000 mg/kg in the first study was significantly greater than that in the vehicle controls by life table analysis. The significance of this effect was essentially unchanged when comparison was based on the pooled vehicle control groups. The incidence of hemangiosarcomas in the vehicle controls in the second study was the same as that in the 1,000 mg/kg group in the first study (Table 19).

Ovary or Uterus: Suppurative inflammation in the first study was observed in 15/50 female vehicle control mice and 6/49 female mice in the 500 mg/kg group. *Klebsiella pneumoniae* was diagnosed in 4/59 uterine lavage samples taken from vehicle control and dosed mice in the first study. Suppurative inflammation in the second study was observed in 17/50 female vehicle control mice and 9/50 female mice in the 250 mg/kg group. Uterine lavage samples were not taken in the second study.

TABLE 17. ANALYSIS OF LUNG LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE (a)

	First Study (b)		Second Study (c)	
	Vehicle Control	500 mg/kg	Vehicle Control	250 mg/kg
Hyperplasia				
Overall Rates	1/50 (2%)	1/50 (2%)	0/50 (0%)	0/50 (0%)
Alveolar/Bronchiolar Adenoma				
Overall Rates	3/50 (6%)	6/50 (12%)	5/50 (10%)	6/50 (12%)
Adjusted Rates	8.6%	18.6%	15.4%	14.9%
Terminal Rates	1/29 (3%)	5/30 (17%)	3/26 (12%)	4/36 (11%)
Week of First Observation	98	76	64	81
Life Table Test		P=0.238		P=0.596N
Incidental Tumor Test		P=0.138		P=0.497
Alveolar/Bronchiolar Carcinoma				
Overall Rates	0/50 (0%)	4/50 (8%)	1/50 (2%)	3/50 (6%)
Adjusted Rates	0.0%	13.3%	3.8%	7.5%
Terminal Rates	0/29 (0%)	4/30 (13%)	1/26 (4%)	2/36 (6%)
Week of First Observation		105	104	81
Life Table Test		P=0.066		P=0.405
Incidental Tumor Test		P=0.066		P=0.342
Alveolar/Bronchiolar Adenoma or Carcinoma (d)				
Overall Rates	3/50 (6%)	9/50 (18%)	6/50 (12%)	8/50 (16%)
Adjusted Rates	8.6%	28.3%	19.0%	20.2%
Terminal Rates	1/29 (3%)	8/30 (27%)	4/26 (15%)	6/36 (17%)
Week of First Observation	98	76	64	81
Life Table Test		P=0.063		P=0.580
Incidental Tumor Test		P=0.028		P=0.437

	Pooled Vehicle Control (e, f)	250 mg/kg	500 mg/kg
Hyperplasia			
Overall Rates	1/100 (1%)	0/50 (0%)	1/50 (2%)
Alveolar/Bronchiolar Adenoma			
Overall Rates	8/100 (8%)	6/50 (12%)	6/50 (12%)
Adjusted Rates	11.8%	14.9%	18.0%
Terminal Rates	4/57 (7%)	4/36 (11%)	5/31 (16%)
Week of First Observation	64	81	76
Life Table Test	P=0.270	P=0.432	P=0.333
Incidental Tumor Test	P=0.225	P=0.300	P=0.277
Alveolar/Bronchiolar Carcinoma			
Overall Rates	1/100 (1%)	3/50 (6%)	4/50 (8%)
Adjusted Rates	1.8%	7.5%	12.9%
Terminal Rates	1/57 (2%)	2/36 (6%)	4/31 (13%)
Week of First Observation	105	81	105
Life Table Test	P=0.030	P=0.151	P=0.048
Incidental Tumor Test	P=0.030	P=0.134	P=0.048
Alveolar/Bronchiolar Adenoma or Carcinoma (d)			
Overall Rates	9/100 (9%)	8/50 (16%)	9/50 (18%)
Adjusted Rates	13.4%	20.2%	27.5%
Terminal Rates	5/57 (9%)	6/36 (17%)	8/31 (26%)
Week of First Observation	64	81	76
Life Table Test	P=0.084	P=0.276	P=0.111
Incidental Tumor Test	P=0.064	P=0.175	P=0.081

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E.
(b) Terminal kill at week 105
(c) Terminal kill at week 104
(d) Historical incidence at testing laboratory (mean ± SD): 15/199 (8% ± 4%); historical incidence in NTP studies: 57/1,087 (5% ± 3%)
(e) Terminal kill regarded as being week 104 for both studies ; thus, one 500 mg/kg and two vehicle control natural deaths at week 104 of the first study are considered as terminal kills in the pooled analysis.
(f) Pooled control groups are not normally used in NTP carcinogenesis studies; they are used here only as a supplemental analysis in the overall data evaluation.

TABLE 18. ANALYSIS OF LIVER TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE (a)

	First Study (b)		Second Study (c)	
	Vehicle Control	500 mg/kg	Vehicle Control	250 mg/kg
Hepatocellular Adenoma				
Overall Rates	1/50 (2%)	4/50 (8%)	8/50 (16%)	4/50 (8%)
Adjusted Rates	3.4%	13.3%	25.9%	10.4%
Terminal Rates	1/29 (3%)	4/30 (13%)	4/26 (15%)	3/36 (8%)
Week of First Observation	105	105	89	88
Life Table Test		P=0.187		P=0.083N
Incidental Tumor Test		P=0.187		P=0.154N
Hepatocellular Carcinoma				
Overall Rates	2/50 (4%)	4/50 (8%)	1/50 (2%)	5/50 (10%)
Adjusted Rates	6.6%	12.9%	2.4%	13.3%
Terminal Rates	1/29 (3%)	3/30 (10%)	0/26 (0%)	4/36 (11%)
Week of First Observation	104	104	88	93
Life Table Test		P=0.349		P=0.179
Incidental Tumor Test		P=0.144		P=0.124
Hepatocellular Adenoma or Carcinoma (d)				
Overall Rates	3/50 (6%)	8/50 (16%)	9/50 (18%)	7/50 (14%)
Adjusted Rates	9.9%	25.8%	27.7%	17.9%
Terminal Rates	2/29 (7%)	7/30 (23%)	4/26 (15%)	5/36 (14%)
Week of First Observation	104	104	88	88
Life Table Test		P=0.109		P=0.207N
Incidental Tumor Test		P=0.038		P=0.369N

	Pooled Vehicle Control (e, f)	250 mg/kg	500 mg/kg
Hepatocellular Adenoma			
Overall Rates	9/100 (9%)	4/50 (8%)	4/50 (8%)
Adjusted Rates	14.0%	10.4%	12.9%
Terminal Rates	5/57 (9%)	3/36 (8%)	4/31 (13%)
Week of First Observation	89	88	105
Life Table Test	P=0.421N	P=0.410N	P=0.510N
Incidental Tumor Test	P=0.544	P=0.541N	P=0.548
Hepatocellular Carcinoma			
Overall Rates	3/100 (3%)	5/50 (10%)	4/50 (8%)
Adjusted Rates	4.6%	13.3%	12.9%
Terminal Rates	2/57 (4%)	4/36 (11%)	4/31 (13%)
Week of First Observation	88	93	104
Life Table Test	P=0.122	P=0.136	P=0.185
Incidental Tumor Test	P=0.091	P=0.102	P=0.190
Hepatocellular Adenoma or Carcinoma (d)			
Overall Rates	12/100 (12%)	7/50 (14%)	8/50 (16%)
Adjusted Rates	18.3%	17.9%	25.8%
Terminal Rates	7/57 (12%)	5/36 (14%)	8/31 (26%)
Week of First Observation	88	88	104
Life Table Test	P=0.343	P=0.571N	P=0.374
Incidental Tumor Test	P=0.190	P=0.477	P=0.226

(a) The incidences of adenomas alone or combined with carcinomas were significantly different for the two vehicle control groups. Adenomas alone (vehicle control group first study, 1/50; vehicle control group second study, 8/50) were significantly different by the life table test (P=0.01), incidental tumor test (P=0.007), and the Fisher exact test (P=0.02). However, when adenomas were combined with carcinomas, the significance was not as great for the life table test (P=0.04) and incidental tumor test (P=0.03). The combined tumors were not significantly different by the Fisher exact test (P=0.06).
(b) Terminal kill at week 105
(c) Terminal kill at week 104
(d) Historical incidence at testing laboratory (mean ± SD): 17/198 (9% ± 5%); historical incidence in NTP studies: 74/1,092 (7% ± 4%)
(e) Terminal kill regarded as being week 104 for both studies; thus, one 500 mg/kg and two vehicle control natural deaths at week 104 of the first study are considered as terminal kills in the pooled analysis.
(f) Pooled control groups are not normally used in NTP carcinogenesis studies; they are used here only as a supplemental analysis in the overall data evaluation.

TABLE 19. ANALYSIS OF CIRCULATORY SYSTEM TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

First Study	Vehicle Control	500 mg/kg	1,000 mg/kg
Hemangiosarcoma (a)			
Overall Rates	1/50 (2%)	3/50 (6%)	4/50 (8%)
Adjusted Rates	3.0%	8.9%	19.3%
Terminal Rates	1/33 (3%)	0/27 (0%)	0/10 (0%)
Week of First Observation	104	91	68
Life Table Tests	P=0.028	P=0.272	P=0.044
Incidental Tumor Tests	P=0.380	P=0.552	P=0.360

Second Study	Vehicle Control	250 mg/kg
Hemangiosarcoma		
Overall Rates	4/50 (8%)	(b) 2/50 (4%)
Adjusted Rates	10.8%	5.7%
Terminal Rates	4/37 (11%)	2/35 (6%)
Week of First Observation	105	104
Life Table Test		P=0.362N
Incidental Tumor Test		P=0.362N

	Pooled Vehicle Control (c)	250 mg/kg	500 mg/kg	1,000 mg/kg
Hemangiosarcoma				
Overall Rates	5/100 (5%)	2/50 (4%)	3/50 (6%)	4/50 (8%)
Adjusted Rates	7.1%	5.7%	8.9%	19.3%
Terminal Rates	5/70 (7%)	2/35 (6%)	0/27 (0%)	0/10 (0%)
Week of First Observation	104	104	91	68
Life Table Test	P=0.024	P=0.555N	P=0.435	P=0.033
Incidental Tumor Test	P=0.281	P=0.555N	P=0.605	P=0.304

(a) Historical incidence of hemangioma or hemangiosarcoma (combined) at testing laboratory (mean ± SD): 4/200 (2% ± 2%); historical incidence in NTP studies: 49/1,097 (4% ± 4%)
(b) A hemangioma (subcutaneous tissue) was also observed in this group.
(c) Pooled control groups are not normally used in NTP carcinogenesis studies; they are used here only as a supplemental analysis in the overall data evaluation.

IV. DISCUSSION AND CONCLUSIONS

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n-Butyl chloride was administered in corn oil by gavage to male and female F344/N rats and B6C3F$_1$ mice at the following doses: 0-3,000 mg/kg for 14 days (rats and mice), 0-500 mg/kg for 13 weeks (rats), 0-1,000 mg/kg for 13 weeks (mice), 0, 60, or 120 mg/kg for 2 years (rats), and 0, 250, 500, or 1,000 mg/kg for 2 years (mice).

Short-Term Studies

In the 14-day studies, all rats that received 1,500 or 3,000 mg/kg and 3/5 males and 1/5 females that received 750 mg/kg *n*-butyl chloride died before the end of the studies. Only males receiving 750 mg/kg had lower body weights than did the vehicle controls. Hyperactivity and convulsions following gavage administration and bloody discharge from the nose and mouth were observed in male rats that received 750 mg/kg or more. One female rat that received 1,500 mg/kg had convulsions. Similar effects occurred in mice, although *n*-butyl chloride appeared to be less toxic. These clinical signs are indicative of central nervous system effects, and they have been reported previously by Smyth et al. (1954). All mice that received 3,000 mg/kg and 3/5 males and 2/5 females that received 1,500 mg/kg died before the end of the studies. No deaths occurred in groups administered 750 mg/kg or less. No compound-related reductions in weight gain occurred. Mice were hyperactive when administered doses of 1,500 mg/kg or more. Furthermore, only 2/10 male mice in the 3,000 mg/kg group had convulsions. There were no compound-related pathologic effects.

In the 13-week studies, all rats survived except for six males in the 500 mg/kg dose group; three of these died as a result of gavage accidents. As in the 14-day studies, animals were hyperactive and convulsed on one or more occasions (5/10 males and 2/10 females at 250 mg/kg and 9/10 males and 8/10 females at 500 mg/kg). Convulsions were not observed in the lower dose groups. Final mean body weights of males that received 250 or 500 mg/kg were 11%-20% lower than those of the vehicle controls, whereas only females in the 500 mg/kg group had 10% lower body weights. Mild to moderate compound-related extramedullary hematopoiesis in the spleen was observed in 3/10 males receiving 500 mg/kg. Because of weight gain depression and convulsions observed at 250 mg/kg and deaths in the male 500 mg/kg group, doses of 60 and 120 mg/kg *n*-butyl chloride were selected for male and female rats in the 2-year studies.

Gavage accidents during the mouse studies killed two vehicle control females, a male and a female in the 60 mg/kg groups, a female in the 120 mg/kg group, and two females in the 1,000 mg/kg group. Only one death, that of a female that received 1,000 mg/kg, was attributed to compound administration. Two females in this same group convulsed during the study. There were no compound-related effects on weight gain and no histopathologic effects. Based on these findings, doses of 500 and 1,000 mg/kg were selected for male and female mice in the 2-year studies. The difference in doses selected for rats and mice in the 2-year studies likely demonstrates a difference in sensitivity to, or in metabolism and disposition of, *n*-butyl chloride.

Two-Year Studies: Rats

In the 2-year studies, survival of both male rats (after week 59) and female rats (after week 41) in the high dose groups was significantly lower than that of the vehicle controls due to *n*-butyl chloride-related toxicity (see Figure 2). Hyperactivity, leading to tremors and convulsions, was noted in some animals before they died; this finding was consistent with the results of the 14-day and 13-week studies in which higher doses were used. Neither gross observations nor histopathologic evaluations revealed toxic morphologic lesions directly attributable to administration of *n*-butyl chloride, but there were incidences of small, usually perivascular hemorrhages in the brain which were consistent with rats dying suddenly during convulsions. Likewise, agonal or terminal congestion, edema, and hemorrhage of the lung were common in such animals. The actual cause of death could not be determined. Similar histopathologic findings were observed in animals dying later in the study but not in those killed at the end of the studies. The excessive mortality in both high dose male and female groups suggests that toxic levels were reached. There was no compound-related decrease in relative weight gain in any dose group. Death was considered to be compound related and not due to errors in gavage

administration. The mortality in the high dose groups was evaluated, and the studies were continued because of good survival in the low dose groups and no apparent compound-related reductions in weight gains in any dose groups. Based on the findings in the 13-week studies, high mortality in the 120 mg/kg high dose groups was not expected and reduced the sensitivity for determining carcinogenic responses in these groups. In retrospect, it might have been desirable to have conducted additional studies at a dose lower than 60 mg/kg.

Despite the low survival of high dose male and female rats, the present studies are considered adequate because survival of male and female rats in the 60 mg/kg dose groups was sufficient to permit evaluation and interpretation of the data. Thirty-two of 50 male rats administered 60 mg/kg *n*-butyl chloride survived to the end of the study (compared with 40/50 vehicle controls), and 38/50 females administered the same dose survived to the end of the study (compared with 35/50 vehicle controls). The mean body weights of high dose males were slightly (less than 9%) lower than those of the vehicle controls throughout most of the study. Mean body weights of dosed females and low dose males and concurrent vehicle controls were comparable throughout the studies. No clinical signs other than convulsions were observed following gavage administration.

There was a marginally ($P = 0.04$) increased incidence of pheochromocytomas of the adrenal gland in low dose female rats (vehicle control, 1/50; low dose, 6/50; high dose, 1/49). There was no supporting increase in the high dose group, and most of the tumors were observed at the end of the study. Pheochromocytomas are late-developing tumors, and this lesion was not observed in the 11 high dose females that survived 2 years. The incidences of hyperplasia of the adrenal medulla were not strongly supportive (vehicle control, 3/50; low dose, 7/50; high dose, 4/49). If these effects were compound-related, higher incidences of hyperplasia and tumors would have been expected. The historical incidence of this tumor is 6%-7%. There was no significant trend for the incidence of this tumor, pairwise statistical significance was marginal, and the incidences of hyperplasia provided limited support. In addition, a negative trend was seen in male rats (vehicle control, 15/50; low dose, 11/50; high dose, 4/50). One vehicle control female rat had a malignant pheochromocytoma. Thus, this marginal increase in female rats is considered unlikely to be the result of *n*-butyl chloride administration.

In male rats, there was a positive trend in the incidences of cytoplasmic vacuolization in the adrenal cortex (vehicle control, 5/50; low dose, 10/50; high dose, 20/50). In female rats, the incidences were lower and not different among the groups (vehicle control, 4/50; low dose, 5/50; high dose, 3/49). Although increased cytoplasmic vacuolization indicates an increased accumulation of lipid material, the biologic significance of this compound-related effect in male rats is not clear. No other compound-related nonneoplastic lesions were seen in the adrenal cortex.

Transitional cell papillomas of the urinary bladder were observed in one low dose male rat and one high dose female rat. The overall historical incidence of this tumor is 0% in male rats and 0.3% in female rats throughout the Program, and none has been observed previously at this laboratory. The significance of this lesion is not clear and is reported here only because it is not normally observed.

Several nonneoplastic effects were observed primarily in high dose male and female rats as a probable result of chemical-related toxicity (see Table 10). Convulsions after dosing, especially in high dose animals, were common throughout the studies. Mortality was excessive in both high dose male and female groups. Toxic effects included hemorrhage in the brain and lung and lymphoid depletion and hemosiderosis of the spleen. Hemorrhage of the brain and alveoli are often observed in animals dying from convulsions. In addition, lymphoid depletion of the spleen is consistent with a stressed state of the animals. The cause of the splenic hemosiderosis is not known. Hemorrhage in the brain and lung and splenic hemosiderosis and lymphoid depletion in high dose animals were observed only in animals dying during the studies except for one high dose rat at the end of the studies that had brain hemorrhage. The other nonneoplastic lesion in rats was nephropathy, which was observed in females (vehicle control, 13/50; low dose, 25/50; high dose, 20/50). Although there

were higher incidences in the dosed animals, the significance of this lesion is not clear, especially since other nonneoplastic kidney effects such as congestion, inflammation, or nephrosis were not present to any degree in either vehicle control or dosed groups.

Two-Year Studies: Mice

Survival of female mice in the 1,000 mg/kg group was reduced to 50% by the 25th week of exposure. Ninety percent of the high dose male mice were alive at that time. No biologically significant decreases in weight gain or survival were observed in the 13-week studies at the doses selected for the 2-year studies. Hyperactivity, tremors, and convulsions were observed in female mice and were seen in the 14-day and 13-week studies. Gross observations and histopathologic evaluation of females dying early did not reveal any morphologic lesions attributable to *n*-butyl chloride; however, hemorrhage of the brain and lung, as reported for rats, was observed.

The poor survival could not be attributed to gavage accidents, disease, or deviations from the study protocol and was therefore considered compound related. Since mortality was excessive, the rest of the high dose females were killed at week 45 and additional 2-year studies with male and female mice were started at a lower dose of 250 mg/kg, with concurrent vehicle controls. At the end of the first 2-year study, a decrease in survival was dose related in male mice. Survival in the high dose male group was reduced (vehicle control, 33/50; 1,000 mg/kg, 10/50), and the mean body weight was 10% lower than that of the vehicle controls. The decline in survival occurred relatively late in the study. Although survival in the low dose male group was lower than that of the vehicle controls, 54% of the animals survived to the end. Survival in the 500 mg/kg female group (first study) and in both male and female 250 mg/kg groups of the second studies was not significantly different from that of the corresponding vehicle control groups. Mean body weights of the animals were the same as or greater than those of the vehicle controls throughout most of the first 2-year studies. Hyperactivity, often followed by tremors and convulsions, was seen primarily in the high dose animals of the first studies. There were no compound-related clinical signs in either male or female mice during the second 2-year studies.

Proliferative lesions were observed in the lung (female), liver (female) and circulatory system (male) with a greater incidence in dosed mice than in the vehicle controls. Alveolar/bronchiolar adenomas or carcinomas (combined) occurred at increased incidences in dosed female mice in the first study but showed little difference in the second study (see Table 17). The incidences of these lesions in vehicle controls were within the range of the historical control incidence for the laboratory and for NTP studies in general. Since there were no significant differences in the incidences of adenomas, carcinomas, or adenomas or carcinomas (combined) between the two vehicle control groups, additional statistical analyses comparing dosed groups to pooled vehicle control groups were performed. The combined incidence of alveolar/bronchiolar adenomas and carcinomas in the 500 mg/kg group was significant ($P=0.03$) by the incidental tumor test, but the incidences of adenomas or carcinomas alone were not significant when compared with the vehicle controls.

When the incidences of alveolar/bronchiolar adenomas and carcinomas from each dose group of the two studies were compared with those in the pooled vehicle control group, the increased incidence of carcinomas alone in the high dose group was of borderline significance ($P=0.05$) (vehicle control, 1/100; 250 mg/kg, 3/50; 500 mg/kg, 4/50). The incidence of adenomas or carcinomas (combined) compared with that in the pooled vehicle controls was not significant (vehicle control, 9/100; 250 mg/kg, 8/50; 500 mg/kg, 9/50). There were no significant increases in the incidences of adenomas or carcinomas (combined) in dosed male mice. A negative trend was found for alveolar/bronchiolar carcinomas in dosed male groups in the first study (vehicle control, 3/50; low dose, 2/50; high dose, 0/50). Hyperplasia of the alveolar/bronchiolar region was present in only one animal of each of the vehicle control male and female groups and of the 500 mg/kg female group. The lack of hyperplasia and insignificant differences in adenomas in dosed versus vehicle control animals did not support a progression of compound-induced neoplasia. Thus, the marginal increase in lung lesions in female mice is

not considered the result of *n*-butyl chloride administration.

A marginally significant (P = 0.04) increased incidence of hepatocellular adenomas or carcinomas (combined) was seen in the 500 mg/kg female mouse group (vehicle control, 3/50; 500 mg/kg, 8/50) (see Table 18). This increase was not significant by logistic regression analysis (P = 0.08). Neither adenomas nor carcinomas alone were significantly increased in either dosed group. Comparison of the vehicle control groups from both studies revealed a significant (P < 0.05) difference in adenomas (1/50 vs 8/50) and adenomas or carcinomas (combined) (3/50 vs 9/50). Even so, when the increased incidence of combined tumors from the dosed groups was compared with that of the pooled vehicle control groups, the incidence was no longer significant. Since the incidences of adenomas and carcinomas were highly variable between the two vehicle control groups, showed no significant effects when the two studies were combined, and showed no dose-related effects in male mice, this marginal increase in females was not considered to be compound related.

A marginal dose-related incidence of hemangiosarcomas was observed in male mice (vehicle control, 1/50; low dose, 3/50; high dose, 4/50) in the first study. The increase in the 1,000 mg/kg group was marginally significant (P = 0.04) by life table analysis; one animal in the low dose group and two in the high dose group had two or more lesions. In the second study, hemangiosarcomas occurred in 4/50 vehicle controls (five tumors) and in 2/50 dosed animals (three tumors). One hemangioma was observed in the 250 mg/kg group. The second study does not support a chemical-induced incidence of hemangiosarcomas, particularly since the vehicle control incidence was equal to the incidence observed in the high dose group in the first study. When the vehicle control groups of the two studies were compared, there was no difference in the incidence of hemangiosarcomas. When the vehicle control groups were pooled and the incidence in dosed animals compared with this pooled vehicle control group (vehicle control, 5/100; 250 mg/kg, 2/50; 500 mg/kg, 3/50; 1,000 mg/kg, 4/50), the statistical significance of the incidence in the 1,000 mg/kg group was essentially unchanged (P = 0.03; by the life table test). Of interest, all hemangiosarcomas observed in both vehicle control groups and in the 250 mg/kg group were observed at the end of the study as opposed to 5/7 hemangiosarcomas in the 500 and 1,000 mg/kg group being observed between weeks 91 and 104. The historical incidence of hemangiosarcomas at this laboratory (1.5%) is lower than the incidence for all NTP studies (4%). Since the incidence of these tumors was only marginally increased and the vehicle control incidence in the first study was lower than the historical incidence for the NTP studies and the incidence in the vehicle controls of the second study, the marginal increase in hemangiosarcomas was not considered to be compound related.

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

Conclusions: Under the conditions of these 2-year gavage studies, there was *no evidence of carcinogenicity** of *n*-butyl chloride for male and female F344/N rats at daily doses of 60 or 120 mg/kg, for male B6C3F$_1$ mice at doses of 250, 500, or 1,000 mg/kg, or for female B6C3F$_1$ mice at doses of 250 or 500 mg/kg. Chemical-induced toxicity in high dose rats (primarily females) reduced the sensitivity of the study for determining carcinogenicity.

