NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 306

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DICHLOROMETHANE (METHYLENE CHLORIDE)

(CAS NO. 75-09-2)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION 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

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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.

CONTENTS

CONTENTS (Continued)

TABLES

TABLES (Continued)

FIGURES

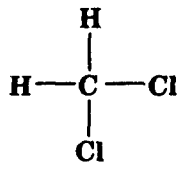
FIGURES (Continued)

APPENDIXES

APPENDIXES (Continued)

APPENDIXES (Continued)

APPENDIXES (Continued)



DICHLOROMETHANE

(Methylene Chloride)

(CAS No. 75-09-2

CH_2Cl_2 Molecular weight 84.94

ABSTRACT

Toxicology and carcinogenesis studies of dichloromethane (DCM, methylene chloride; 99% pure) were conducted by inhalation exposure of groups of 50 male and 50 female F344/N rats and B6C3F_1 mice 6 hours per day, 5 days per week, for 102 weeks. The exposure concentrations used (0, 1,000, 2,000, or 4,000 ppm for rats and 0, 2,000, or 4,000 ppm for mice) were selected on the basis of results from 13-week inhalation studies in which groups of 10 rats and 10 mice of each sex were exposed to dichloromethane at concentrations of 525-8,400 ppm 6 hours per day, 5 days per week.

During the 2-year studies in rats, body weight gains for exposed males and females were comparable to those of the chamber controls. The survival of exposed male rats was comparable to that of the chamber controls; however, the survival of all groups of males at the termination of the study was low (control, 16/50; low dose, 16/50; mid dose, 17/50; high dose, 9/50). Most of the early deaths among male rats occurred during the final weeks of the study; the survival of male rats through week 86 of the study was 36/50, 39/50, 37/50, and 33/50. This decreased survival is believed to be related to the high incidence of leukemia (34/50; 26/50; 32/50; 35/50). Survival of female rats exposed at 4,000 ppm was reduced relative to that of the chamber controls (30/50; 22/50; 22/50; 15/50); leukemia occurred frequently in all female rat groups. Final mean body weights of high dose male mice and low and high dose female mice were 10%-17% lower than those of the chamber controls; these reductions occurred during the last 16 weeks of the study. The survival of dosed male mice and high dose female mice was reduced relative to that of the chamber controls (male: control, 39/50; low dose, 24/50; high dose, 11/50; female: 25/50; 25/50; 8/50). This reduced survival may have been due to the chemically induced development of liver and lung neoplasia in male and female mice.

Increased incidences of benign mammary gland lesions (adenomas and fibroadenomas) occurred in male and female rats exposed to dichloromethane (male: 0/50; 0/50; 2/50; 5/50; female: 5/50; 11/50; 13/50; 23/50). The incidence of malignant mammary gland neoplasms was not increased in female rats (2/50; 2/50; 2/50; 0/50); none was observed in male rats. In addition, integumentary system tumors in the area of the mammary chain occurred with a positive trend in male rats (subcutaneous tissue fibroma or sarcoma: 1/50; 1/50; 2/50; 5/50); the combined incidence of all tumors in the mammary area in male rats was 1/50, 1/50, 4/50, and 9/50.

Exposure to dichloromethane was associated with increased incidences of hepatic hemosiderosis, cytomegaly, cytoplasmic vacuolization, necrosis, granulomatous inflammation, and bile duct fibrosis

in both male and female rats. There was a positive but marginal trend in the incidence of hepatocellular neoplastic nodules or hepatocellular carcinomas (combined) in female rats (2/50; 1/50; 4/50; 5/50). The incidence of squamous metaplasia of the nasal cavity was increased in female rats exposed at 4,000 ppm (1/50; 2/50; 3/50; 9/50) but not in males (4/50; 5/50; 3/50; 3/50). No nasal cavity tumors were observed in rats. The increased incidences of mononuclear cell leukemia in mid dose and high dose female rats (17/50; 17/50; 23/50; 23/50) were statistically significant by age-adjusted analyses. In male rats, mesotheliomas (arising primarily from the tunica vaginalis) occurred at increased incidences (0/50; 2/50; 5/50; 4/50).

Lung tumors occurred at increased incidences in male and female mice exposed to dichloromethane (alveolar/bronchiolar adenomas: male--3/50; 19/50; 24/50; female--2/50; 23/48; 28/48; alveolar/bronchiolar carcinomas: male--2/50; 10/50; 28/50; female--1/50; 13/48; 29/48). Cytologic degeneration of the liver was observed at increased incidences in high dose male and dosed female mice (male: 0/50; 0/49; 22/49; female: 0/50; 23/48; 21/48). Incidences of hepatocellular adenomas or hepatocellular carcinomas (combined) were increased in high dose male and dosed female mice (male: 22/50; 24/49; 33/49; female: 3/50; 16/48; 40/48). There were also dose-related increases in the numbers of mice bearing multiple lung or liver neoplasms. Dose-related increases were observed in the incidences of testicular atrophy in male mice and uterine and ovarian atrophy in female mice; these effects are considered to be secondary responses to neoplasia.

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

Under the conditions of these inhalation studies, there was *some evidence of carcinogenicity** of dichloromethane for male F344/N rats as shown by an increased incidence of benign neoplasms of the mammary gland. There was *clear evidence of carcinogenicity* of dichloromethane for female F344/N rats as shown by increased incidences of benign neoplasms of the mammary gland. There was *clear evidence of carcinogenicity* of dichloromethane for male and female $B6C3F_1$ mice, as shown by increased incidences of alveolar/bronchiolar neoplasms and of hepatocellular neoplasms.

*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 Dichloromethane is based on the 13-week studies that began in March 1980 and ended in June 1980 and on the 2-year studies that began in April 1981 and ended in April 1983 at Battelle Pacific Northwest Laboratories.

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on dichloromethane on March 29, 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.

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

On March 29, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of dichloromethane 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. Swenberg, a principal reviewer, agreed with the conclusions for three of the four studies. He did not agree with the proposed conclusion for female rats (clear evidence of carcinogenicity) because the increase in neoplasia was for benign mammary gland fibroadenomas. He said the significant and dose-related increases in these tumors and the induction of this same type of tumor in two other studies supported a conclusion of some evidence of carcinogenicity for female rats. Dr. Swenberg said statements on causal relationships between leukemia and survival in female rats and between liver and lung tumors and survival in mice should be better supported. Dr. Hooper also asked for clarification as to whether the high incidence of leukemia in rats may have caused increased mortality. Dr. J. Mennear, NTP, presented data that supported causal relationships. For example, 22 of 35 (63%) high dose female rats dying before the termination of the study had leukemia versus 9 of 20 (45%) controls.

As a second principal reviewer, Dr. Hooper agreed with the conclusions. He asked whether the NTP had looked for a dose-related increase in multiplicity of mammary fibroadenomas in rats. Such an examination might influence the strength of the evidence for carcinogenicity, especially in male rats. He suggested inclusion of a table summarizing the experimental conditions and tumor findings for the various reported long-term dichloromethane studies [see Table 26, p. 59]. Dr. Hooper asked whether the testicular atrophy in male mice and the ovarian/uterine atrophy in female mice could be attributed to direct or indirect effects of the chemical. Dr. E. McConnell, NTP, replied that these effects were believed to be secondary to neoplasia.

As a third principal reviewer, Dr. Turnbull agreed with the conclusions as written. He asked that a statement in the Technical Report clarify whether the histopathology slides were identified during diagnoses. [The original pathologist and quality assessment laboratory use fully labeled slides; the NTP Pathology Working Group evaluates slides in a blind fashion.]

The discussion focused primarily on whether the appropriate descriptor for the conclusions in female rats was clear evidence of carcinogenicity, as written, or some evidence of carcinogenicity. The key issues centered on: (1) the relative weight given to concurrent control data versus historical (laboratory and Program) control data; (2) the interpretation of "a substantially increased incidence of benign neoplasms"; and (3) the issue of whether a conclusion of clear evidence of carcinogenicity based on benign neoplasms was appropriate. With regard to (1) and (2), Dr. Kociba, Dr. Purchase, and Dr. Swenberg argued that historical rates should be emphasized, since the concurrent rate (10%) was lower than the mean Program-wide rates (28%). Thus, Dr. Swenberg maintained that the rate in the high dose group for fibroadenomas (22/50; 44%) was less than double the historical average and not a "substantial" increase. Dr. J. Haseman, NIEHS, said the historical data base came primarily from feed studies and there was no good data base of chamber controls from inhalation studies. Dr. J. Huff, NIEHS, stated that the concurrent control data are given more weight by the NTP, whereas historical control data are for comparison. He noted that the rates for fibroadenomas for two previous inhalation studies at Battelle Northwest Laboratories were 14% and 18%. With regard to (3), Dr. Hook and Dr. Kotelchuck commented that the definitions of the categories for strength of evidence have been used by the Panel since June 1983. Dr. Kociba spoke for being able to factor in qualitative

considerations such as tumor types and their commonality and absence of malignancy. Dr. McConnell said that the NTP's stance mirrored that of the International Agency for Research on Cancer, i.e., "If a substance is found to induce only benign tumors in experimental animals, it should nevertheless be suspected of being a carcinogen..." Dr. Huff summarized the NTP's reasoning for the conclusion: With concurrent controls, there was a significant positive trend, a dose-related effect in which the incidence in the high dose animals was significantly greater than that in the controls; the effects were observed in both sexes; and these findings were supported by studies in the literature.

Dr. Kotelchuck moved that the conclusion of clear evidence of carcinogenicity in female rats be accepted with the addition of the word "benign" in front of "neoplasms." Dr. Perera seconded the motion, and it was approved with six affirmative votes; there were two negative votes (Dr. Crowley and Dr. Swenberg) and two abstentions by reason of company affiliation (Dr. Kociba and Dr. Purchase). Dr. Hooper then moved that the conclusion of some evidence of carcinogenicity in male rats be accepted also with inclusion of the "benign" in front of "neoplasms." Dr. Perera seconded the motion, and it was approved by seven affirmative votes; there were one negative vote (Dr. Crowley) and two abstentions (Dr. Kociba and Dr. Purchase). Dr. Swenberg moved that the conclusions of clear evidence of carcinogenicity in male and female mice be accepted as written. Dr. Hooper seconded the motion, and it was approved by eight affirmative votes; there were two abstentions (Dr. Kociba and Dr. Purchase).

I. INTRODUCTION

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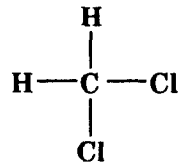

DICHLOROMETHANE

(Methylene Chloride)

(CAS No. 75-09-2

CH_2Cl_2 Molecular weight 84.94

Dichloromethane (DCM, methylene chloride) is widely used in industrial processes, food preparation, and agriculture. In industry, dichloromethane is used as a solvent in paint removers, degreasing agents, aerosol propellants, and triacetate solutions; as a blowing agent in flexible urethane foams; and as a process solvent in the manufacture of steroids, antibiotics, vitamins, and tablet coatings (Merck Index, 1976; Kirk-Othmer, 1964, 1966, 1967, 1979a,b, 1980; Simmons and Levitt, 1979). The use of dichloromethane as an extraction solvent for spice oleoresins, hops, and caffeine from coffee has been approved by the U.S. Food and Drug Administration (USCFR, 1974). Dichloromethane has been used as an inhalation anesthetic and as a fumigant for grain and strawberries (Valle-Riestra, 1974; Farm Chemicals Handbook, 1977; Merck Index, 1976). The International Program on Chemical Safety has recently published an environmental health criteria document on dichloromethane (WHO, 1984).

In 1980, 564 million pounds of dichloromethane was produced in the United States (USITC, 1981). Dichloromethane has been identified in drinking water, bottled artesian water, and water from the Mississippi River (Dowty et al., 1975).

Humans and laboratory animals readily absorb dichloromethane by inhalation and ingestion. Dermal absorption of dichloromethane has been observed in rats (Schutz, 1958) and humans (Stewart and Dodd, 1964). In humans, absorption of dichloromethane following dermal exposure occurs more slowly than absorption occurring after ingestion or inhalation.

Dichloromethane is distributed throughout the body after being inhaled or ingested by humans or laboratory animals. Dichloromethane has been detected in the urine of dogs and humans (MacEwen et al., 1972; DiVincenzo et al., 1972) and in human milk (Vozovaya et al., 1974). The solvent has been detected in the kidney (Moskowitz and Shapiro, 1952), liver, and brain (Bonventre et al., 1977) of humans accidentally poisoned by the chemical. Anesthesia and central nervous system depression have accompanied accidental dichloromethane poisoning, indicating that the chemical crosses the blood/brain barrier (Moskowitz and Shapiro, 1952; Hughes, 1954). Dichloromethane also crosses the placental barrier, but teratogenic effects were not observed when dichloromethane was administered by inhalation to Swiss-Webster mice and to Long Evans and Sprague-Dawley rats (Leong et al., 1975; Schwetz et al., 1975; Hardin and Manson, 1980).

Elimination of dichloromethane from the body occurs primarily through pulmonary excretion; approximately 85% is excreted unchanged. Small amounts of dichloromethane are eliminated via the kidney. The plasma half-life of inhaled dichloromethane in humans is estimated to be 40 minutes (DiVincenzo et al., 1972). Elimination of dichloromethane from human muscle and adipose tissue has been estimated to occur in 60-80 minutes and 240 minutes, respectively (Stewart et al., 1972a,b).

Carbon monoxide and carbon dioxide are known metabolites of dichloromethane in humans and laboratory animals (Stewart et al., 1972a,b; Kubic and Anders, 1975; Ahmed and Anders, 1976). Carboxyhemoglobin is formed when dichloromethane is metabolized to carbon monoxide (Stewart et al., 1972a,b). The biotransformation of dichloromethane to carbon monoxide has been postulated to occur through the process of microsomal oxidative dechlorination (Kubic and Anders, 1975); it takes place primarily in the liver, but microsomes in the lung and kidney can carry out this metabolic reaction. Dichloromethane is metabolized in the liver cytosol via a glutathione-dependent enzyme to formaldehyde (Ahmed and Anders, 1976). Formaldehyde can be oxidized to carbon dioxide. The detection of formic acid in the urine of workers exposed to dichloromethane has led investigators to suggest that dichloromethane is first metabolized to formaldehyde and then to formic acid (Kuzelova and Vlask, 1966).

Various in vivo toxicity experiments have established the liver as the primary target organ for dichloromethane and central nervous system depression as the major grossly observable effect. In cases of accidental poisoning in humans, the prominent effects include central nervous system depression, behavioral changes, irritation of the mucous membranes, cardiovascular effects, pulmonary irritation and edema, and carboxyhemoglobinemia.

In single-dose experiments in mice, the subcutaneous and intraperitoneal LD_{50} values for dichloromethane were found to be 6,452 and 1,987 mg/kg, respectively (Kutob and Plaa, 1962; Klaassen and Plaa, 1966).

When dogs, rabbits, guinea pigs, and rats were exposed to air containing 5,000 ppm dichloromethane (7 hours per day, 5 days per week) for up to 6 months, only the guinea pigs were affected (Heppel et al., 1944). Decreased growth in the guinea pigs was the only observable effect; no compound-related lesions were seen. Exposure to dichloromethane at a concentration of 10,000 ppm (4 hours per day, 5 days per week) for up to 8 weeks produced fatty metamorphosis of the liver in guinea pigs and dogs, but no compound-related lesions were seen in rats and rabbits.

Exposure of male and female Syrian hamsters to air containing 0, 500, 1,500, or 3,500 ppm dichloromethane (6 hours per day, 5 days per week) for 2 years did not adversely affect survival or produce compound-related lesions (Burek et al., 1980). When male and female Sprague-Dawley rats were exposed under the same conditions, reduced survival was seen in the group of females exposed at the highest concentration. Dose-related increases were observed in the total number of fibromas or fibroadenomas in the mammary gland of females. The increase in fibromas reflected an increase in the number of tumors found in individual animals, since the number of females with mammary tumors did not increase. Increased incidences of mammary tumors were also found in male rats exposed at 1,500 or 3,500 ppm dichloromethane, although the increases were not as pronounced as those seen in females.

The male rats exposed to dichloromethane at 1,500 or 3,500 ppm had increased incidences of sarcomas of the salivary gland (Burek et al., 1980). This effect might have been related to a viral salivary gland infection (sialodacryoadenitis) in these animals, although these tumors were not detected among similarly infected females.

In a subsequent inhalation study, male and female Sprague-Dawley rats were exposed to dichloromethane at concentrations of 0, 50, 200, or 500 ppm (Nitschke et al., 1982). The compound at the 500-ppm concentration produced mammary fibroma/fibroadenomas in males and females, but salivary gland tumors were not observed. Exposure to dichloromethane at concentrations of 200 ppm or less was not associated with tumor production.

In 2-year studies sponsored by the National Coffee Association (1982, 1983), F344 rats were administered 0, 5, 50, 125, or 250 mg/kg per day of dichloromethane in drinking water and $B6C3F_1$ mice were administered 0, 60, 125, 185, or 250 mg/kg per day in drinking water. There was no evidence of chemically induced carcinogenesis;

however, it is probable that the test animals could have tolerated higher doses of dichloromethane.

Although Theiss et al. (1977) reported a slight, but not statistically significant, increase in the incidence of lung adenomas in strain A mice, IARC found the study to be inadequate because of poor survival of the test animals.

When mortality in a group of 751 workers exposed to dichloromethane at 30-1,200 ppm for up to 30 years was compared with that in a group of workers not exposed to dichloromethane, no increase in cancer-related deaths was noted in the exposed group (Friedlander et al., 1978); these data were considered inadequate to assess the carcinogenicity of dichloromethane in humans (IARC, 1982).

Dichloromethane is mutagenic in *Salmonella typhimurium* in the presence and absence of S9 when the cells are exposed to dichloromethane vapor in a desiccator. The International Agency for Research on Cancer (IARC) has concluded that dichloromethane is mutagenic in *S. typhimurium* TA98 and TA100. The vapor is also mutagenic in the plant Tradescantia and causes mitotic recombination and gene conversion in yeast. Dichloromethane has given mixed results in the sex-linked recessive lethal assay in Drosophila and in cell transformation studies in vitro. Most in vivo or in vitro studies in mammalian systems have given negative results. Dichloromethane, however, did induce chromosomal aberrations in Chinese hamster ovary (CHO) cells (Table 1).

Investigation of the role of bacterial metabolism in the mutagenicity of dichloromethane revealed that *S. typhimurium* strain TA100 metabolized this compound to water-soluble metabolites and to both carbon monoxide and carbon dioxide. The detection of these gases suggests that metabolism by the bacteria occurs by pathways similar to those known in the rat. Brunner et al. (1980) have shown dichloromethane to be a C-1 substrate for bacterial strain DM-1, the metabolic pathways again being very similar to those in mammalian systems. The finding of a large number of water-soluble metabolites in the metabolism of dichloromethane by TA100 is consistent with the use of the compound as a C-1 substrate by these bacteria also.

Deactivation of the mutagenic metabolites occurs mainly by rapid chemical decomposition and is relatively independent of the site of formation or the distribution of deactivating enzymes (Green, 1983). Consequently, the lack of mutagenicity in mammalian systems (see Table 1) may be due to the inability of the target cells to metabolize dichloromethane or to the instability of mutagenic metabolities (if formed by the S9) preventing transport into the cell and interaction with the DNA.

Study Rationale: Dichloromethane was selected for study because of its widespread use and potential for human exposure and because other halogenated hydrocarbons have shown evidence of carcinogenic activity. These studies complement other studies (Burek et al., 1980, 1984; Nitschke et al., 1982; National Coffee Association, 1982, 1983) whose results were incomplete at the time these studies were initiated.

TABLE 1. SUMMARY OF RESULTS FROM GENETIC TOXICOLOGY TESTING OF DICHLOROMETHANE

Short-Term Test	Result	Reference
Salmonella typhimurium		
TA1535	+	McGregor, 1979
(+/– S9)	–	Nestmann et al., 1980
	+	Nestmann et al., 1981
TA98	+	Jongen et al., 1978
	+	Nestmann et al., 1981
	+	Gocke et al., 1981
TA100	+	Jongen et al., 1978
	+	Kanada and Uyeta, 1978
	+	Simmon, 1978
	–	Nestmann et al., 1980
	+	Nestmann et al., 1981
	+	Gocke et al., 1981
	+	Jongen et al., 1982
	+	Green (1983)
Bacillus subtilis		
Rec assay	–	Kanada and Uyeta, 1978
Tradescantia (plant)	+	Schairer and Sautkulis, 1982
Yeast D7		
Mitotic recombination	+	Callen et al.,1980
Mitotic gene conversion	+	Callen et al., 1980
Yeast D3		
Mitotic recombination	–	Simmon et al., 1977
Drosophila		
SLRL	+	Gocke et al., 1981
	–	Abrahamson and Valencia, 1980
CHO/HGPRT and V79/HGPRT	–	Jongen et al., 1981
V79 and human fibroblasts		
UDS	–	Jongen et al., 1981
DNA-synthesis inhibition	–	Jongen et al., 1981
V79		
Sister-chromatid exchange	–	Jongen et al., 1981
CHO		
Sister-chromatid exchange	–	Thilager and Kumaroo, 1983
Rat		
Chromosome aberration in vivo	–	Johnston et al., 1980
CHO		
Chromosome aberration in vitro	+	Thilager and Kumaroo, 1983
Mouse		
Micronucleus	–	Gocke et al., 1981
Fischer rat		
Cell transformation in vitro	+	Price et al., 1978
Mice B/C 3T3		
Cell transformation in vitro	–	Sivak, 1978
Syrian hamster embryo cells		
SA7 viral enhanced transformation	+	Hatch et al., 1983

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF DICHLOROMETHANE

GENERATION AND MEASUREMENT OF CHAMBER CONCENTRATIONS IN THE TWO-YEAR STUDIES

SINGLE-EXPOSURE STUDIES

NINETEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

PROCUREMENT AND CHARACTERIZATION OF DICHLOROMETHANE

Dichloromethane was obtained from Fisher Scientific Company or Dow Chemical USA in five different lots (Table 2). Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, Missouri). The identities of all lots were confirmed by spectroscopic analyses (Appendix G). The infrared and nuclear magnetic resonance spectra were consistent with the literature spectra. The ultraviolet spectrum was consistent with that expected for the structure. The cumulative data from elemental analysis and gas chromatography indicated that the purity of each of the five lots was greater than 99%.

A stability test demonstrated that dichloromethane was found to be stable for 2 weeks at temperatures up to 35° C (Appendix G). The testing laboratory performing the 2-year studies stored the chemical at room temperature in steel drums and periodically reanalyzed it by infrared spectroscopy and gas chromatography. These analyses indicated that no degradation of the stored chemical occurred during the course of the 2-year studies.

GENERATION AND MEASUREMENT OF CHAMBER CONCENTRATIONS IN THE TWO-YEAR STUDIES

Dichloromethane was vaporized at 38°-42° C, diluted with air, and introduced into the chambers (Table 3; Appendix H). Concentrations in each exposure chamber were monitored 8-12 times per exposure period with a Hewlett-Packard 5840A Gas Chromatograph. Average weekly exposure concentrations are presented in Appendix H, Figures 16, 17, and 18. The weekly mean vapor concentrations were within 10% of the target concentrations at all positions sampled within the chamber. A summary of the chamber concentrations for the 2-year studies is presented in Tables 4 and 5.

TABLE 2. IDENTITY AND SOURCE OF LOTS IN THE INHALATION STUDIES OF DICHLOROMETHANE

	Single-Exposure Studies	Nineteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers	766062	767132, 77-26-22, 775007	775007	D112480
Date of Initial Use of Each Lot	6/9/77	10/7/77; 10/23/77; 10/24/77	NA	4/29/81
Supplier	Fisher Scientific Co. (St. Louis, MO)	Fisher Scientific Co. (St. Louis, MO)	Fisher Scientific Co. (St. Louis, MO)	Dow Chemical USA (Midland, MI)

TABLE 3. GENERATION OF CHAMBER CONCENTRATIONS IN THE INHALATION STUDIES OF DICHLOROMETHANE

Single-Exposure Studies	Nineteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Clean, dry air (−40° C dewpoint) was introduced into the exposure chamber through all-glass impingers containing the test material. Concentrations were achieved by varying the amount of air that passed through the test material.	Same as single-exposure studies	Dichloromethane liquid was metered onto a heated wick vaporizer located in the chamber fresh air duct.	Same as 13-wk studies

TABLE 4. SUMMARY OF CHAMBER CONCENTRATIONS OF DICHLOROMETHANE DURING THE TWO-YEAR INHALATION STUDIES

Target Concentration (ppm)	Total Number of Readings	Mean Concentration (a) (ppm)	Maximum Concentration Observed (b)
1,000	5,238	1,004 ± 51	1,559
2,000	5,188	2,009 ± 13	2,411
4,000	5,199	3,982 ± 213	5,293

(a) Mean ± standard deviation
(b) Single observation, not daily mean

TABLE 5. DISTRIBUTION OF MEAN DAILY CONCENTRATIONS OF DICHLOROMETHANE DURING THE TWO-YEAR INHALATION STUDIES

Range of Concentration (percent of target)	Number of Days Mean within Range		
	1,000 ppm	2,000 ppm	4,000 ppm
>110	0	0	0
100-110	291	312	239
90-100	194	172	245
80-90	7	7	7
70-80	0	1	1
<70	0	0	0

II. MATERIALS AND METHODS

SINGLE-EXPOSURE STUDIES

Two shipments of male and female F344/N rats and B6C3F$_1$ mice were obtained from Frederick Cancer Research Center and observed for 7 days before being placed on study. The studies were conducted at Industrial Biotest Laboratories.

Groups of five rats and mice of each sex were exposed for 4 hours to air containing 15,500, 16,500, 16,800, 17,250, 18,500, or 19,000 ppm dichloromethane (three groups at 19,000 ppm). Controls were not used. Animals were observed daily and were weighed on days 0 and 15. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 6.

NINETEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and observed for 16 days before being placed on study. The studies were conducted at Industrial Biotest Laboratories.

Groups of five rats and mice of each sex were exposed to air containing dichloromethane at target concentrations of 0, 1,625, 3,250, 6,500, 13,000, or 16,000 ppm for 6 hours per day, 5 days per week for 19 days (11 exposures). Rats and mice were observed daily and were weighed on days 0, 5, 10, 15, and 19. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 6.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated exposure to dichloromethane and to determine the concentrations to be used in the 2-year studies. The 13-week studies were conducted at Battelle Pacific Northwest Laboratories

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 21 days, and assigned to test groups according to a table of random numbers. Feed was available ad libitum during nonexposure periods; water was available at all times.

Groups of 10 rats and 10 mice of each sex were exposed to air containing dichloromethane at target concentrations of 0, 525, 1,050, 2,100, 4,200, or 8,400 ppm, 6 hours per day, 5 days per week for 13 weeks (63 exposures). Further experimental details are summarized in Table 6.

Animals were observed 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. Liver fat:liver weight ratios were determined for all survivors. Tissues and groups examined are listed in Table 6.

TWO-YEAR STUDIES

Study Design

Two-year studies were conducted at Battelle Pacific Northwest Laboratories. Groups of 50 rats of each sex were exposed to air containing dichloromethane at target concentrations of 0 (chamber controls), 1,000, 2,000, or 4,000 ppm, 6 hours per day, 5 days per week for 102 weeks. Groups of 50 mice of each sex were exposed to dichloromethane at concentrations of 0, 2,000, or 4,000 ppm on the same schedule. Actual concentrations are summarized in Table 4 and Appendix H, Figures 16, 17, and 18. During week 3 of the studies, the 1,000-ppm rats (both sexes) were exposed at 2,000 ppm and the 2,000-ppm rats and mice (both sexes) were exposed at 1,000 ppm.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female, × C3H/HeN MTV$^-$, male) mice used in this study were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding 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. Animals were shipped to the

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF DICHLOROMETHANE

	Single-Exposure Studies	Nineteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN				
Testing Laboratory	Industrial Biotest Laboratories (Northbrook, IL)	Industrial Biotest Laboratories (Northbrook, IL)	Battelle Pacific Northwest Laboratories (Richland, WA)	Battelle Pacific Northwest Laboratories (Richland, WA)
Size of Test Groups	5 males and 5 females of each species	Same as single-exposure studies	10 males and 10 females of each species	50 males and 50 females of each species
Doses	Target: 15,500, 16,500, 16,800, 17,250, 18,500, or 19,000 ppm dichloromethane by inhalation	Target: 0, 1,625, 3,250, 6,500, 13,000, or 16,000 ppm dichloromethane by inhalation	Target: 0, 525, 1,050, 2,100, 4,200, or 8,400 ppm dichloromethane by inhalation	Rats--0, 1,000, 2,000, or 4,000 ppm dichloromethane by inhalation; mice--0, 2,000 or 4,000 ppm
Date of First Dose	6/9/77-6/23/77	10/7/77	3/19/80	4/29/81
Date of Last Dose	N/A	10/24/77	6/17/80	4/15/83
Duration of Dosing	Single 4-h exposure	6-h/d, 5 d/wk on 11 d over a 19-d period	6 h/d, 5 d/wk for 13 wk	6 h/d, 5 d/wk for 102 wk
Type and Frequency of Observation	All animals were observed throughout exposure period and for 14 d thereafter; weighed before exposure and on d 15	All animals were observed 1 × d during exposure period; weighed on d 0, 5, 10, 15, and 19	Animals were weighed just before exposure and 1 × wk thereafter	Observed 2 × d; clinically examined 1 × wk for 3.5 mo, then 2 × mo until mo 8; after mo 8, palpated and clinically examined 1 × mo; weighed 1 × wk for 12 wk, then 1 × mo
Necropsy and Histologic Examination	Complete necropsy performed on all animals; tissues were not examined histologically	Complete necropsy performed on all animals; tissues were not examined histologically	Complete necropsy performed on all animals; complete histologic exam performed on high dose and controls; lower dose groups examined to determine no-effect level	Necropsy performed on all animals; the following tissues were examined histologically: gross lesions and tissue masses, regional lymph nodes, tracheobronchial lymph nodes, mandibular lymph nodes, salivary glands, sternebrae including marrow, thyroid gland, parathyroids, larynx, small intestine, colon, duodenum, liver, heart, trachea, prostate/testes or ovaries/uterus, lungs and mainstem bronchi, skin, trachea gallbladder (mice), kidneys, spleen, stomach, brain, thymus, colon, adrenal glands, urinary bladder, pituitary gland, nasal cavity/turbinates, mammary glands, preputial gland (male rats), clitoral gland (female rats)