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

V. REFERENCES

V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	CONTROL (VEH)	60 mg/kg	120 mg/kg
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Fibrous histiocytoma, malignant		1 (2%)	
*Pelvis	(50)	(50)	(50)
Fibrous histiocytoma, malignant	1 (2%)		
*Skin	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	2 (4%)
Basal cell carcinoma		1 (2%)	1 (2%)
Keratoacanthoma	3 (6%)	2 (4%)	2 (4%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma	2 (4%)	1 (2%)	
Fibrosarcoma		1 (2%)	
Lipoma		2 (4%)	
Neurofibroma	1 (2%)	1 (2%)	2 (4%)
Neurofibrosarcoma	1 (2%)	3 (6%)	1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
Alveolar/bronchiolar adenoma	1 (2%)	2 (4%)	
Alveolar/bronchiolar carcinoma		1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malig. lymphoma, lymphocytic type		1 (2%)	1 (2%)
Leukemia, mononuclear cell	11 (22%)	7 (14%)	6 (12%)
#Mediastinal lymph node	(49)	(50)	(49)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
#Jejunum	(50)	(50)	(50)
Granulocytic sarcoma	1 (2%)		
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
#Salivary gland	(48)	(50)	(46)
Mixed tumor, malignant			1 (2%)
#Liver	(50)	(50)	(50)
Neoplastic nodule	2 (4%)	1 (2%)	1 (2%)
Hepatocellular carcinoma	1 (2%)	2 (4%)	
#Pancreas	(50)	(50)	(48)
Acinar cell adenoma	4 (8%)	9 (18%)	5 (10%)
#Forestomach	(50)	(49)	(50)
Squamous cell papilloma	1 (2%)	1 (2%)	2 (4%)
#Ileum	(50)	(50)	(50)
Leiomyoma	1 (2%)		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	60 mg/kg	120 mg/kg
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Lipoma		1 (2%)	
#Urinary bladder	(50)	(50)	(49)
Transitional cell papilloma		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary intermedia	(48)	(49)	(47)
Adenoma, NOS	3 (6%)		
#Anterior pituitary	(48)	(49)	(47)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	18 (38%)	14 (29%)	8 (17%)
#Adrenal	(50)	(50)	(50)
Cortical adenoma	2 (4%)		
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	14 (28%)	11 (22%)	4 (8%)
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(49)	(49)	(46)
Follicular cell adenoma	4 (8%)	3 (6%)	
C-cell adenoma	5 (10%)	1 (2%)	2 (4%)
C-cell carcinoma	1 (2%)	1 (2%)	3 (7%)
#Pancreatic islets	(50)	(50)	(48)
Islet cell adenoma	2 (4%)	2 (4%)	
Islet cell carcinoma	2 (4%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma	5 (10%)	3 (6%)	3 (6%)
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	2 (4%)	2 (4%)	2 (4%)
Adenoma, NOS	1 (2%)		
#Prostate	(40)	(42)	(49)
Adenoma, NOS		1 (2%)	
#Testis	(50)	(49)	(49)
Interstitial cell tumor	46 (92%)	45 (92%)	39 (80%)
Fibrous histiocytoma, metastatic		1 (2%)	
NERVOUS SYSTEM			
#Brain	(49)	(50)	(49)
Carcinoma, NOS, invasive	1 (2%)		
Ependymoma	1 (2%)		
#Cerebellum	(49)	(50)	(49)
Astrocytoma	1 (2%)		
SPECIAL SENSE ORGANS			
*Zymbal gland	(50)	(50)	(50)
Ceruminous carcinoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	60 mg/kg	120 mg/kg
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metastatic		1 (2%)	
*Peritoneum	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive			1 (2%)
Fibrosarcoma, metastatic		1 (2%)	
Fibrous histiocytoma, metastatic	1 (2%)		
Mesothelioma, NOS		1 (2%)	
Neurofibrosarcoma, invasive	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	8	22
Moribund sacrifice	6	10	11
Terminal sacrifice	40	32	17
TUMOR SUMMARY			
Total animals with primary tumors**	48	48	42
Total primary tumors	142	125	87
Total animals with benign tumors	48	47	42
Total benign tumors	113	101	69
Total animals with malignant tumors	20	20	14
Total malignant tumors	25	22	17
Total animals with secondary tumors##	3	3	1
Total secondary tumors	3	3	2
Total animals with tumors uncertain-- benign or malignant	4	2	1
Total uncertain tumors	4	2	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 A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	CONTROL (VEH)	60 mg/kg	120 mg/kg
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Basal cell carcinoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosarcoma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type	2 (4%)		
Malignant lymphoma, histiocytic type			1 (2%)
Leukemia, mononuclear cell	12 (24%)	10 (20%)	5 (10%)
CIRCULATORY SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Angiolipoma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic			1 (2%)
Neoplastic nodule	1 (2%)	4 (8%)	
#Pancreas	(50)	(49)	(50)
Acinar cell adenoma	1 (2%)	1 (2%)	
#Forestomach	(49)	(50)	(49)
Squamous cell papilloma	2 (4%)	1 (2%)	
#Duodenum	(50)	(50)	(50)
Adenocarcinoma, NOS			1 (2%)
URINARY SYSTEM			
#Urinary bladder	(49)	(50)	(49)
Transitional cell papilloma			1 (2%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	60 mg/kg	120 mg/kg
ENDOCRINE SYSTEM			
#Pituitary intermedia	(49)	(50)	(49)
Adenoma, NOS	1 (2%)	4 (8%)	1 (2%)
#Anterior pituitary	(49)	(50)	(49)
Carcinoma, NOS	2 (4%)	2 (4%)	1 (2%)
Adenoma, NOS	22 (45%)	21 (42%)	10 (20%)
#Adrenal	(50)	(50)	(49)
Cortical adenoma		2 (4%)	1 (2%)
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma		6 (12%)	1 (2%)
Pheochromocytoma, malignant	1 (2%)		
#Thyroid	(48)	(49)	(46)
Follicular cell adenoma	1 (2%)	1 (2%)	
Follicular cell carcinoma	1 (2%)		
C-cell adenoma	4 (8%)	3 (6%)	2 (4%)
C-cell carcinoma	2 (4%)	2 (4%)	
#Pancreatic islets	(50)	(49)	(50)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)	3 (6%)	
Fibroadenoma	16 (32%)	17 (34%)	8 (16%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	3 (6%)	1 (2%)	1 (2%)
Adenoma, NOS	1 (2%)	1 (2%)	
#Uterus	(50)	(50)	(50)
Adenocarcinoma, NOS	3 (6%)	2 (4%)	
Leiomyosarcoma	1 (2%)		
Endometrial stromal polyp	12 (24%)	16 (32%)	8 (16%)
Endometrial stromal sarcoma		1 (2%)	
#Cervix uteri	(50)	(50)	(50)
Fibroma	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Carcinoma, NOS, invasive		1 (2%)	
#Brain	(50)	(50)	(50)
Carcinoma, NOS, invasive	1 (2%)	1 (2%)	
Glioma, NOS			1 (2%)
#Cerebellum	(50)	(50)	(50)
Granular cell tumor, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
*Zymbal gland	(50)	(50)	(50)
Ceruminous carcinoma	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	60 mg/kg	120 mg/kg
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Liposarcoma	1 (2%)		
*Mesentery	(50)	(50)	(50)
Sarcoma, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Adenocarcinoma, NOS, metastatic	1 (2%)	1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	2	3	29
Moribund sacrifice	14	9	10
Terminal sacrifice	34	38	11
TUMOR SUMMARY			
Total animals with primary tumors**	47	46	25
Total primary tumors	94	101	45
Total animals with benign tumors	40	42	18
Total benign tumors	62	75	33
Total animals with malignant tumors	28	19	11
Total malignant tumors	31	22	11
Total animals with secondary tumors##	2	3	1
Total secondary tumors	2	3	1
Total animals with tumors uncertain--benign or malignant	1	4	1
Total uncertain tumors	1	4	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 A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: VEHICLE CONTROL

ANIMAL NUMBER	0036	0046	0003	0411	0007	0119	0400	0200	0034	0112	0001	0002	0004	0005	0006	0008	0009	0110	0111	0113	0114	0115	0116	0221	0222
WEEKS ON STUDY	048	066	081	084	088	097	099	100	100	103	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																					X				
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																			X						
Neurofibroma																									
Neurofibrosarcoma																X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
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			X		
Esophagus	+	+	−	+	−	−	+	+	−	+	−	−	−	+	+	+	+	+	+	+	+	+	−	−	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma							X																		
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma									X																
Granulocytic sarcoma																							X		
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS															X										
Adenoma, NOS				X	X	X	X	X		X	X	X				X	X					X	X		
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma											X														
Pheochromocytoma					X					X		X	X									X			
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma														X											
C-cell adenoma							X						X				X								
C-cell carcinoma						X																			
Parathyroid	−	−	+	−	+	+	−	+	−	+	+	+	+	+	−	−	+	+	−	−	+	−	−	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	+	N	N	+	N	N	+	N	N	+	N	N	N	N	+	N	N	N	N
Fibroadenoma							X			X			X												
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	+	+	−	+	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	−	+
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																									
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive															X										
Ependymoma																									
Astrocytoma																									
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
Ceruminous carcinoma								X																	
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
Fibrous histiocytoma, malignant			X																						
Mesothelioma, NOS																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, 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
Fibrous histiocytoma, metastatic			X																						
Neurofibrosarcoma, invasive																X									
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 A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	031	017	018	023	024	025	026	027	028	029	030	032	033	035	037	038	039	042	043	044	045	047	048	049	050	TOTAL:
WEEKS ON STUDY	105	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma										X			X													3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma						X																				2
Neurofibroma				X																						1
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma															X											1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	−	−	−	−	+	+	+	+	+	+	−	−	−	−	+	+	+	−	−	−	−	−	+	+	+	26
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										2
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						4
Esophagus	+	−	−	+	+	+	−	+	+	+	−	−	−	+	+	+	−	+	−	+	−	+	+	+	+	31
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Granulocytic sarcoma																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	48
Carcinoma, NOS																										1
Adenoma, NOS	X		X	X		X			X			X					X	X				X				21
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										2
Pheochromocytoma			X		X	X			X						X				X	X				X	X	14
Pheochromocytoma, malignant																						X				1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma						X							X							X						4
C-cell adenoma		X																			X					5
C-cell carcinoma																										1
Parathyroid	+	+	−	−	−	−	−	+	+	+	−	−	−	−	−	+	−	+	+	−	+	+	+	−	−	25
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma						X						X														2
Islet cell carcinoma					X																	X				2
REPRODUCTIVE SYSTEM																										
Mammary gland	N	+	N	N	N	+	+	N	N	N	N	N	+	N	+	+	+	N	N	N	N	N	+	+	N	*50
Fibroadenoma															X									X		5
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	X	X	X	46
Prostate	−	+	−	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	40
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
Carcinoma, NOS	X																							X		2
Adenoma, NOS										X																1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	49
Carcinoma, NOS, invasive																										1
Ependymoma																							X			1
Astrocytoma					X																					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	N	*50
Ceruminous carcinoma																										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
Fibrous histiocytoma, malignant																										1
Mesothelioma, NOS																					X					1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										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
Fibrous histiocytoma, metastatic																										1
Neurofibrosarcoma, invasive																										1
Leukemia, mononuclear cell		X		X			X			X				X						X			X	X	11

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: 60 mg/kg

ANIMAL NUMBER	023	014	026	036	007	033	029	037	044	001	002	013	055	046	022	035	041	043	003	004	006	008	009	010	011
WEEKS ON STUDY	040	050	061	080	081	082	086	086	089	091	092	092	098	098	099	100	101	101	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Basal cell carcinoma																									
Keratoacanthoma																								X	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma															X										
Fibrosarcoma							X																		
Lipoma						X																			
Neurofibroma																									X
Neurofibrosarcoma	\			X					X	X															
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma			X																						
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma															X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	−	+	−	+	−	+	+	+	−	+	+	+	−	−	+	+	+	+	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									X
Hepatocellular carcinoma								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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lipoma						X																			
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X				X		X		X				X	X			X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma							X				X				X		X			X					
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																						X		X	
C-cell adenoma																									
C-cell carcinoma																									
Parathyroid	−	−	−	−	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	−	−	+	+	−	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma					X																				
Islet cell carcinoma																									
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
Fibroadenoma																X									
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
Fibrous histiocytoma, metastatic																X									
Prostate	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−
Adenoma, NOS																									
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																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																									
Mediastinum	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
Alveolar/bronchiolar ca, 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
Fibrosarcoma, metastatic							X																		
Fibrous histiocytoma, malignant																X									
Mesothelioma, NOS														X											
Malig. lymphoma, lymphocytic type											X														
Leukemia, mononuclear cell														X				X		X					

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 60 mg/kg (Continued)

ANIMAL NUMBER	0 1 2	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 4	0 2 5	0 2 7	0 2 8	0 3 0	0 3 1	0 3 2	0 3 4	0 3 8	0 3 9	0 4 0	0 4 2	0 4 5	0 4 7	0 4 8	0 4 9	0 5 0	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																						X				1
Basal cell carcinoma											X															1
Keratoacanthoma										X																2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
Fibrosarcoma																										1
Lipoma												X														2
Neurofibroma																										1
Neurofibrosarcoma																										3
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Alveolar/bronchiolar adenoma																X		X								2
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	−	−	+	+	+	−	−	+	+	−	−	−	−	−	+	+	+	+	−	−	−	−	+	+	28
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Hepatocellular carcinoma																										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	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma	X				X				X		X		X		X			X								9
Esophagus	−	+	−	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	−	−	+	+	+	35
Stomach	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																	X									1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lipoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell papilloma									X																	1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X					X		X				X	X								X			X		14
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma					X			X				X		X									X	X		11
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma															X											3
C-cell adenoma							X																			1
C-cell carcinoma																									X	1
Parathyroid	+	−	+	−	+	+	+	−	−	+	−	−	−	+	−	−	−	+	−	−	−	−	−	−	−	24
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma										X																2
Islet cell carcinoma	X																									1
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
Fibroadenoma				X					X																	3
Testis	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	X	X	45
Fibrous histiocytoma, metastatic																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	−	−	+	+	+	42
Adenoma, NOS																X										1
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
Carcinoma, NOS			X											X												2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
Mediastinum	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
Alveolar/ronchiolar carcinoma, metastatic																										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
Fibrosarcoma, metastatic																										1
Fibrous histiocytoma, malignant																										1
Mesothelioma, NOS																										1
Malig. lymphoma, lymphocytic type																										1
Leukemia, mononuclear cell											X		X				X				X					7

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: 120 mg/kg

ANIMAL NUMBER	01 17	01 13	01 11	00 04	01 12	02 23	01 19	03 35	04 43	01 16	03 33	02 24	03 37	03 36	03 38	01 14	00 05	03 31	04 47	00 06	02 25	00 03	03 32	04 45	01 15
WEEKS ON STUDY	02 99	03 88	04 22	04 55	04 88	04 99	05 44	05 99	05 99	06 00	06 82	07 11	07 11	07 72	07 22	07 55	07 77	07 77	08 00	08 86	08 87	08 99	08 99	08 99	09 00
INTEGUMENTARY SYSTEM																									
Skin	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Basal cell carcinoma																									
Keratoacanthoma																									
Subcutaneous tissue	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurofibroma																									
Neurofibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																			X						
Trachea	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	–	–	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar ca, metastatic																			X						
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	–	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	–	+	+	+	+
Mixed tumor, malignant																									
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																									
Esophagus	+	+	+	–	–	+	+	–	+	+	+	–	+	+	+	–	+	+	+	–	–	+	–	+	–
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																X									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, *NOS*																X		X							
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	–	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+
C-cell adenoma																									
C-cell carcinoma																							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
Fibroadenoma																						X			
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor								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*																									
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
Alveolar/bronchiolar ca, invasive																			X						
Malig. lymphoma, lymphocytic type																							X		
Leukemia, mononuclear cell																									

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 120 mg/kg (Continued)

ANIMAL NUMBER	049	022	028	008	027	041	002	001	007	009	010	018	020	021	026	029	030	034	039	040	042	044	046	048	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	090	091	095	097	097	099	100	102	104	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma								X				X														2
Basal cell carcinoma																						X				1
Keratoacanthoma		X		X																						2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Neurofibroma										X										X						2
Neurofibrosarcoma																		.					X			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma									X																	2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
Alveolar/bronchiolar carcinoma, metastatic																										1
Thymus	+	−	+	+	+	+	−	+	+	−	+	−	+	+	+	+	−	−	−	−	−	−	−	−	+	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Mixed tumor, malignant									X																	1
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Acinar cell adenoma													X			X	X			X		X				5
Esophagus	+	−	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	36
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma						X																				2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	47
Adenoma, NOS		X									X		X	X						X				X		8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma						X	X							X									X			4
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
C cell adenoma																X			X							2
C cell carcinoma											X			X												3
Parathyroid	+	−	−	−	−	+	−	−	−	+	+	−	+	−	−	+	+	+	+	−	−	−	+	−	+	19
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	N	N	N	+	+	N	N	N	N	+	N	N	N	+	N	N	N	+	N	+	N	N	*50
Fibroadenoma																	X				X					3
Testis	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	X	39
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	N	*50
Carcinoma, NOS										X			X													2
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
Alveolar/bronchiolar carcinoma, invasive																										1
Malignant lymphoma, lymphocytic type																										1
Leukemia, mononuclear cell				X	X	X		X			X	X														6

*Animals necropsied

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

ANIMAL NUMBER	0171	0281	0139	0339	0389	0008	0489	0332	0379	0422	0144	0550	0004	0227	0244	0001	0029	0039	0055	0269	0299	0311	0355	0406	0006
WEEKS ON STUDY	0777	0788	0800	0800	0833	0855	0877	0888	0899	0900	0911	0911	0955	1000	1011	1015	1035	1055	1055	1055	1055	1055	1055	1055	1066
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																									
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																									
Esophagus	+	+	+	+	+	+	+	+	+	−	−	+	−	+	+	−	+	−	−	+	−	−	−	+	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Squamous cell papilloma						X							X												
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	−	−	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS						X																			
Adenoma, NOS								X		X	X	X	X	X	X	X		X	X	X		X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma		X																							
Follicular cell carcinoma							X																		
C-cell adenoma																				X					
C-cell carcinoma																									
Parathyroid	−	+	−	+	+	−	+	−	−	+	+	−	−	−	+	−	+	+	−	−	−	−	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+
Adenocarcinoma, NOS											X														
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
Carcinoma, NOS						X										X				X					
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																		X							
Fibroma																	X								
Leiomyosarcoma																									
Endometrial stromal polyp						X				X			X		X	X				X					
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive						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
Ceruminous carcinoma									X																
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
Liposarcoma				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
Sarcoma, 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
Adenocarcinoma, NOS, metastatic																									
Malig. lymphoma, lymphocytic type					X																X				
Leukemia, mononuclear cell	X	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	0007	0009	0110	0111	0112	0115	0116	0118	0119	0120	0121	0122	0123	0125	0130	0134	0136	0139	0141	0143	0144	0145	0146	0147	0149	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	106	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	−	−	+	+	+	+	−	−	−	−	−	−	−	−	−	+	+	+	−	+	+	−	−	−	24
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																					X					1
Esophagus	−	+	−	+	+	+	+	−	−	−	−	−	−	−	−	−	+	+	−	+	+	+	−	−	−	26
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
Carcinoma, NOS															X											2
Adenoma, NOS	X	X	X	X			X	X	X		X	X					X				X					23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma, malignant											X															1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	48
Follicular cell adenoma																										1
Follicular cell carcinoma																										1
C-cell adenoma			X									X				X										4
C-cell carcinoma																	X					X				2
Parathyroid	+	−	+	−	−	−	−	+	−	+	−	+	+	+	−	−	−	+	−	+	−	−	−	−	−	19
REPRODUCTIVE SYSTEM																										
Mammary gland	+	N	+	+	+	+	+	N	N	+	N	N	+	+	+	+	+	N	N	N	+	+	+	+	N	*50
Adenocarcinoma, NOS																										1
Fibroadenoma	X		X			X							X	X	X	X	X				X		X	X		16
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
Carcinoma, NOS																										3
Adenoma, NOS					X																					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS			X														X									3
Fibroma																										1
Leiomyosarcoma													X													1
Endometrial stromal polyp						X		X	X									X		X		X				12
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										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	N	*50
Ceruminous carcinoma																										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
Liposarcoma																										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
Sarcoma, NOS																										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
Adenocarcinoma, NOS, metastatic																	X									1
Malig. lymphoma, lymphocytic type																										2
Leukemia, mononuclear cell		X							X			X			X			X			X				12

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: 60 mg/kg

ANIMAL NUMBER	043	038	007	030	048	012	029	037	011	004	047	009	001	002	003	005	006	008	010	013	014	015	016	017	018
WEEKS ON STUDY	060	062	079	088	088	095	097	097	099	100	101	102	105	105	105	105	105	105	105	105	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	+	−	+	−	−	+	+	−	+	+	−	+	+	−	−	−	−	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
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																									
Esophagus	+	+	+	+	+	−	+	+	−	+	+	+	+	+	−	−	−	−	+	−	−	+	−	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma	X																								
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS						X	X																		
Adenoma, NOS				X	X							X		X		X	X	X	X				X	X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma										X															
Pheochromocytoma				X										X											
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																						X			
C-cell adenoma					X																				
C-cell carcinoma																									
Parathyroid	+	−	−	+	+	−	+	−	+	+	+	+	−	−	+	+	+	+	−	−	−	−	−	+	−
Pancreatic islets	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	N	+	+	N	+	+	+	+	N	+	N	N	N	+	N	+	N	+	+	+	N
Adenocarcinoma						X						X												X	
Fibroadenoma			X				X		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
Carcinoma, NOS																									
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS					X																				
Endometrial stromal polyp				X				X					X			X				X	X		X		X
Endometrial stromal sarcoma	X																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive						X	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
Adenocarcinoma, NOS, metastatic					X																				
Leukemia, mononuclear cell				X					X		X						X								

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 60 mg/kg (Continued)

ANIMAL NUMBER	0019	0020	0021	0022	0023	0024	0025	0026	0027	0028	0031	0032	0033	0034	0035	0036	0039	0040	0041	0042	0044	0045	0046	0049	0050	TOTAL:
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell carcinoma													X													1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	−	+	+	+	+	−	−	−	−	+	+	+	+	+	+	+	+	+	+	+	−	−	−	−	−	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule				X											X											4
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Acinar cell adenoma			X																							1
Esophagus	+	+	+	+	+	+	+	−	−	+	+	−	+	−	−	+	+	+	+	+	+	−	+	+	+	35
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS																										2
Adenoma, NOS	X		X			X		X	X			X	X	X	X	X		X		X		X		X	X	25
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																			X							2
Pheochromocytoma									X				X									X			X	6
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell adenoma																										1
C-cell adenoma				X													X									3
C-cell carcinoma										X							X									2
Parathyroid	+	−	−	+	+	−	+	+	+	−	+	−	−	−	+	−	+	+	−	−	−	+	−	−	−	24
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																			X							1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	N	N	+	+	+	N	+	+	+	+	+	+	+	N	+	N	N	+	N	*50
Adenocarcinoma																										3
Fibroadenoma	X								X				X	X	X		X	X	X		X			X		17
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
Carcinoma, NOS											X															1
Adenoma, NOS										X																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS					X																					2
Endometrial stromal polyp		X	X			X						X	X		X		X					X			16
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										2
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
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
Adenocarcinoma, NOS, metastatic																										1
Leukemia, mononuclear cell	X		X						X				X				X					X				10

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: 120 mg/kg

ANIMAL NUMBER	0232	0404	0110	0116	0224	0550	0220	0114	0442	0449	0001	0007	0113	0225	0446	0409	0445	0435	0119	0332	0008	0117	0115	0334	0448
WEEKS ON STUDY	0337	0337	0338	0338	0400	0411	0422	0455	0466	0466	0477	0477	0511	0511	0511	0538	0553	0555	0557	0557	0600	0600	0601	0601	0601
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																									
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	+	+	+	+	+	+	+	+	−	−	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Transitional cell papilloma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	−	+	+	+	+	+
C-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
Fibroadenoma																									
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																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp	X																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granular cell tumor, NOS																									
Glioma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Muscle	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
Angiolipoma																									
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																				X					
Leukemia, mononuclear cell																		X							

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 120 mg/kg (Continued)

ANIMAL NUMBER	041	018	044	031	021	005	111	006	033	002	037	022	038	039	003	004	012	026	027	028	029	030	035	036	047	TOTAL TISSUES TUMORS
WEEKS ON STUDY	068	074	078	080	081	082	082	090	092	097	100	101	104	104	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																	X									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	−	+	−	−	−	+	+	+	+	+	+	−	−	−	−	+	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																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
Esophagus	+	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	−	−	−	+	−	+	+	+	+	38
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																X										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Transitional cell papilloma										X																1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																			X							1
Adenoma, NOS		X				X		X	X		X	X				X	X				X	X		X		11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																				X						1
Pheochromocytoma											X															1
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
C-cell adenoma									X		X															2
Parathyroid	−	−	−	+	−	−	−	+	+	+	+	+	+	+	−	+	+	−	−	−	−	+	−	−	−	16
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	+	+	+	N	N	N	+	+	+	N	+	+	+	N	+	N	N	+	N	N	+	N	*50
Fibroadenoma				X		X					X	X				X		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
Carcinoma, NOS															X											1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp				X					X	X							X			X				X	X	8
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granular cell tumor, NOS																							X			1
Glioma, NOS							X																			1
MUSCULOSKELETAL SYSTEM																										
Muscle	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
Angiolipoma													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																										1
Leukemia, mononuclear cell				X									X	X							X					5

* Animals necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	CONTROL (VEH)	500 mg/kg	1,000 mg/kg
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	2 (4%)	1 (2%)	3 (6%)
Fibroma	1 (2%)	4 (8%)	1 (2%)
Fibrosarcoma	14 (28%)	12 (24%)	7 (14%)
Neurofibrosarcoma	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Hepatocellular carcinoma, metastatic	2 (4%)	2 (4%)	2 (4%)
Alveolar/bronchiolar adenoma	3 (6%)	8 (16%)	4 (8%)
Alveolar/bronchiolar carcinoma	3 (6%)	2 (4%)	
Sarcoma, NOS, metastatic	1 (2%)		
Fibrosarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	7 (14%)	6 (12%)	
Malignant lymphoma, histiocytic type		1 (2%)	
#Spleen	(50)	(48)	(49)
Malignant lymphoma, NOS	1 (2%)		
#Mesenteric lymph node	(44)	(47)	(44)
Malignant lymphoma, histiocytic type		2 (4%)	
#Liver	(50)	(50)	(50)
Malignant lymphoma, NOS	1 (2%)		
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma		1 (2%)	1 (2%)
*Thorax	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
#Bone marrow	(50)	(50)	(49)
Hemangiosarcoma		1 (2%)	
#Spleen	(50)	(48)	(49)
Hemangiosarcoma		2 (4%)	1 (2%)
#Liver	(50)	(50)	(50)
Hemangiosarcoma			2 (4%)
#Omentum	(50)	(49)	(49)
Hemangiosarcoma	1 (2%)		
#Kidney/pelvis	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(50)
Hepatocellular adenoma	4 (8%)	4 (8%)	5 (10%)
Hepatocellular carcinoma	9 (18%)	10 (20%)	10 (20%)
#Forestomach	(50)	(49)	(49)
Squamous cell papilloma			2 (4%)
Squamous cell carcinoma		1 (2%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	500 mg/kg	1,000 mg/kg
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma		1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
#Adrenal medulla	(50)	(47)	(49)
Pheochromocytoma	1 (2%)		
#Thyroid	(48)	(45)	(47)
Follicular cell adenoma		1 (2%)	
#Pancreatic islets	(49)	(49)	(50)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
None			
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Adenoma, NOS	5 (10%)	3 (6%)	
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Fibrosarcoma		1 (2%)	
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	11	33
Moribund sacrifice	9	12	7
Terminal sacrifice	32	27	10