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF DICHLOROMETHANE (Continued)

	Single-Exposure Studies	Nineteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE				
Strain and Species	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice	F344/N rats; $B6C3F_1$ mice
Animal Source	Frederick Cancer Research Center (Frederick, MD)	Harlan Industries (Cumberland, IN)	Charles River Breeding Laboratories (Portage, MI)	Same as 13-wk studies
Time Held BeforeTest	7 d	16 d	21-22 d	21 d
Age When Placed on Study			7-9 wk	Rats--7-8 wk; mice--8-9 wk
Age When Killed			20-22 wk	Rats--111-112 wk; mice--112-113 wk
Necropsy Dates	14 d after exposure	10/25/77		4/25/83-4/29/83
Method of Animal Distribution	Assigned to groups according to computer-generated tables of random numbers	Same as single-exposure studies	Same as single-exposure studies	Same as single-exposure studies
Animal Identification	Ear notch number	Same as single-exposure studies	Ear tag	Ear tag
Feed	Wayne Lab-Blox® (Allied Mills, Chicago, IL); ad libitum but feed removed during exposure	Same as single-exposure studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum except during exposure	Same as 13-wk studies except for 4/23/81-5/9/81 when Wayne Lab-Blox® was used
Bedding				San-i-cell: ground corncob bedding (Paxton Processing, Paxton, IL); during quarantine only
Water	Ad libitum	Ad libitum	Automatic watering system (Edstrom Industries, Waterford, WI)	Automatic watering system (quarantine--Systems Engineering, Napa, CA; study--Edstrom Industries, Waterford, WI)
Cages	Stainless steel mesh (Unifab Corp., Kalamazoo, MI)	Same as single-exposure studies	Stainless steel wire (Hazleton Systems, Aberdeen, MD)	Quarantine: solid bottom polycarbonate and wire bottom (Lab Products, Inc., Rochelle Park, NJ); chamber cages: stainless steel mesh (Hazleton Systems, Aberdeen, MD)
Chambers				Hazleton-200 (Hazleton Systems, Aberdeen, MD)

TABLE 6. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE INHALATION STUDIES OF DICHLOROMETHANE (Continued)

	Single-Exposure Studies	Nineteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Animals per Cage	1	Rats 1, mice--3 during quarantine, 1 during exposure	1	5 (rats), 10 (mice) for 2 wk during quarantine, 1 animal per cage thereafter
Other Chemicals on Test in Same Room		Tetrachloroethylene		Tetrachloroethylene
Animal Room Environment	Temp humidity fluorescent light 12 h/d	Temp humidity	Chamber--72° 79° F, 43% 70% humidity, room 72° 76° F, 40% 60% humidity, fluorescent light 12 h/d	Chamber 77° ± 2° F (a), 58% ± 6% humidity, room- 23° 25° C, 45% 65% humidity, fluorescent light 12 h/d, 20 room air changes/h

(a) Excursions to 69° F and 83° F

testing laboratory at 4-6 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 rats were placed on study at 7-8 weeks of age and mice at 8-9 weeks of age

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

All animals were housed individually Feed and water were available ad libitum except during exposure periods, during exposure periods, water but not feed was available Details of animal maintenance are given in Table 6. Serologic analyses were performed as described in Appendix I

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 study. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 6.

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 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 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 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.)

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

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

III. RESULTS

RATS

SINGLE-EXPOSURE STUDIES

NINETEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

MICE

SINGLE-EXPOSURE STUDIES

NINETEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Survival

Pathology and Statistical Analyses of Results

SINGLE-EXPOSURE STUDIES

The incidence of deaths in the various groups is given in Table 7. No compound-related effects were observed at necropsy.

NINETEEN-DAY STUDIES

Four of five males and 5/5 females that were exposed to dichloromethane at 16,000 ppm and 1/5 males and 1/5 females exposed at 13,000 ppm died before the end of the studies (Table 8). The final mean body weight of male rats that were exposed at 13,000 ppm and that lived to the end of the study was 17% lower than that of the controls. The final mean body weights of females exposed at 6,500 and 13,000 ppm were 5% and 8% lower than that of the controls. Intermittent scratching, ataxia, and hyperactivity were observed in all but the two lowest dose groups. Dyspnea and anesthesia were observed in the two highest dosed groups.

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SINGLE-EXPOSURE INHALATION STUDIES OF DICHLOROMETHANE

Target Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)
MALE				
15,500	4/5	105 ± 3	168 ± 6	+ 62 ± 3
16,500	5/5	105 ± 2	169 ± 4	+ 64 ± 2
16,800	4/5	119 ± 1	186 ± 1	+ 68 ± 1
17,250	3/5	106 ± 2	170 ± 2	+ 61 ± 2
18,500	3/5	84 ± 5	147 ± 5	+ 61 ± 3
19,000	2/5	99 ± 13	175 ± 1	+ 60 ± 7
19,000	5/5	118 ± 4	178 ± 4	+ 60 ± 1
19,000	2/5	112 ± 3	188 ± 2	+ 73 ± 6
FEMALE				
15,500	5/5	89 ± 2	124 ± 2	+ 35 ± 0.2
16,500	5/5	94 ± 3	126 ± 4	+ 32 ± 1
16,800	5/5	96 ± 3	124 ± 3	+ 28 ± 1
17,250	5/5	87 ± 3	118 ± 3	+ 31 ± 2
18,500	4/5	74 ± 3	112 ± 2	+ 37 ± 3
19,000	3/5	90 ± 3	123 ± 1	+ 32 ± 1
19,000	5/5	95 ± 3	126 ± 3	+ 31 ± 1
19,000	4/5	102 ± 1	130 ± 2	+ 29 ± 0.3

(a) Number surviving/number initially 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 of the group ± standard error of the mean

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE NINETEEN-DAY INHALATION STUDIES OF DICHLOROMETHANE

Target Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	140 ± 5	201 ± 7	+ 61 ± 3	--
1,625	5/5	142 ± 4	213 ± 5	+ 71 ± 5	106
3,250	5/5	141 ± 4	197 ± 5	+ 56 ± 2	98
6,500	5/5	142 ± 4	197 ± 5	+ 55 ± 4	98
13,000	4/5	140 ± 5	167 ± 4	+ 24 ± 5	83
16,000	1/5	135 ± 2	149	+ 21	74
FEMALE					
0	5/5	109 ± 3	136 ± 3	+ 27 ± 1	--
1,625	5/5	109 ± 3	138 ± 5	+ 29 ± 2	101
3,250	5/5	111 ± 4	139 ± 5	+ 28 ± 2	102
6,500	5/5	107 ± 3	129 ± 5	+ 22 ± 2	95
13,000	4/5	110 ± 4	125 ± 4	+ 13 ± 2	92
16,000	0/5	103 ± 2	(d)	(d)	--

(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
(d) No data are reported due to the 100% mortality in this group.

THIRTEEN-WEEK STUDIES

One of 10 males and 1/10 females exposed to dichloromethane at 8,400 ppm died before the end of the studies (Table 9). The final mean body weights of males and females exposed at 8,400 ppm were 23% and 11% lower than those of the controls. Foreign body pneumonia (focal accumulation of mononuclear and multinucleated inflammatory cells) was present in 4/10 males and 6/10 females exposed at 8,400 and in 1/10 females exposed at 4,011 ppm. The liver lipid:liver weight ratios for male and female rats exposed at 8,400 ppm and females exposed at 4,200 ppm were significantly ($P<0.05$) lower than those of the controls by Dunnett's test (Table 10).

Dose Selection Rationale: A maximum exposure concentration of 4,000 ppm was selected for the 2-year studies because of the minimal severity of the histopathologic changes as noted after exposure at 4,000 ppm for 13 weeks. The second exposure concentration selected was 2,000 ppm for both species, and a third, lower, concentration (1,000 ppm) was added for rats because, in an earlier inhalation study (Burek et al., 1980, 1984), exposure at 3,500 ppm had reduced the survival of male and female Sprague-Dawley rats.

TABLE 9. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK INHALATION STUDIES OF DICHLOROMETHANE

Target Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (c)	Change (d)	Final Weight Relative to Controls (percent)
MALE					
0	10/10	142 ± 5	306 ± 8	+ 164 ± 8	--
525	10/10	161 ± 3	315 ± 7	+ 154 ± 5	103
1,050	10/10	154 ± 4	317 ± 3	+ 163 ± 4	104
2,100	10/10	155 ± 4	322 ± 5	+ 167 ± 4	105
4,200	10/10	153 ± 3	318 ± 5	+ 165 ± 3	104
8,400	(e) 10/10	157 ± 3	237 ± 5	+ 80 ± 4	77
FEMALE					
0	10/10	105 ± 2	175 ± 5	+ 70 ± 6	--
525	10/10	117 ± 3	184 ± 5	+ 67 ± 3	105
1,050	10/10	114 ± 3	187 ± 4	+ 73 ± 3	107
2,100	10/10	112 ± 2	188 ± 4	+ 76 ± 2	107
4,200	10/10	110 ± 3	181 ± 3	+ 71 ± 3	103
8,400	(f) 9/10	111 ± 2	156 ± 4	+ 46 ± 2	89

(a) Number surviving/number in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on those animals that survived through the final weighing.
(c) Final body weights taken after 12 weeks of exposure
(d) Mean body weight change of the survivors ± standard error of the mean
(e) One animal died during week 12 after the final body weights were taken.
(f) Week of death: 10

TABLE 10. RATIO OF LIVER LIPID WEIGHT TO LIVER WEIGHT IN RATS EXPOSED TO DICHLOROMETHANE IN THE THIRTEEN-WEEK INHALATION STUDIES

Target Concentration (ppm)	Milligrams Lipid/Gram Liver (a) Male	Female
0	35 ± 10	30 ± 8
525	31 ± 6	25 ± 5
1,050	28 ± 3	26 ± 5
2,100	34 ± 6	24 ± 4
4,200	32 ± 7	(b) 24 ± 3
8,400	(c) 25 ± 7	(c) 22 ± 4

(a) Mean ± standard deviation
(b) $P<0.05$ vs the controls by Dunnett's test
(c) $P<0.01$ vs the controls by Dunnett's test

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of dosed and control rats of each sex were comparable throughout the studies (Table 11 and Figure 1). Rats exposed at 4,000 ppm were restless and pawed at the eyes and muzzle during the exposure period.

TABLE 11. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

Weeks on Study	Control		1,000 ppm			2,000 ppm			4,000 ppm		
	Av Wt (grams)	No. of Survivors	Av Wt (grams)	Wt (percent of controls)	No. of Survivors	Av Wt (grams)	Wt (percent of controls)	No. of Survivors	Av Wt (grams)	Wt (percent of controls)	No. of Survivors
MALE											
0	166	50	162	98	50	163	98	50	166	100	50
1	202	50	205	101	50	202	100	50	198	98	50
2	226	50	232	103	50	229	101	50	223	99	50
3	246	50	248	101	50	244	99	50	242	98	50
4	269	50	272	101	50	271	101	50	265	99	50
5	280	50	285	102	50	280	100	50	278	99	50
6	291	50	296	102	50	289	99	50	289	99	50
7	304	50	312	103	50	311	102	50	312	103	50
8	318	50	324	102	50	323	102	50	314	99	50
9	327	50	332	102	50	327	100	50	322	98	50
10	344	50	342	99	50	336	98	50	331	96	50
11	350	50	351	100	50	348	99	50	347	99	50
12	355	50	358	101	50	357	101	50	353	99	50
16	376	50	382	102	50	377	100	50	377	100	50
21	395	50	392	99	50	390	99	50	390	99	50
25	414	50	413	100	50	408	99	50	406	98	50
29	421	50	426	101	50	418	99	50	417	99	50
34	432	50	434	100	50	425	98	50	432	100	50
38	441	50	446	101	50	440	100	50	440	100	50
42	455	50	458	101	50	451	99	50	451	99	50
46	462	50	465	101	50	454	98	50	460	100	50
51	461	50	469	102	50	459	100	50	462	100	50
55	469	50	473	101	50	467	100	50	467	100	50
60	475	49	479	101	50	469	99	50	470	99	50
64	478	49	485	101	48	476	100	50	480	100	48
68	476	47	489	103	46	479	101	50	482	101	48
73	480	45	490	102	44	485	101	48	484	101	48
77	484	42	485	100	43	484	100	44	476	98	46
81	475	41	472	99	43	471	99	41	477	100	40
86	471	36	489	104	39	475	101	37	479	102	33
90	467	34	481	103	35	473	101	34	482	103	28
95	475	26	476	100	28	467	98	28	471	99	19
99	465	21	464	100	23	462	99	21	456	98	16
FEMALE											
0	127	50	127	100	50	126	99	50	127	100	50
1	142	50	146	103	50	145	102	50	142	100	50
2	152	50	155	102	50	155	102	50	152	100	50
3	161	50	160	99	50	161	100	50	159	99	50
4	173	50	170	98	50	174	101	50	173	100	50
5	177	50	178	101	50	180	102	50	178	101	50
6	181	50	185	102	50	186	103	50	183	101	50
7	189	50	191	101	50	190	101	50	190	101	50
8	193	50	196	102	50	197	102	50	194	101	50
9	198	50	200	101	50	201	102	50	195	98	50
10	201	50	203	101	50	204	101	50	200	100	50
11	203	50	208	102	50	209	103	50	207	102	50
12	208	50	210	101	50	210	101	50	209	100	50
16	216	50	219	101	50	216	100	50	217	100	50
21	224	50	224	100	50	223	100	50	222	99	50
25	233	50	234	100	50	231	99	50	232	100	50
29	240	50	242	101	50	237	99	50	238	99	50
34	246	50	245	100	50	241	98	50	243	99	50
38	252	50	253	100	50	251	100	50	248	98	50
42	260	50	261	100	50	259	100	50	257	99	50
46	269	50	267	99	50	265	99	50	265	99	50
51	279	49	280	100	50	277	99	50	277	99	50
55	289	49	288	100	50	290	100	50	284	98	50
60	300	49	299	100	50	302	101	50	295	98	49
64	304	49	305	100	49	309	102	48	304	100	48
68	312	49	314	101	49	315	101	46	312	100	48
73	318	49	322	101	49	323	102	44	323	102	45
77	322	47	330	102	45	325	101	42	328	102	44
81	317	45	326	103	44	320	101	42	322	102	41
86	322	42	336	104	41	324	101	33	322	100	38
90	324	40	337	104	39	337	104	30	327	101	32
95	335	36	347	104	33	342	102	27	335	100	27
99	332	31	345	104	26	337	102	26	334	101	21

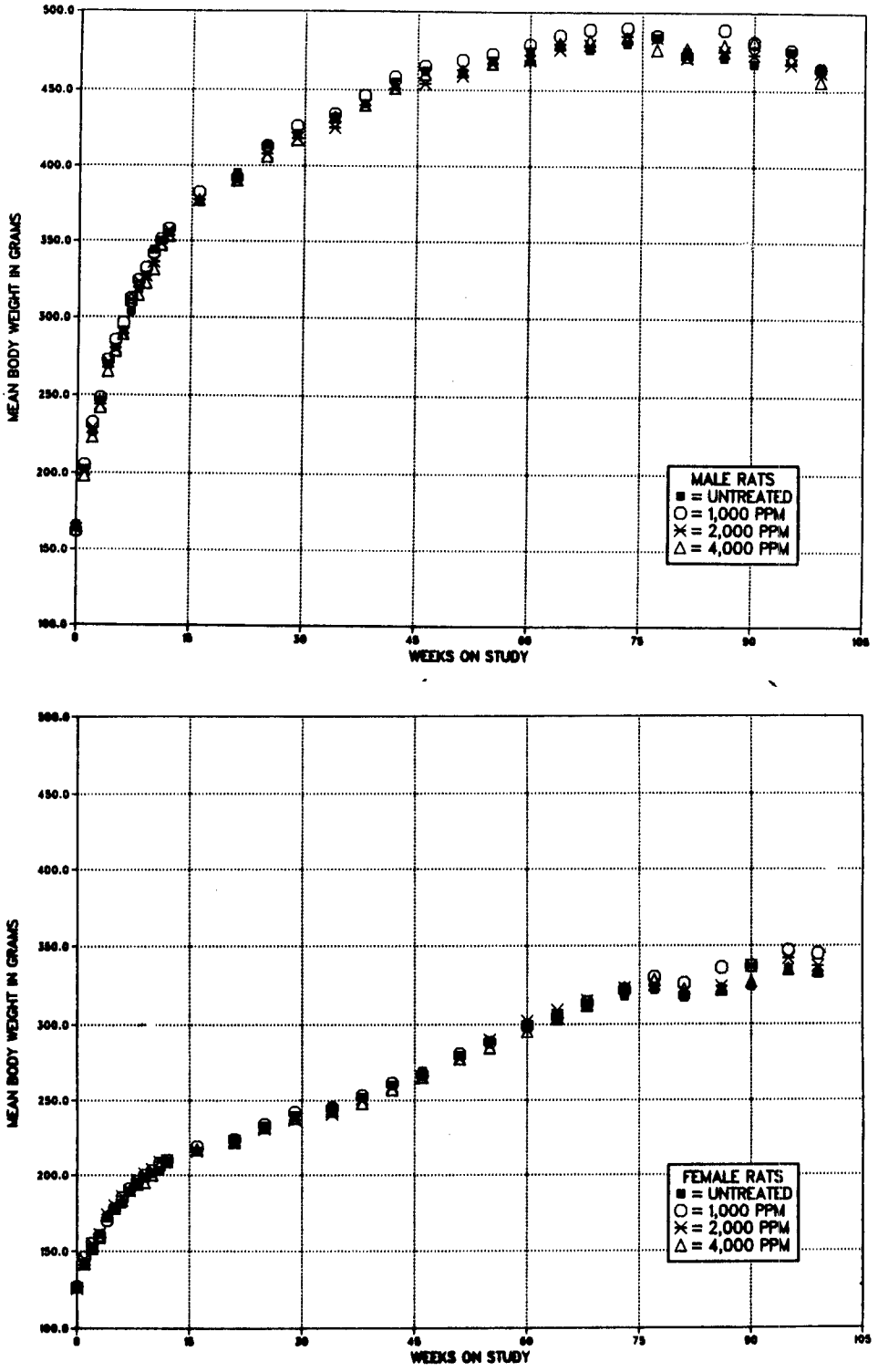

FIGURE 1. GROWTH CURVES FOR RATS EXPOSED TO DICHLOROMETHANE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of the survival of male and female rats exposed to dichloromethane at the concentrations used in these studies and those of the controls are shown in the Kaplan and Meier curves in Figure 2. The survival of the high dose group of female rats was significantly lower than that of the controls (Table 12) after week 100. No other significant differences in survival were observed between any groups of either sex. Survival of all groups of males was low (18%-34%). Most of the early deaths among males occurred during the final 16 weeks of the study.

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 mammary gland, integumentary system, liver, multiple organs, tunica vaginalis, hematopoietic system, nasal cavity, kidney, spleen, prostate, parathyroid, adrenal gland, testis, and pituitary gland. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1 and E2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the four groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in control animals are listed in Appendix F.

TABLE 12. SURVIVAL OF RATS IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

	Control	1,000 ppm	2,000 ppm	4,000 ppm
MALE (a)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (b)	34	34	33	41
Killed at termination	16	16	17	9
Survival P values (c)	0.116	0.945	0.935	0.163
FEMALE (a)				
Animals initially in study	50	50	50	50
Nonaccidental deaths before termination (b)	20	28	28	35
Killed at termination	30	22	22	15
Survival P values (c)	0.006	0.223	0.118	0.006

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

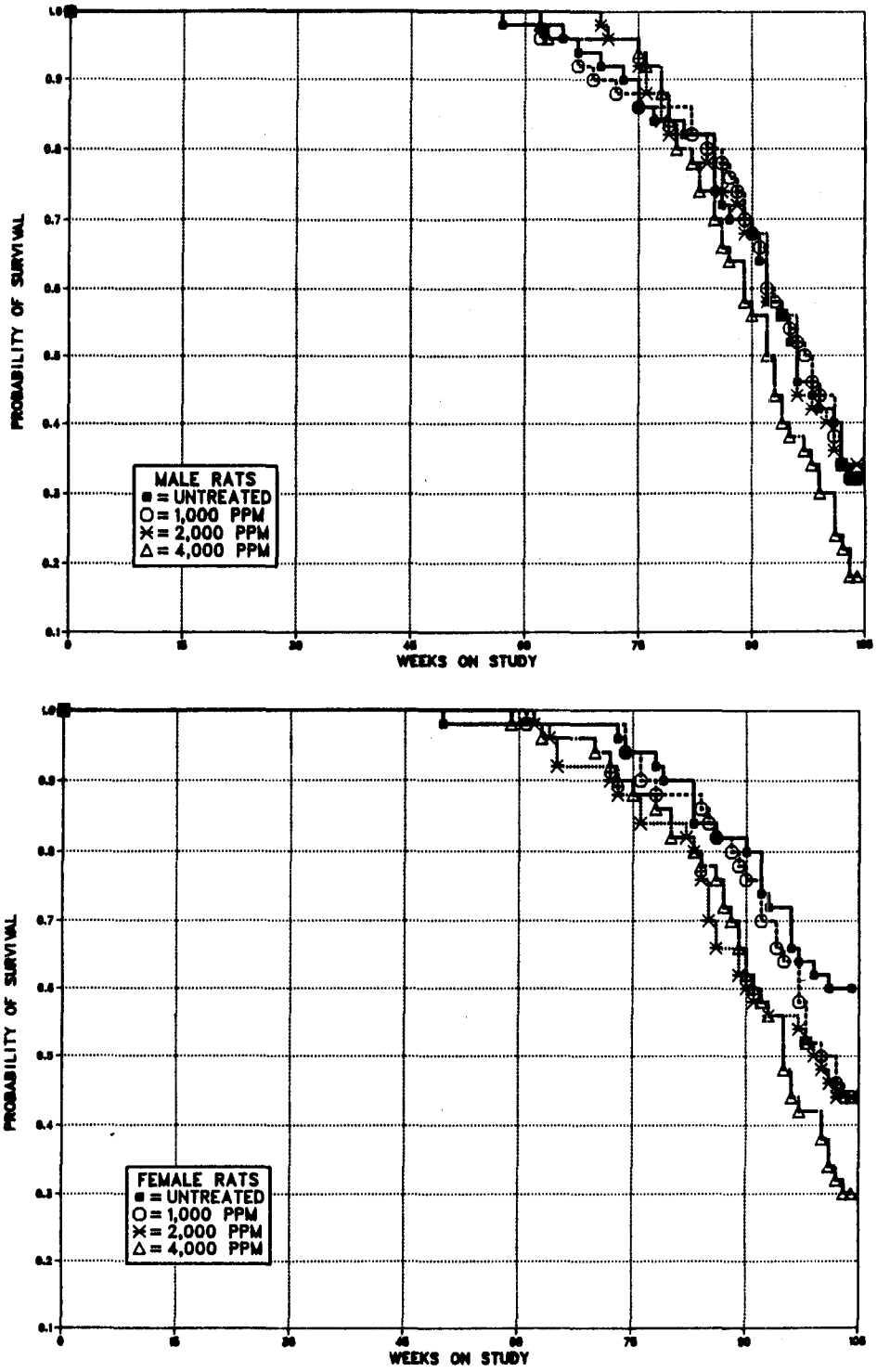

FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS EXPOSED TO DICHLOROMETHANE BY INHALATION FOR TWO YEARS

Mammary Gland: Fibroadenomas and adenomas or fibroadenomas (combined) in male and female rats occurred with significant positive trends, and the incidences in high dose males and dosed females were significantly greater than those in the controls (Table 13). Subcutaneous fibromas and fibromas or sarcomas (combined) located in the mammary area in male rats occurred with significant positive trends; the incidences in the dosed groups were not significantly greater than those in the controls. These subcutaneous tumors all occurred in the area of the mammary chain and may have been derived from nonglandular mammary tissue. Therefore, the subcutaneous tumors and the mammary gland tumors were combined for comparative purposes. When combined, the tumors occurred in male rats with a significant positive trend and the incidence in the high dose group was significantly greater than that in the controls (Table 13).

Except for a single adenoma in a high dose female rat, all mammary tumors were visible at necropsy. The neoplasms ranged from 1 to 8 cm in diameter and were primarily located in the axillary and inguinal areas. Grossly, they appeared to be cystic and rubbery or firm and many contained a milky fluid.

The diagnosis of fibroadenoma was based on the presence of a prominent fibrous stroma made up of mature collagenous fibrous tissue and proliferating mammary epithelium forming acini and solid masses of columnar, cuboidal, or round epithelial cells with abundant, often foamy cytoplasm. The mitotic rate was low. The amount of these two components in tumors diagnosed as fibroadenomas varied from masses of mature collagen with small islands of proliferating mammary epithelium to masses made up largely of proliferating mammary epithelium but with a mature fibrous stroma.

A diagnosis of carcinoma of the mammary gland in a low dose female was based on the presence of solid sheets and nests of proliferating epithelial cells that were basophilic and had a high nuclear-to-cytoplasmic ratio and a high rate of mitosis. The diagnosis of a malignant mixed tumor in one control female rat was based on the presence of a dominant bone-forming sarcomatous component, accompanied by a small squamous epithelial component.

TABLE 13. ANALYSIS OF MAMMARY GLAND OR SUBCUTANEOUS TISSUE LESIONS IN RATS IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE (a)

	Control	1,000 ppm	2,000 ppm	4,000 ppm
MALE				
Mammary Gland: Fibroadenoma (b)				
Overall Rates	0/50 (0%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted Rates	0.0%	0.0%	11.8%	34.0%
Terminal Rates	0/16 (0%)	0/16 (0%)	2/17 (12%)	2/9 (22%)
Week of First Observation			104	101
Life Table Tests	P<0.001	(c)	P=0.250	P=0.020
Incidental Tumor Tests	P=0.003	(c)	P=0.250	P=0.040
Mammary Gland: Adenoma				
Overall Rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Mammary Gland: Adenoma or Fibroadenoma				
Overall Rates	0/50 (0%)	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted Rates	0.0%	0.0%	11.8%	36.6%
Terminal Rates	0/16 (0%)	0/16 (0%)	2/17 (12%)	2/9 (22%)
Week of First Observation			104	93
Life Table Tests	P<0.001	(c)	P=0.250	P=0.010
Incidental Tumor Tests	P<0.001	(c)	P=0.250	P=0.023

TABLE 13. ANALYSIS OF MAMMARY GLAND OR SUBCUTANEOUS TISSUE LESIONS IN RATS IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE (Continued)

	Control	1,000 ppm	2,000 ppm	4,000 ppm
MALE (Continued)				
Subcutaneous Tissue: Fibroma (d)				
Overall Rates	1/50 (2%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted Rates	6.3%	6.3%	9.2%	19.5%
Terminal Rates	1/16 (6%)	1/16 (6%)	1/17 (6%)	0/9 (0%)
Week of First Observation	104	104	96	89
Life Table Tests	P=0.024	P=0.764	P=0.523	P=0.095
Incidental Tumor Tests	P=0.064	P=0.764	P=0.505	P=0.204
Subcutaneous Tissue: Sarcoma				
Overall Rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Subcutaneous Tissue: Fibroma or Sarcoma				
Overall Rates	1/50 (2%)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted Rates	6.3%	6.3%	9.2%	22.7%
Terminal Rates	1/16 (6%)	1/16 (6%)	1/17 (6%)	0/9 (0%)
Week of First Observation	104	104	96	89
Life Table Tests	P=0.008	P=0.764	P=0.523	P=0.050
Incidental Tumor Tests	P=0.026	P=0.764	P=0.505	P=0.125
Mammary Gland or Subcutaneous Tissue: Adenoma, Fibroadenoma, or Fibroma				
Overall Rates	1/50 (2%)	1/50 (2%)	4/50 (8%)	9/50 (18%)
Adjusted Rates	6.3%	6.3%	20.6%	49.0%
Terminal Rates	1/16 (6%)	1/16 (6%)	3/17 (18%)	2/9 (22%)
Week of First Observation	104	104	96	89
Life Table Tests	P<0.001	P=0.764	P=0.196	P=0.002
Incidental Tumor Tests	P=0.001	P=0.764	P=0.186	P=0.008
FEMALE				
Mammary Gland: Epithelial Hyperplasia				
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
Mammary Gland: Fibroadenoma (e)				
Overall Rates	5/50 (10%)	11/50 (22%)	13/50 (26%)	22/50 (44%)
Adjusted Rates	15.7%	41.2%	43.6%	79.4%
Terminal Rates	4/30 (13%)	8/22 (36%)	7/22 (32%)	10/15 (67%)
Week of First Observation	96	74	65	73
Life Table Tests	P<0.001	P=0.028	P=0.009	P<0.001
Incidental Tumor Tests	P<0.001	P=0.049	P=0.025	P<0.001
Mammary Gland: Adenoma				
Overall Rates	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%)
Mammary Gland: Adenoma or Fibroadenoma				
Overall Rates	5/50 (10%)	11/50 (22%)	13/50 (26%)	23/50 (46%)
Adjusted Rates	15.7%	41.2%	43.6%	83.5%
Terminal Rates	4/30 (13%)	8/22 (36%)	7/22 (32%)	11/15 (73%)
Week of First Observation	96	74	65	73
Life Table Tests	P<0.001	P=0.028	P=0.009	P<0.001
Incidental Tumor Tests	P<0.001	P=0.049	P=0.025	P<0.001
Mammary Gland: Adenocarcinoma or Carcinoma				
Overall Rates	1/50 (2%)	2/50 (4%)	2/50 (4%)	0/50 (0%)
Mammary Gland: Mixed Tumors, Malignant				
Overall Rates	1/50 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence at testing laboratory: 0/100; historical incidence in NTP studies (mean ± SD): 51/1,727 (3% ± 3%)
(c) No P value is reported because no tumors were observed in the 1,000-ppm and control groups.
(d) Historical incidence at testing laboratory: 6/100 (6%); historical incidence in NTP studies (mean ± SD): 91/1,727 (5% ± 3%)
(e) Historical incidence at testing laboratory: 16/99 (16%); historical incidence in NTP studies (mean ± SD): 492/1,772 (28% ± 10%)

Liver: Hemosiderosis, hepatocytomegaly, cytoplasmic vacuolization, and necrosis were observed at increased incidences in dosed male and female rats (Appendix C, Tables C1 and C2). Bile duct fibrosis was observed at increased incidences in dosed male rats and mid dose female rats. Neoplastic nodules and neoplastic nodules or hepatocellular carcinomas (combined) in female rats occurred with significant positive trends by the life table test; the incidences in the high dose group were not significantly greater than those in the controls (Table 14).