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	500 mg/kg	1,000 mg/kg
TUMOR SUMMARY			
Total animals with primary tumors**	32	38	29
Total primary tumors	53	62	39
Total animals with benign tumors	14	19	11
Total benign tumors	14	22	13
Total animals with malignant tumors	29	31	23
Total malignant tumors	39	40	26
Total animals with secondary tumors##	3	3	2
Total secondary tumors	3	3	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 B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	CONTROL (VEH)	250 mg/kg
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50
INTEGUMENTARY SYSTEM		
*Skin	(50)	(50)
Squamous cell papilloma		1 (2%)
Keratoacanthoma	1 (2%)	
*Subcutaneous tissue	(50)	(50)
Fibroma	3 (6%)	2 (4%)
Fibrosarcoma	8 (16%)	5 (10%)
RESPIRATORY SYSTEM		
#Lung	(50)	(50)
Hepatocellular carcinoma, metastatic	3 (6%)	5 (10%)
Alveolar/bronchiolar adenoma	12 (24%)	6 (12%)
Alveolar/bronchiolar carcinoma	2 (4%)	5 (10%)
HEMATOPOIETIC SYSTEM		
*Multiple organs	(50)	(50)
Malignant lymphoma, NOS	5 (10%)	5 (10%)
Malig. lymphoma, histiocytic type	1 (2%)	
#Mesenteric lymph node	(47)	(44)
Malig. lymphoma, histiocytic type	1 (2%)	
CIRCULATORY SYSTEM		
*Subcut tissue	(50)	(50)
Hemangioma		1 (2%)
#Spleen	(50)	(50)
Hemangiosarcoma		1 (2%)
#Heart	(50)	(50)
Hemangiosarcoma	1 (2%)	
#Liver	(50)	(50)
Hemangiosarcoma	3 (6%)	2 (4%)
#Kidney	(50)	(50)
Hemangiosarcoma	1 (2%)	
DIGESTIVE SYSTEM		
#Liver	(50)	(50)
Hepatocellular adenoma	5 (10%)	10 (20%)
Hepatocellular carcinoma	10 (20%)	11 (22%)
Fibrosarcoma, metastatic	1 (2%)	
#Forestomach	(50)	(50)
Squamous cell papilloma		2 (4%)
Squamous cell carcinoma, in situ	1 (2%)	
Squamous cell carcinoma		1 (2%)
URINARY SYSTEM		
#Kidney	(50)	(50)
Tubular cell adenoma	1 (2%)	
ENDOCRINE SYSTEM		
#Pituitary intermedia	(40)	(45)
Adenoma, NOS	1 (3%)	
#Anterior pituitary	(40)	(45)
Adenoma, NOS	2 (5%)	

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	250 mg/kg
ENDOCRINE SYSTEM (Continued)		
#Pituitary posterior	(40)	(45)
Glioma, NOS		1 (2%)
#Adrenal medulla	(49)	(49)
Pheochromocytoma	2 (4%)	
#Thyroid	(46)	(47)
Follicular cell adenoma	1 (2%)	
REPRODUCTIVE SYSTEM		
#Testis	(50)	(50)
Interstitial cell tumor	1 (2%)	1 (2%)
NERVOUS SYSTEM		
None		
SPECIAL SENSE ORGANS		
*Harderian gland	(50)	(50)
Adenoma, NOS		1 (2%)
Adenocarcinoma, NOS		1 (2%)
MUSCULOSKELETAL SYSTEM		
None		
BODY CAVITIES		
None		
ALL OTHER SYSTEMS		
*Multiple organs	(50)	(50)
Hepatocellular carcinoma, metastatic		1 (2%)
ANIMAL DISPOSITION SUMMARY		
Animals initially in study	50	50
Natural death	9	9
Moribund sacrifice	6	6
Terminal sacrifice	35	35
TUMOR SUMMARY		
Total animals with primary tumors**	41	39
Total primary tumors	62	56
Total animals with benign tumors	24	19
Total benign tumors	29	24
Total animals with malignant tumors	27	26
Total malignant tumors	33	32
Total animals with secondary tumors##	4	6
Total secondary tumors	4	6

* 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. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	CONTROL (VEH)	500 mg/kg
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50
INTEGUMENTARY SYSTEM		
*Subcutaneous tissue	(50)	(50)
Fibrosarcoma		1 (2%)
RESPIRATORY SYSTEM		
#Lung	(50)	(50)
Alveolar/bronchiolar adenoma	3 (6%)	6 (12%)
Alveolar/bronchiolar carcinoma		4 (8%)
HEMATOPOIETIC SYSTEM		
*Multiple organs	(50)	(50)
Malignant lymphoma, NOS	16 (32%)	13 (26%)
Malignant lymphoma, histiocytic type	1 (2%)	
#Spleen	(50)	(50)
Malignant lymphoma, NOS		2 (4%)
#Jejunum	(49)	(50)
Malignant lymphoma, NOS	1 (2%)	
#Thymus	(21)	(19)
Malignant lymphoma, NOS	1 (5%)	
CIRCULATORY SYSTEM		
#Liver	(50)	(50)
Hemangiosarcoma		1 (2%)
#Uterine serosa	(50)	(49)
Hemangioma	1 (2%)	
DIGESTIVE SYSTEM		
#Liver	(50)	(50)
Hepatocellular adenoma	1 (2%)	4 (8%)
Hepatocellular carcinoma	2 (4%)	4 (8%)
#Forestomach	(50)	(50)
Squamous cell papilloma		1 (2%)
URINARY SYSTEM		
None		
ENDOCRINE SYSTEM		
#Pituitary	(43)	(46)
Carcinoma, NOS	2 (5%)	1 (2%)
Adenoma, NOS	12 (28%)	8 (17%)
#Adrenal	(49)	(50)
Pheochromocytoma	1 (2%)	
#Thyroid	(48)	(48)
Follicular cell carcinoma		1 (2%)

TABLE B3. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	500 mg/kg
REPRODUCTIVE SYSTEM		
#Uterus	(50)	(49)
Leiomyoma	1 (2%)	
Endometrial stromal polyp	1 (2%)	
#Ovary	(48)	(48)
Granulosa cell tumor	1 (2%)	
NERVOUS SYSTEM		
None		
SPECIAL SENSE ORGANS		
*Harderian gland	(50)	(50)
Adenoma, NOS		3 (6%)
*External ear	(50)	(50)
Sarcoma, NOS		1 (2%)
MUSCULOSKELETAL SYSTEM		
None		
BODY CAVITIES		
None		
ALL OTHER SYSTEMS		
*Multiple organs	(50)	(50)
Sarcoma, NOS	1 (2%)	
ANIMAL DISPOSITION SUMMARY		
Animals initially in study	50	50
Natural death	16	13
Moribund sacrifice	6	5
Terminal sacrifice	28	30
Dosing accident		2
TUMOR SUMMARY		
Total animals with primary tumors**	31	29
Total primary tumors	45	50
Total animals with benign tumors	14	15
Total benign tumors	20	22
Total animals with malignant tumors	22	23
Total malignant tumors	24	28
Total animals with tumors uncertain--benign or malignant	1	
Total uncertain tumors	1	

* Number of animals necropsied
** Primary tumors: all tumors except secondary tumors
# Number of animals with tissue examined microscopically

TABLE B4. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	CONTROL (VEH)	250 mg/kg
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50
INTEGUMENTARY SYSTEM		
*Skin	(50)	(50)
Squamous cell carcinoma		1 (2%)
*Subcutaneous tissue	(50)	(50)
Sarcoma, NOS		1 (2%)
RESPIRATORY SYSTEM		
#Lung	(50)	(50)
Hepatocellular carcinoma, metastatic		3 (6%)
Alveolar/bronchiolar adenoma	5 (10%)	6 (12%)
Alveolar/bronchiolar carcinoma	1 (2%)	3 (6%)
HEMATOPOIETIC SYSTEM		
*Multiple organs	(50)	(50)
Malignant lymphoma, NOS	13 (26%)	11 (22%)
Malig. lymphoma, histiocytic type	1 (2%)	2 (4%)
#Spleen	(49)	(49)
Malignant lymphoma, NOS	1 (2%)	
#Liver	(50)	(50)
Malignant lymphoma, NOS		1 (2%)
#Uterus	(50)	(50)
Malig. lymphoma, histiocytic type		1 (2%)
CIRCULATORY SYSTEM		
#Spleen	(49)	(49)
Hemangiosarcoma		2 (4%)
#Liver	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)
DIGESTIVE SYSTEM		
#Liver	(50)	(50)
Hepatocellular adenoma	8 (16%)	4 (8%)
Hepatocellular carcinoma	1 (2%)	5 (10%)
#Forestomach	(48)	(49)
Squamous cell papilloma	3 (6%)	3 (6%)
URINARY SYSTEM		
None		
ENDOCRINE SYSTEM		
#Anterior pituitary	(39)	(41)
Carcinoma, NOS	1 (3%)	1 (2%)
Adenoma, NOS	7 (18%)	7 (17%)
#Thyroid	(44)	(46)
Follicular cell adenoma	1 (2%)	
#Pancreatic islets	(45)	(49)
Islet cell carcinoma	1 (2%)	

TABLE B4. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	250 mg/kg
REPRODUCTIVE SYSTEM		
#Uterus	(50)	(50)
Leiomyosarcoma		2 (4%)
#Ovary	(48)	(50)
Adenocarcinoma, NOS		1 (2%)
Papillary cystadenoma, NOS		2 (4%)
Luteoma		1 (2%)
Tubular adenoma	1 (2%)	
NERVOUS SYSTEM		
None		
SPECIAL SENSE ORGANS		
*Harderian gland	(50)	(50)
Adenoma, NOS		1 (2%)
MUSCULOSKELETAL SYSTEM		
None		
BODY CAVITIES		
None		
ALL OTHER SYSTEMS		
*Multiple organs	(50)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)
Tail		
Osteoma		1
ANIMAL DISPOSITION SUMMARY		
Animals initially in study	50	50
Natural death	23	13
Moribund sacrifice	2	1
Terminal sacrifice	25	36

TABLE B4. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	250 mg/kg
TUMOR SUMMARY		
Total animals with primary tumors**	35	35
Total primary tumors	45	57
Total animals with benign tumors	19	21
Total benign tumors	25	25
Total animals with malignant tumors	20	25
Total malignant tumors	20	32
Total animals with secondary tumors##		3
Total secondary tumors		4

* 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 B5. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: VEHICLE CONTROL

ANIMAL NUMBER	0022	0034	0027	0048	0009	0005	0026	0043	0045	0033	0041	0012	0008	0023	0047	0001	0028	0002	0003	0004	0006	0007	0010	0011	0013
WEEKS ON STUDY	005	012	024	041	054	061	066	072	076	083	084	085	088	091	097	101	102	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																X									
Fibroma																									
Fibrosarcoma							X	X	X				X	X		X					X				
Neurofibrosarcoma											X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																	X								
Alveolar/bronchiolar adenoma																		X		X				X	
Alveolar/bronchiolar carcinoma															X	X									
Sarcoma, NOS, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																						X			
Lymph nodes	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	+	−	+	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																						X			X
Hepatocellular carcinoma										X	X			X			X	X							X
Malignant lymphoma, NOS																					X				
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	+	+	+	N	+	+
Pancreas	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	−	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																	X								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	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																									
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
Malignant lymphoma, NOS													X											X	

TABLE B5. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 4	0 2 5	0 2 9	0 3 0	0 3 1	0 3 2	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 0	0 4 2	0 4 4	0 4 6	0 4 9	0 5 0	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Sarcoma, NOS	X																									2
Fibroma															X											1
Fibrosarcoma		X							X	X					X				X		X				X	14
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																					X					2
Alveolar/bronchiolar adenoma																										3
Alveolar/bronchiolar carcinoma											X															3
Sarcoma, NOS, metastatic	X																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, NOS																										1
Lymph nodes	−	+	+	−	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	44
Thymus	−	+	−	−	−	+	−	+	−	−	+	−	−	+	+	+	−	−	−	+	−	+	−	−	+	19
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma													X				X									4
Hepatocellular carcinoma																					X	X		X		9
Malignant lymphoma, NOS																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	−	+	−	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	−	−	+	+	+	+	+	38
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma																										1
Thyroid	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	+	−	+	−	+	+	+	−	−	−	−	+	−	−	−	−	−	+	−	+	+	−	−	−	+	29
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	+	+	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	47
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			X						X		X							X					X			5
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
Malignant lymphoma, NOS			X								X		X										X		X	7

* Animals necropsied

TABLE B5. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: 500 mg/kg

ANIMAL NUMBER	011	016	028	001	038	033	024	050	034	012	017	045	015	022	002	042	005	030	018	021	037	014	047	003	004
WEEKS ON STUDY	022	030	059	078	081	083	084	084	086	089	089	089	091	092	094	094	096	096	098	098	098	099	102	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma													X						X						
Fibrosarcoma				X				X		X	X		X		X	X				X	X	X			
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																							X		X
Alveolar/bronchiolar adenoma								X			X			X	X							X			X
Alveolar/bronchiolar carcinoma																									
Fibrosarcoma, metastatic																				X					
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																							X		
Spleen	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma													X										X		
Lymph nodes	+	+	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig lymphoma, histiocytic type																									
Thymus	+	−	−	−	−	−	−	+	−	−	−	−	−	+	−	−	+	−	−	−	−	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma					X		X							X									X	X	X
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	+	N	N	+	+	+	N	N	N	+	+	+	+	N	+	+	N	+	+	N	+	+
Pancreas	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																	X								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	−	+	+	+
Follicular cell adenoma																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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								
MUSCULOSKELETAL SYSTEM																									
Muscle	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
Fibrosarcoma																								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
Hemangiosarcoma																	X								
Malignant lymphoma, NOS									X			X									X			X	
Malig. lymphoma, histiocytic type																									

TABLE B5. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 500 mg/kg (Continued)

ANIMAL NUMBER	006	007	008	009	010	013	019	020	023	025	026	027	029	031	032	035	036	039	040	041	043	044	046	048	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS											X															1
Fibroma				X					X																	4
Fibrosarcoma						X												X								12
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										2
Alveolar/bronchiolar adenoma		X																X								8
Alveolar/bronchiolar carcinoma	X																					X				2
Fibrosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangiosarcoma																										2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malig. lymphoma, histiocytic type								X										X								2
Thymus	+	+	+	+	+	−	−	−	−	+	+	−	−	−	−	−	−	+	−	−	−	−	−	−	+	13
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma									X							X										4
Hepatocellular carcinoma														X						X	X		X			10
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	N	N	N	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	−	+	−	+	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	45
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	47
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	45
Follicular cell adenoma															X											1
Parathyroid	−	+	−	+	+	+	−	+	+	+	−	−	−	−	+	−	−	−	+	−	+	−	−	+	+	22
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma																										1
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	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	−	39
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								X															X			3
MUSCULOSKELETAL SYSTEM																										
Muscle	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
Fibrosarcoma																										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
Hemangiosarcoma																										1
Malignant lymphoma, NOS			X							X																6
Malig. lymphoma, histiocytic type				X																						1

* Animals necropsied

TABLE B5. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: 1,000 mg/kg

ANIMAL NUMBER	027	006	023	017	028	044	003	021	046	029	038	015	019	025	037	030	048	049	022	004	032	043	001	002	041
WEEKS ON STUDY	003	020	022	023	023	038	051	055	066	068	068	076	076	077	078	079	084	084	086	087	087	087	089	089	090
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS											X				X									X	
Fibroma																									
Fibrosarcoma								X												X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																									
Alveolar/bronchiolar adenoma								X				X													
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																X									
Lymph nodes	+	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+
Thymus	−	+	−	+	−	+	+	+	+	+	−	+	−	+	−	−	−	−	−	−	+	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X	X								X				
Hepatocellular carcinoma																									
Hemangiosarcoma																X									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	+	+	+	N	+	+	N	+	N	+	+	+	+	+	N	N	+	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																X									
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma										X															
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	−	−	−	−	−	+	+	−	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+
Adrenal	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Hemangiosarcoma																									
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
Hemangiosarcoma																									

TABLE B5. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 1,000 mg/kg (Continued)

ANIMAL NUMBER	0 2 6	0 0 8	0 1 1	0 4 7	0 1 4	0 4 2	0 2 4	0 3 6	0 0 7	0 1 2	0 1 3	0 3 5	0 3 9	0 2 0	0 4 5	0 0 5	0 0 9	0 1 0	0 1 6	0 1 8	0 3 1	0 3 3	0 3 4	0 4 0	0 5 0	TOTAL:
WEEKS ON STUDY	0 9 1	0 9 2	0 9 2	0 9 2	0 9 4	0 9 5	0 9 6	0 9 7	0 9 8	0 9 8	0 9 8	0 9 9	1 0 0	1 0 2	1 0 2	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																									3
Fibroma																							X		1
Fibrosarcoma	X	X									X									X		X			7
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic					X				X																2
Alveolar/bronchiolar adenoma						X															X				4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																									1
Lymph nodes	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	44
Thymus	−	−	+	−	−	−	−	+	−	−	−	−	+	−	−	−	−	−	−	−	−	+	−	−	14
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma										X													X		5
Hepatocellular carcinoma		X			X			X	X						X	X	X	X	X		X				10
Hemangiosarcoma														X											2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	+	+	N	+	+	+	N	+	N	+	N	N	N	N	+	+	+	N	+	N	N	+	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	−	+	+	+	−	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	43
Stomach	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma	X													X											2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	−	−	+	+	+	+	+	+	−	43
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																									1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	39
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	47
Parathyroid	+	+	−	+	−	+	+	+	−	+	−	+	−	+	−	−	−	+	−	+	−	−	+	−	21
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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	−	+	−	+	−	+	+	+	+	+	−	+	+	+	+	+	−	−	+	+	44
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	*50
Hemangiosarcoma														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	*50
Hemangiosarcoma												X													1

* Animals necropsied

TABLE B6. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: VEHICLE CONTROL

ANIMAL NUMBER	0028	0040	0036	0002	0003	0032	0026	0022	0004	0005	0021	0030	0042	0110	0111	0001	0006	0007	0008	0009	0012	0013	0014	0015	0016
WEEKS ON STUDY	0811	0811	0822	0844	0887	0887	0888	0933	0998	1000	1011	1022	1033	1044	1044	1055	1055	1055	1055	1055	1055	1055	1055	1055	1055
INTEGUMENTARY SYSTEM																									
Skin	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma													X												
Fibrosarcoma	X				X	X		X		X		X						X		X					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic			X				X																		X
Alveolar/bronchiolar adenoma								X			X		X	X		X									X
Alveolar/bronchiolar carcinoma																									
Trachea	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	−	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig. lymphoma, histiocytic type																									X
Thymus	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	+	+	−	+	+	+	−	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma				X																					
Hepatocellular carcinoma		X	X				X				X				X		X								X
Fibrosarcoma, metastatic					X																				
Hemangiosarcoma																				X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Pancreas	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, in situ																									
Small intestine	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Hemangiosarcoma																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	−	+	+	+	+	−	−	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																				X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	−	+	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma				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	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																					X				
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Malignant lymphoma, NOS									X									X		X					
Malignant lymphoma, histiocytic 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 B6. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0017	0018	0019	0020	0023	0024	0025	0027	0029	0031	0033	0034	0035	0037	0038	0039	0041	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma	X																									1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma						X																				3
Fibrosarcoma														X												8
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										3
Alveolar/bronchiolar adenoma														X	X		X	X					X	X		12
Alveolar/bronchiolar carcinoma										X									X							2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malignant lymphoma, histiocytic type																										1
Thymus	+	+	+	+	–	+	–	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	29
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																								X		1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma			X					X														X			X	5
Hepatocellular carcinoma					X			X					X													10
Fibrosarcoma, metastatic																										1
Hemangiosarcoma									X																X	3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	+	N	N	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, in situ														X												1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma										X																1
Hemangiosarcoma																								X		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	+	+	+	+	+	–	+	+	+	–	+	+	–	+	+	+	+	+	+	+	–	+	40
Adenoma, NOS								X		X																3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma		X																	X							2
Thyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell adenoma																										1
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
Interstitial cell tumor																										1
Prostate	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Malignant lymphoma, NOS												X												X		5
Malig. lymphoma, histiocytic type																										1

* Animals necropsied

TABLE B6. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: 250 mg/kg

ANIMAL NUMBER	012	014	050	211	016	004	005	008	007	032	013	010	026	031	038	001	002	003	006	009	011	015	017	018	019
WEEKS ON STUDY	075	079	079	084	091	093	095	096	097	098	099	100	102	102	102	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									X
Fibrosarcoma							X		X	X	X														
Hemangioma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic													X	X											
Alveolar/bronchiolar adenoma						X																			X
Alveolar/bronchiolar carcinoma				X								X				X									
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
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											
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	N	N	+	+	+	+	+	N	+	N	N	+	+	+	N	N	+	+	+	+	+	+
Pancreas	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																					X				
Squamous cell carcinoma																								X	
Small intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+	+
Glioma, NOS																									X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
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				
Adenocarcinoma, 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
Hepatocellular carcinoma, metastatic					X																				
Malignant lymphoma, NOS															X	X	X								

TABLE B6. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 250 mg/kg (Continued)

ANIMAL NUMBER	020	022	023	024	025	027	028	029	030	033	034	035	036	037	039	040	041	042	043	044	045	046	047	048	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma			X																							2
Fibrosarcoma				X																						5
Hemangioma																				X						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic	X								X												X					5
Alveolar/bronchiolar adenoma	X											X				X				X						6
Alveolar/bronchiolar carcinoma																							X		X	5
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																		X								1
Lymph nodes	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	44
Thymus	−	+	+	+	+	−	−	−	−	−	+	−	+	+	−	+	+	−	−	+	−	−	+	+	−	19
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma				X			X	X																	X	10
Hepatocellular carcinoma	X									X								X	X		X	X				11
Hemangiosarcoma														X				X								2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	N	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma								X																		2
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	45
Glioma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	47
Parathyroid	−	+	+	−	−	−	+	+	+	−	−	+	−	+	+	−	+	−	−	+	+	+	−	−		25
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
Interstitial cell tumor					X																					1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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																										1
Adenocarcinoma, 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
Hepatocellular carcinoma, metastatic																										1
Malignant lymphoma, NOS															X										X	5

* Animals necropsied

TABLE B7. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: VEHICLE CONTROL

ANIMAL NUMBER	0015	0040	0044	0041	0043	0048	0045	0033	0022	0004	0016	0024	0008	0017	0018	0009	0023	0032	0012	0025	0039	0001	0002	0003	0005
WEEKS ON STUDY	0466	0711	0711	0777	0884	0886	0888	0889	0891	0892	0893	0897	0898	0899	1000	1001	1002	1002	1003	1004	1004	1005	1005	1005	1005
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X		X										
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Thymus	−	+	−	+	−	−	−	−	+	+	−	+	+	−	−	+	−	−	−	+	−	+	−	+	+
Malignant lymphoma, NOS																									
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																				X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	N	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	−	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	−	−	+	+
Carcinoma, NOS																									
Adenoma, NOS															X			X	X	X					
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
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
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																									
Endometrial stromal polyp																									
Hemangioma	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
Sarcoma, NOS									X																
Malignant lymphoma, NOS				X		X		X			X			X		X	X	X					X		
Malig. lymphoma, histiocytic type																									

\+ 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 B7. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	007	008	010	011	013	014	019	020	021	026	027	028	029	030	031	032	034	035	036	037	042	046	047	049	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma														X												3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	45
Thymus	−	−	−	−	−	+	+	+	−	−	−	−	−	−	−	+	+	+	−	+	−	−	+	−	+	21
Malignant lymphoma, NOS								X																		1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma											X															1
Hepatocellular carcinoma										X																2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+	+	+	+	N	N	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS							X																			1
Large intestine	−	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	48
Carcinoma, NOS															X		X									2
Adenoma, NOS				X			X	X			X			X		X					X				X	12
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma														X												1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	+	+	+	−	+	−	+	+	+	+	+	−	−	−	+	+	+	+	−	−	+	+	+	−	+	30
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	+	+	+	+	N	+	N	N	N	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma				X																						1
Endometrial stromal polyp																					X					1
Hemangioma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Granulosa cell tumor														X												1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Sarcoma, NOS																										1
Malignant lymphoma, NOS						X			X				X		X	X			X					X		16
Malig lymphoma, histiocytic type																	X									1

* Animals necropsied

TABLE B7. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: 500 mg/kg

ANIMAL NUMBER	016	023	008	039	024	028	033	001	044	003	047	032	009	017	042	030	031	027	048	013	002	004	005	008	007
WEEKS ON STUDY	000	000	047	058	073	073	076	077	078	080	082	083	084	084	084	089	089	091	101	104	105	105	105	105	105
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma							X																		
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	+	+	−	+	+	−	−	+	−	−	−	+	−	−	−	−	−	−	+	−	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								X	
Hepatocellular carcinoma																				X					
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	+	+	+	+	N	+	N	+	+	+	+	N	+	+	+	N	+	+	N	N	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	−
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	−	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																X								X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
Parathyroid	−	−	+	−	+	−	+	+	+	+	+	+	−	+	−	+	−	−	+	−	+	+	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	+	N	N	N	+	N	N	+	+	N	N	N	+	N	N	N	N	+	N	N	N	N
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
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
Ear	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																									
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
Malignant lymphoma, NOS											X							X	X						X

TABLE B7. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 500 mg/kg (Continued)

ANIMAL NUMBER	0110	0111	0112	0114	0115	0118	0119	0220	0221	0222	0225	0226	0229	0234	0235	0236	0237	0238	0240	0241	0243	0245	0246	0249	0250	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X										X	X							X			X	6
Alveolar/bronchiolar carcinoma					X						X	X		X												4
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, NOS					X																X					2
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	49
Thymus	−	+	−	−	−	+	+	−	+	+	+	−	−	+	+	+	−	+	+	−	−	−	−	+	−	19
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma								X													X	X				4
Hepatocellular carcinoma	X											X				X										4
Hemangiosarcoma										X																1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																	X									1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Carcinoma, NOS												X														1
Adenoma, NOS					X		X	X							X				X			X				8
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell carcinoma							X																			1
Parathyroid	−	+	−	+	−	−	+	−	+	−	−	+	−	+	+	−	+	+	+	+	+	+	+	−	+	29
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	+	+	N	+	+	+	+	N	N	N	N	N	+	N	+	+	+	+	N	N	N	+	N	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	48
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			X																			3
Ear	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																							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
Malignant lymphoma, NOS						X		X	X			X		X	X				X					X	X	13