TABLE 14. ANALYSIS OF LIVER TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE

	Control	1,000 ppm	2,000 ppm	4,000 ppm
Neoplastic Nodule				
Overall Rates	2/50 (4%)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted Rates	6.7%	2.0%	10.2%	19.6%
Terminal Rates	2/30 (7%)	0/22 (0%)	1/22 (5%)	1/15 (7%)
Week of First Observation	104	61	85	73
Life Table Tests	P=0.030	P=0.569N	P=0.382	P=0.080
Incidental Tumor Tests	P=0.097	P=0.494N	P=0.482	P=0.229
Hepatocellular Carcinoma				
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Neoplastic Nodule or Hepatocellular Carcinoma (a)				
Overall Rates	2/50 (4%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted Rates	6.7%	2.0%	14.4%	19.6%
Terminal Rates	2/30 (7%)	0/22 (0%)	2/22 (9%)	1/15 (7%)
Week of First Observation	104	61	85	73
Life Table Tests	P=0.027	P=0.569N	P=0.223	P=0.080
Incidental Tumor Tests	P=0.086	P=0.494N	P=0.297	P=0.229

(a) Historical incidence at testing laboratory: 1/98 (1%); historical incidence in NTP studies (mean ± SD): 48/1,766 (3% ± 3%)

Multiple Organs: Mesotheliomas of the tunica vaginalis or multiple organs in male rats occurred with significant positive trends, and the incidences in the mid dose and high dose groups were significantly greater than that in the controls (Table 15).

Hematopoietic System: Mononuclear cell leukemia in male and female rats occurred with significant positive trends by the life table test; the incidences in the mid dose and high dose female rats were significantly greater than those in the controls by the life table test (Table 16). The incidence in low dose male rats was significantly lower than that in the controls.

TABLE 15. ANALYSIS OF MESOTHELIOMAS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE

	Control	1,000 ppm	2,000 ppm	4,000 ppm
Tunica Vaginalis: All Types				
Overall Rates	0/50 (0%)	1/50 (2%)	4/50 (8%)	4/50 (8%)
Adjusted Rates	0.0%	2.2%	19.2%	24.4%
Terminal Rates	0/16 (0%)	0/16 (0%)	2/17 (12%)	0/9 (0%)
Week of First Observation		69	96	92
Life Table Tests	P=0.009	P=0.496	P=0.070	P=0.031
Incidental Tumor Tests	P=0.030	P=0.473	P=0.062	P=0.097
All Sites: All Types (a)				
Overall Rates	0/50 (0%)	2/50 (4%)	5/50 (10%)	4/50 (8%)
Adjusted Rates	0.0%	4.4%	22.8%	24.4%
Terminal Rates	0/16 (0%)	0/16 (0%)	2/17 (12%)	0/9 (0%)
Week of First Observation		69	96	92
Life Table Tests	P=0.020	P=0.243	P=0.038	P=0.031
Incidental Tumor Tests	P=0.063	P=0.225	P=0.030	P=0.097

(a) Historical incidence at testing laboratory: 4/100 (4%); historical incidence in NTP studies (mean ± SD): 44/1,727 (3% ± 2%)

TABLE 16. ANALYSIS OF HEMATOPOIETIC SYSTEM TUMORS IN RATS IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

	Control	1,000 ppm	2,000 ppm	4,000 ppm
MALE				
Mononuclear Cell Leukemia (a)				
Overall Rates	34/50 (68%)	26/50 (52%)	32/50 (64%)	35/50 (70%)
Adjusted Rates	80.3%	77.0%	80.2%	89.4%
Terminal Rates	8/16 (50%)	9/16 (56%)	10/17 (59%)	6/9 (67%)
Week of First Observation	57	82	71	75
Life Table Tests	P=0.045	P=0.147N	P=0.400N	P=0.134
Incidental Tumor Tests	P=0.399	P=0.049N	P=0.434N	P=0.487N
FEMALE				
Mononuclear Cell Leukemia (b)				
Overall Rates	17/50 (34%)	17/50 (34%)	23/50 (46%)	23/50 (46%)
Adjusted Rates	41.1%	44.4%	63.6%	58.1%
Terminal Rates	8/30 (27%)	4/22 (18%)	10/22 (45%)	1/15 (7%)
Week of First Observation	73	76	73	63
Life Table Tests	P=0.009	P=0.402	P=0.049	P=0.028
Incidental Tumor Tests	P=0.273	P=0.425N	P=0.189	P=0.579

(a) Historical incidence at testing laboratory: 36/100 (36%); historical incidence in NTP studies (mean ± SD): 458/1,727 (27% ± 9%)
(b) Historical incidence at testing laboratory: 27/99 (27%); historical incidence in NTP studies (mean ± SD): 307/1,772 (17% ± 6%)

Nasal Cavity: Squamous metaplasia was observed at an increased incidence in high dose female rats (male: control, 4/50, 8%; low dose, 5/50, 10%; mid dose, 3/50, 6%; high dose, 3/50, 6%; female: control, 1/50, 2%; low dose, 2/50, 4%; mid dose, 3/50, 6%; high dose, 9/50, 18%).

Kidney: Degeneration of the kidney tubule was observed at an increased incidence in mid dose male rats and high dose female rats (male: control, 11/50, 22%; low dose, 13/50, 26%; mid dose, 23/50, 46%; high dose, 10/50, 20%; female: control, 14/50, 28%; low dose, 20/50, 40%; mid dose, 22/50, 44%; high dose, 25/49, 51%).

Spleen: Fibrosis was observed at increased incidences in dosed male and female rats (male: control, 2/50, 4%; low dose, 6/49, 12%; mid dose, 11/50, 22%; high dose, 8/50, 16%; female: control, 0/50; low dose, 2/50, 4%; mid dose, 4/50, 8%; high dose, 4/49, 8%).

Prostate: Suppurative inflammation was observed at increased incidences in dosed male rats (control, 1/44, 2%; low dose, 4/42, 10%; mid dose, 10/46, 22%; high dose, 5/45, 11%).

Parathyroid: Hyperplasia was observed at increased incidences in dosed male rats (male: control, 0/29; low dose, 6/35, 17%; mid dose, 2/30, 7%; high dose, 4/32, 13%; female: control, 2/26, 18%; low dose, 0/19; mid dose, 1/26, 4%; high dose, 0/26).

Other Increased Tumor Incidences: Other tumors occurred at marginally significant increased incidences in the dosed groups relative to the controls. These increases were characterized by a significant trend but no significant pairwise effect, a pairwise difference that was significant only by life table analysis, or a significant effect at the low dose but no significant trend or effect at the high dose. These tumors included adrenal gland pheochromocytomas and interstitial cell tumors of the testis in males and pituitary gland adenomas or carcinomas (combined) in males and females (Appendix E, Tables E1 and E2).

SINGLE-EXPOSURE STUDIES

The incidence of deaths in the various groups is given in Table 17. The LC_{50} value for male mice was calculated on the basis of time-weighted average concentrations of 15,975, 16,356, 16,948, 17,175, 18,035, 18,670, 19,271, and 20,398 by probit analysis (Finney, 1971) to be 17,703 ppm (95% confidence limit range, 16,163-18,505 ppm). No meaningful LC_{50} value could be determined for the female mice. No compound-related effects were observed at necropsy.

NINETEEN-DAY STUDIES

All mice exposed to dichloromethane at 16,000 ppm and 3/5 males and 4/5 females exposed at 13,000 ppm died before the end of the studies (Table 18). The female mouse in the 13,000-ppm group that survived to the end of the study lost weight. Final mean body weights of other groups of dosed and control male and female mice were comparable. Hyperactivity was considered to be compound related. No compound-related effects were observed at necropsy.

TABLE 17. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SINGLE-EXPOSURE INHALATION STUDIES OF DICHLOROMETHANE

Target Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)
MALE				
15,500	5/5	20.4 ± 0.7	25.8 ± 0.6	+ 5.4 ± 0.2
16,500	5/5	21.0 ± 0.7	25.2 ± 0.7	+ 4.2 ± 0.2
16,800	5/5	20.2 ± 2.1	27.4 ± 0.2	+ 7.2 ± 2.2
17,250	1/5	19.8 ± 0.6	24.0	+ 5.0
18,500	3/5	18.6 ± 0.5	24.3 ± 0.3	+ 6.3 ± 0.7
19,000	1/5	20.8 ± 0.2	26.0	+ 5.0
19,000	1/5	22.0 ± 0.9	24.0	+ 1.0
19,000	0/5	22.0 ± 0.4	(d)	(d)
FEMALE				
15,500	5/5	17.2 ± 0.4	20.8 ± 0.2	+ 3.6 ± 0.2
16,500	5/5	16.6 ± 0.6	20.0 ± 0.7	+ 3.4 ± 0.2
16,800	5/5	19.4 ± 0.2	21.2 ± 0.4	+ 1.8 ± 0.5
17,250	2/5	18.6 ± 0.7	20.0 ± 0.0	+ 2.0 ± 0.0
18,500	2/5	16.4 ± 0.4	22.5 ± 0.5	+ 5.5 ± 0.5
19,000	4/5	18.8 ± 0.4	21.3 ± 0.3	+ 2.3 ± 0.5
19,000	4/5	19.2 ± 0.6	20.3 ± 0.5	+ 1.3 ± 0.5
19,000	2/5	18.2 ± 0.7	20.5 ± 0.5	+ 2.0 ± 1.0

(a) Number surviving/number initially 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 of the group ± standard error of the mean
(d) No data are reported due to the 100% mortality in this group.

TABLE 18. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE NINETEEN-DAY INHALATION STUDIES OF DICHLOROMETHANE

Target Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)
MALE					
0	5/5	24.8 ± 0.6	26.8 ± 0.6	+ 2.0 ± 0.0	--
1,625	4/5	24.6 ± 0.4	27.8 ± 0.3	+ 2.8 ± 0.3	103.7
3,250	5/5	24.6 ± 0.2	26.8 ± 1.0	+ 2.2 ± 1.0	100.0
6,500	5/5	24.4 ± 0.2	28.0 ± 0.3	+ 3.6 ± 0.4	104.5
13,000	2/5	25.4 ± 0.5	26.5 ± 0.5	+ 1.0 ± 0.0	98.9
16,000	0/5	25.0 ± 0.4	(d)	(d)	--
FEMALE					
0	5/5	19.2 ± 0.4	22.6 ± 0.5	+ 3.4 ± 0.4	--
1,625	5/5	19.4 ± 0.7	23.0 ± 0.5	+ 3.6 ± 0.2	101.8
3,250	5/5	19.8 ± 0.5	24.8 ± 0.6	+ 5.0 ± 0.3	109.7
6,500	5/5	19.4 ± 0.2	24.8 ± 0.6	+ 5.4 ± 0.6	109.7
13,000	1/5	19.2 ± 0.5	17.0	− 2.0	75.2
16,000	0/5	19.0 ± 0.3	(d)	(d)	--

(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 change of the survivors of the group ± standard error of the mean
(d) No data are reported due to the 100% mortality in this group.

THIRTEEN-WEEK STUDIES

The deaths of 4/10 males and 2/10 females exposed to dichloromethane at 8,400 ppm were considered to be compound related (Table 19). The final mean body weight of females exposed at 8,400 ppm was 8% lower than that of the controls. Centrilobular hydropic degeneration (pale perinuclear cytoplasm of centrilobular hepatocytes) of minimal-to-mild severity was observed in 3/10 males and 8/10 females exposed at 8,400 ppm and in 9/10 females exposed at 4,200 ppm. This lesion was considered to be due to differences in glycogen storage and a consequence of the sequence in which the animals were killed. The liver lipid:liver weight ratio for female mice that were exposed at 8,400 ppm was significantly lower than that of the controls ($P<0.05$, Dunnett's test) (Table 20).

Dose Selection Rationale: Based on deaths observed at 8,400 ppm and the severity of histologic changes noted in mice exposed at 4,000 ppm for 13 weeks, concentrations selected for mice for the 2-year inhalation studies of dichloromethane were 2,000 and 4,000 ppm.

TABLE 19. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK INHALATION STUDIES OF DICHLOROMETHANE

Target Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (c)	Change (d)	Final Weight Relative to Controls (percent)
MALE					
0	(e) 9/10	27.3 ± 0.4	33.0 ± 0.8	+ 5.7 ± 0.8	--
525	10/10	25.5 ± 0.7	32.1 ± 0.6	+ 6.6 ± 0.8	97.3
1,050	(f) 9/10	27.2 ± 0.6	33.7 ± 0.8	+ 6.4 ± 0.4	102.1
2,100	10/10	26.9 ± 0.7	34.4 ± 0.6	+ 7.5 ± 0.6	104.2
4,200	10/10	26.1 ± 0.5	32.9 ± 0.7	+ 6.8 ± 0.5	99.7
8,400	(g) 6/10	25.4 ± 0.7	34.0 ± 1.0	+ 7.7 ± 1.0	103.0
FEMALE					
0	(h) 7/10	20.9 ± 0.6	27.7 ± 0.6	+ 6.3 ± 0.4	--
525	10/10	21.0 ± 0.5	28.1 ± 0.8	+ 7.1 ± 0.9	101.4
1,050	10/10	21.0 ± 0.4	28.9 ± 0.5	+ 7.9 ± 0.7	104.3
2,100	10/10	21.3 ± 0.6	29.2 ± 0.8	+ 7.9 ± 0.4	105.4
4,200	10/10	20.6 ± 0.4	28.7 ± 0.5	+ 8.1 ± 0.5	103.6
8,400	(i) 7/10	19.6 ± 0.4	25.4 ± 0.6	+ 5.6 ± 0.5	91.7

(a) Number surviving/number initially in group
(b) Initial group body weight ± standard error of the mean. Subsequent calculations are based on those animals that survived through the final weighing.
(c) Final body weights taken after 12 weeks of exposure
(d) Mean body weight change of the survivors ± standard error of the mean
(e) Week of death: 8
(f) Week of death: 5
(g) Week of death: 2, 9, 12, 12
(h) Week of death: 8
(i) Week of death: 12; one death was accidental.

TABLE 20. RATIO OF LIVER LIPID WEIGHT TO LIVER WEIGHT IN MICE EXPOSED TO DICHLOROMETHANE IN THE THIRTEEN-WEEK INHALATION STUDIES

Target Concentration (ppm)	Milligrams Lipid/Gram Liver (a) Male	Female
0	36 ± 4	41 ± 9
525	45 ± 12	44 ± 7
1,050	36 ± 4	36 ± 5
2,100	43 ± 19	42 ± 9
4,200	32 ± 4	40 ± 7
8,400	34 ± 6	(b) 30 ± 4

(a) Mean ± standard deviation
(b) $P<0.01$ vs controls by Dunnett's test

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The initial weight of the high dose male mice was 15% lower than that of the controls (Table 21 and Figure 3). The mean body weight of the high dose group was generally comparable to that of the controls until week 90, after which they were 8%-11% lower than those of the controls. The initial mean body weight of the high dose female mice was 7% greater than that of the controls and remained greater until week 51. From week 51 to week 95, mean body weights of the high dose female mice were 0%-9% lower than those of the controls; at week 99, the mean body weight of the high dose female group was 17% lower than that of the controls. During exposure periods, high dose female mice (and to a lesser extent, high dose male mice and low dose female mice) were hyperactive. During the second year of the study, high dose female mice were lethargic.

TABLE 21. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

Weeks on Study	Control		2,000 ppm			4,000 ppm		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	24.7	50	24.3	98	50	21.0	85	50
1	24.3	50	26.3	108	50	25.8	106	49
2	25.6	50	26.6	104	50	27.4	107	49
3	26.3	50	27.5	105	50	27.6	105	49
4	28.1	50	29.0	103	50	28.2	100	49
5	28.0	50	29.1	104	50	28.9	103	49
6	24.7	50	30.3	123	50	29.9	121	49
7	27.6	50	31.9	116	50	29.7	108	49
8	28.8	50	30.7	107	50	30.6	106	49
9	30.6	50	32.2	105	50	31.4	103	49
10	29.4	50	31.3	106	50	31.0	105	49
11	30.3	50	31.6	104	50	31.4	104	49
12	29.9	50	31.2	104	50	31.1	104	49
16	30.0	50	33.0	110	50	32.9	110	49
21	32.1	50	34.7	108	50	32.5	101	49
25	33.5	50	34.5	103	50	34.3	102	49
29	33.2	50	35.0	105	50	35.5	107	49
34	34.6	50	35.6	103	47	35.6	103	49
38	35.8	50	36.4	102	47	37.9	106	48
42	33.8	50	31.7	94	47	36.0	107	48
46	34.9	50	36.9	106	47	36.1	103	47
51	36.7	50	38.4	105	47	36.1	98	47
55	37.1	50	39.3	106	47	38.3	103	47
60	36.4	50	39.1	107	46	36.7	101	47
64	37.0	50	38.9	105	46	36.7	99	45
68	37.9	50	39.6	104	46	36.4	96	44
73	37.8	48	41.0	108	44	36.8	97	42
77	35.4	46	40.1	113	42	35.7	101	36
81	36.4	44	39.7	109	40	36.1	99	35
86	36.1	43	40.7	113	37	35.0	97	33
90	36.6	42	38.8	106	32	33.5	92	30
95	35.7	41	37.9	106	30	33.5	94	25
99	35.3	39	39.3	111	28	31.3	89	21
FEMALE								
0	16.8	50	17.6	105	50	18.0	107	50
1	21.9	50	22.2	101	50	22.1	101	49
2	21.6	49	23.3	108	47	22.9	106	49
3	22.8	49	21.7	95	47	24.8	109	49
4	24.7	49	25.2	102	47	25.1	102	48
5	24.5	49	25.3	103	47	26.0	106	48
6	24.3	49	25.7	106	47	27.4	113	48
7	25.0	49	26.8	107	47	26.4	106	47
8	26.0	49	27.3	105	47	28.1	108	47
9	27.0	49	27.7	103	47	27.5	102	46
10	25.2	49	27.6	110	47	28.6	113	46
11	25.6	49	28.2	110	46	28.7	112	46
12	26.5	49	26.8	101	46	28.1	106	46
16	25.5	49	28.9	113	46	28.9	113	46
21	27.9	48	29.2	105	46	28.9	104	46
25	30.7	48	30.6	100	46	31.7	103	46
29	29.0	48	30.5	105	46	31.2	108	46
34	31.5	48	31.1	99	46	32.0	102	46
38	31.0	47	31.8	102	46	32.5	105	46
42	31.9	47	32.6	102	46	32.1	101	46
46	31.6	47	31.2	99	46	31.8	101	46
51	33.3	47	32.2	97	46	32.4	97	46
55	34.2	47	33.6	98	46	34.2	100	46
60	34.7	46	34.2	99	46	32.9	95	46
64	33.2	45	33.0	99	46	32.2	97	46
68	34.0	45	34.5	101	45	32.2	95	46
73	35.6	44	35.5	100	45	33.2	93	43
77	33.9	42	34.0	100	44	32.9	97	39
81	34.7	40	34.9	101	43	32.9	95	36
86	34.6	36	35.2	102	41	32.0	92	31
90	34.8	32	34.0	98	36	31.5	91	21
95	32.7	29	33.7	103	32	32.6	100	20
99	37.2	26	33.5	90	26	30.8	83	12

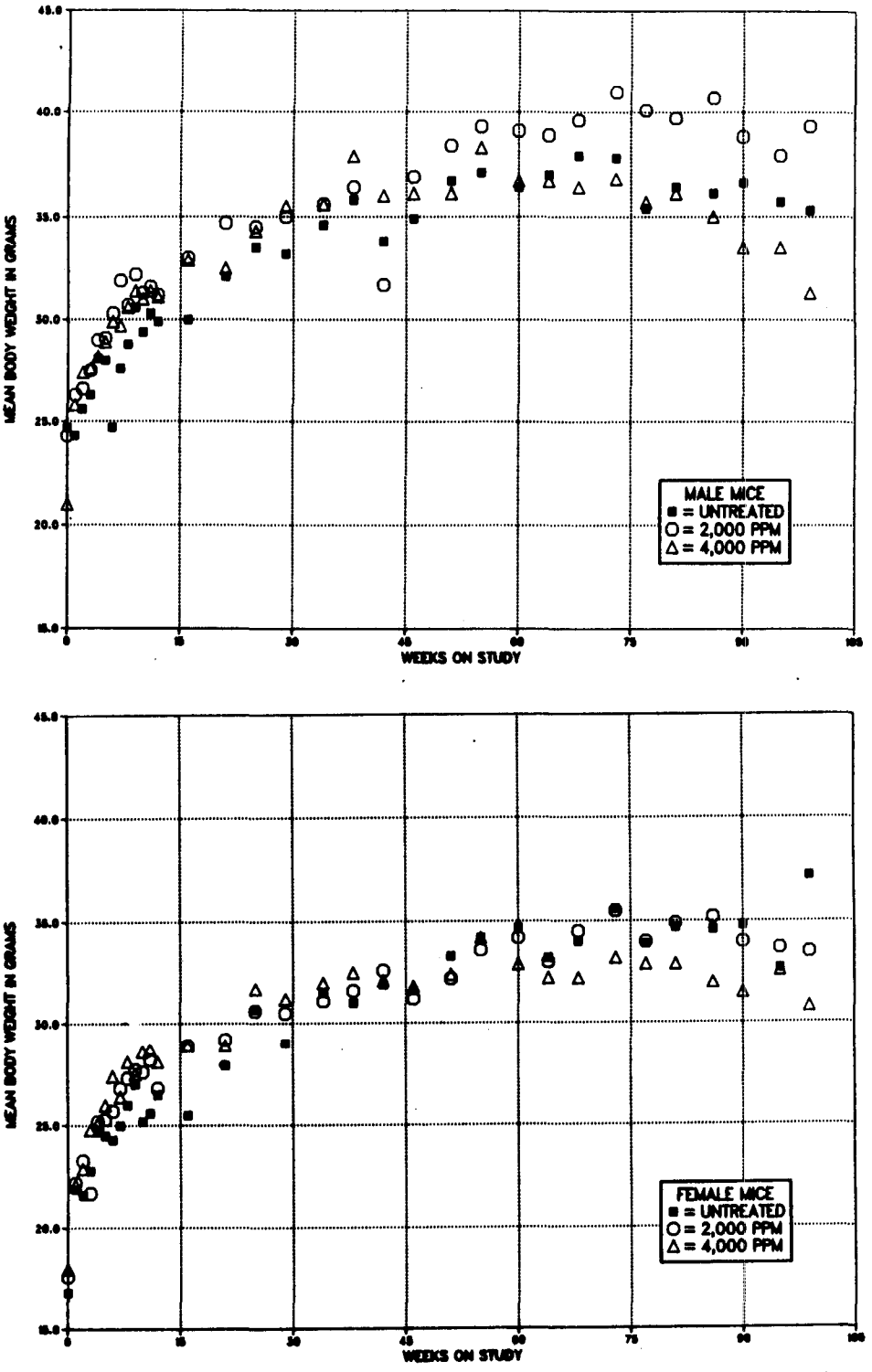

FIGURE 3. GROWTH CURVES FOR MICE EXPOSED TO DICHLOROMETHANE BY INHALATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival of male and female mice exposed to dichloromethane at the concentrations used in these studies and those of the controls are shown in the Kaplan and Meier curves in Figure 4. The survival of both dosed groups of male mice (low dose after week 101, high dose after week 89) was significantly lower than that of the controls, and the survival of the high dose group was significantly lower than that of the low dose group ($P = 0.016$) (Table 22). The survival of the high dose group of female mice was significantly lower than that of both the controls (after week 98) and the low dose group ($P < 0.01$).

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, testis, ovary, uterus, kidney, stomach, and spleen. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in control animals are listed in Appendix F.

TABLE 22. SURVIVAL OF MICE IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

	Control	2,000 ppm	4,000 ppm
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	11	24	38
Accidentally killed	0	2	1
Killed at termination	39	24	9
Died during termination period	0	0	2
Survival P values (c)	<0.001	0.010	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	24	22	40
Accidentally killed	1	2	1
Animals missing	0	1	1
Killed at termination	25	25	8
Survival P values (c)	0.002	0.678	0.004

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

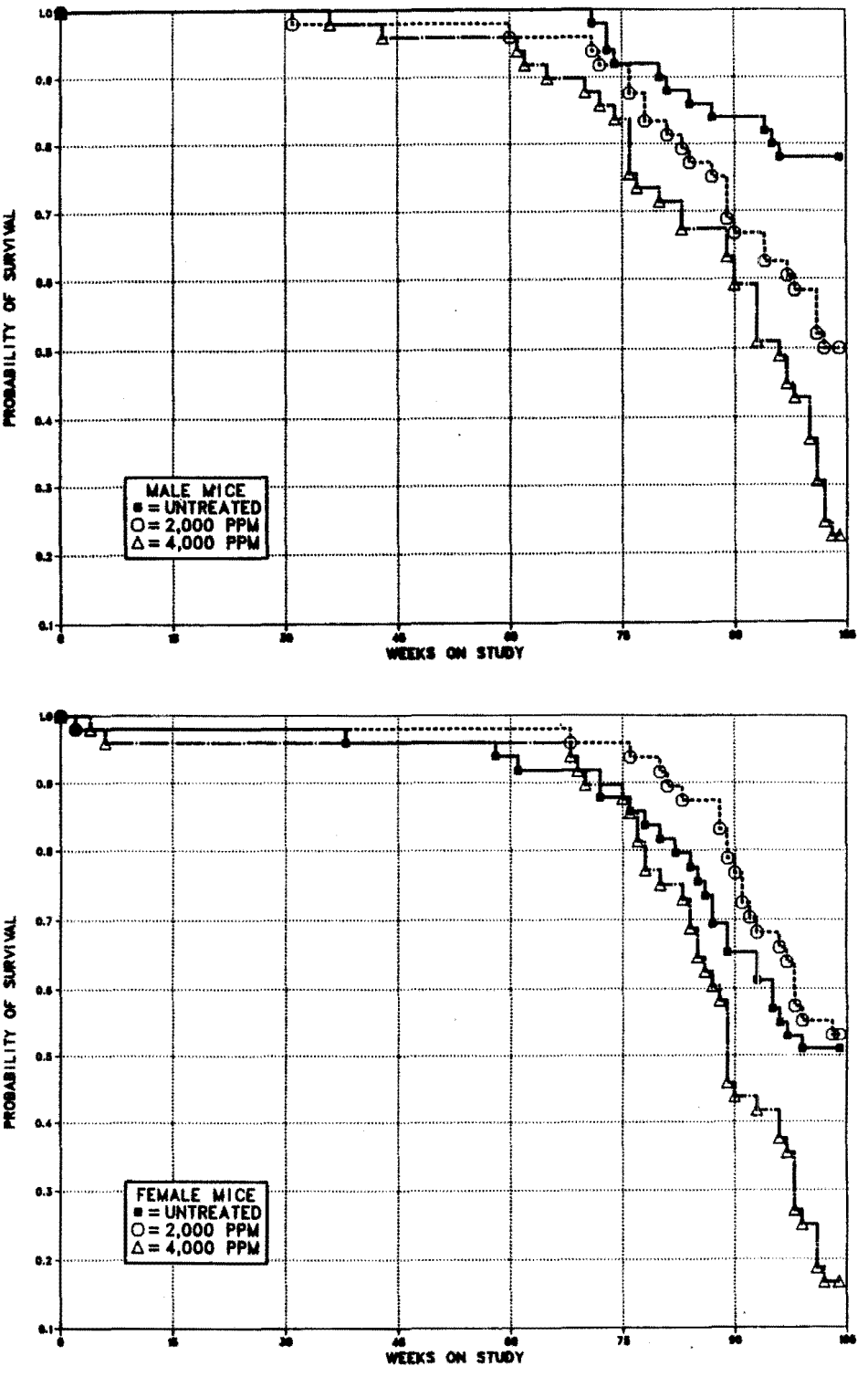

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE EXPOSED TO DICHLOROMETHANE BY INHALATION FOR TWO YEARS

Lung: Alveolar/bronchiolar adenomas, alveolar bronchiolar carcinomas, and alveolar/bronchiolar adenomas or carcinomas (combined) in male and female mice occurred with significant positive trends, and the incidences in the dosed groups were significantly greater than those in the controls (Table 23).