* Animals necropsied

TABLE B8. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: VEHICLE CONTROL

ANIMAL NUMBER	0048	0019	0114	0117	0003	0189	0339	0009	0455	0111	0448	0226	0355	0255	0110	0550	0002	0115	0443	0363	0367	0272	0422	0005	0440
WEEKS ON STUDY	0133	0664	0866	0722	0755	0800	0822	0877	0877	0888	0888	0899	0899	0900	0911	0911	0922	0922	0922	0927	0997	0999	1001	1002	1044
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma		X						X																	
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																									
Lymph nodes	+	+	+	−	+	−	−	−	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
Thymus	−	−	−	−	−	−	−	−	−	+	−	+	+	−	−	−	+	−	−	−	+	+	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	−	+	+	+	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X								X			X	X	
Hepatocellular carcinoma										X															
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	N	N	+	+	+	+	N	N	N	+	+	+	+	N	+	+	+	+	N	N	N	+
Pancreas	+	−	+	−	+	+	+	+	+	−	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+
Esophagus	+	+	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+
Stomach	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	−	+	+	−	−	+	+	+	−	−	−	+	+	+	+	−	+	+	+
Carcinoma, NOS																									
Adenoma, NOS																							X		X
Adrenal	+	+	+	+	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+
Follicular cell adenoma																									
Parathyroid	−	+	+	−	+	+	−	−	+	−	−	−	+	+	−	−	+	+	+	+	−	+	−	−	−
Pancreatic islets	+	−	+	−	+	+	+	+	+	−	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+
Islet cell carcinoma														X											
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	N	N	N	N	N	N	+	+	N	N	N	N	N	N	+	+	N	N	N	N	+
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular adenoma																									
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
Malignant lymphoma, NOS					X				X		X					X		X	X						X
Malig. lymphoma, histiocytic 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 B8. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0001	0004	0006	0007	0008	0012	0013	0016	0020	0021	0022	0023	0024	0028	0029	0030	0031	0032	0033	0034	0038	0041	0046	0047	0049	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma							X							X						X						5
Alveolar/bronchiolar carcinoma																X										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS																					X					1
Lymph nodes	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	−	+	−	+	+	+	+	−	39
Thymus	+	+	−	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+	−	+	+	−	+	+	−	25
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma							X		X								X							X		8
Hepatocellular carcinoma																										1
Hemangiosarcoma																			X							1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell papilloma							X											X			X					3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	−	+	+	−	39
Carcinoma, NOS								X																		1
Adenoma, NOS							X			X					X	X				X						7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	44
Follicular cell adenoma					X																					1
Parathyroid	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	33
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Islet cell carcinoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	+	N	+	+	N	N	N	+	N	N	+	N	N	N	+	+	N	N	N	N	N	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tubular adenoma																	X									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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
Malignant lymphoma, NOS		X				X					X	X	X	X												13
Malig. lymphoma, histiocytic type																										1

* Animals necropsied

TABLE B8. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE: 250 mg/kg

ANIMAL NUMBER	0372	0299	0099	0033	0126	0266	0288	0308	0089	0211	0550	0388	0233	0092	0101	0404	0055	0086	0077	0110	0111	0113	0145	0156	0168
WEEKS ON STUDY	074	076	081	083	086	086	088	089	091	091	093	097	100	102	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																			X						
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic											X					X						X			
Alveolar/bronchiolar adenoma			X			X									X										X
Alveolar/bronchiolar carcinoma			X																			X			
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma				X									X												
Lymph nodes	−	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Thymus	−	−	−	+	−	−	−	−	−	+	−	+	−	−	+	+	+	−	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma							X										X		X						
Hepatocellular carcinoma											X					X			X			X			
Hemangiosarcoma													X												
Malignant lymphoma, NOS																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	N	+	+	+	+	+	N	+	N	+	+	N	+	N	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	−	+	+	+	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																						X		X	
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	−	+	−	+	+	+	+	−	−	−	+	+	+	−	+	+	−	+	+	+	+
Carcinoma, NOS																									X
Adenoma, NOS															X	X						X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+
Parathyroid	+	−	+	+	−	+	−	−	+	−	−	+	−	−	−	−	−	−	+	−	+	+	+	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	+	N	+	N	N	N	N	N	+	+	+	N	N	+	N	N	+	+	N	N	N
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																	X								
Malig. lymphoma, histiocytic type																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS											X														
Papillary cystadenoma, NOS																									
Luteoma																									
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		
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
Adenocarcinoma, NOS, metastatic											X														
Malignant lymphoma, NOS									X			X		X						X					
Malig. lymphoma, histiocytic type																					X				
Tail																									
Osteoma																X									

TABLE B8. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 250 mg/kg (Continued)

ANIMAL NUMBER	017	018	019	020	022	024	025	027	031	032	033	034	035	036	039	040	041	042	043	046	044	045	047	048	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	105	105	105	105	105	
INTEGUMENTARY SYSTEM																										
Skin	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																				X						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										3
Alveolar/bronchiolar adenoma						X										X										6
Alveolar/bronchiolar carcinoma												X														3
Trachea	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Hemangiosarcoma																										2
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	−	+	+	+	+	+	34
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																	X									4
Hepatocellular carcinoma																	X									5
Hemangiosarcoma																										1
Malignant lymphoma, NOS													X													1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	N	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma					X																					3
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	−	+	+	41
Carcinoma, NOS																										1
Adenoma, NOS					X		X				X										X					7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid	+	+	+	+	−	+	−	−	−	−	+	+	−	+	+	+	−	+	−	−	+	−	−	+	+	25
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	+	+	N	N	N	N	+	+	+	N	N	N	N	N	+	N	N	+	N	N	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma														X												2
Malig. lymphoma, histiocytic type																				X						1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS																										1
Papillary cystadenoma, NOS		X						X																		2
Luteoma													X													1
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																										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
Adenocarcinoma, NOS, metastatic																										1
Malignant lymphoma, NOS			X			X	X							X	X	X	X									11
Malig. lymphoma, histiocytic type								X																		2
Tail																										
Osteoma																										1

* Animals necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	CONTROL (VEH)	60 mg/kg	120 mg/kg
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%)	1 (2%)	
Polyp	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhage			1 (2%)
Abscess, NOS		1 (2%)	
RESPIRATORY SYSTEM			
#Lung/bronchiole	(50)	(50)	(50)
Metaplasia, NOS	1 (2%)		2 (4%)
#Lung	(50)	(50)	(50)
Aspiration, NOS	1 (2%)	1 (2%)	
Emphysema, NOS			1 (2%)
Congestion, NOS			2 (4%)
Edema, NOS			2 (4%)
Hemorrhage	1 (2%)		
Bronchopneumonia, NOS			1 (2%)
Granuloma, foreign body	1 (2%)	1 (2%)	1 (2%)
#Lung/alveoli	(50)	(50)	(50)
Hemorrhage		2 (4%)	19 (38%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Lymphoid depletion		1 (2%)	
#Bone marrow	(50)	(50)	(46)
Fibrosis		1 (2%)	
Hypoplasia, NOS	2 (4%)	1 (2%)	
Hyperplasia, NOS	6 (12%)	5 (10%)	4 (9%)
Hyperplasia, hematopoietic		1 (2%)	
#Spleen	(50)	(50)	(50)
Accessory structure	1 (2%)	1 (2%)	
Congestion, NOS			1 (2%)
Fibrosis, focal		2 (4%)	
Necrosis, focal		1 (2%)	
Infarct, NOS	1 (2%)	1 (2%)	
Hemosiderosis	6 (12%)	3 (6%)	16 (32%)
Lymphoid depletion	1 (2%)	1 (2%)	15 (30%)
Hematopoiesis	1 (2%)	5 (10%)	
#Lymph node	(49)	(50)	(49)
Hemosiderosis			1 (2%)
#Mandibular lymph node	(49)	(50)	(49)
Congestion, NOS		1 (2%)	
Plasmacytosis		1 (2%)	
#Mediastinal lymph node	(49)	(50)	(49)
Congestion, NOS	4 (8%)	2 (4%)	1 (2%)
Hemosiderosis	1 (2%)		
#Mesenteric lymph node	(49)	(50)	(49)
Congestion, NOS	1 (2%)		
Lymphoid depletion			1 (2%)
#Thymus	(26)	(28)	(34)
Congestion, NOS			2 (6%)
Atrophy, NOS	2 (8%)		3 (9%)
Lymphoid depletion			1 (3%)
Plasmacytosis	1 (4%)		

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

	CONTROL (VEH)	60 mg/kg	120 mg/kg
CIRCULATORY SYSTEM			
#Lymph node	(49)	(50)	(49)
Lymphangiectasis			1 (2%)
#Mandibular lymph node	(49)	(50)	(49)
Lymphangiectasis		2 (4%)	
#Mesenteric lymph node	(49)	(50)	(49)
Lymphangiectasis	1 (2%)	1 (2%)	
#Heart	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, chronic focal		1 (2%)	
Degeneration, NOS	1 (2%)		
#Auricular appendage	(50)	(50)	(50)
Dilatation, NOS		1 (2%)	
#Right ventricle	(50)	(50)	(50)
Hypertrophy, NOS		1 (2%)	
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	44 (88%)	45 (90%)	41 (82%)
*Mesenteric artery	(50)	(50)	(50)
Hypertrophy, NOS	1 (2%)		
*Pulmonary vein	(50)	(50)	(50)
Calcification, NOS		1 (2%)	
#Liver	(50)	(50)	(50)
Perivasculitis	1 (2%)		
#Urinary bladder	(50)	(50)	(49)
Perivasculitis	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(48)	(50)	(46)
Inflammation, chronic	1 (2%)	2 (4%)	1 (2%)
Metaplasia, squamous		1 (2%)	
#Liver	(50)	(50)	(50)
Hernia, NOS	1 (2%)	1 (2%)	1 (2%)
Congestion, NOS	1 (2%)	1 (2%)	4 (8%)
Inflammation, focal	2 (4%)		
Inflammation, chronic focal			1 (2%)
Cholangiofibrosis	2 (4%)	1 (2%)	4 (8%)
Necrosis, focal	1 (2%)	1 (2%)	5 (10%)
Metamorphosis fatty	21 (42%)	15 (30%)	11 (22%)
Cytoplasmic change, NOS	5 (10%)	6 (12%)	
Basophilic cyto change	11 (22%)	3 (6%)	1 (2%)
Clear cell change	2 (4%)	4 (8%)	5 (10%)
Atypia, NOS			1 (2%)
Angiectasis	2 (4%)	2 (4%)	1 (2%)
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, NOS		1 (2%)	
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	40 (80%)	34 (68%)	28 (56%)
#Pancreas	(50)	(50)	(48)
Hemorrhage		1 (2%)	
Fibrosis			1 (2%)
Fibrosis, focal	1 (2%)		
Necrosis, fat		2 (4%)	
Atrophy, focal	15 (30%)	13 (26%)	1 (2%)
Hyperplasia, focal	1 (2%)		
#Pancreatic acinus	(50)	(50)	(48)
Atrophy, NOS	1 (2%)		
Hyperplasia, NOS			1 (2%)
Hyperplasia, focal	3 (6%)	2 (4%)	

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

	CONTROL (VEH)	60 mg/kg	120 mg/kg
DIGESTIVE SYSTEM (Continued)			
#Stomach	(50)	(49)	(50)
Epidermal inclusion cyst			1 (2%)
Ulcer, NOS		1 (2%)	
Inflammation, focal	1 (2%)		
Inflammation, acute focal		1 (2%)	
Inflammation, chronic focal			1 (2%)
Ulcer, perforated			1 (2%)
#Gastric submucosa	(50)	(49)	(50)
Inflammation, NOS	1 (2%)		
Inflammation, focal		1 (2%)	
Inflammation, acute	1 (2%)	1 (2%)	
Inflammation, acute focal		1 (2%)	
Inflammation, chronic	1 (2%)	1 (2%)	
Granulation, tissue	2 (4%)		1 (2%)
Fibrosis		2 (4%)	
#Forestomach	(50)	(49)	(50)
Ulcer, NOS	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	1 (2%)		
Ulcer, perforated			1 (2%)
Hyperplasia, basal cell	4 (8%)	3 (6%)	4 (8%)
Hyperkeratosis	3 (6%)	1 (2%)	5 (10%)
#Peyer's patch	(50)	(50)	(50)
Hypertrophy, NOS		1 (2%)	
#Colon	(48)	(49)	(45)
Parasitism	6 (13%)	5 (10%)	7 (16%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Congestion, NOS	3 (6%)		2 (4%)
Nephropathy	44 (88%)	45 (90%)	43 (86%)
Nephrosis, NOS	2 (4%)	1 (2%)	3 (6%)
Nephrosis, cholemic		1 (2%)	2 (4%)
Metamorphosis fatty	1 (2%)		
Calcification, focal	4 (8%)	5 (10%)	3 (6%)
#Renal papilla	(50)	(50)	(50)
Necrosis, NOS			1 (2%)
#Kidney/tubule	(50)	(50)	(50)
Regeneration, NOS			1 (2%)
#Kidney/pelvis	(50)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder	(50)	(50)	(49)
Calculus, gross observation only			1 (2%)
Calculus, microscopic examination		2 (4%)	3 (6%)
Inflammation, chronic focal	1 (2%)		
Necrosis, hemorrhagic			1 (2%)
Hyperplasia, epithelial		1 (2%)	2 (4%)
#Urinary bladder/submucosa	(50)	(50)	(49)
Inflammation, chronic focal		2 (4%)	2 (4%)
ENDOCRINE SYSTEM			
#Pituitary	(48)	(49)	(47)
Cyst, NOS	1 (2%)		
#Anterior pituitary	(48)	(49)	(47)
Cyst, NOS	3 (6%)	2 (4%)	2 (4%)
Multiple cysts			1 (2%)
Hemorrhagic cyst	1 (2%)		

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

	CONTROL (VEH)	60 mg/kg	120 mg/kg
ENDOCRINE SYSTEM			
#Anterior pituitary (Continued)	(48)	(49)	(47)
Hyperplasia, focal	5 (10%)	9 (18%)	3 (6%)
Angiectasis			1 (2%)
#Adrenal	(50)	(50)	(50)
Congestion, NOS		1 (2%)	1 (2%)
#Adrenal cortex	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
Degeneration, lipoid	1 (2%)	1 (2%)	2 (4%)
Cytoplasmic vacuolization	5 (10%)	10 (20%)	20 (40%)
Hyperplasia, NOS			2 (4%)
Hyperplasia, focal	1 (2%)		4 (8%)
#Adrenal medulla	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Hyperplasia, NOS	18 (36%)	12 (24%)	8 (16%)
Hyperplasia, focal			1 (2%)
#Thyroid	(49)	(49)	(46)
Congestion, NOS		1 (2%)	
Hyperplasia, C-cell	8 (16%)	7 (14%)	4 (9%)
#Parathyroid	(25)	(24)	(19)
Hyperplasia, NOS			1 (5%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele			1 (2%)
Lactation	7 (14%)	2 (4%)	3 (6%)
*Preputial gland	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
#Prostate	(40)	(42)	(49)
Dilatation, NOS			1 (2%)
Inflammation, NOS	1 (3%)	3 (7%)	
Inflammation, focal	1 (3%)	1 (2%)	
Inflammation, acute	4 (10%)	5 (12%)	3 (6%)
Inflammation, acute focal	1 (3%)		2 (4%)
Inflammation, acute/chronic	1 (3%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (3%)	4 (10%)	1 (2%)
Inflammation, chronic focal	2 (5%)		1 (2%)
Atrophy, NOS	20 (50%)	11 (26%)	18 (37%)
Hyperplasia, focal		5 (12%)	
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS			2 (4%)
Inflammation, acute			1 (2%)
Atrophy, NOS	33 (66%)	28 (56%)	24 (48%)
#Testis	(50)	(49)	(49)
Edema, NOS			1 (2%)
Atrophy, NOS	33 (66%)	16 (33%)	24 (49%)
Atrophy, focal		3 (6%)	
Hypospermatogenesis	2 (4%)	2 (4%)	
Hyperplasia, interstitial cell	1 (2%)	3 (6%)	5 (10%)
NERVOUS SYSTEM			
#Brain/meninges	(49)	(50)	(49)
Inflammation, acute			1 (2%)
#Subdural space	(49)	(50)	(49)
Hematoma, NOS	1 (2%)		
#Subarachnoid space	(49)	(50)	(49)
Hemorrhage	1 (2%)		1 (2%)
#Brain/ependyma	(49)	(50)	(49)
Inflammation, chronic focal	1 (2%)		

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

	CONTROL (VEH)	60 mg/kg	120 mg/kg
NERVOUS SYSTEM (Continued)			
#Brain	(49)	(50)	(49)
Hydrocephalus, NOS	4 (8%)		
Congestion, NOS	1 (2%)		1 (2%)
Hemorrhage	2 (4%)	4 (8%)	18 (37%)
Granulation, tissue		1 (2%)	
Psammoma bodies		1 (2%)	
#Cerebellum	(49)	(50)	(49)
Hemorrhage			2 (4%)
*Spinal cord	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute			1 (2%)
SPECIAL SENSE ORGANS			
*Eye/retina	(50)	(50)	(50)
Degeneration, NOS	2 (4%)		
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	4 (8%)		
*Harderian gland	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Hemorrhage		1 (2%)	
*Peritoneum	(50)	(50)	(50)
Inflammation, NOS	1 (2%)		1 (2%)
*Pericardium	(50)	(50)	(50)
Inflammation, NOS			1 (2%)
Inflammation, chronic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Dilatation/ducts			1 (2%)
Congestion, NOS	2 (4%)	6 (12%)	15 (30%)
Fibrosis			1 (2%)
Calcification, focal			1 (2%)
Omentum			
Necrosis, fat	3	2	2
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 *n*-BUTYL CHLORIDE

	CONTROL (VEH)	60 mg/kg	120 mg/kg
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%)		
*Subcutaneous tissue	(50)	(50)	(50)
Granulation, tissue	1 (2%)		
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Aspiration, NOS			2 (4%)
Congestion, NOS	2 (4%)		
Fibrosis, focal			1 (2%)
Infarct, NOS			1 (2%)
#Lung/alveoli	(50)	(50)	(50)
Hemorrhage			26 (52%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(47)	(50)	(48)
Fibrosis		1 (2%)	
Fibrosis, focal	1 (2%)		
Hyperplasia, NOS	7 (15%)	3 (6%)	3 (6%)
#Spleen	(50)	(50)	(50)
Accessory structure		1 (2%)	
Hemorrhage			1 (2%)
Infarct, NOS	1 (2%)		
Infarct, healed	1 (2%)		
Hemosiderosis	3 (6%)	3 (6%)	27 (54%)
Lymphoid depletion	1 (2%)	1 (2%)	24 (48%)
Hematopoiesis	6 (12%)	5 (10%)	2 (4%)
#Mandibular lymph node	(50)	(48)	(50)
Congestion, NOS	1 (2%)		
Lymphoid depletion			1 (2%)
#Mediastinal lymph node	(50)	(48)	(50)
Congestion, NOS	3 (6%)		
Hemosiderosis		1 (2%)	
#Mesenteric lymph node	(50)	(48)	(50)
Congestion, NOS	1 (2%)	1 (2%)	1 (2%)
Hemorrhage	1 (2%)		
Hypertrophy, NOS	1 (2%)		
Hyperplasia, NOS		1 (2%)	
#Inguinal lymph node	(50)	(48)	(50)
Hyperplasia, NOS	1 (2%)		
#Liver	(50)	(50)	(50)
Hematopoiesis	1 (2%)		
#Thymus	(24)	(29)	(39)
Multiple cysts	1 (4%)		
Congestion, NOS	1 (4%)		
Lymphoid depletion			1 (3%)
CIRCULATORY SYSTEM			
#Mandibular lymph node	(50)	(48)	(50)
Lymphangiectasis			1 (2%)
#Mediastinal lymph node	(50)	(48)	(50)
Lymphangiectasis		1 (2%)	

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

	CONTROL (VEH)	60 mg/kg	120 mg/kg
CIRCULATORY SYSTEM (Continued)			
#Lung	(50)	(50)	(50)
Perivasculitis		1 (2%)	
#Heart	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, chronic focal		1 (2%)	3 (6%)
#Auricular appendage	(50)	(50)	(50)
Dilatation, NOS			1 (2%)
#Myocardium	(50)	(50)	(50)
Degeneration, NOS	30 (60%)	42 (84%)	27 (54%)
#Liver	(50)	(50)	(50)
Perivasculitis	1 (2%)	2 (4%)	5 (10%)
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(50)	(50)
Dilatation/ducts		1 (2%)	
Hemorrhage			1 (2%)
Inflammation, acute	1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)	
Fibrosis, focal	2 (4%)		
#Liver	(50)	(50)	(50)
Hernia, NOS	1 (2%)	2 (4%)	3 (6%)
Hemorrhage			1 (2%)
Inflammation, focal	5 (10%)		
Inflammation, chronic focal			2 (4%)
Inflammation, granulomatous focal	1 (2%)	2 (4%)	
Cholangiofibrosis	3 (6%)		1 (2%)
Necrosis, focal	3 (6%)	2 (4%)	5 (10%)
Metamorphosis fatty	14 (28%)	6 (12%)	3 (6%)
Cytoplasmic change, NOS	1 (2%)		
Cytoplasmic vacuolization	1 (2%)		
Basophilic cyto change	31 (62%)	38 (76%)	10 (20%)
Focal cellular change		2 (4%)	2 (4%)
Angiectasis	1 (2%)	1 (2%)	
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, NOS		1 (2%)	
#Bile duct	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Hyperplasia, NOS	15 (30%)	19 (38%)	10 (20%)
#Pancreas	(50)	(49)	(50)
Dilatation/ducts	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal		4 (8%)	
Fibrosis	1 (2%)		
Fibrosis, focal		1 (2%)	
Atrophy, focal	7 (14%)	5 (10%)	1 (2%)
#Pancreatic acinus	(50)	(49)	(50)
Focal cellular change		1 (2%)	
Hyperplasia, focal	2 (4%)	4 (8%)	
#Stomach	(49)	(50)	(49)
Ulcer, NOS			2 (4%)
Inflammation, chronic focal	1 (2%)		1 (2%)
Hyperkeratosis		1 (2%)	
#Gastric submucosa	(49)	(50)	(49)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic	1 (2%)		
Inflammation, chronic focal		1 (2%)	
Granulation, tissue		2 (4%)	

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

	CONTROL (VEH)	60 mg/kg	120 mg/kg
DIGESTIVE SYSTEM (Continued)			
#Forestomach	(49)	(50)	(49)
Ulcer, NOS	2 (4%)	1 (2%)	1 (2%)
Inflammation, chronic focal			1 (2%)
Ulcer, perforated	2 (4%)		
Hyperplasia, basal cell	1 (2%)	1 (2%)	1 (2%)
Hyperkeratosis	4 (8%)	2 (4%)	2 (4%)
Acanthosis	1 (2%)	1 (2%)	
#Duodenum	(50)	(50)	(50)
Ulcer, NOS			1 (2%)
#Ileum	(50)	(50)	(50)
Parasitism	1 (2%)		
#Colon	(46)	(50)	(50)
Parasitism	6 (13%)	4 (8%)	5 (10%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Congestion, NOS			2 (4%)
Pyelonephritis, focal			1 (2%)
Inflammation, chronic focal	1 (2%)		1 (2%)
Nephropathy	13 (26%)	25 (50%)	20 (40%)
Nephrosis, NOS		1 (2%)	
Nephrosis, cholemic	2 (4%)		2 (4%)
Calcification, focal	19 (38%)	21 (42%)	18 (36%)
#Kidney/tubule	(50)	(50)	(50)
Necrosis, NOS			1 (2%)
#Urinary bladder	(49)	(50)	(49)
Inflammation, chronic focal	1 (2%)		
Hyperplasia, epithelial	1 (2%)		1 (2%)
#Urinary bladder/submucosa	(49)	(50)	(49)
Inflammation, chronic focal	2 (4%)	3 (6%)	1 (2%)
ENDOCRINE SYSTEM			
#Pituitary	(49)	(50)	(49)
Cyst, NOS	2 (4%)	2 (4%)	1 (2%)
Multiple cysts			1 (2%)
Hemorrhagic cyst	1 (2%)		
Angiectasis			1 (2%)
#Pituitary intermedia	(49)	(50)	(49)
Multiple cysts		1 (2%)	
#Anterior pituitary	(49)	(50)	(49)
Cyst, NOS	2 (4%)	2 (4%)	3 (6%)
Multiple cysts	3 (6%)	2 (4%)	4 (8%)
Hemorrhage			1 (2%)
Hemorrhagic cyst	4 (8%)	1 (2%)	1 (2%)
Cytoplasmic vacuolization		1 (2%)	
Hyperplasia, focal	5 (10%)	3 (6%)	3 (6%)
Angiectasis	1 (2%)	3 (6%)	
#Adrenal	(50)	(50)	(49)
Necrosis, focal			1 (2%)
#Adrenal cortex	(50)	(50)	(49)
Hemorrhage			1 (2%)
Degeneration, lipoid	3 (6%)	2 (4%)	1 (2%)
Cytoplasmic vacuolization	4 (8%)	5 (10%)	3 (6%)
Focal cellular change		1 (2%)	
Hyperplasia, focal	1 (2%)	3 (6%)	4 (8%)
#Adrenal medulla	(50)	(50)	(49)
Hyperplasia, NOS	3 (6%)	6 (12%)	4 (8%)
Hyperplasia, focal		1 (2%)	

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

	CONTROL (VEH)	60 mg/kg	120 mg/kg
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(48)	(49)	(46)
Ultimobranchial cyst		1 (2%)	
Hemorrhage	1 (2%)		1 (2%)
Hyperplasia, C-cell	3 (6%)	8 (16%)	3 (7%)
#Pancreatic islets	(50)	(49)	(50)
Hyperplasia, NOS	1 (2%)		
Metaplasia, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Galactocele	7 (14%)	12 (24%)	2 (4%)
Lactation	17 (34%)	19 (38%)	5 (10%)
*Clitoral gland	(50)	(50)	(50)
Dilatation, NOS		2 (4%)	
#Uterus	(50)	(50)	(50)
Dilatation, NOS	1 (2%)	4 (8%)	4 (8%)
Granuloma, foreign body		1 (2%)	
Metaplasia, squamous		1 (2%)	
#Uterus/endometrium	(50)	(50)	(50)
Hyperplasia, cystic	3 (6%)	5 (10%)	2 (4%)
#Ovary	(50)	(50)	(50)
Cyst, NOS	2 (4%)	6 (12%)	4 (8%)
Multiple cysts			1 (2%)
Parovarian cyst			1 (2%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Hemorrhage			1 (2%)
#Brain	(50)	(50)	(50)
Hydrocephalus, NOS	3 (6%)		1 (2%)
Hemorrhage	1 (2%)	1 (2%)	25 (50%)
Inflammation, focal	1 (2%)		
Calcification, focal			1 (2%)
#Medulla oblongata	(50)	(50)	(50)
Hemorrhage			1 (2%)
*Spinal cord	(50)	(50)	(50)
Hemorrhage			1 (2%)
Degeneration, NOS			1 (2%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage			1 (2%)
*Eye anterior chamber	(50)	(50)	(50)
Hemorrhage	1 (2%)		
*Eye/iris	(50)	(50)	(50)
Inflammation, NOS		1 (2%)	
*Eye/crystalline lens	(50)	(50)	(50)
Cataract	2 (4%)	2 (4%)	2 (4%)
*Harderian gland	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
Hypertrophy, NOS		1 (2%)	

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

	CONTROL (VEH)	60 mg/kg	120 mg/kg
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Necrosis, NOS	1 (2%)		
*Skull	(50)	(50)	(50)
Osteosclerosis		2 (4%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage	1 (2%)		1 (2%)
Granuloma, foreign body			1 (2%)
*Pleural cavity	(50)	(50)	(50)
Hemorrhage			1 (2%)
*Pleura	(50)	(50)	(50)
Hemorrhage			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Congestion, NOS		1 (2%)	28 (56%)
Necrosis, NOS			1 (2%)
Necrosis, focal	1 (2%)		
Foot			
Crystals, NOS	1		
Omentum			
Reaction, foreign body			1
Necrosis, fat	3	6	8
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 *n*-BUTYL CHLORIDE

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	CONTROL (VEH)	500 mg/kg	1,000 mg/kg
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, NOS	3 (6%)		1 (2%)
Ulcer, NOS	5 (10%)	4 (8%)	2 (4%)
Inflammation, acute			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic	‡3 (6%)		3 (6%)
Inflammation, chronic focal	1 (2%)		
Fibrosis	1 (2%)	4 (8%)	1 (2%)
Calcification, focal	1 (2%)		
Acanthosis	2 (4%)	2 (4%)	1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, acute	1 (2%)	1 (2%)	
Abscess, NOS	2 (4%)		1 (2%)
Inflammation, chronic	1 (2%)		
Fibrosis		1 (2%)	1 (2%)
Calcification, NOS	1 (2%)		
Metaplasia, osseous		1 (2%)	
RESPIRATORY SYSTEM			
#Lung/bronchiole	(50)	(50)	(50)
Aspiration, foreign body			1 (2%)
#Lung	(50)	(50)	(50)
Fibrosis, diffuse	1 (2%)		
Hyperplasia, alveolar epithelium	1 (2%)		
Metaplasia, osseous		1 (2%)	
#Lung/alveoli	(50)	(50)	(50)
Histiocytosis	2 (4%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(50)	(50)	(49)
Hematopoiesis	1 (2%)		
#Spleen	(50)	(48)	(49)
Hyperplasia, lymphoid	1 (2%)		
Hematopoiesis	9 (18%)	8 (17%)	5 (10%)
#Lymph node	(44)	(47)	(44)
Hyperplasia, lymphoid	1 (2%)		
#Mandibular lymph node	(44)	(47)	(44)
Hyperplasia, plasma cell		1 (2%)	1 (2%)
#Mesenteric lymph node	(44)	(47)	(44)
Congestion, NOS	9 (20%)	5 (11%)	8 (18%)
Inflammation, acute		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
#Axillary lymph node	(44)	(47)	(44)
Hyperplasia, lymphoid	1 (2%)		
#Inguinal lymph node	(44)	(47)	(44)
Hyperplasia, plasma cell	1 (2%)		
#Liver	(50)	(50)	(50)
Hematopoiesis	2 (4%)	3 (6%)	1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	500 mg/kg	1,000 mg/kg
CIRCULATORY SYSTEM			
#Lung	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
Thrombus, organized			1 (2%)
#Heart	(50)	(50)	(50)
Calcification, focal		1 (2%)	
#Heart/atrium	(50)	(50)	(50)
Thrombus, mural			1 (2%)
*Pancreatic artery	(50)	(50)	(50)
Inflammation, chronic		2 (4%)	
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(49)	(50)
Inflammation, chronic focal	21 (42%)	18 (37%)	24 (48%)
#Liver	(50)	(50)	(50)
Necrosis, NOS			1 (2%)
Necrosis, focal	1 (2%)	1 (2%)	1 (2%)
Infarct, NOS		1 (2%)	
Metamorphosis fatty	3 (6%)	7 (14%)	1 (2%)
Eosinophilic cyto change	2 (4%)		
Hepatocytomegaly	3 (6%)		1 (2%)
#Liver/centrilobular	(50)	(50)	(50)
Necrosis, NOS	3 (6%)		
Metamorphosis fatty	1 (2%)		
Hepatocytomegaly	1 (2%)		
Atrophy, NOS		1 (2%)	
#Pancreas	(49)	(49)	(50)
Cyst, NOS		1 (2%)	
Inflammation, acute focal		1 (2%)	
Inflammation, chronic	1 (2%)		
#Pancreatic acinus	(49)	(49)	(50)
Atrophy, NOS	1 (2%)		
Atrophy, focal		1 (2%)	
#Gastric mucosa	(50)	(49)	(49)
Inflammation, acute focal		1 (2%)	
Calcification, focal	1 (2%)		
#Jejunum	(49)	(50)	(50)
Mucocele	1 (2%)		
Hyperplasia, adenomatous	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Pyelonephritis, acute		1 (2%)	
Inflammation, chronic focal	30 (60%)	32 (64%)	25 (50%)
Glomerulosclerosis, NOS		4 (8%)	
#Renal papilla	(50)	(50)	(50)
Necrosis, NOS	1 (2%)		
#Perirenal tissue	(50)	(50)	(50)
Necrosis, fat	2 (4%)		
#Kidney/tubule	(50)	(50)	(50)
Necrosis, NOS	1 (2%)		
Calcification, NOS	1 (2%)		
Hyperplasia, cystic		1 (2%)	
#Kidney/pelvis	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, acute necrotizing	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	500 mg/kg	1,000 mg/kg
URINARY SYSTEM (Continued)			
#Urinary bladder	(49)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	1 (2%)	1 (2%)	
Inflammation, chronic diffuse	1 (2%)		
#Urinary bladder/submucosa	(49)	(50)	(50)
Inflammation, chronic focal	10 (20%)	18 (36%)	5 (10%)
ENDOCRINE SYSTEM			
#Pituitary	(47)	(47)	(39)
Hyperplasia, focal		3 (6%)	
#Adrenal cortex	(50)	(47)	(49)
Hypertrophy, focal			1 (2%)
Hyperplasia, nodular	1 (2%)		
Hyperplasia, focal			1 (2%)
#Adrenal medulla	(50)	(47)	(49)
Hyperplasia, focal	3 (6%)	3 (6%)	1 (2%)
#Thyroid	(48)	(45)	(47)
Hyperplasia, follicular cell	4 (8%)	5 (11%)	4 (9%)
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Dilatation/ducts	1 (2%)		
Inflammation, chronic	4 (8%)	1 (2%)	
#Prostate	(47)	(39)	(44)
Inflammation, acute	2 (4%)		
*Seminal vesicle	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Infection, bacterial	1 (2%)		
#Testis	(50)	(49)	(49)
Calcification, focal	1 (2%)		
Atrophy, NOS	1 (2%)		
Hyperplasia, interstitial cell			1 (2%)
#Testis/tubule	(50)	(49)	(49)
Degeneration, NOS	3 (6%)	3 (6%)	2 (4%)
Calcification, NOS	2 (4%)	2 (4%)	2 (4%)
Calcification, focal		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Granuloma, foreign body	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	500 mg/kg	1,000 mg/kg
BODY CAVITIES			
*Pleura	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)		
*Mesentery	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, granulomatous		1 (2%)	
Necrosis, fat		2 (4%)	
ALL OTHER SYSTEMS			
Foot			
Ankylosis	1		
Omentum			
Necrosis, fat	2		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported	1		5

Number of animals with tissue examined microscopically
* Number of animals necropsied
‡ Multiple occurence of morphology in the same organ. Tissue is counted only once.

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	CONTROL (VEH)	250 mg/kg
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50
INTEGUMENTARY SYSTEM		
*Skin	(50)	(50)
Ulcer, NOS		3 (6%)
Inflammation, acute		2 (4%)
Inflammation, chronic focal	1 (2%)	
Necrosis, focal		2 (4%)
*Subcut tissue	(50)	(50)
Inflammation, chronic	1 (2%)	
Fibrosis, focal		1 (2%)
RESPIRATORY SYSTEM		
*Nasal cavity	(50)	(50)
Inflammation, chronic		1 (2%)
Inflammation, chronic focal		3 (6%)
#Lung	(50)	(50)
Pneumonia, interstitial chronic		1 (2%)
#Lung/alveoli	(50)	(50)
Histiocytosis	2 (4%)	3 (6%)
HEMATOPOIETIC SYSTEM		
*Subcut tissue	(50)	(50)
Hyperplasia, plasma cell	1 (2%)	
Hyperplasia, lymphoid	1 (2%)	
#Bone marrow	(50)	(50)
Hyperplasia, hematopoietic		1 (2%)
Hematopoiesis		1 (2%)
#Spleen	(50)	(50)
Amyloidosis		1 (2%)
Angiectasis	1 (2%)	1 (2%)
Hyperplasia, lymphoid	1 (2%)	
Hematopoiesis	8 (16%)	6 (12%)
#Lymph node	(47)	(44)
Hyperplasia, plasma cell	1 (2%)	
#Mandibular lymph node	(47)	(44)
Hyperplasia, lymphoid	1 (2%)	
#Mesenteric lymph node	(47)	(44)
Congestion, NOS	13 (28%)	20 (45%)
Hyperplasia, lymphoid	6 (13%)	4 (9%)
#Renal lymph node	(47)	(44)
Hyperplasia, lymphoid	1 (2%)	
#Inguinal lymph node	(47)	(44)
Hyperplasia, plasma cell	1 (2%)	
#Liver	(50)	(50)
Hematopoiesis	1 (2%)	
#Peyers patch	(49)	(49)
Hyperplasia, lymphoid		1 (2%)
CIRCULATORY SYSTEM		
#Lung	(50)	(50)
Perivasculitis	1 (2%)	
#Pancreas	(49)	(49)
Periarteritis	1 (2%)	
#Perirenal tissue	(50)	(50)
Perivasculitis		1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	250 mg/kg
CIRCULATORY SYSTEM (Continued)		
#Urinary bladder	(49)	(49)
Perivasculitis		1 (2%)
DIGESTIVE SYSTEM		
#Salivary gland	(48)	(50)
Inflammation, chronic focal	31 (65%)	30 (60%)
Hyperplasia, intraductal		1 (2%)
#Liver	(50)	(50)
Inflammation, chronic focal	1 (2%)	
Necrosis, NOS	2 (4%)	1 (2%)
Necrosis, focal	1 (2%)	
Amyloidosis		1 (2%)
Metamorphosis, fatty	3 (6%)	2 (4%)
Eosinophilic cyto change		1 (2%)
Clear cell change		1 (2%)
#Bile duct	(50)	(50)
Cyst, NOS	1 (2%)	
Inflammation, chronic		1 (2%)
#Pancreas	(49)	(49)
Inflammation, acute focal	1 (2%)	
Inflammation, chronic focal	1 (2%)	
Necrosis, focal		1 (2%)
#Forestomach	(50)	(50)
Ulcer, NOS	1 (2%)	4 (8%)
Inflammation, chronic focal	1 (2%)	1 (2%)
Necrosis, focal	1 (2%)	
Hyperkeratosis	1 (2%)	
Acanthosis	3 (6%)	3 (6%)
#Small intestine /serosa	(49)	(49)
Inflammation, chronic		1 (2%)
*Anus	(50)	(50)
Prolapse		1 (2%)
URINARY SYSTEM		
#Kidney	(50)	(50)
Hydronephrosis		1 (2%)
Cyst, NOS		1 (2%)
Inflammation, suppurative		1 (2%)
Pyelonephritis, acute		1 (2%)
Glomerulonephritis, chronic		1 (2%)
Inflammation, chronic focal	38 (76%)	32 (64%)
Glomerulosclerosis, NOS	3 (6%)	2 (4%)
Hemosiderosis		1 (2%)
Hyperplasia, tubular cell	1 (2%)	
#Kidney/tubule	(50)	(50)
Cyst, NOS	1 (2%)	
Calcification, NOS		1 (2%)
Hyperplasia, cystic		1 (2%)
#Urinary bladder	(49)	(49)
Inflammation, chronic		1 (2%)
Inflammation, chronic focal		1 (2%)
ENDOCRINE SYSTEM		
#Anterior pituitary	(40)	(45)
Multiple cysts		1 (2%)
Hyperplasia, focal		2 (4%)
#Adrenal/capsule	(49)	(49)
Hyperplasia, focal	1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	250 mg/kg
ENDOCRINE SYSTEM (Continued)		
#Adrenal serosa	(49)	(49)
Inflammation, fibrinous		1 (2%)
#Adrenal cortex	(49)	(49)
Degeneration, NOS	1 (2%)	
Hyperplasia, nodular		1 (2%)
Hyperplasia, focal	1 (2%)	1 (2%)
#Thyroid	(46)	(47)
Cystic follicles		1 (2%)
Inflammation, acute focal		1 (2%)
Hyperplasia, follicular cell		1 (2%)
#Thyroid follicle	(46)	(47)
Hyperplasia, cystic		1 (2%)
REPRODUCTIVE SYSTEM		
*Preputial gland	(50)	(50)
Dilatation/ducts		1 (2%)
Cystic ducts		1 (2%)
Inflammation, suppurative	2 (4%)	4 (8%)
Inflammation, chronic	5 (10%)	3 (6%)
#Prostate	(49)	(48)
Inflammation, chronic		1 (2%)
Inflammation, chronic focal	1 (2%)	
#Testis/tubule	(50)	(50)
Degeneration, NOS		3 (6%)
Calcification, focal	2 (4%)	2 (4%)
NERVOUS SYSTEM		
#Cerebral ventricle	(50)	(50)
Inflammation, suppurative		1 (2%)
SPECIAL SENSE ORGANS		
*Nasolacrimal duct	(50)	(50)
Inflammation, suppurative		1 (2%)
MUSCULOSKELETAL SYSTEM		
*Tarsal joint	(50)	(50)
Ankylosis	31 (62%)	17 (34%)
BODY CAVITIES		
*Mesentery	(50)	(50)
Necrosis, fat		1 (2%)
ALL OTHER SYSTEMS		
*Multiple organs	(50)	(50)
Amyloidosis		1 (2%)
SPECIAL MORPHOLOGY SUMMARY		
None		

Number of animals with tissue examined microscopically
* Number of animals necropsied

TABLE D3. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	CONTROL (VEH)	500 mg/kg
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50
INTEGUMENTARY SYSTEM		
*Skin	(50)	(50)
Ulcer, NOS		3 (6%)
Inflammation, acute		1 (2%)
Inflammation, acute/chronic		1 (2%)
Fibrosis		1 (2%)
Acanthosis		2 (4%)
RESPIRATORY SYSTEM		
#Lung/bronchiole	(50)	(50)
Inflammation, chronic		1 (2%)
#Lung	(50)	(50)
Inflammation, interstitial	2 (4%)	
Hyperplasia, alveolar epithelium	1 (2%)	1 (2%)
#Lung/alveoli	(50)	(50)
Hemorrhage	1 (2%)	
Histiocytosis		3 (6%)
HEMATOPOIETIC SYSTEM		
#Spleen	(50)	(50)
Hyperplasia, lymphoid	2 (4%)	3 (6%)
Hematopoiesis	13 (26%)	7 (14%)
#Lymph node	(45)	(49)
Cyst, NOS	1 (2%)	
Congestion, NOS	1 (2%)	
Hemorrhagic cyst	2 (4%)	
Hyperplasia, lymphoid	1 (2%)	
#Lumbar lymph node	(45)	(49)
Hyperplasia, plasma cell		1 (2%)
#Mesenteric lymph node	(45)	(49)
Congestion, NOS	1 (2%)	1 (2%)
Hyperplasia, plasma cell	1 (2%)	
#Renal lymph node	(45)	(49)
Hyperplasia, plasma cell	1 (2%)	
#Liver	(50)	(50)
Hematopoiesis	7 (14%)	1 (2%)
#Adrenal	(49)	(50)
Hematopoiesis	1 (2%)	
#Adrenal cortex	(49)	(50)
Hematopoiesis	1 (2%)	
CIRCULATORY SYSTEM		
*Skin	(50)	(50)
Perivasculitis		1 (2%)
#Lung	(50)	(50)
Perivasculitis	2 (4%)	3 (6%)
#Heart	(50)	(50)
Calcification, focal	1 (2%)	
*Coronary artery	(50)	(50)
Inflammation, acute	1 (2%)	
#Hepatic sinusoid	(50)	(50)
Infection, bacterial		1 (2%)

TABLE D3. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)		500 mg/kg	
DIGESTIVE SYSTEM				
#Salivary gland	(49)		(48)	
Inflammation, chronic focal	19	(39%)	16	(33%)
#Liver	(50)		(50)	
Cyst, NOS	1	(2%)		
Inflammation, acute focal			1	(2%)
Inflammation, chronic	1	(2%)		
Inflammation, chronic focal	2	(4%)		
Necrosis, focal			2	(4%)
Necrosis, midzonal			1	(2%)
Metamorphosis fatty	3	(6%)	1	(2%)
Hepatocytomegaly	1	(2%)		
#Hepatic serosa	(50)		(50)	
Inflammation, acute	4	(8%)	2	(4%)
#Liver/centrilobular	(50)		(50)	
Necrosis, NOS	1	(2%)	1	(2%)
#Bile duct	(50)		(50)	
Inflammation, chronic focal	1	(2%)		
Hyperplasia, NOS	1	(2%)		
#Pancreas	(49)		(49)	
Inflammation, suppurative			1	(2%)
Inflammation, acute	1	(2%)		
Inflammation, chronic	3	(6%)		
#Esophagus	(46)		(47)	
Acanthosis			1	(2%)
#Forestomach	(50)		(50)	
Inflammation, chronic			1	(2%)
Hyperplasia, epithelial	1	(2%)		
Hyperkeratosis			1	(2%)
Acanthosis	1	(2%)	2	(4%)
URINARY SYSTEM				
#Kidney	(50)		(50)	
Pyelonephritis, acute	1	(2%)	1	(2%)
Inflammation, acute focal	1	(2%)		
Glomerulonephritis, chronic	2	(4%)		
Inflammation, chronic focal	19	(38%)	23	(46%)
Infection, bacterial	1	(2%)		
Glomerulosclerosis, NOS	1	(2%)	1	(2%)
#Urinary bladder	(49)		(50)	
Inflammation, chronic	1	(2%)		
#Urinary bladder/submucosa	(49)		(50)	
Inflammation, chronic focal	25	(51%)	22	(44%)
ENDOCRINE SYSTEM				
#Pituitary	(43)		(46)	
Hyperplasia, focal	2	(5%)	4	(9%)
#Periadrenal tissue	(49)		(50)	
Inflammation, acute	1	(2%)		
Inflammation, chronic	1	(2%)		
#Thyroid	(48)		(48)	
Cystic follicles			2	(4%)
Inflammation, chronic focal	1	(2%)		
Hyperplasia, follicular cell	7	(15%)	8	(17%)

TABLE D3. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	500 mg/kg
REPRODUCTIVE SYSTEM		
*Mammary gland	(50)	(50)
Hyperplasia, cystic		1 (2%)
#Uterus	(50)	(49)
Inflammation, suppurative	2 (4%)	2 (4%)
Amyloidosis	1 (2%)	
#Uterus/endometrium	(50)	(49)
Hemorrhage	1 (2%)	
Inflammation, suppurative	8 (16%)	
Hyperplasia, cystic	36 (72%)	33 (67%)
#Ovary/parovarian	(48)	(48)
Steatitis		1 (2%)
Necrosis, fat		1 (2%)
#Ovary	(48)	(48)
Cyst, NOS	10 (21%)	19 (40%)
Hemorrhage		1 (2%)
Hematoma, NOS	1 (2%)	
Hemorrhagic cyst	3 (6%)	2 (4%)
Inflammation, suppurative	12 (25%)	6 (13%)
Inflammation, chronic	3 (6%)	5 (10%)
Hyperplasia, adenomatous	5 (10%)	1 (2%)
NERVOUS SYSTEM		
None		
SPECIAL SENSE ORGANS		
None		
MUSCULOSKELETAL SYSTEM		
*Skeletal muscle	(50)	(50)
Inflammation, acute	2 (4%)	1 (2%)
BODY CAVITIES		
*Mediastinum	(50)	(50)
Vegetable foreign body		1 (2%)
Inflammation, acute	1 (2%)	
Abscess, NOS	1 (2%)	1 (2%)
Infection, bacterial		1 (2%)
*Pleura	(50)	(50)
Inflammation, acute focal	1 (2%)	
Inflammation, chronic	1 (2%)	
*Epicardium	(50)	(50)
Inflammation, acute focal	1 (2%)	
*Mesentery	(50)	(50)
Necrosis, fat	1 (2%)	2 (4%)

TABLE D3. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	500 mg/kg
ALL OTHER SYSTEMS		
*Multiple organs	(50)	(50)
Inflammation, acute	4 (8%)	1 (2%)
Inflammation, chronic focal	1 (2%)	2 (4%)
Adipose tissue		
Inflammation, acute	1	2
Omentum		
Inflammation, suppurative		1
Inflammation, acute	1	
Abscess, NOS	1	
Necrosis, fat	1	1
SPECIAL MORPHOLOGY SUMMARY		
No lesion reported		1

Number of animals with tissue examined microscopically
* Number of animals necropsied

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	CONTROL (VEH)	250 mg/kg
ANIMALS INITIALLY IN STUDY	50	50
ANIMALS NECROPSIED	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50
INTEGUMENTARY SYSTEM		
None		
RESPIRATORY SYSTEM		
*Nasal cavity	(50)	(50)
Inflammation, chronic	1 (2%)	
#Lung	(50)	(50)
Inflammation, acute	1 (2%)	2 (4%)
Bacterial septicemia	1 (2%)	
Infection, bacterial	1 (2%)	
#Lung/alveoli	(50)	(50)
Histiocytosis		1 (2%)
HEMATOPOIETIC SYSTEM		
#Spleen	(49)	(49)
Hyperplasia, lymphoid	1 (2%)	2 (4%)
Hematopoiesis	5 (10%)	3 (6%)
#Mediastinal lymph node	(39)	(45)
Inflammation, suppurative	1 (3%)	
Inflammation, acute	1 (3%)	
#Lumbar lymph node	(39)	(45)
Inflammation, suppurative		1 (2%)
#Mesenteric lymph node	(39)	(45)
Congestion, NOS	1 (3%)	2 (4%)
Hyperplasia, lymphoid		1 (2%)
#Renal lymph node	(39)	(45)
Hyperplasia, plasma cell	1 (3%)	
#Liver	(50)	(50)
Hematopoiesis	4 (8%)	4 (8%)
CIRCULATORY SYSTEM		
#Brain	(50)	(50)
Embolus, septic	1 (2%)	
#Lung	(50)	(50)
Thrombosis, NOS	1 (2%)	
Perivasculitis	1 (2%)	
#Heart	(50)	(50)
Embolus, septic	1 (2%)	
Fibrosis, focal		1 (2%)
Necrosis, focal	1 (2%)	
Calcification, focal		1 (2%)
Angiectasis		1 (2%)
#Cardiac valve	(50)	(50)
Inflammation, acute	1 (2%)	
#Ovary	(48)	(50)
Thrombus, organized		1 (2%)
#Thyroid	(44)	(46)
Embolus, septic	1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	250 mg/kg
DIGESTIVE SYSTEM		
*Root of tooth	(50)	(50)
Abscess, NOS	1 (2%)	
#Salivary gland	(46)	(48)
Inflammation, chronic focal	13 (28%)	25 (52%)
#Liver	(50)	(50)
Dilatation/sinus		1 (2%)
Inflammation, acute focal		1 (2%)
Inflammation, chronic focal	2 (4%)	3 (6%)
Necrosis, focal	1 (2%)	1 (2%)
Metamorphosis, fatty	2 (4%)	1 (2%)
Basophilic cyto change		1 (2%)
Hepatocytomegaly	1 (2%)	
#Hepatic serosa	(50)	(50)
Inflammation, fibrinous		1 (2%)
Inflammation, acute	3 (6%)	1 (2%)
Inflammation, acute focal		1 (2%)
#Bile duct	(50)	(50)
Inflammation, chronic	7 (14%)	6 (12%)
#Pancreas	(45)	(49)
Cystic ducts		1 (2%)
Inflammation, fibrinous	1 (2%)	
Inflammation, acute	1 (2%)	
Inflammation, chronic	3 (7%)	1 (2%)
#Pancreatic acinus	(45)	(49)
Atrophy, NOS		1 (2%)
#Peripancreatic tissue	(45)	(49)
Inflammation, acute		2 (4%)
#Gastric mucosa	(48)	(49)
Calcification, focal	1 (2%)	
#Glandular stomach	(48)	(49)
Inflammation, chronic	1 (2%)	
#Forestomach	(48)	(49)
Inflammation, acute focal	1 (2%)	
Inflammation, chronic		1 (2%)
Inflammation, chronic focal	1 (2%)	
Hyperplasia, focal		1 (2%)
Hyperkeratosis		2 (4%)
Acanthosis	1 (2%)	1 (2%)
#Small intestine	(49)	(50)
Amyloidosis	1 (2%)	
#Ileum	(49)	(50)
Amyloidosis	1 (2%)	
URINARY SYSTEM		
#Kidney	(50)	(49)
Inflammation, chronic focal	27 (54%)	31 (63%)
Infection, bacterial	1 (2%)	1 (2%)
Glomerulosclerosis, NOS	3 (6%)	3 (6%)
#Kidney/glomerulus	(50)	(49)
Amyloidosis	1 (2%)	1 (2%)
#Urinary bladder	(48)	(49)
Inflammation, acute focal		1 (2%)
Inflammation, chronic focal	10 (21%)	19 (39%)
#Urinary bladder/serosa	(48)	(49)
Inflammation, acute	1 (2%)	

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	250 mg/kg
ENDOCRINE SYSTEM		
#Anterior pituitary	(39)	(41)
Dilatation/sinus		2 (5%)
Hyperplasia, focal	8 (21%)	10 (24%)
#Adrenal serosa	(47)	(50)
Inflammation, fibrinous	2 (4%)	
#Periadrenal tissue	(47)	(50)
Inflammation, acute	1 (2%)	1 (2%)
Infection, bacterial	1 (2%)	
#Thyroid	(44)	(46)
Cystic follicles	1 (2%)	
Hyperplasia, follicular cell	1 (2%)	
REPRODUCTIVE SYSTEM		
#Uterus	(50)	(50)
Inflammation, suppurative	1 (2%)	
Inflammation, acute	1 (2%)	
#Uterus/endometrium	(50)	(50)
Inflammation, suppurative	8 (16%)	7 (14%)
Hyperplasia, cystic	26 (52%)	35 (70%)
#Ovary/parovarian	(48)	(50)
Inflammation, suppurative		1 (2%)
Inflammation, chronic		2 (4%)
#Ovary	(48)	(50)
Cyst, NOS	8 (17%)	8 (16%)
Follicular cyst, NOS	1 (2%)	
Hemorrhagic cyst	1 (2%)	1 (2%)
Inflammation, suppurative	15 (31%)	5 (10%)
Inflammation, chronic		1 (2%)
#Mesovarium	(48)	(50)
Inflammation, chronic	1 (2%)	
NERVOUS SYSTEM		
#Brain/meninges	(50)	(50)
Inflammation, suppurative		1 (2%)
SPECIAL SENSE ORGANS		
None		
MUSCULOSKELETAL SYSTEM		
None		
BODY CAVITIES		
*Mediastinum	(50)	(50)
Inflammation, acute	2 (4%)	
*Pleura	(50)	(50)
Inflammation, fibrinous	4 (8%)	1 (2%)
Inflammation, acute	1 (2%)	
*Pericardium	(50)	(50)
Inflammation, fibrinous	2 (4%)	
*Mesentery	(50)	(50)
Inflammation, suppurative	1 (2%)	
Necrosis, fat	1 (2%)	1 (2%)