TABLE 23. ANALYSIS OF LUNG LESIONS IN MICE IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE (a)

	Control	2,000 ppm	4,000 ppm
MALE			
Epithelial Hyperplasia			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Alveolar/Bronchiolar Adenoma			
Overall Rates	3/50 (6%)	19/50 (38%)	24/50 (48%)
Adjusted Rates	7.7%	55.6%	78.5%
Terminal Rates	3/39 (8%)	10/24 (42%)	6/11 (55%)
Week of First Observation	104	71	70
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Alveolar/Bronchiolar Carcinoma			
Overall Rates	2/50 (4%)	10/50 (20%)	28/50 (56%)
Adjusted Rates	4.9%	34.0%	92.9%
Terminal Rates	1/39 (3%)	6/24 (25%)	9/11 (82%)
Week of First Observation	94	78	72
Life Table Tests	P<0.001	P=0.002	P<0.001
Incidental Tumor Tests	P<0.001	P=0.016	P<0.001
Alveolar/Bronchiolar Adenoma or Carcinoma (b)			
Overall Rates	5/50 (10%)	27/50 (54%)	40/50 (80%)
Adjusted Rates	12.4%	74.2%	100.0%
Terminal Rates	4/39 (10%)	15/24 (63%)	11/11 (100%)
Week of First Observation	94	71	70
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
FEMALE			
Epithelial Hyperplasia			
Overall Rates	0/50 (0%)	1/48 (2%)	0/48 (0%)
Alveolar/Bronchiolar Adenoma			
Overall Rates	2/50 (4%)	23/48 (48%)	28/48 (58%)
Adjusted Rates	6.7%	66.5%	91.1%
Terminal Rates	1/25 (4%)	14/25 (56%)	6/8 (75%)
Week of First Observation	87	83	68
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Alveolar/Bronchiolar Carcinoma			
Overall Rates	1/50 (2%)	13/48 (27%)	29/48 (60%)
Adjusted Rates	4.0%	45.9%	92.2%
Terminal Rates	1/25 (4%)	10/25 (40%)	6/8 (75%)
Week of First Observation	104	89	68
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Alveolar/Bronchiolar Adenoma or Carcinoma (c)			
Overall Rates	3/50 (6%)	30/48 (63%)	41/48 (85%)
Adjusted Rates	10.6%	82.9%	100.0%
Terminal Rates	2/25 (8%)	19/25 (76%)	8/8 (100%)
Week of First Observation	87	83	68
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001

(a) The statistical methods used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence at testing laboratory: 31/100 (31%); historical incidence in NTP studies (mean ± SD): 296/1,780 (17% ± 8%)
(c) Historical incidence at testing laboratory: 10/100 (10%); historical incidence in NTP studies (mean ± SD): 122/1,777 (7% ± 4%)

Liver: Cytologic degeneration was observed at increased incidences in high dose male mice and dosed female mice (male: control, 0/50; low dose, 0/49; high dose, 22/49, 45%; female: control, 0/50; low dose, 23/48, 48%; high dose, 21/48, 44%). Hepatocellular adenomas, hepatocellular carcinomas, and hepatocellular adenomas or carcinomas (combined) in male and female mice occurred with significant positive trends. The incidences of hepatocellular adenomas in high dose male and high dose female mice, hepatocellular carcinomas in high dose male and dosed female mice, hepatocellular adenomas and hepatocellular adenomas or carcinomas (combined) in dosed male mice, and hepatocellular adenomas or carcinomas (combined) in dosed female mice were significantly greater than those in the controls (Table 24).

TABLE 24. ANALYSIS OF LIVER TUMORS IN MICE IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

	Control	2,000 ppm	4,000 ppm
MALE			
Hepatocellular Adenoma			
Overall Rates	10/50 (20%)	14/49 (29%)	14/49 (29%)
Adjusted Rates	23.0%	46.9%	68.3%
Terminal Rates	7/39 (18%)	9/24 (38%)	6/11 (55%)
Week of First Observation	73	71	80
Life Table Tests	P<0.001	P=0.041	P=0.001
Incidental Tumor Tests	P=0.075	P=0.161	P=0.095
Hepatocellular Carcinoma			
Overall Rates	13/50 (26%)	15/49 (31%)	26/49 (53%)
Adjusted Rates	29.7%	43.7%	76.4%
Terminal Rates	9/39 (23%)	7/24 (29%)	5/11 (45%)
Week of First Observation	73	72	61
Life Table Tests	P<0.001	P=0.111	P<0.001
Incidental Tumor Tests	P=0.016	P=0.422	P=0.042
Hepatocellular Adenoma or Carcinoma (a)			
Overall Rates	22/50 (44%)	24/49 (49%)	33/49 (67%)
Adjusted Rates	48.3%	66.8%	93.0%
Terminal Rates	16/39 (41%)	13/24 (54%)	9/11 (82%)
Week of First Observation	73	71	61
Life Table Tests	P<0.001	P=0.048	P<0.001
Incidental Tumor Tests	P=0.010	P=0.305	P=0.020
FEMALE			
Hepatocellular Adenoma			
Overall Rates	2/50 (4%)	6/48 (13%)	22/48 (46%)
Adjusted Rates	6.5%	21.3%	83.0%
Terminal Rates	1/25 (4%)	4/25 (16%)	5/8 (63%)
Week of First Observation	84	96	68
Life Table Tests	P<0.001	P=0.151	P<0.001
Incidental Tumor Tests	P<0.001	P=0.155	P<0.001
Hepatocellular Carcinoma			
Overall Rates	1/50 (2%)	11/48 (23%)	32/48 (67%)
Adjusted Rates	4.0%	34.0%	96.5%
Terminal Rates	1/25 (4%)	6/25 (24%)	7/8 (88%)
Week of First Observation	104	83	68
Life Table Tests	P<0.001	P=0.005	P<0.001
Incidental Tumor Tests	P<0.001	P=0.004	P<0.001
Hepatocellular Adenoma or Carcinoma (b)			
Overall Rates	3/50 (6%)	16/48 (33%)	40/48 (83%)
Adjusted Rates	10.4%	48.0%	100.0%
Terminal Rates	2/25 (8%)	9/25 (36%)	8/8 (100%)
Week of First Observation	84	83	68
Life Table Tests	P<0.001	P=0.002	P<0.001
Incidental Tumor Tests	P<0.001	P=0.002	P<0.001

(a) Historical incidence at testing laboratory: 28/100 (28%); historical incidence in NTP studies (mean ± SD): 540/1,784 (30% ± 8%)
(b) Historical incidence at testing laboratory: 5/100 (5%); historical incidence in NTP studies (mean ± SD): 147/1,781 (8% ± 5%)

Circulatory System: Hemangiosarcomas in male mice occurred with a significant positive trend by the life table test; the incidence in the 4,000-ppm group was significantly greater than that in the controls in life table pairwise comparisons (Table 25). The following incidences of hemangioma or hemangiosarcoma (combined) were observed in female mice: control, 0/50; low dose, 2/49 (4%); high dose, 2/49 (4%).

Testis: Testicular atrophy was observed at increased incidences in dosed male mice (control, 0/50; low dose, 4/50, 8%; high dose, 31/50, 62%).

Ovary and Uterus: Ovarian atrophy was observed at increased incidences in dosed female mice (control, 6/50, 12%; low dose, 28/47, 60%; high dose, 32/43, 74%). Uterine atrophy was observed at increased incidence in high dose female mice (control, 0/50; low dose, 1/48, 2%; high dose, 8/47, 17%).

Kidney: The incidence of kidney/tubule casts was increased in high dose male mice (male: control, 6/50, 12%; low dose, 11/49, 22%; high dose, 20/50, 40%; female: control, 8/49, 16%; low dose, 23/48, 48%; high dose, 23/47, 49%).

Stomach: Dilatation of the stomach was observed at an increased incidence in high dose male and female mice (male: control, 3/49, 6%; low dose, 7/47, 15%; high dose, 9/49, 18%; female: control, 1/49, 2%; low dose, 2/47, 4%; high dose, 10/48, 21%).

Spleen: Atrophy of the splenic follicles was observed at increased incidence in high dose male mice (male: control, 0/49; low dose, 3/49, 6%; high dose, 7/48, 15%; female: control, 0/49; low dose, 0/48; high dose, 1/47, 2%).

TABLE 25. ANALYSIS OF CIRCULATORY SYSTEM TUMORS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE

	Control	2,000 ppm	4,000 ppm
Hemangioma			
Overall Rates	1/50 (2%)	0/50 (0%)	1/50 (2%)
Hemangiosarcoma			
Overall Rates	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted Rates	2.6%	7.6%	21.4%
Terminal Rates	1/39 (3%)	1/24 (4%)	1/11 (9%)
Week of First Observation	104	101	70
Life Table Tests	P=0.007	P=0.352	P=0.017
Incidental Tumor Tests	P=0.083	P=0.495	P=0.142
Hemangioma or Hemangiosarcoma (a)			
Overall Rates	2/50 (4%)	2/50 (4%)	6/50 (12%)
Adjusted Rates	4.8%	7.6%	25.8%
Terminal Rates	1/39 (3%)	1/24 (4%)	1/11 (9%)
Week of First Observation	87	101	70
Life Table Tests	P=0.010	P=0.558	P=0.022
Incidental Tumor Tests	P=0.170	P=0.643N	P=0.301

(a) Historical incidence at testing laboratory: 2/100 (2%); historical incidence in NTP studies (mean ± SD): 78/1,791 (4% ± 4%)

IV. DISCUSSION AND CONCLUSIONS

Toxicology and carcinogenesis studies were conducted by exposing rodents to dichloromethane (99% pure) by inhalation. For the 2-year studies, groups of 50 male and 50 female F344/N rats and $B6C3F_1$ mice were exposed for 6 hours per day, 5 days per week. The exposure concentrations used in these studies (0 [chamber controls], 1,000, 2,000, or 4,000 ppm in rats and 0, 2,000, or 4,000 ppm in mice) were selected on the basis of the results of 13-week inhalation studies in which groups of rats and mice of each sex were exposed to dichloromethane at concentrations ranging from 500 to 8,400 ppm for 6 hours per day, 5 days per week.

Thirteen-Week Studies

In the 13-week studies in rats, exposure at 8,200 ppm decreased body weight gain in both sexes; one male rat died before the end of the study. Body weight gains by dosed mice were comparable to those of chamber controls; four males in the 8,400-ppm group and two females in the 8,200-ppm and chamber control groups died before the end of the studies. The 8,200-ppm and 4,000-ppm concentrations produced mild to minimal lung changes in rats and hydropic changes in the livers of mice.

A maximum exposure concentration of 4,000 ppm was selected for the 2-year studies because of the minimal severity of the histopathologic changes noted in both rats and mice after exposure at 4,000 ppm for 13 weeks. The second exposure concentration selected was 2,000 ppm for both species, and a third, lower concentration (1,000 ppm) was added for rats because, in an earlier inhalation study (Burek et al., 1980, 1984), exposure at 3,500 ppm had reduced the survival of female Sprague-Dawley rats.

Two-Year Studies

The results of the present studies as well as of other available long-term studies conducted on dichloromethane are summarized for ease of comparison in Table 26. In male rats, exposure at 1,000, 2,000, or 4,000 ppm dichloromethane had no effect on survival compared with the chamber controls; however, the survival of all groups of male rats was unusually low relative to historical data (chamber control, 16/50; low dose, 16/50; mid dose, 17/50; high dose, 9/50). Most of these early deaths occurred during the last 16 weeks of the study; the survival at week 86 was considered average (control, 36/50; low dose, 39/50; mid dose, 37/50; high dose, 33/50). There was an unusually high incidence of advanced mononuclear cell leukemia in all groups of male rats (control, 34/50; low dose, 26/50; mid dose, 32/50; high dose, 35/50). The leukemia may have contributed to the early deaths. The survival of female rats exposed at 4,000 ppm was reduced (control, 30/50; low dose, 22/50; mid dose, 22/50; high dose, 15/50), and there was an increase in the incidence of leukemia in the 2,000-ppm and 4,000-ppm groups (control, 17/50; low dose, 17/50; mid dose, 23/50; high dose, 23/50). The advanced leukemia, which may have reduced survival of high dose females, may have been due to administration of dichloromethane. In light of the unusually high incidence of leukemia in all groups of males, it is not possible to make an unequivocal conclusion concerning the relationship between dichloromethane exposure and the marginally increased incidence of the disease in the mid dose and high dose female rats. Body weights for dosed male and female rats were comparable to those of chamber controls.

In mice, the survival of dosed males and high dose females was reduced relative to that of the chamber controls (see Table 22 and Figure 4). This reduced survival may have been because of the high incidences of liver and lung neoplasia in dosed animals. Total deaths increased in a dose-related manner during the final 16 weeks (male: control, 4/43, 9%; low dose, 9/37, 24%; high dose, 12/33, 36%; female: control, 10/36, 28%; low dose, 15/41, 37%; high dose, 19/31, 61%). Final mean body weights of high dose male mice and dosed female mice were 10%-17% lower than those of the chamber controls. These differences in body weight occurred during the last 16 weeks of the studies.

Mammary Gland Effects in Rats

The administration of dichloromethane produced increased incidences of mammary gland neoplasms in both male and female rats (male:

TABLE 26. SUMMARY OF RESULTS OF TWO-YEAR STUDIES ON DICHLOROMETHANE

Reference	Route	Species	Strain	Concentration	Tumor Site
Burek et al. (1980, 1984)	Inhalation	Rat	Sprague-Dawley	0, 500, 1,500, 3500 ppm	Mammary gland (both sexes)
	Inhalation	Hamster	Syrian	0, 500, 1,500, 3,500 ppm	No reported effect
Nitschke et al. (1982)	Inhalation	Rat	Sprague-Dawley	0, 50, 200, 500 ppm	Mammary gland (females)
National Coffee Association (1982)	Drinking water	Rat	F344	0, 5, 50, 125, 250 mg/kg	No reported effects
National Coffee Association (1983)	Drinking water	Mouse	$B6C3F_1$	0, 60, 125, 185, 250 mg/kg	No reported effects
Current studies	Inhalation	Rat	F344/N	0, 1,000, 2,000, 4,000 ppm	Mammary gland (both sexes)
	Inhalation	Mouse	$B6C3F_1$	0, 2,000, 4,000 ppm	Liver and lung (both sexes)

control, 0/50; low dose, 0/50; mid dose, 2/50; high dose, 5/50; female: control, 7/50; low dose, 13/50; mid dose, 14/50; high dose, 23/50). In addition, there was a marginal increase in the incidence of subcutaneous tissue fibromas in the region of the mammary chain in male rats (control, 1/50; low dose, 1/50; mid dose, 2/50; high dose, 4/50). Since these fibromas were all found in the axillary and inguinal areas, they probably arose from mammary tissue. The incidences of the combined mammary tumors were: control, 1/50; low dose, 1/50; mid dose, 4/50; high dose, 9/50. The historical incidences of mammary gland tumors in chamber control rats at the same laboratory are 1/100 in males and 17/99 in females. Throughout the Program, the historical incidences for animals receiving no treatment are 54/1,727 (3%) in males and 520/1,772 (29%) in females (Tables F4 and F11).

Burek et al. (1980, 1984) exposed Sprague-Dawley rats to dichloromethane at concentrations of 0, 500, 1,500, or 3,500 ppm for 6 hours per day, 5 days per week for 2 years (see Table 26). The Sprague-Dawley rat strain has control incidences of mammary gland tumors of 10% in males and 80% in females (Burek et al., 1984). This high background incidence in females makes it difficult to detect significant increases in the number of tumor-bearing animals in 2-year studies. Burek et al. (1980, 1984) reported that the number of animals with mammary gland tumors was not increased by exposure to dichloromethane (male: control, 7/92; low dose, 3/95; mid dose, 7/95; high dose, 14/97; female: control, 79/96; low dose, 81/95; mid dose, 80/96; high dose, 83/97) but that all exposure concentrations increased the number of mammary gland tumors per mammary gland-tumor-bearing female (mean number of tumors per tumor-bearing female: control, 2.1; low dose, 2.7; mid dose, 3.1; high dose, 3.5). The same effect, although less pronounced, was produced in male rats exposed at 1,500 or 3,500 ppm. Burek et al. (1984) reported no evidence of carcinogenicity of dichloromethane in Syrian golden hamsters (exposures up to 3,500 ppm for 2 years).