TABLE D4. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	CONTROL (VEH)	250 mg/kg
ALL OTHER SYSTEMS		
*Multiple organs	(50)	(50)
Inflammation, suppurative	1 (2%)	
Inflammation, acute	1 (2%)	
Inflammation, chronic focal	3 (6%)	1 (2%)
Omentum		
Inflammation, acute		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 *n*-BUTYL CHLORIDE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	Vehicle Control	60 mg/kg	120 mg/kg
Skin: Keratoacanthoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	7.5%	6.3%	8.5%
Terminal Rates (c)	3/40 (7%)	2/32 (6%)	0/17 (0%)
Week of First Observation	104	104	91
Life Table Tests (d)	P=0.459	P=0.602N	P=0.528
Incidental Tumor Tests (d)	P=0.592N	P=0.602N	P=0.619N
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Subcutaneous Tissue: Neurofibrosarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	2.5%	6.8%	5.9%
Terminal Rates (c)	1/40 (3%)	0/32 (0%)	1/17 (6%)
Week of First Observation	104	80	104
Life Table Tests (d)	P=0.392	P=0.271	P=0.560
Incidental Tumor Tests (d)	P=0.551N	P=0.619	P=0.560
Cochran-Armitage Trend Test (d)	P=0.610		
Fisher Exact Test (d)		P=0.309	P=0.753
Subcutaneous Tissue: Fibrosarcoma or Neurofibrosarcoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	2.5%	9.0%	5.9%
Terminal Rates (c)	1/40 (3%)	0/32 (0%)	1/17 (6%)
Week of First Observation	104	80	104
Life Table Tests (d)	P=0.376	P=0.158	P=0.560
Incidental Tumor Tests (d)	P=0.482N	P=0.510	P=0.560
Cochran-Armitage Trend Test (d)	P=0.601		
Fisher Exact Test (d)		P=0.181	P=0.753
Subcutaneous Tissue: Fibroma or Neurofibroma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	7.5%	5.9%	11.8%
Terminal Rates (c)	3/40 (7%)	1/32 (3%)	2/17 (12%)
Week of First Observation	104	100	104
Life Table Tests (d)	P=0.439	P=0.599N	P=0.496
Incidental Tumor Tests (d)	P=0.502	P=0.581N	P=0.496
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
Subcutaneous Tissue: Neurofibroma or Neurofibrosarcoma			
Overall Rates (a)	2/50 (4%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	5.0%	9.8%	17.6%
Terminal Rates (c)	2/40 (5%)	1/32 (3%)	3/17 (18%)
Week of First Observation	104	80	104
Life Table Tests (d)	P=0.133	P=0.277	P=0.153
Incidental Tumor Tests (d)	P=0.281	P=0.552	P=0.153
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Test (d)		P=0.339	P=0.500
Subcutaneous Tissue: Fibroma, Neurofibroma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	4/50 (8%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	10.0%	14.3%	17.6%
Terminal Rates (c)	4/40 (10%)	1/32 (3%)	3/17 (18%)
Week of First Observation	104	80	104
Life Table Tests (d)	P=0.302	P=0.283	P=0.359
Incidental Tumor Tests (d)	P=0.564N	P=0.585	P=0.359
Cochran-Armitage Trend Test (d)	P=0.429N		
Fisher Exact Test (d)		P=0.370	P=0.500N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	2.5%	8.9%	8.8%
Terminal Rates (c)	1/40 (3%)	2/32 (6%)	1/17 (6%)
Week of First Observation	104	99	80
Life Table Tests (d)	P=0.152	P=0.233	P=0.266
Incidental Tumor Tests (d)	P=0.257	P=0.249	P=0.421
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.309	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	11/50 (22%)	7/50 (14%)	6/50 (12%)
Adjusted Rates (b)	26.1%	20.3%	28.0%
Terminal Rates (c)	9/40 (23%)	5/32 (16%)	2/17 (12%)
Week of First Observation	100	98	97
Life Table Tests (d)	P=0.436	P=0.394N	P=0.423
Incidental Tumor Tests (d)	P=0.398N	P=0.315N	P=0.487N
Cochran-Armitage Trend Test (d)	P=0.110N		
Fisher Exact Test (d)		P=0.218N	P=0.144N
Liver: Neoplastic Nodule or Hepatocellular Carcinoma			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	6.9%	7.8%	5.9%
Terminal Rates (c)	1/40 (3%)	1/32 (3%)	1/17 (6%)
Week of First Observation	99	86	104
Life Table Tests (d)	P=0.518N	P=0.578	P=0.622N
Incidental Tumor Tests (d)	P=0.239N	P=0.526N	P=0.420N
Cochran-Armitage Trend Test (d)	P=0.238N		
Fisher Exact Test (d)		P=0.661	P=0.309N
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	4/50 (8%)	9/50 (18%)	5/48 (10%)
Adjusted Rates (b)	10.0%	27.1%	29.4%
Terminal Rates (c)	4/40 (10%)	8/32 (25%)	5/17 (29%)
Week of First Observation	104	99	104
Life Table Tests (d)	P=0.040	P=0.051	P=0.076
Incidental Tumor Tests (d)	P=0.050	P=0.054	P=0.076
Cochran-Armitage Trend Test (d)	P=0.409		
Fisher Exact Test (d)		P=0.117	P=0.474
Pituitary Intermedia: Adenoma			
Overall Rates (a)	3/48 (6%)	0/49 (0%)	0/47 (0%)
Adjusted Rates (b)	7.6%	0.0%	0.0%
Terminal Rates (c)	2/38 (5%)	0/32 (0%)	0/15 (0%)
Week of First Observation	103		
Life Table Tests (d)	P=0.095N	P=0.160N	P=0.322N
Incidental Tumor Tests (d)	P=0.064N	P=0.144N	P=0.223N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.117N	P=0.125N
Pituitary Gland: Adenoma			
Overall Rates (a)	18/48 (38%)	14/49 (29%)	8/47 (17%)
Adjusted Rates (b)	41.2%	38.4%	39.8%
Terminal Rates (c)	13/38 (34%)	10/32 (31%)	5/15 (33%)
Week of First Observation	84	89	75
Life Table Tests (d)	P=0.531N	P=0.473N	P=0.593N
Incidental Tumor Tests (d)	P=0.103N	P=0.286N	P=0.113N
Cochran-Armitage Trend Test (d)	P=0.017N		
Fisher Exact Test (d)		P=0.236N	P=0.022N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	19/48 (40%)	14/49 (29%)	8/47 (17%)
Adjusted Rates (b)	43.6%	38.4%	39.8%
Terminal Rates (c)	14/38 (37%)	10/32 (31%)	5/15 (33%)
Week of First Observation	84	89	75
Life Table Tests (d)	P=0.462N	P=0.401N	P=0.540N
Incidental Tumor Tests (d)	P=0.074N	P=0.223N	P=0.089N
Cochran-Armitage Trend Test (d)	P=0.010N		
Fisher Exact Test (d)		P=0.176N	P=0.013N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	14/50 (28%)	11/50 (22%)	4/50 (8%)
Adjusted Rates (b)	33.2%	29.8%	20.6%
Terminal Rates (c)	12/40 (30%)	7/32 (22%)	2/17 (12%)
Week of First Observation	88	86	99
Life Table Tests (d)	P=0.264N	P=0.549N	P=0.291N
Incidental Tumor Tests (d)	P=0.074N	P=0.349N	P=0.118N
Cochran-Armitage Trend Test (d)	P=0.008N		
Fisher Exact Test (d)		P=0.323N	P=0.009N
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	15/50 (30%)	11/50 (22%)	4/50 (8%)
Adjusted Rates (b)	35.6%	29.8%	20.6%
Terminal Rates (c)	13/40 (33%)	7/32 (22%)	2/17 (12%)
Week of First Observation	88	86	99
Life Table Tests (d)	P=0.206N	P=0.470N	P=0.239N
Incidental Tumor Tests (d)	P=0.051N	P=0.278N	P=0.091N
Cochran-Armitage Trend Test (d)	P=0.004N		
Fisher Exact Test (d)		P=0.247N	P=0.005N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	4/49 (8%)	3/49 (6%)	0/46 (0%)
Adjusted Rates (b)	10.0%	9.4%	0.0%
Terminal Rates (c)	4/40 (10%)	3/32 (9%)	0/17 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.191N	P=0.621N	P=0.218N
Incidental Tumor Tests (d)	P=0.191N	P=0.621N	P=0.218N
Cochran-Armitage Trend Test (d)	P=0.055N		
Fisher Exact Test (d)		P=0.500N	P=0.067N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	5/49 (10%)	1/49 (2%)	2/46 (4%)
Adjusted Rates (b)	12.0%	3.1%	11.8%
Terminal Rates (c)	4/40 (10%)	1/32 (3%)	2/17 (12%)
Week of First Observation	99	104	104
Life Table Tests (d)	P=0.414N	P=0.162N	P=0.634N
Incidental Tumor Tests (d)	P=0.347N	P=0.141N	P=0.537N
Cochran-Armitage Trend Test (d)	P=0.148N		
Fisher Exact Test (d)		P=0.102N	P=0.245N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	1/49 (2%)	1/49 (2%)	3/46 (7%)
Adjusted Rates (b)	2.2%	3.1%	14.8%
Terminal Rates (c)	0/40 (0%)	1/32 (3%)	2/17 (12%)
Week of First Observation	97	104	89
Life Table Tests (d)	P=0.061	P=0.713	P=0.102
Incidental Tumor Tests (d)	P=0.128	P=0.762	P=0.266
Cochran-Armitage Trend Test (d)	P=0.184		
Fisher Exact Test (d)		P=0.753	P=0.285

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/49 (12%)	2/49 (4%)	5/46 (11%)
Adjusted Rates (b)	14.0%	6.3%	26.2%
Terminal Rates (c)	4/40 (10%)	2/32 (6%)	4/17 (24%)
Week of First Observation	97	104	89
Life Table Tests (d)	P=0.262	P=0.218N	P=0.230
Incidental Tumor Tests (d)	P=0.412	P=0.171N	P=0.449
Cochran-Armitage Trend Test (d)	P=0.467N		
Fisher Exact Test (d)		P=0.134N	P=0.545N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	3/50 (6%)	0/48 (0%)
Adjusted Rates (b)	10.0%	8.3%	0.0%
Terminal Rates (c)	4/40 (10%)	2/32 (6%)	0/17 (0%)
Week of First Observation	104	81	
Life Table Tests (d)	P=0.178N	P=0.606N	P=0.218N
Incidental Tumor Tests (d)	P=0.128N	P=0.521N	P=0.218N
Cochran-Armitage Trend Test (d)	P=0.053N		
Fisher Exact Test (d)		P=0.500N	P=0.064N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	11.8%	8.9%	14.8%
Terminal Rates (c)	3/40 (7%)	2/32 (6%)	2/17 (12%)
Week of First Observation	99	100	89
Life Table Tests (d)	P=0.468	P=0.483N	P=0.496
Incidental Tumor Tests (d)	P=0.475N	P=0.433N	P=0.553N
Cochran-Armitage Trend Test (d)	P=0.283N		
Fisher Exact Test (d)		P=0.357N	P=0.357N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	46/50 (92%)	45/49 (92%)	39/49 (80%)
Adjusted Rates (b)	100.0%	100.0%	97.4%
Terminal Rates (c)	40/40 (100%)	31/31 (100%)	16/17 (94%)
Week of First Observation	81	80	59
Life Table Tests (d)	P<0.001	P=0.032	P<0.001
Incidental Tumor Tests (d)	P=0.148	P=0.334	P=0.284
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.631N	P=0.068N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	2/50 (4%)
Adjusted Rates (b)	7.5%	6.3%	11.8%
Terminal Rates (c)	3/40 (7%)	2/32 (6%)	2/17 (12%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.437	P=0.602N	P=0.496
Incidental Tumor Tests (d)	P=0.437	P=0.602N	P=0.496
Cochran-Armitage Trend Test (d)	P=0.406N		
Fisher Exact Test (d)		P=0.500N	P=0.500N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences 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 tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	Vehicle Control	60 mg/kg	120 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	12/50 (24%)	10/50 (20%)	5/50 (10%)
Adjusted Rates (b)	29.3%	24.0%	28.8%
Terminal Rates (c)	8/35 (23%)	7/38 (18%)	1/11 (9%)
Week of First Observation	77	88	55
Life Table Tests (d)	P=0.554	P=0.340N	P=0.535
Incidental Tumor Tests (d)	P=0.148N	P=0.422N	P=0.159N
Cochran-Armitage Trend Test (d)	P=0.045N		
Fisher Exact Test (d)		P=0.405N	P=0.054N
Liver: Neoplastic Nodule			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	2.9%	9.8%	0.0%
Terminal Rates (c)	1/35 (3%)	2/38 (5%)	0/11 (0%)
Week of First Observation	105	99	
Life Table Tests (d)	P=0.545	P=0.213	P=0.730N
Incidental Tumor Tests (d)	P=0.524N	P=0.304	P=0.730N
Cochran-Armitage Trend Test (d)	P=0.390N		
Fisher Exact Test (d)		P=0.181	P=0.500N
Intermediate Pituitary: Adenoma			
Overall Rates (a)	1/49 (2%)	4/50 (8%)	1/49 (2%)
Adjusted Rates (b)	2.9%	10.5%	9.1%
Terminal Rates (c)	1/34 (3%)	4/38 (11%)	1/11 (9%)
Week of First Observation	105	105	105
Life Table Tests (d)	P=0.236	P=0.214	P=0.493
Incidental Tumor Tests (d)	P=0.236	P=0.214	P=0.493
Cochran-Armitage Trend Test (d)	P=0.601		
Fisher Exact Test (d)		P=0.187	P=0.753
Pituitary Gland: Adenoma			
Overall Rates (a)	22/49 (45%)	21/50 (42%)	10/49 (20%)
Adjusted Rates (b)	53.4%	50.9%	55.4%
Terminal Rates (c)	15/34 (44%)	18/38 (47%)	4/11 (36%)
Week of First Observation	88	88	74
Life Table Tests (d)	P=0.367	P=0.327N	P=0.326
Incidental Tumor Tests (d)	P=0.423N	P=0.483N	P=0.348N
Cochran-Armitage Trend Test (d)	P=0.008N		
Fisher Exact Test (d)		P=0.465N	P=0.009N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	24/49 (49%)	23/50 (46%)	11/49 (22%)
Adjusted Rates (b)	56.8%	53.1%	61.7%
Terminal Rates (c)	16/34 (47%)	18/38 (47%)	5/11 (45%)
Week of First Observation	85	88	74
Life Table Tests (d)	P=0.352	P=0.319N	P=0.294
Incidental Tumor Tests (d)	P=0.376N	P=0.457N	P=0.375N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P=0.462N	P=0.005N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	0/50 (0%)	6/50 (12%)	1/49 (2%)
Adjusted Rates (b)	0.0%	15.0%	6.7%
Terminal Rates (c)	0/35 (0%)	5/38 (13%)	0/11 (0%)
Week of First Observation		88	100
Life Table Tests (d)	P=0.091	P=0.023	P=0.320
Incidental Tumor Tests (d)	P=0.143	P=0.011	P=0.602
Cochran-Armitage Trend Test (d)	P=0.398		
Fisher Exact Test (d)		P=0.013	P=0.495

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	1/50 (2%)	6/50 (12%)	1/49 (2%)
Adjusted Rates (b)	2.9%	15.0%	6.7%
Terminal Rates (c)	1/35 (3%)	5/38 (13%)	0/11 (0%)
Week of First Observation	105	88	100
Life Table Tests (d)	P=0.189	P=0.074	P=0.518
Incidental Tumor Tests (d)	P=0.258	P=0.043	P=0.714
Cochran-Armitage Trend Test (d)	P=0.579		
Fisher Exact Test (d)		P=0.056	P=0.747
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	4/48 (8%)	3/49 (6%)	2/46 (4%)
Adjusted Rates (b)	11.8%	7.4%	12.2%
Terminal Rates (c)	4/34 (12%)	2/37 (5%)	0/11 (0%)
Week of First Observation	105	88	92
Life Table Tests (d)	P=0.527	P=0.454N	P=0.529
Incidental Tumor Tests (d)	P=0.570N	P=0.539N	P=0.678N
Cochran-Armitage Trend Test (d)	P=0.280N		
Fisher Exact Test (d)		P=0.488N	P=0.359N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/48 (13%)	4/49 (8%)	2/46 (4%)
Adjusted Rates (b)	17.6%	10.1%	12.2%
Terminal Rates (c)	6/34 (18%)	3/37 (8%)	0/11 (0%)
Week of First Observation	105	88	92
Life Table Tests (d)	P=0.449N	P=0.317N	P=0.644N
Incidental Tumor Tests (d)	P=0.374N	P=0.383N	P=0.503N
Cochran-Armitage Trend Test (d)	P=0.108N		
Fisher Exact Test (d)		P=0.357N	P=0.148N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	16/50 (32%)	17/50 (34%)	8/50 (16%)
Adjusted Rates (b)	41.3%	40.0%	50.0%
Terminal Rates (c)	13/35 (37%)	13/38 (34%)	4/11 (36%)
Week of First Observation	77	79	80
Life Table Tests (d)	P=0.250	P=0.558	P=0.238
Incidental Tumor Tests (d)	P=0.458N	P=0.489	P=0.517N
Cochran-Armitage Trend Test (d)	P=0.046N		
Fisher Exact Test (d)		P=0.500	P=0.050N
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.5%	7.2%	0.0%
Terminal Rates (c)	0/35 (0%)	1/38 (3%)	0/11 (0%)
Week of First Observation	91	95	
Life Table Tests (d)	P=0.636N	P=0.351	P=0.670N
Incidental Tumor Tests (d)	P=0.428N	P=0.348	P=0.602N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	17/50 (34%)	20/50 (40%)	8/50 (16%)
Adjusted Rates (b)	42.8%	45.2%	50.0%
Terminal Rates (c)	13/35 (37%)	14/38 (37%)	4/11 (36%)
Week of First Observation	77	79	80
Life Table Tests (d)	P=0.263	P=0.464	P=0.296
Incidental Tumor Tests (d)	P=0.381N	P=0.537	P=0.435N
Cochran-Armitage Trend Test (d)	P=0.032N		
Fisher Exact Test (d)		P=0.339	P=0.032N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	Vehicle Control	60 mg/kg	120 mg/kg
Clitoral Gland: Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	7.8%	2.6%	9.1%
Terminal Rates (c)	2/35 (6%)	1/38 (3%)	1/11 (9%)
Week of First Observation	85	105	105
Life Table Tests (d)	P=0.471N	P=0.281N	P=0.720N
Incidental Tumor Tests (d)	P=0.464N	P=0.379N	P=0.680N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.309N	P=0.309N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	10.6%	5.3%	9.1%
Terminal Rates (c)	3/35 (9%)	2/38 (5%)	1/11 (9%)
Week of First Observation	85	105	105
Life Table Tests (d)	P=0.380N	P=0.304N	P=0.608N
Incidental Tumor Tests (d)	P=0.378N	P=0.387N	P=0.570N
Cochran-Armitage Trend Test (d)	P=0.118N		
Fisher Exact Test (d)		P=0.339N	P=0.181N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	12/50 (24%)	16/50 (32%)	8/50 (16%)
Adjusted Rates (b)	30.3%	39.6%	47.5%
Terminal Rates (c)	8/35 (23%)	14/38 (37%)	4/11 (36%)
Week of First Observation	85	88	37
Life Table Tests (d)	P=0.090	P=0.352	P=0.133
Incidental Tumor Tests (d)	P=0.250	P=0.284	P=0.440
Cochran-Armitage Trend Test (d)	P=0.206N		
Fisher Exact Test (d)		P=0.252	P=0.227N
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	12/50 (24%)	17/50 (34%)	8/50 (16%)
Adjusted Rates (b)	30.3%	40.8%	47.5%
Terminal Rates (c)	8/35 (23%)	14/38 (37%)	4/11 (36%)
Week of First Observation	85	60	37
Life Table Tests (d)	P=0.088	P=0.280	P=0.133
Incidental Tumor Tests (d)	P=0.313	P=0.218	P=0.440
Cochran-Armitage Trend Test (d)	P=0.208N		
Fisher Exact Test (d)		P=0.189	P=0.227N
Uterus: Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	8.6%	4.7%	0.0%
Terminal Rates (c)	3/35 (9%)	1/38 (3%)	0/11 (0%)
Week of First Observation	105	88	
Life Table Tests (d)	P=0.229N	P=0.462N	P=0.382N
Incidental Tumor Tests (d)	P=0.238N	P=0.570N	P=0.382N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences 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 tests 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 FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	Vehicle Control	500 mg/kg	1,000 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	3.0%	12.7%	10.0%
Terminal Rates (c)	1/33 (3%)	2/27 (7%)	1/10 (10%)
Week of First Observation	104	91	104
Life Table Tests (d)	P=0.258	P=0.145	P=0.476
Incidental Tumor Tests (d)	P=0.464	P=0.245	P=0.476
Cochran-Armitage Trend Test (d)	P=0.601		
Fisher Exact Test (d)		P=0.181	P=0.753
Subcutaneous Tissue: Fibrosarcoma			
Overall Rates (a)	14/50 (28%)	12/50 (24%)	7/50 (14%)
Adjusted Rates (b)	35.0%	29.9%	34.5%
Terminal Rates (c)	8/33 (24%)	2/27 (7%)	2/10 (20%)
Week of First Observation	66	78	55
Life Table Tests (d)	P=0.497N	P=0.490N	P=0.583
Incidental Tumor Tests (d)	P=0.010N	P=0.205N	P=0.077N
Cochran-Armitage Trend Test (d)	P=0.058N		
Fisher Exact Test (d)		P=0.410N	P=0.070N
Subcutaneous Tissue: Sarcoma			
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	5.8%	3.7%	8.5%
Terminal Rates (c)	1/33 (3%)	1/27 (4%)	0/10 (0%)
Week of First Observation	101	104	68
Life Table Tests (d)	P=0.192	P=0.572N	P=0.277
Incidental Tumor Tests (d)	P=0.479	P=0.428N	P=0.689
Cochran-Armitage Trend Test (d)	P=0.399		
Fisher Exact Test (d)		P=0.500N	P=0.500
Subcutaneous Tissue: Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	16/50 (32%)	13/50 (26%)	10/50 (20%)
Adjusted Rates (b)	39.2%	32.7%	40.1%
Terminal Rates (c)	9/33 (27%)	3/27 (11%)	2/10 (20%)
Week of First Observation	66	78	55
Life Table Tests (d)	P=0.429	P=0.425N	P=0.412
Incidental Tumor Tests (d)	P=0.019N	P=0.144N	P=0.094N
Cochran-Armitage Trend Test (d)	P=0.105N		
Fisher Exact Test (d)		P=0.330N	P=0.127N
Subcutaneous Tissue: Fibroma, Sarcoma, Fibrosarcoma, or Neurofibrosarcoma			
Overall Rates (a)	16/50 (32%)	16/50 (32%)	11/50 (22%)
Adjusted Rates (b)	39.2%	40.3%	47.6%
Terminal Rates (c)	9/33 (27%)	5/27 (19%)	3/10 (30%)
Week of First Observation	66	78	55
Life Table Tests (d)	P=0.261	P=0.479	P=0.289
Incidental Tumor Tests (d)	P=0.055N	P=0.344N	P=0.184N
Cochran-Armitage Trend Test (d)	P=0.160N		
Fisher Exact Test (d)		P=0.585	P=0.184N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	9.1%	22.6%	18.6%
Terminal Rates (c)	3/33 (9%)	3/27 (11%)	1/10 (10%)
Week of First Observation	104	84	55
Life Table Tests (d)	P=0.096	P=0.078	P=0.146
Incidental Tumor Tests (d)	P=0.439	P=0.194	P=0.311
Cochran-Armitage Trend Test (d)	P=0.434		
Fisher Exact Test (d)		P=0.100	P=0.500

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	8.4%	7.4%	0.0%
Terminal Rates (c)	1/33 (3%)	2/27 (7%)	0/10 (0%)
Week of First Observation	97	104	
Life Table Tests (d)	P=0.268N	P=0.584N	P=0.338N
Incidental Tumor Tests (d)	P=0.077N	P=0.367N	P=0.031N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	10/50 (20%)	4/50 (8%)
Adjusted Rates (b)	17.0%	29.0%	18.6%
Terminal Rates (c)	4/33 (12%)	6/27 (22%)	1/10 (10%)
Week of First Observation	97	84	55
Life Table Tests (d)	P=0.246	P=0.145	P=0.381
Incidental Tumor Tests (d)	P=0.338N	P=0.398	P=0.423N
Cochran-Armitage Trend Test (d)	P=0.330N		
Fisher Exact Test (d)		P=0.207	P=0.370N
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	11.1%	0.0%
Terminal Rates (c)	0/33 (0%)	3/27 (11%)	0/10 (0%)
Week of First Observation		104	
Life Table Tests (d)	P=0.345	P=0.087	(e)
Incidental Tumor Tests (d)	P=0.345	P=0.087	(e)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Test (d)		P=0.121	(e)
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	9/50 (18%)	9/50 (18%)	0/50 (0%)
Adjusted Rates (b)	26.2%	28.2%	0.0%
Terminal Rates (c)	8/33 (24%)	6/27 (22%)	0/10 (0%)
Week of First Observation	88	86	
Life Table Tests (d)	P=0.113N	P=0.468	P=0.068N
Incidental Tumor Tests (d)	P=0.032N	P=0.596N	P=0.037N
Cochran-Armitage Trend Test (d)	P=0.004N		
Fisher Exact Test (d)		P=0.603N	P=0.002N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	3.0%	8.9%	19.3%
Terminal Rates (c)	1/33 (3%)	0/27 (0%)	0/10 (0%)
Week of First Observation	104	91	68
Life Table Tests (d)	P=0.028	P=0.272	P=0.044
Incidental Tumor Tests (d)	P=0.380	P=0.552	P=0.360
Cochran-Armitage Trend Test (d)	P=0.133		
Fisher Exact Test (d)		P=0.309	P=0.181
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/50 (8%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	12.1%	14.8%	22.2%
Terminal Rates (c)	4/33 (12%)	4/27 (15%)	1/10 (10%)
Week of First Observation	104	104	76
Life Table Tests (d)	P=0.069	P=0.530	P=0.115
Incidental Tumor Tests (d)	P=0.175	P=0.530	P=0.322
Cochran-Armitage Trend Test (d)	P=0.429		
Fisher Exact Test (d)		P=0.643N	P=0.500

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	Vehicle Control	500 mg/kg	1,000 mg/kg
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	9/50 (18%)	10/50 (20%)	10/50 (20%)
Adjusted Rates (b)	23.8%	30.2%	62.8%
Terminal Rates (c)	5/33 (15%)	6/27 (22%)	5/10 (50%)
Week of First Observation	83	81	92
Life Table Tests (d)	P=0.018	P=0.398	P=0.017
Incidental Tumor Tests (d)	P=0.331	P=0.511N	P=0.427
Cochran-Armitage Trend Test (d)	P=0.450		
Fisher Exact Test (d)		P=0.500	P=0.500
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	12/50 (24%)	13/50 (26%)	15/50 (30%)
Adjusted Rates (b)	31.9%	40.2%	74.4%
Terminal Rates (c)	8/33 (24%)	9/27 (33%)	6/10 (60%)
Week of First Observation	83	81	76
Life Table Tests (d)	P=0.002	P=0.355	P=0.002
Incidental Tumor Tests (d)	P=0.113	P=0.576N	P=0.195
Cochran-Armitage Trend Test (d)	P=0.286		
Fisher Exact Test (d)		P=0.500	P=0.326
Harderian Gland: Adenoma			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	15.2%	10.1%	0.0%
Terminal Rates (c)	5/33 (15%)	2/27 (7%)	0/10 (0%)
Week of First Observation	104	96	
Life Table Tests (d)	P=0.152N	P=0.460N	P=0.230N
Incidental Tumor Tests (d)	P=0.093N	P=0.381N	P=0.230N
Cochran-Armitage Trend Test (d)	P=0.023N		
Fisher Exact Test (d)		P=0.357N	P=0.028N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences 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 tests 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 1,000 mg/kg and vehicle control groups.

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	Vehicle Control	250 mg/kg
Subcutaneous Tissue: Fibroma		
Overall Rates (a)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	7.9%	5.7%
Terminal Rates (c)	2/37 (5%)	2/35 (6%)
Week of First Observation	103	104
Life Table Test (d)		P=0.528N
Incidental Tumor Test (d)		P=0.475N
Fisher Exact Test (d)		P=0.500N
Subcutaneous Tissue: Fibrosarcoma		
Overall Rates (a)	8/50 (16%)	5/50 (10%)
Adjusted Rates (b)	17.7%	11.8%
Terminal Rates (c)	2/37 (5%)	1/35 (3%)
Week of First Observation	81	95
Life Table Test (d)		P=0.301N
Incidental Tumor Test (d)		P=0.172N
Fisher Exact Test (d)		P=0.277N
Subcutaneous Tissue: Fibroma or Fibrosarcoma		
Overall Rates (a)	11/50 (22%)	7/50 (14%)
Adjusted Rates (b)	24.4%	17.0%
Terminal Rates (c)	4/37 (11%)	3/35 (9%)
Week of First Observation	81	95
Life Table Test (d)		P=0.257N
Incidental Tumor Test (d)		P=0.131N
Fisher Exact Test (d)		P=0.218N
Lung: Alveolar/Bronchiolar Adenoma		
Overall Rates (a)	12/50 (24%)	6/50 (12%)
Adjusted Rates (b)	29.8%	16.2%
Terminal Rates (c)	9/37 (24%)	5/35 (14%)
Week of First Observation	93	93
Life Table Test (d)		P=0.121N
Incidental Tumor Test (d)		P=0.070N
Fisher Exact Test (d)		P=0.096N
Lung: Alveolar/Bronchiolar Carcinoma		
Overall Rates (a)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	5.4%	12.8%
Terminal Rates (c)	2/37 (5%)	3/35 (9%)
Week of First Observation	104	84
Life Table Test (d)		P=0.202
Incidental Tumor Test (d)		P=0.200
Fisher Exact Test (d)		P=0.218
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma		
Overall Rates (a)	14/50 (28%)	11/50 (22%)
Adjusted Rates (b)	34.8%	28.1%
Terminal Rates (c)	11/37 (30%)	8/35 (23%)
Week of First Observation	93	84
Life Table Test (d)		P=0.375N
Incidental Tumor Test (d)		P=0.285N
Fisher Exact Test (d)		P=0.322N
Hematopoietic System: Lymphoma, All Malignant		
Overall Rates (a)	7/50 (14%)	5/50 (10%)
Adjusted Rates (b)	18.2%	13.8%
Terminal Rates (c)	6/37 (16%)	4/35 (11%)
Week of First Observation	98	102
Life Table Test (d)		P=0.416N
Incidental Tumor Test (d)		P=0.353N
Fisher Exact Test (d)		P=0.380N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	Vehicle Control	250 mg/kg
Circulatory System: Hemangiosarcoma		
Overall Rates (a)	4/50 (8%)	2/50 (4%)
Adjusted Rates (b)	10.8%	5.7%
Terminal Rates (c)	4/37 (11%)	2/35 (6%)
Week of First Observation	105	104
Life Table Test (d)		P=0.362N
Incidental Tumor Test (d)		P=0.362N
Fisher Exact Test (d)		P=0.339N
Circulatory System: Hemangioma or Hemangiosarcoma		
Overall Rates (a)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	10.8%	8.6%
Terminal Rates (c)	4/37 (11%)	3/35 (9%)
Week of First Observation	105	104
Life Table Test (d)		P=0.531N
Incidental Tumor Test (d)		P=0.531N
Fisher Exact Test (d)		P=0.500N
Liver: Hepatocellular Adenoma		
Overall Rates (a)	5/50 (10%)	10/50 (20%)
Adjusted Rates (b)	12.7%	24.2%
Terminal Rates (c)	4/37 (11%)	6/35 (17%)
Week of First Observation	84	79
Life Table Test (d)		P=0.124
Incidental Tumor Test (d)		P=0.099
Fisher Exact Test (d)		P=0.131
Liver: Hepatocellular Carcinoma		
Overall Rates (a)	10/50 (20%)	11/50 (22%)
Adjusted Rates (b)	23.4%	27.0%
Terminal Rates (c)	6/37 (16%)	6/35 (17%)
Week of First Observation	81	91
Life Table Test (d)		P=0.464
Incidental Tumor Test (d)		P=0.483
Fisher Exact Test (d)		P=0.500
Liver: Hepatocellular Adenoma or Carcinoma		
Overall Rates (a)	15/50 (30%)	21/50 (42%)
Adjusted Rates (b)	34.7%	47.0%
Terminal Rates (c)	10/37 (27%)	12/35 (34%)
Week of First Observation	81	79
Life Table Test (d)		P=0.148
Incidental Tumor Test (d)		P=0.109
Fisher Exact Test (d)		P=0.149
Forestomach: Squamous Cell Papilloma or Carcinoma		
Overall Rates (a)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	8.6%
Terminal Rates (c)	0/37 (0%)	3/35 (9%)
Week of First Observation		104
Life Table Test (d)		P=0.111
Incidental Tumor Test (d)		P=0.111
Fisher Exact Test (d)		P=0.121

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the 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 Fisher exact test compares directly the overall incidence rates. A lower incidence in the dosed group is indicated by (N).

TABLE E5. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	Vehicle Control	500 mg/kg
Lung: Alveolar/Bronchiolar Adenoma		
Overall Rates (a)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	8.6%	18.6%
Terminal Rates (c)	1/29 (3%)	5/30 (17%)
Week of First Observation	98	76
Life Table Test (d)		P=0.238
Incidental Tumor Test (d)		P=0.138
Fisher Exact Test (d)		P=0.243
Lung: Alveolar/Bronchiolar Carcinoma		
Overall Rates (a)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	0.0%	13.3%
Terminal Rates (c)	0/29 (0%)	4/30 (13%)
Week of First Observation		105
Life Table Test (d)		P=0.066
Incidental Tumor Test (d)		P=0.066
Fisher Exact Test (d)		P=0.059
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma		
Overall Rates (a)	3/50 (6%)	9/50 (18%)
Adjusted Rates (b)	8.6%	28.3%
Terminal Rates (c)	1/29 (3%)	8/30 (27%)
Week of First Observation	98	76
Life Table Test (d)		P=0.063
Incidental Tumor Test (d)		P=0.028
Fisher Exact Test (d)		P=0.061
Hematopoietic System: Lymphoma, All Malignant		
Overall Rates (a)	19/50 (38%)	15/50 (30%)
Adjusted Rates (b)	49.7%	45.0%
Terminal Rates (c)	11/29 (38%)	12/30 (40%)
Week of First Observation	77	82
Life Table Test (d)		P=0.305N
Incidental Tumor Test (d)		P=0.467N
Cochran-Armitage Trend Test (d)		
Fisher Exact Test (d)		P=0.264N
Liver: Hepatocellular Adenoma		
Overall Rates (a)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	3.4%	13.3%
Terminal Rates (c)	1/29 (3%)	4/30 (13%)
Week of First Observation	105	105
Life Table Test (d)		P=0.187
Incidental Tumor Test (d)		P=0.187
Fisher Exact Test (d)		P=0.181
Liver: Hepatocellular Carcinoma		
Overall Rates (a)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	6.6%	12.9%
Terminal Rates (c)	1/29 (3%)	3/30 (10%)
Week of First Observation	104	104
Life Table Test (d)		P=0.349
Incidental Tumor Test (d)		P=0.144
Fisher Exact Test (d)		P=0.339
Liver: Hepatocellular Adenoma or Carcinoma		
Overall Rates (a)	3/50 (6%)	8/50 (16%)
Adjusted Rates (b)	9.9%	25.8%
Terminal Rates (c)	2/29 (7%)	7/30 (23%)
Week of First Observation	104	104
Life Table Test (d)		P=0.109
Incidental Tumor Test (d)		P=0.038
Fisher Exact Test (d)		P=0.100

TABLE E5. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE FIRST TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	Vehicle Control	500 mg/kg
Pituitary Gland: Adenoma		
Overall Rates (a)	12/43 (28%)	8/46 (17%)
Adjusted Rates (b)	39.9%	26.3%
Terminal Rates (c)	8/25 (32%)	7/29 (24%)
Week of First Observation	100	89
Life Table Test (d)		P=0.164N
Incidental Tumor Test (d)		P=0.322N
Fisher Exact Test (d)		P=0.175N
Pituitary Gland: Adenoma or Carcinoma		
Overall Rates (a)	14/43 (33%)	9/46 (20%)
Adjusted Rates (b)	47.0%	29.7%
Terminal Rates (c)	10/25 (40%)	8/29 (28%)
Week of First Observation	100	89
Life Table Test (d)		P=0.108N
Incidental Tumor Test (d)		P=0.223N
Fisher Exact Test (d)		P=0.124N
Harderian Gland: Adenoma		
Overall Rates (a)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	10.0%
Terminal Rates (c)	0/29 (0%)	3/30 (10%)
Week of First Observation		105
Life Table Test (d)		P=0.126
Incidental Tumor Test (d)		P=0.126
Fisher Exact Test (d)		P=0.121

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the 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 Fisher exact test compares directly the overall incidence rates. A lower incidence in the dosed group is indicated by (N).

TABLE E6. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE

	Vehicle Control	250 mg/kg
Lung: Alveolar/Bronchiolar Adenoma		
Overall Rates (a)	5/50 (10%)	6/50 (12%)
Adjusted Rates (b)	15.4%	14.9%
Terminal Rates (c)	3/26 (12%)	4/36 (11%)
Week of First Observation	64	81
Life Table Test (d)		P=0.596N
Incidental Tumor Test (d)		P=0.497
Fisher Exact Test (d)		P=0.500
Lung: Alveolar/Bronchiolar Carcinoma		
Overall Rates (a)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	3.8%	7.5%
Terminal Rates (c)	1/26 (4%)	2/36 (6%)
Week of First Observation	104	81
Life Table Test (d)		P=0.405
Incidental Tumor Test (d)		P=0.342
Fisher Exact Test (d)		P=0.309
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma		
Overall Rates (a)	6/50 (12%)	8/50 (16%)
Adjusted Rates (b)	19.0%	20.2%
Terminal Rates (c)	4/26 (15%)	6/36 (17%)
Week of First Observation	64	81
Life Table Test (d)		P=0.580
Incidental Tumor Test (d)		P=0.437
Fisher Exact Test (d)		P=0.387
Hematopoietic System: Malignant Lymphoma, Histiocytic Type		
Overall Rates (a)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	3.2%	8.3%
Terminal Rates (c)	0/26 (0%)	3/36 (8%)
Week of First Observation	97	104
Life Table Test (d)		P=0.418
Incidental Tumor Test (d)		P=0.374
Cochran-Armitage Trend Test (d)		
Fisher Exact Test (d)		P=0.309
Hematopoietic System: Lymphoma, All Malignant		
Overall Rates (a)	15/50 (30%)	15/50 (30%)
Adjusted Rates (b)	42.9%	38.3%
Terminal Rates (c)	8/26 (31%)	12/36 (33%)
Week of First Observation	75	91
Life Table Test (d)		P=0.267N
Incidental Tumor Test (d)		P=0.507N
Cochran-Armitage Trend Test (d)		
Fisher Exact Test (d)		P=0.586N
Liver: Hepatocellular Adenoma		
Overall Rates (a)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	25.9%	10.4%
Terminal Rates (c)	4/26 (15%)	3/36 (8%)
Week of First Observation	89	88
Life Table Test (d)		P=0.083N
Incidental Tumor Test (d)		P=0.154N
Fisher Exact Test (d)		P=0.178N

TABLE E6. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE SECOND TWO-YEAR GAVAGE STUDY OF *n*-BUTYL CHLORIDE (Continued)

	Vehicle Control	250 mg/kg
Liver: Hepatocellular Carcinoma		
Overall Rates (a)	1/50 (2%)	5/50 (10%)
Adjusted Rates (b)	2.4%	13.3%
Terminal Rates (c)	0/26 (0%)	4/36 (11%)
Week of First Observation	88	93
Life Table Test (d)		P=0.179
Incidental Tumor Test (d)		P=0.124
Fisher Exact Test (d)		P=0.102
Liver: Hepatocellular Adenoma or Carcinoma		
Overall Rates (a)	9/50 (18%)	7/50 (14%)
Adjusted Rates (b)	27.7%	17.9%
Terminal Rates (c)	4/26 (15%)	5/36 (14%)
Week of First Observation	88	88
Life Table Test (d)		P=0.207N
Incidental Tumor Test (d)		P=0.369N
Fisher Exact Test (d)		P=0.393N
Forestomach: Squamous Cell Papilloma		
Overall Rates (a)	3/48 (6%)	3/49 (6%)
Adjusted Rates (b)	11.5%	8.6%
Terminal Rates (c)	3/26 (12%)	3/35 (9%)
Week of First Observation	104	104
Life Table Test (d)		P=0.520N
Incidental Tumor Test (d)		P=0.520N
Fisher Exact Test (d)		P=0.651N
Pituitary Gland: Adenoma		
Overall Rates (a)	7/39 (18%)	7/41 (17%)
Adjusted Rates (b)	29.9%	21.9%
Terminal Rates (c)	6/22 (27%)	7/32 (22%)
Week of First Observation	101	104
Life Table Test (d)		P=0.318N
Incidental Tumor Test (d)		P=0.401N
Fisher Exact Test (d)		P=0.575N
Pituitary Gland: Adenoma or Carcinoma		
Overall Rates (a)	8/39 (21%)	8/41 (20%)
Adjusted Rates (b)	34.3%	25.0%
Terminal Rates (c)	7/22 (32%)	8/32 (25%)
Week of First Observation	101	104
Life Table Test (d)		P=0.287N
Incidental Tumor Test (d)		P=0.363N
Fisher Exact Test (d)		P=0.566N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between the 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 Fisher exact test compares directly the overall incidence rates. A lower incidence in the 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 PANCREATIC ACINAR CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	Incidence of Adenoma or Carcinoma in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
Diglycidyl resorcinol ether	2/49
Diglycidyl resorcinol ether	1/49
1,2-Dichloropropane	1/48
Chlorodibromomethane	1/50
TOTAL	(b) 5/196 (2.6%)
SD (c)	1.02%
Range (d)	
High	2/49
Low	1/50
Overall Historical Incidence	
TOTAL	(e) 47/1,086 (4.3%)
SD (c)	7.37%
Range (d)	
High	(f) 14/50
Low	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes one acinar cell carcinoma and four acinar cell adenomas
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes 45 acinar cell adenomas, 1 adenoma, NOS, and 2 acinar cell carcinomas. One of the animals that had an acinar cell carcinoma also had an acinar cell adenoma.
(f) Second high, 11/50; third high, 5/49

TABLE F2. HISTORICAL INCIDENCE OF URINARY BLADDER TRANSITIONAL CELL TUMORS IN F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

MALE

No urinary bladder tumors have been observed in 200 male vehicle control animals at EG&G Mason Research Institute or in 1,070 male vehicle control animals in all NTP studies.

FEMALE

No urinary bladder tumors have been observed in 200 vehicle control animals at EG&G Mason Research Institute.

Overall Historical Incidence

Number of Animals Examined	Number of Tumors	Diagnosis
1,060	1	Papilloma, NOS
	2	Transitional cell papilloma
Total	3 (0.3%)	

(a) Data as of August 3, 1984, for studies of at least 104 weeks. No more than one tumor was observed in any vehicle control group.

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

Study	Incidence of Pheochromocytoma or Pheochromocytoma, Malignant in Vehicle Controls
Historical Incidence at EG&G Mason Research Institute	
Diglycidyl resorcinol ether	3/50
Diglycidyl resorcinol ether	5/50
1,2-Dichloropropane	2/49
Chlorodibromomethane	3/50
TOTAL	13/199 (6.5%)
SD (b)	2.49%
Range (c)	
High	5/50
Low	2/49
Overall Historical Incidence	
TOTAL	(d) 65/1,093 (5.9%)
SD (b)	2.99%
Range (c)	
High	6/50
Low	1/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes two malignant tumors, one of which was in an animal also bearing a benign tumor. The reported range is the same as for benign tumors only.

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

Study	Incidence in Vehicle Controls		
	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	1/50	0/50	1/50
1,2-Dichloropropane	0/50	2/50	2/50
Chlorodibromomethane	0/50	0/50	0/50
Bis(2-chloro-1-methylethyl)ether	1/50	1/50	1/50
TOTAL	2/200 (1.0%)	3/200 (1.5%)	4/200 (2.0%)
SD (b)	1.15%	1.91%	1.63%
Range (c)			
High	1/50	2/50	2/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	5/1,097 (0.5%)	46/1,097 (4.2%)	49/1,097 (4.5%)
SD (b)	0.86%	3.90%	3.75%
Range (c)			
High	1/50	7/50	7/50
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984, 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 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 EG&G Mason Research Institute			
Diglycidyl resorcinol ether	7/49	7/49	13/49
1,2-Dichloropropane	7/50	11/50	18/50
Chlorodibromomethane	14/50	10/50	23/50
Bis(2-chloro-1-methylethyl)ether	8/50	5/50	13/50
TOTAL	36/199 (18.1%)	33/199 (16.6%)	67/199 (33.7%)
SD (b)	6.68%	5.47%	9.44%
Range (c)			
High	14/50	11/50	23/50
Low	7/50	5/50	13/50
Overall Historical Incidence			
TOTAL	140/1,091 (12.8%)	238/1,091 (21.8%)	357/1,091 (32.7%)
SD (b)	6.82%	7.75%	9.63%
Range (c)			
High	14/50	19/50	25/50
Low	0/50	5/50	7/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

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

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	3/48	0/48	3/48
1,2-Dichloropropane	0/50	1/50	1/50
Chlorodibromomethane	2/50	4/50	6/50
Bis(2-chloro-1-methylethyl)ether	5/50	2/50	7/50
TOTAL	10/198 (5.1%)	7/198 (3.5%)	17/198 (8.6%)
SD (b)	4.19%	3.42%	5.47%
Range (c)			
High	5/50	4/50	7/50
Low	0/50	0/48	1/50
Overall Historical Incidence			
TOTAL	41/1,092 (3.8%)	34/1,092 (3.1%)	74/1,092 (6.8%)
SD (b)	2.65%	2.29%	3.63%
Range (c)			
High	5/50	4/50	7/50
Low	0/50	0/50	1/50

(a) Data as of August 3, 1984, 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 ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidyl resorcinol ether	3/49	0/49	3/49
1,2-Dichloropropane	5/50	1/50	6/50
Chlorodibromomethane	3/50	2/50	5/50
Bis(2-chloro-1-methylethyl)ether	1/50	0/50	1/50
TOTAL	12/199 (6.0%)	3/199 (1.5%)	15/199 (7.5%)
SD (b)	3.27%	1.91%	4.42%
Range (c)			
High	5/50	2/50	6/50
Low	1/50	0/50	1/50
Overall Historical Incidence			
TOTAL	45/1,087 (4.1%)	12/1,087 (1.1%)	57/1,087 (5.2%)
SD (b)	2.88%	1.60%	3.47%
Range (c)			
High	5/50	2/50	6/50
Low	0/50	0/50	0/49

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

APPENDIX G

GENETIC TOXICOLOGY OF *n*-BUTYL CHLORIDE

TABLE G1. MUTAGENICITY OF *n*-BUTYL CHLORIDE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b)		
		−S9	+S9 (rat)	+S9 (hamster)
TA100	0	114 ± 3.8	109 ± 6.7	99 ± 3.3
	10	112 ± 10.6	120 ± 8.1	95 ± 2.9
	33	131 ± 1.0	118 ± 5.8	105 ± 7.8
	100	122 ± 7.7	110 ± 9.9	102 ± 3.5
	333	122 ± 8.0	106 ± 7.8	97 ± 3.5
	666	119 ± 9.6	93 ± 6.5	91 ± 7.0
TA1535	0	24 ± 3.1	10 ± 2.6	12 ± 1.5
	10	25 ± 4.2	11 ± 1.2	5 ± 0.7
	33	24 ± 2.0	12 ± 1.2	11 ± 2.6
	100	29 ± 3.3	8 ± 1.9	9 ± 1.5
	333	27 ± 1.9	11 ± 2.5	6 ± 0.9
	666	23 ± 2.6	9 ± 1.9	9 ± 0.9
TA1537	0	6 ± 0.9	7 ± 1.5	7 ± 2.8
	10	8 ± 1.8	7 ± 1.7	9 ± 1.0
	33	7 ± 2.1	6 ± 1.2	9 ± 2.7
	100	5 ± 0.6	8 ± 0.9	11 ± 0.6
	333	4 ± 1.2	6 ± 1.7	8 ± 1.2
	666	7 ± 1.9	9 ± 1.7	12 ± 1.8
TA98	0	20 ± 1.0	18 ± 1.7	24 ± 2.2
	10	17 ± 1.9	25 ± 4.6	21 ± 3.0
	33	20 ± 2.0	21 ± 2.6	23 ± 0.9
	100	19 ± 2.3	24 ± 1.2	22 ± 2.0
	333	13 ± 1.2	22 ± 3.5	27 ± 3.0
	666	11 ± 1.2	26 ± 3.6	22 ± 3.8

(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 (dimethyl sulfoxide) 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 was poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Mean ± standard error

TABLE G2. MUTAGENICITY OF *n*-BUTYL CHLORIDE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

Compound	Dose (μg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
DMSO	--				
		109	69	100	52
		117	72	100	54
		96	67	100	48
		134	60	100	74
Methyl Methanesulfonate					
	15	518	30	22	527
		600	37	25	541
n-Butyl Chloride					
	350	128	83	83	52
		113	66	90	57
	400	184	94	57	66
		176	84	60	70
	450	286	97	50	99
		204	56	44	121
	500	769	65	16	394
		255	83	91	103
	550	523	52	24	335
		826	64	13	430

(a) Experiments were performed twice, all doses were tested in duplicate, except the solvent control dimethyl sulfoxide (DMSO), which was tested in quadruplicate. 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 G3. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY *n*-BUTYL CHLORIDE (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	SCE/Cell	Dose (µg/ml)	SCE/Cell
DMSO		DMSO	
10 µl	8.44	10 µl	8.86
n-Butyl Chloride		*n*-Butyl Chloride	
500	8.04	1,600	9.14
1,600	9.30	3,000	8.98
3,000	7.92	4,000	9.68
4,000	8.38	5,000	9.64
5,000	9.06		
Mitomycin C		Cyclophosphamide	
0.001	26.06	0.3	10.54
0.010	51.00	2.0	25.60

(a) SCE = sister-chromatid exchange; CHO = Chinese hamster ovary
(b) 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 24 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 KCl (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).
(c) 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 G4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY *n*-BUTYL CHLORIDE (a)

−S9 (b)		+S9 (c)	
Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)	Dose (µg/ml)	Abs/100 Cells (percent cells w/abs)
DMSO		DMSO	
10 µl	1 (1)	10 µl	5 (3)
n-Butyl Chloride		*n*-Butyl Chloride	
1,600	1 (1)	1,600	2 (2)
3,000	3 (3)	3,000	4 (4)
4,000	1 (1)	4,000	3 (3)
5,000	1 (1)	5,000	2 (2)
Mitomycin C		Cyclophosphamide	
0.25	21 (16)	15	56 (42)
1.00	48 (38)	50	87 (51)

(a) Abs = aberrations; CHO = Chinese hamster ovary
(b) 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.
(c) 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 H

CHEMICAL CHARACTERIZATION OF

n-BUTYL CHLORIDE

APPENDIX H. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of *n*-Butyl Chloride Lot No. 780135-3 Performed by the Analytical Chemistry Laboratory

	Determined	Literature Values
A. Physical properties		
1. Boiling point:	79° C (visual)	78° C (CRC, 44th ed.)
2. Density:	$^{24}_{25}$d: 0.88214 ± 0.00004(δ) g/ml	0.884 g/ml (CRC, 44th ed.)
3. Appearance:	Clear, colorless liquid	Colorless liquid (CRC, 44th ed.)
B. Spectral data		
1. Infrared		
Instrument:	Perkin-Elmer Infracord	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 7	Identical to literature spectrum (Sadtler Standard Spectra)
2. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	1% Methanol (v/v)	
Results:	No absorbance exhibited between 800 and 220 nm	Consistent with structure

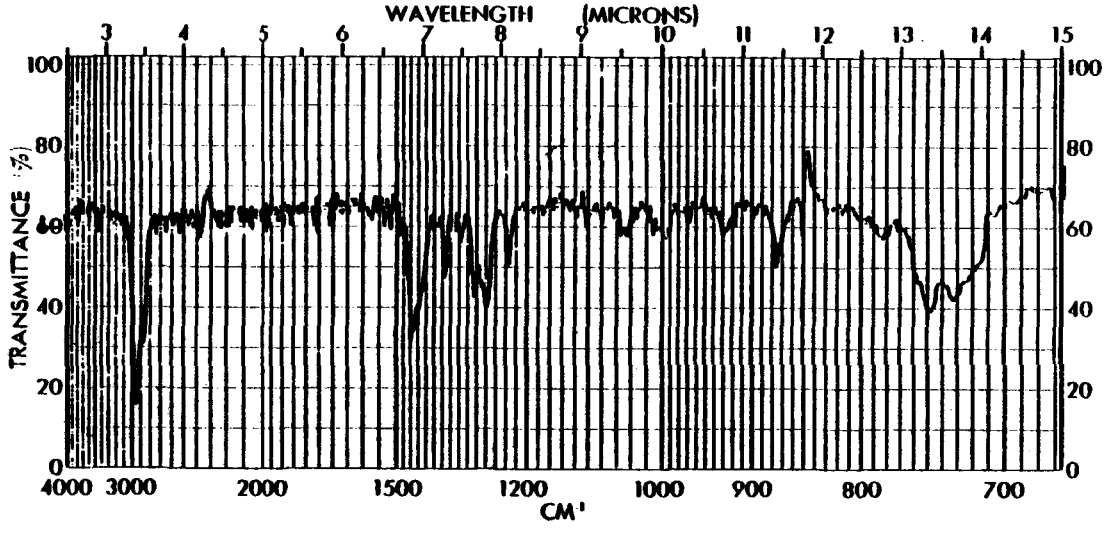

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF *n*-BUTYL CHLORIDE (LOT NO. 780135-3)

	Determined	Literature Values
3. Nuclear magnetic resonance		
Instrument:	Varian EM360-A	
Solvent:	Neat, tetramethylsilane added as an internal standard	
Assignments:	See Figure 8	Identical to literature spectrum (Sadtler Standard Spectra)
Chemical shift (δ):	a m, 1.00 J_{a-b} = 6 Hz b m, 1.20-1.90 c t, 3.49 J_{b-c} = 6 Hz	
Integration ratios:	a 3.03 b 4.04 c 1.93	

C. Water analysis (Karl Fischer): 0.46% ± 0.14(δ)%

D. Elemental analysis

Element	C	H	Cl
Theory (T)	51.90	9.80	38.30
Determined (D)	51.64 51.80	9.70 9.78	38.29 38.42
Percent D/T	99.7	99.4	100.1

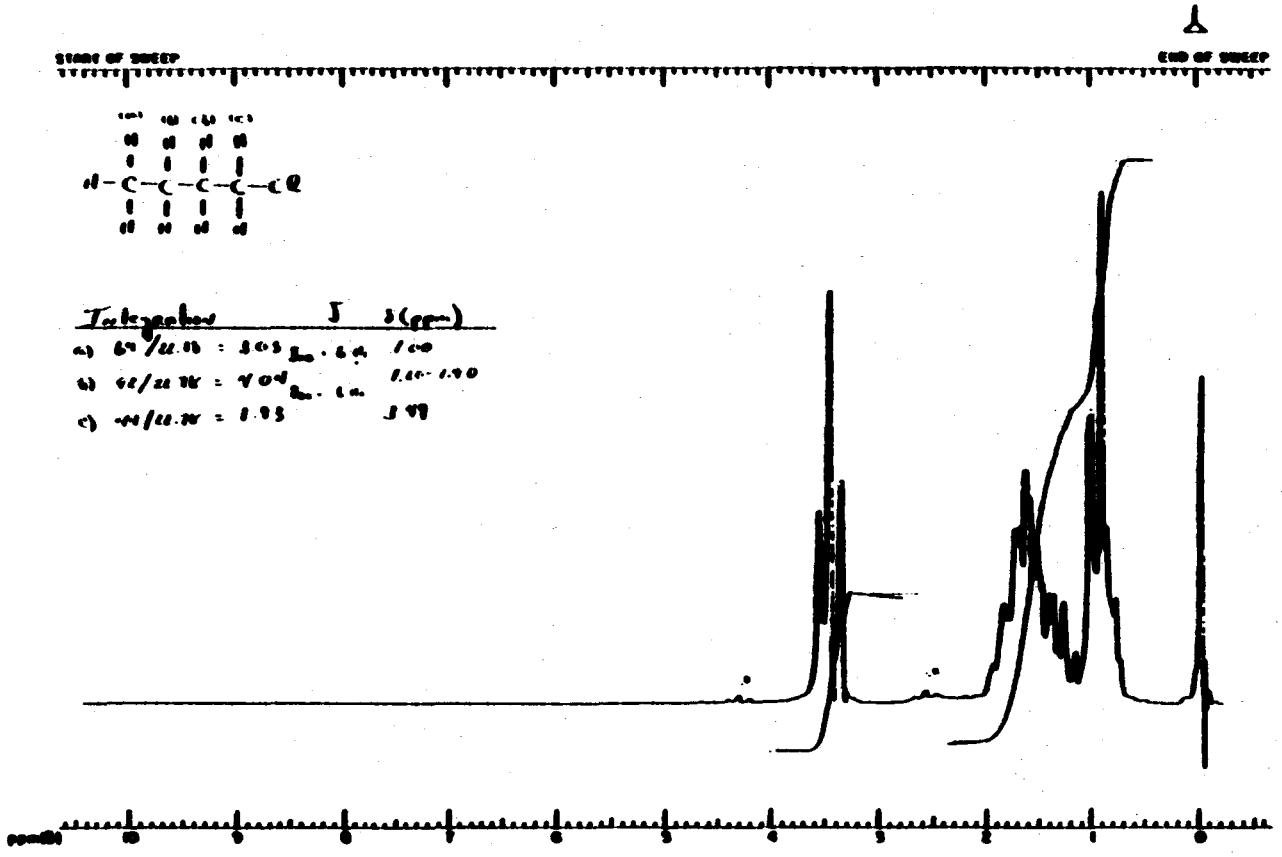

FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF *n*-BUTYL CHLORIDE (LOT NO. 780135-3)

E. **Free acid titration:** 25 ± 4(δ) ppm (as hydrochloric acid)

F. **Chromatographic analyses:** Gas chromatography

System 1

Instrument: Varian 3700
Detector: Flame ionization
Column: Carbopack C/0.1% SP1000, 1.8 m × 4 mm ID, glass
Inlet temperature: 250° C
Detector temperature: 330° C
Carrier gas: Nitrogen, 70 ml/min
Sample injected: 5.6 µl of the neat compound, and 1% (v/v) and 0.5% (v/v) to quantitate the impurity and check the linearity of detector response

Results: A major peak preceded by one impurity

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	9.2	0.81	0.27
2	11.4	1.00	100

System 2

Instrument: Perkin-Elmer 3920
Detector: Flame ionization
Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport; 1.8 m × 4 mm ID, glass
Inlet temperature: 200° C
Detector temperature: 260° C
Carrier gas: Nitrogen, 45 ml/min
Sample injected: 3.0 µl of the neat compound, and 1.0% (v/v) and 0.5% (v/v) to quantitate the impurity and check the linearity of detector response

Results: A major peak preceded by one impurity

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	1.8	0.69	0.40
2	2.6	1.00	100

G. **Conclusions:** The results of the elemental analysis for carbon, hydrogen, and chlorine were in agreement with theoretical values. The water content by Karl Fischer analysis was 0.46% ± 0.14(δ)%. Free acid titration indicated a concentration of 25 ± 4 ppm (as hydrochloric acid). Gas chromatography, with a Carbopack C/0.1% SP1000 column, detected a major peak preceded by one impurity with a relative area of 0.27%. A second gas chromatographic system, with a 20% SP2100/0.1% Carbowax 1500 column, detected a major peak preceded by one impurity with a relative area of 0.40%. The infrared and nuclear magnetic resonance spectra were identical to literature spectra. The ultraviolet and visible spectra were consistent with the structure.

II. Test Chemical Stability Study of *n*-Butyl Chloride Lot No. 780135-3 Performed by the Analytical Chemistry Laboratory

A. **Sample storage:** Samples of *n*-butyl chloride were stored in glass vessels with Teflon®-lined lids for 2 weeks at temperatures of −20°, 5°, 25°, and 60° C.

B. **Analytical method:** Samples were analyzed by gas chromatography with the following system:

Instrument: Varian 3700 (autosampler)
Detector: Flame ionization
Column: Carbopack C/0.1% SP1000, 1.8 m × 4 mm ID, glass
Inlet temperature: 250° C
Detector temperature: 330° C
Carrier gas: Nitrogen, 60 ml/min
Oven temperature: 110° C
Retention times: *n*-butyl chloride--3.4 min; internal standard--7.8 min
Sample injected: Samples (1 ml) from each storage temperature were dissolved in methylene chloride (100 ml) containing 0.7% pentane internal standard.

C. **Results:** The results were compared with the values obtained for the −20° C sample.

Storage Temperature	Percent Recovery
−20° C	100.0
5° C	100.0 ± 0.4(δ)
25° C	99.3 ± 0.3(δ)
60° C	98.8 ± 1.4(δ)

D. **Conclusion:** *n*-Butyl chloride is stable as the bulk chemical for 2 weeks at temperatures up to 60° C.

III. Test Chemical Stability Study of *n*-Butyl Chloride Lot No. 780135-3 Performed by the Testing Laboratory

A. Storage conditions

Bulk: 4° C until 2/1/80, then 0° C
Reference: −18° C until 12/2/81, then −20° C or lower

B. Analytical methods

1. Gas chromatography

Instrument: Varian 1400
Detection: Flame ionization
Column: 0.1% SP1000 on Carbopack C, 6 ft × 2 mm ID, glass
Oven temperature program: 50° -170° C (or 190° C) at 6° C/minute
Inlet temperature: 170°-230° C
Detector temperature: 205°-240° C

2. Infrared spectroscopy

Instrument: Perkin-Elmer Infracord #137
Cell: Liquid film between silver chloride plates

C. Results

1. Gas chromatography

	Percent Purity	
Date	Bulk	Reference
02/27/79	99.74	99.68
06/11/79	99.69	99.62
10/03/79	99.85	99.76
02/27/80	99.78	99.76
06/23/80	99.79	99.76
10/07/80	99.73	99.75
02/27/81	99.73	99.74
04/15/81	99.67	99.70
08/11/81	99.66	99.67
12/14/81	99.73	99.73
03/26/82	99.71	99.72
08/09/82	99.72	--
12/13/82	99.73	99.73
04/29/83	99.73	99.73

2. Infrared spectroscopy: All bulk spectra were consistent with those of the reference sample.

D. Conclusion: No notable degradation was observed during the studies.

APPENDIX I

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX I. PREPARATION AND CHARACTERIZATION

I. Room Temperature Stability Study of *n*-Butyl Chloride (Lot No. 780135-3) in Corn Oil Performed by the Analytical Chemistry Laboratory

A. Sample preparation and storage: *n*-Butyl chloride (3.0137 ± 0.0001 g) was placed in a 50-ml volumetric flask and diluted to the mark with corn oil. The chemical dissolved readily after manual shaking. The solution concentration was 6.02% w/v.

As soon as the solution had been prepared, 10 accurately weighed 1.59 g aliquots (the total solution weighed 45.804 ± 0.001 g; therefore, each aliquot contained 104.6 mg of *n*-butyl chloride) were removed and sealed in separate 60-ml septum vials. Duplicate aliquots were used as initial, or zero-time, samples and for storage for 1, 2, 5, or 7 days.

B. Sample extraction and analysis: A solution containing an internal reference standard was prepared by weighing 1.6092 ± 0.0001 g of *n*-amyl alcohol, transferring it to a 25-ml volumetric flask, and diluting to the mark with absolute methanol. This solution was further diluted 10/100 with absolute methanol. The concentration of reference standard was 6.437 ± 0.008 mg/ml.

To extract each sample aliquot, the septum vial was opened, 25 ml of methanol was added by volumetric pipette, and the vial was resealed immediately. The corn oil/methanol mixture was manually shaken for 30 seconds and sonicated for 30 seconds; then 10 ml of the resulting suspension was decanted into a 12-ml centrifuge tube and centrifuged for 5 minutes. A portion of the clear, methanolic supernatant solution (3 ml) was transferred to an 8.5-ml septum vial, and 3 ml of the internal standard solution was added for subsequent analysis by the gas chromatographic system outlined below:

Instrument: Varian 3700 with CDS 111 microprocessor
Column: 20% SP2100/10.1% Carbowax 1500 on 100/120 mesh Supelcoport; 1.8 m × 2 mm ID, glass, silanized
Detection: Flame ionization
Temperatures:
Inlet, 150° C
Oven, 50° C, isothermal
Detector, 250° C
Carrier gas: Nitrogen, 30 ml/min
Volume of solution injected: 4 µl
Retention times:
Test chemical, 2.5 minutes
Reference standard, 7.2 minutes

C. Quality control protocol: Analyses were performed in duplicate with *n*-amyl alcohol as an internal reference standard. Zero-time recovery studies were performed in duplicate at the same concentration level as the test samples. Gas chromatographic linearity was determined with standard solutions in methanol for the *n*-butyl chloride and the internal reference.

D. Results

Storage Time (days)	Average Percent Chemical Found in Chemical/Vehicle Mixture (a, b)
0	(c) 6.6 ± 0.2
1	6.5 ± 0.2
2	6.6 ± 0.2
5	6.6 ± 0.2
7	6.4 ± 0.2

(a) Zero-time recovery yield, 87% ± 2%.
(b) Target concentration of chemical in corn oil, 6.580% ± 0.001% (w/w) or 6.02% (w/v)
(c) The error values in this table are average deviations obtained in the analytic measurements of the test solutions.

E. **Conclusion:** *n*-Butyl chloride is stable when dissolved in corn oil at a concentration of 6% and stored at room temperature for 7 days.

APPENDIX J

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX J. METHODS OF ANALYSIS

I. Testing Laboratory

Procedure: Dose mixtures were stored at 4° C during the 13-week studies and at 0° C during the 2-year studies.

Duplicate 1-ml samples were extracted with methanol containing 2 mg/ml of *n*-amyl alcohol as an internal standard.

Instrument: Varian 1400
Column: 20% SP2100/0.1% Carbowax 1500 on 100/200 mesh Supelcoport (100/120 Supelcoport before 6/25/80), 6 ft × 2 mm ID, glass
Detector temperature: 70° C (50° C before 6/25/80)

II. Analytical Chemistry Laboratory

A. **Preparation of standard spiked corn oil:** Two standard solutions of *n*-butyl chloride were prepared independently in methanol. The solutions were diluted with methanol to make three or four additional standards. Aliquots (10 or 20 ml) of the five or six standard solutions were pipetted into individual septum vials (30 or 35 ml) containing 2 g of undosed corn oil to make spiked corn oil standards bracketing the specified concentration range of the referee sample. Undosed corn oil (2 g) in a septum vial (30 or 35 ml) was treated with methanol (10 or 20 ml) for use as a blank. After the vials were sealed with Teflon®-lined septa, the spiked corn oil standards and the corn oil blank were analyzed.

B. **Preparation of referee sample:** Three portions (approximately 2 g each) of the referee corn oil sample were transferred to individually tared septum vials (30 or 35 ml) and weighed to the nearest 0.001 g. Methanol (10 or 20 ml) was pipetted into each vial, the vials were sealed, and the samples were analyzed.

C. **Analysis:** Vials containing the samples, standards, and the blank were agitated for 10 seconds on a vortex mixer and shaken for 15 minutes at maximum stroke on a wrist-action shaker. After being centrifuged for 3 minutes, an aliquot of the methanol layer from each vial was combined with an aliquot of internal standard solution (*n*-amyl alcohol in methanol) and diluted with methanol. The solutions were mixed, and the *n*-butyl chloride content was determined by the gas chromatography system described below.

The samples were determined from the linear regression equation computed from the standard data. To obtain the regression equation, peak areas from each injection of the spiked corn oil standards were divided by the corresponding internal standard peak areas and related to the milligrams of chemical in the respective spiked corn oil standard.

Instrument: Varian 3700 Gas Chromatograph with Autosampler and Varian CDS 111-C integrator
Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 1.8 m × 2 mm ID, glass, silanized
Detection: Flame ionization
Inlet temperature: 100° C or 150° C
Oven temperature: 50° C or 60° C, isothermal
Detector temperature: 200° C or 250° C
Carrier gas: Nitrogen, 30 ml/min
Volume of solution injected: 2 or 3 µl

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

APPENDIX K

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE K1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

Date Mixed	Concentration (a) of *n*-Butyl Chloride in Corn Oil (mg/ml)		Determined as a Percent of Target
	Target	Determined	
03/27/79	200	214.7	107
	100	106.5	107
	50	51.7	103
	24	24.5	102
	12	11.4	95
	6	(b) 4.0	67
05/11/79	6	(b) 5.3	89
06/08/79	6	5.9	99

(a) Results of duplicate analysis
(b) Out of specifications

TABLE K2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

Date Mixed	Concentration (a) of *n*-Butyl Chloride in Corn Oil for Target Concentration (mg/ml)				
	12	24	50	100	200
03/11/80	11.2	22.4		93.5	192.0
04/23/80	11.25	22.0		100.5	200.0
06/25/80	11.5	22.5		96.0	196.5
08/07/80	(b) 7.75	22.5		95.0	203.0
	(c) 11.25				
10/29/80	11.5	22.5		100.0	199.0
12/10/80	10.9	22.0		102.0	202.5
03/04/81	11.4	22.8		105.0	206.0
03/25/81	11.25	22.0	50.0		
05/29/81	11.9	23.8	50.5	99.0	204.9
07/15/81	10.8	22.3	48.1	100.9	194.5
09/09/81	11.8	23.8	50.0	102.5	192.5
12/02/81	11.7	23.1	50.2	102.7	206.9
01/13/82	10.8	23.3	51.7	97.5	194.5
03/03/82			49.0		
05/12/82			50.8		
07/14/82			49.25		
08/25/82			50.75		
10/27/82			49.0		
12/08/82			50.6		
03/09/83			49.9		
Mean (mg/ml)	11.1	22.7	50.0	99.6	199.4
Standard deviation	1.06	0.63	0.95	3.46	5.33
Coefficient of variation (percent)	9.5	2.8	1.9	3.5	2.7
Range (mg/ml)	7.75-11.9	22.0-23.8	48.1-51.7	93.5-105.0	192.0-206.9
Number of samples	13	13	13	12	12

(a) Results of duplicate analysis
(b) Out of specifications; not used in the study.
(c) Remix; not included in the mean.

TABLE K3. RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration	
		Testing Laboratory (a)	Referee Laboratory (b)
06/25/80	200	196.5	188.1
12/10/80	24	22.0	23.1
03/25/81	50	50.0	52.2
12/02/81	12	11.7	11.8
05/12/82	50	50.8	50.2
12/08/82	50	50.6	50.1
03/09/83	50	49.9	48.4

(a) Results of duplicate analysis
(b) Results of triplicate analysis

APPENDIX L

SENTINEL ANIMAL PROGRAM

APPENDIX L. SENTINEL ANIMAL PROGRAM

I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect 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 are untreated, and these animals and the test animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

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

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	(First Study) 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, 24 mo)	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (6 mo) MHV (6, 12, 18 mo)	MHV (mouse hepatitis virus) (24 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 L1.

TABLE L1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF *n*-BUTYL CHLORIDE (a)

	Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS			
	6	10/10	Sendai
		10/10	RCV
	12	6/10	Sendai
		9/10	RCV
	18	5/9	Sendai
		4/9	RCV
	24	8/10	Sendai
		3/10	RCV
MICE	**First Study**		
	6	8/10	Sendai
	12	1/10	Sendai
	18	4/10	Sendai
	24	3/5	MHV
	Second Study		
	6	--	None positive
	12	--	None positive
	18	--	None positive
	24	6/9	MHV

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

APPENDIX M

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

Meal Diet: December 1979 to January 1983

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

TABLE M1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mi ›ral)	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 NIH 07 RAT AND MOUSE RATION (a)

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

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

TABLE M3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	24.23 ± 0.99	22.6-26.3	36
Crude fat (percent by weight)	5.01 ± 0.44	4.2-6.0	36
Crude fiber (percent by weight)	3.35 ± 0.49	1.4-4.3	36
Ash (percent by weight)	6.71 ± 0.38	6.0-7.4	36
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	0.827-0.840	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			
Vitamin A (IU/kg)	10,589 ± 2,042	6,700-17,000	36
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	16.2 ± 0.428	7.8-23.0	(b) 35
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)	1.28 ± 0.17	0.81-1.6	24
Phosphorous (percent)	0.99 ± 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 IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	No. of Samples
Arsenic (ppm)	0.41 ± 0.17	<0.05-0.93	36
Cadmium (ppm) (a)	0.11 ± 0.06	<0.05-0.40	36
Lead (ppm)	0.97 ± 0.64	0.27-2.93	36
Mercury (ppm) (b)	< 0.05		
Selenium (ppm)	0.27 ± 0.07	0.10-0.48	36
Aflatoxins (ppb) (b,c)	<10	<5.0-10.0	36
Nitrate nitrogen (ppm) (d)	8.18 ± 4.48	<0.1-18.0	36
Nitrite nitrogen (ppm) (d)	1.84 ± 1.23	<0.1-5.3	36
BHA (ppm) (e,f)	4.33 ± 4.72	<0.2-20.0	36
BHT (ppm) (e)	3.21 ± 2.35	<1.0-7.6	36
Aerobic plate count (CFU/g)	105,483 ± 91,644	7,000-320,000	36
Coliform (MPN/g)	835 ± 944	<3-2,400	36
E. Coli (MPN/g) (g)	6.4 ± 6.0	<3-23	35
E. Coli (MPN/g) (h)	10.3 ± 24.8	<3-150	36
Total nitrosamines (ppb) (i,j)	5.59 ± 4.93	0.9-18.8	34
Total nitrosamines (ppb) (i,k)	11.22 ± 24.19	0.9-118.4	36
N-Nitrosodimethylamine (ppb) (i,j)	4.83 ± 4.75	0.7-16.0	34
N-Nitrosodimethylamine (ppb) (i,k)	10.39 ± 23.90	0.7-117.0	36
N-Nitrosopyrrolidine (ppb) (l)	1.15 ± 0.74	<0.3-3.2	35
Pesticides (ppm)			
Alpha-BHC (b,m)	<0.01		36
Beta-BHC (b)	<0.02		36
Gamma-BHC-Lindane (b)	<0.01		36
Delta-BHC (b)	<0.01		36
Heptachlor (b)	<0.01		36
Aldrin (b)	<0.01		36
Heptachlor epoxide (b)	<0.01		36
DDE (b,n)	<0.01	0.05 (7/14/81)	36
DDD (b)	<0.01		36
DDT (b)	<0.01		36
HCB (b)	<0.01		36
Mirex (b)	<0.01		36
Methoxychlor (b,o)	<0.05	0.13 (4/26/82) 0.6 (6/24/82)	36
Dieldrin (b)	<0.01		36
Endrin (b)	<0.01		36
Telodrin (b)	<0.01		24
Chlordane (b)	<0.05		26
Toxaphene (b)	<0.1		36
Estimated PCB's (b)	<0.2		36
Ronnel (b)	<0.01		36
Ethion (b)	<0.02		36
Trithion (b)	<0.05		36
Diazinon (b,n)	<0.1	0.1 (4/27/81)	36
Methyl parathion (b)	<0.02		36
Ethyl parathion (b)	<0.02		36
Malathion (p)	0.09 ± 0.06	<0.05-0.25	36
Endosulfan I (b)	<0.01		14
Endosulfan II (b)	<0.01		14
Endosulfan sulfate (b)	<0.03		14

TABLE M4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) Three batches contained more than 0.1 ppm.
(b) All values were less than the detection limit, which is given in the table as the mean.
(c) Detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(d) Source of contamination: Alfalfa, grains, and fish meal
(e) Source of contamination: Soy oil and fish meal
(f) Six batches contained less than 0.5 ppm.
(g) Excludes one very high value of 150 obtained in the batch produced on 8/26/82.
(h) Includes the high values listed in footnote (g).
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range exclude two very high values in the range of 95.6 and 118.4 ppb obtained in batches produced on 1/26/81 and 4/27/81.
(k) Mean, standard deviation, and range include the high values listed in footnote (j).
(l) Not detectable on 6/24/82
(m) BHC = hexachlorocyclohexane or benzene hexachloride
(n) One observation was above the detection limit. The value and the date it was obtained are listed under the range.
(o) Two observations were above the detection limit. The values and the dates are listed under the range.
(p) Fourteen batches contained more than 0.05 ppm.

APPENDIX N

DATA AUDIT SUMMARY

APPENDIX N. DATA AUDIT SUMMARY

The experimental data and pathology materials for the toxicology and carcinogenesis studies of *n*-butyl chloride 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 experimental data audit was conducted by Argus Research Laboratories, Inc., in November 1984 and April 1985. Audit team members were Dr. J. Goeke, Dr. A. Haberman, Ms. C. Veigle, Dr. D. Copeland, Mr. M. Pielmeier, and Ms. R. Joftes. The first and second studies on *n*-butyl chloride were initiated at EG&G Mason Research Institute as follows: rats, started in March 1980 and completed in March 1982; first mouse study, started in February 1980 and completed in February 1982; second mouse study, started in March 1981 and completed in March 1983. The studies were started before the October 1981 NTP requirements for full compliance with Good Laboratory Practices regulations.

The full report of the audit of these studies is on file at the NIEHS, Research Triangle Park, North Carolina. 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 vehicle control groups.

The review of the toxicology data found minor discrepancies in the documentation of clinical observations. Several temperature and humidity readings outside the accepted range occurred during the studies. A review of the available chemistry data found no discrepancies. A review of the pathology data found no substantial problems or discrepancies. Animal identification was good; however, because of mutilated or missing ears, the following mice could not be identified: three high dose males, one vehicle control female in each study, and one dosed female in each study. The tissue bag for high dose male rat no. 39 was missing. Four blocks were missing for rats (one vehicle control female and three high dose females) and five for mice (one vehicle control female in each study, one dosed female in the second study, and a vehicle control male and a dosed male in the second study). One slide from each of two rats (vehicle control male, high dose female) and four mice (vehicle control male and female and two high dose males) were missing. Seven slide/block matches were uncertain (three vehicle control male rats, two vehicle control male mice, and two dosed male mice in the second study). A few untrimmed lesions were found in wet tissues of rats and mice. The untrimmed lesions were not in target organs. The slides were read, and the diagnoses of three neoplasms in mice were included in the final tables of this report.

A few discrepancies between gross and microscopic diagnoses of lesions were noted; these were distributed among dose groups and tissues and were determined to have no impact on the final interpretation of the studies and therefore were not pursued.

In summary, a few discrepancies were found during the audit; some that were considered not to affect the interpretation of the studies were not necessarily pursued to final conclusion but are listed in the final audit report. The data presented in this Technical Report are considered adequate to support the conclusions of the studies.

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