In a followup study, Nitschke et al. (1982) exposed Sprague-Dawley rats at 0, 50, 200, or 500 ppm for 6 hours per day, 5 days per week for 2 years (see Table 26). An increase in the number of mammary gland tumors per mammary gland-tumor-bearing female was observed at 500 ppm (control, 2.0; 50 ppm, 2.3; 200 ppm, 2.2; 500 ppm, 2.7). In male rats, no effects on the mammary gland were reported.

In 2-year drinking water studies (National Coffee Association, 1982, 1983), dichloromethane was made available to F344 rats (5-250 mg/kg per day) and B6C3F$_1$ mice (60-250 mg/kg per day) (see Table 26). This dosing regimen was not reported to be associated with neoplasia in either species; however, it is probable that the animals could have tolerated higher doses.

The increased incidences of mammary gland tumors in female rats in the present study are consistent with the findings of Burek et al. (1980, 1984) and of Nitschke et al. (1982). These observations in females lend support to the dichloromethane-associated increased incidences of mammary gland tumors and subcutaneous fibromas in male rats. The weight of the evidence for the mammary gland effect in male rats is considered to be less than that for female rats.

Hepatic Effects in Rats

Burek et al. (1984) reported that inhalation of dichloromethane at 500-3,500 ppm by Sprague-Dawley rats produced minimal, nonproliferative changes in the liver. The reported changes included hemosiderosis, focal necrosis of hepatocytes, basophilic change (females only), and cytoplasmic vacuolization. These changes were also noted in the present inhalation studies and were accompanied by hepatocytomegaly in males and females, bile duct fibrosis in males, and granulomatous inflammation in females. In addition, dichloromethane exposure produced a positive trend in the incidence of hepatocellular neoplastic nodules or carcinomas (combined) in female rats (control, 2/50; low dose, 1/50; mid dose, 4/50; high dose, 5/50). The liver neoplasia may have been due to dichloromethane exposure.

Other Effects in Rats

The incidence of mesotheliomas (originating primarily in the tunica vaginalis) was increased in male rats (control, 0/50; low dose, 1/50; mid dose, 4/50; high dose, 4/50). This increase is not considered to be related to the administration of dichloromethane because the concurrent control incidence was low relative to earlier inhalation studies conducted at this laboratory (4/100, 4%).

Dose-related increases in the incidences of squamous metaplasia of the nasal mucosal epithelium in female rats and suppurative inflammation of the nasal cavity in male rats were noted. The metaplasia and inflammation may have been due to irritant properties of dichloromethane. No nasal cavity neoplasms were observed.

Other neoplasms that occurred with marginally increased incidences in dosed groups of rats included adrenal gland pheochromocytomas and interstitial cell tumors of the testis in males (Table E1) and pituitary gland adenomas/carcinomas in both sexes (Tables E1 and E2). The increases in pituitary gland, adrenal gland, and testicular tumors were significant only by life table analyses, which are inappropriate for these generally nonlethal tumors. An exception occurred in low dose male rats, where the increase in pituitary gland adenomas was significant by both life table and incidental tumor tests, and the incidence was substantially above concurrent and historical controls. Similar increases, however, were not observed in mid dose and high dose male rats, and diagnostic differences between pituitary gland hyperplasia (reduced in low dose males) and adenomas can be slight. Therefore, none of these marginally increased incidences was considered compound related.

Pulmonary Effects in Mice

Exposure to dichloromethane increased the incidences of alveolar/bronchiolar adenomas in both male and female mice (male: control, 3/50; low dose, 19/50; high dose, 24/50; female: control, 2/50; low dose, 23/48; high dose, 28/48) and carcinomas (male: control, 2/50; low dose, 10/50; high dose, 28/50; female: control, 1/50; low dose, 13/48; high dose, 29/48). The observed incidences of alveolar/bronchiolar neoplasia in the chamber control groups were lower than those reported for other chamber control groups at this laboratory and for untreated controls throughout the Program (Tables F14 and F18).

In addition to dose-related increases in the number of male and female mice with lung tumors, there were dose-related increases in the incidences of dosed animals bearing multiple

lung tumors (Table 27). No chamber control animal had more than one lung tumor, whereas 38% of all dosed male mice and 42% of all dosed female mice had multiple lung tumors; in those mice with lung tumors, 38/67 (57%) dosed males and 40/71 (56%) dosed females had multiple lung tumors. Lung tumor multiplicity included both alveolar/bronchiolar adenomas and carcinomas (see Table 27). In cases of lung tumor multiplicity, it was not possible to differentiate definitively between multiple primary carcinomas and primary carcinomas with multiple intrapulmonary metastatic lesions. However, the presence of numerous cases of multiple adenomas (15/100 dosed males and 16/96 dosed females) suggests that some of the carcinomas were multiple primary lesions rather than metastatic lesions.

TABLE 27. MULTIPLICITY OF PULMONARY TUMORS IN MICE EXPOSED TO DICHLOROMETHANE

Diagnoses	Exposure Groups (ppm) 0	2,000	4,000
MALE			
One adenoma and one carcinoma	0/50	1/50	3/50
Multiple adenomas	0/50	5/50	4/50
Multiple carcinomas	0/50	3/50	12/50
Multiple adenomas and multiple carcinomas	0/50	0/50	3/50
One adenoma and multiple carcinomas	0/50	1/50	3/50
Multiple adenomas and one carcinoma	0/50	0/50	3/50
Incidence of mice with multiple tumors	0/50 (0%)	10/50 (20%)	28/50 (56%)
No. of mice with multiple tumors/ no. of mice with pulmonary tumors	0/5 (0%)	10/27 (37%)	28/40 (70%)
FEMALE			
One adenoma and one carcinoma	0/50	2/48	4/48
Multiple adenomas	0/50	4/48	5/48
Multiple carcinomas	0/50	1/48	8/48
Multiple adenomas and multiple carcinomas	0/50	0/48	2/48
One adenoma and multiple carcinomas	0/50	2/48	7/48
Multiple adenomas and one carcinoma	0/50	2/48	3/48
Incidence of mice with multiple tumors	0/50 (0%)	11/48 (23%)	29/48 (60%)
No. of mice with multiple tumors/ no. of mice with pulmonary tumors	0/3 (0%)	11/30 (37%)	29/41 (71%)

Hepatic Effects in Mice

Dichloromethane produced cytologic degeneration of the liver in both male and female mice; this change was not observed in chamber control animals (Tables D1 and D2). Exposure to dichloromethane increased the incidence of hepatocellular carcinomas and of adenomas or carcinomas (combined) in male mice exposed to dichloromethane at 4,000 ppm (see Table 24). In female mice, dichloromethane produced dose-related increases in the incidences of both hepatocellular adenomas and hepatocellular carcinomas (see Table 24). The incidences of these tumors in the chamber control group were consistent with historical control incidences at this laboratory and in the overall Program (Table F19).

As was the case for lung tumors in mice, multiplicity of hepatocellular tumors in dichloromethane-exposed male and female mice was common (Table 28). The incidence of animals with multiple hepatocellular tumors was increased in both males and females in a dose-related manner (male: control, 2/50; low dose, 11/49; high dose, 16/49; female: control, 0/50; low dose, 3/48; high dose, 28/48). Hepatocellular tumor multiplicity was found in 4% of the male chamber control mice and in none of the female chamber controls, whereas 28% of all exposed males and 32% of all exposed females had multiple liver tumors. In the chamber control groups, 2/22 (9%) hepatocellular tumor-bearing males and 0/3 (0%) hepatocellular tumor-bearing females had multiple liver tumors. In contrast, 27/57 (47%) liver tumor-bearing

TABLE 28. MULTIPLICITY OF LIVER TUMORS IN MICE EXPOSED TO DICHLOROMETHANE

Diagnoses	Exposure Groups (ppm) 0	2,000	4,000
MALE			
One adenoma and one carcinoma	1/50	2/49	3/49
Multiple adenomas	0/50	3/49	3/49
Multiple carcinomas	1/50	3/49	6/49
Multiple adenomas and multiple carcinomas	0/50	0/49	1/49
One adenoma and multiple carcinomas	0/50	0/49	2/49
Multiple adenomas and one carcinoma	0/50	3/49	1/49
Incidence of mice with multiple tumors	2/50 (4%)	11/49 (22%)	16/49 (33%)
No. of mice with multiple tumors/ no. of mice with liver tumors	2/22 (9%)	11/24 (46%)	16/33 (48%)
FEMALE			
One adenoma and one carcinoma	0/50	1/48	6/48
Multiple adenomas	0/50	0/48	4/48
Multiple carcinomas	0/50	2/48	10/48
Multiple adenomas and multiple carcinomas	0/50	0/48	3/48
One adenoma and multiple carcinomas	0/50	0/48	1/48
Multiple adenomas and one carcinoma	0/50	0/48	4/48
Incidence mice with multiple tumors	0/50 (0%)	3/48 (6%)	28/48 (58%)
No. of mice with multiple tumors/ no. of mice with liver tumors	0/3 (0%)	3/16 (19%)	28/40 (70%)

dichloromethane-exposed males and 31/56 (55%) liver tumor-bearing exposed females had hepatocellular tumor multiplicity.

In earlier studies, the National Coffee Association (1983) found no association between dichloromethane administration and liver tumors in mice (see Table 26). In the studies conducted by Burek et al. (1984) and by Nitschke et al. (1982), mice were not used as experimental animals.

Other Effects in Mice

Increased incidences of testicular atrophy in males and ovarian and uterine atrophy in females were detected in dichloromethane-exposed mice. These changes may be secondary to the extensive lung and liver neoplasia produced by the inhalation exposures.

An increase in the incidence of hemangiomas or hemangiosarcomas (combined) was detected in high dose male mice (control, 2/50; low dose, 2/50; high dose, 6/50). Five of the six tumors in the high dose group were hemangiosarcomas of the liver. The apparent increase in hemangiosarcomas was not considered to be clearly compound related.

Salivary Glands

Burek et al. (1984) reported an increased incidence of sarcomas in the ventral neck region (in or around the salivary glands) in male rats exposed to dichloromethane at 1,500 or 3,500 ppm. These authors speculated that exposure to dichloromethane in combination with an early infection of sialodacryoadenitis may have caused these lesions. In the present studies, there was no evidence of dichloromethane-related anomalies of the salivary glands in either sex of either species.

Conclusions: Under the conditions of these inhalation studies, there was *some evidence of carcinogenicity** of dichloromethane for male F344/N rats as shown by an increased incidence of benign neoplasms of the mammary gland. There was *clear evidence of carcinogenicity* of dichloromethane for female F344/N rats as shown by increased incidences of benign neoplasms of the mammary gland. There was *clear evidence of carcinogenicity* of dichloromethane for male and female B6C3F$_1$ mice, as shown by increased incidences of alveolar/bronchiolar neoplasms and of hepatocellular neoplasms.

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

V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOG	50	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(50)
Papilloma, NOS	4 (8%)		1 (2%)	
Basal cell carcinoma		1 (2%)	1 (2%)	
Trichoepithelioma	1 (2%)	2 (4%)	1 (2%)	
Sebaceous adenocarcinoma	1 (2%)			
Keratoacanthoma	2 (4%)	2 (4%)‡		3 (6%)
*Subcut tissue	(50)	(50)	(50)	(50)
Sarcoma, NOS				1 (2%)
Fibroma	1 (2%)	1 (2%)	2 (4%)	4 (8%)
Neurilemoma, malignant				1 (2%)
RESPIRATORY SYSTEM				
#Lung	(50)	(49)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)		1 (2%)	
Alveolar/bronchiolar carcinoma		1 (2%)	1 (2%)	1 (2%)
Pheochromocytoma, metastatic			1 (2%)	
Osteosarcoma, metastatic		1 (2%)		
HEMATOPOIETIC SYSTEM				
*Multiple organs	(50)	(50)	(50)	(50)
Leukemia, mononuclear cell	34 (68%)	26 (52%)	32 (64%)	35 (70%)
#Spleen	(50)	(49)	(50)	(50)
Sarcoma, NOS		1 (2%)		
Mesothelioma, invasive				1 (2%)
Malignant lymphoma, NOS		1 (2%)		
CIRCULATORY SYSTEM				
None				
DIGESTIVE SYSTEM				
#Liver	(50)	(49)	(50)	(50)
Neoplastic nodule		2 (4%)	2 (4%)	
Hepatocellular carcinoma	2 (4%)	1 (2%)	2 (4%)	1 (2%)
*Rectum	(50)	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)	
Neurofibrosarcoma			1 (2%)	
URINARY SYSTEM				
#Urinary bladder	(50)	(47)	(50)	(48)
Mesothelioma, invasive				1 (2%)
ENDOCRINE SYSTEM				
#Anterior pituitary	(50)	(47)	(49)	(49)
Carcinoma, NOS		1 (2%)		
Adenoma, NOS	20 (40%)	31 (66%)	27 (55%)	24 (49%)
#Adrenal	(50)	(50)	(50)	(50)
Neoplasm, NOS		1 (2%)		
#Adrenal medulla	(50)	(50)	(50)	(50)
Pheochromocytoma	5 (10%)	11 (22%)	10 (20%)	10 (20%)
Pheochromocytoma, malignant			1 (2%)	
Ganglioneuroma				2 (4%)

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)				
#Thyroid	(49)	(48)	(49)	(50)
Neoplasm, NOS		1 (2%)		
Follicular cell adenoma				1 (2%)
Follicular cell carcinoma		1 (2%)	2 (4%)	
C-cell adenoma	1 (2%)	3 (6%)	6 (12%)	2 (4%)
C-cell carcinoma	1 (2%)	1 (2%)	1 (2%)	
#Pancreatic islets	(48)	(46)	(48)	(48)
Islet cell adenoma	3 (6%)	6 (13%)	2 (4%)	2 (4%)
Islet cell carcinoma		1 (2%)		
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(50)
Adenoma, NOS				1 (2%)
Fibroadenoma			2 (4%)	4 (8%)
*Preputial gland	(50)	(50)	(50)	(50)
Carcinoma, NOS	3 (6%)	1 (2%)	3 (6%)	2 (4%)
Adenoma, NOS				2 (4%)
#Testis	(50)	(49)	(50)	(50)
Interstitial cell tumor	39 (78%)	37 (76%)	41 (82%)	43 (86%)
NERVOUS SYSTEM				
#Brain	(50)	(50)	(50)	(49)
Carcinoma, NOS, invasive		1 (2%)		
SPECIAL SENSE ORGANS				
*External ear	(50)	(50)	(50)	(50)
Papilloma, NOS		1 (2%)		
*Ear canal	(50)	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)	
*Zymbal gland	(50)	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	2 (4%)	1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM				
*Femur	(50)	(50)	(50)	(50)
Osteosarcoma		1 (2%)		
BODY CAVITIES				
*Peritoneal cavity	(50)	(50)	(50)	(50)
Fibrosarcoma		1 (2%)		
Liposarcoma	1 (2%)			
*Tunica vaginalis	(50)	(50)	(50)	(50)
Mesothelioma, NOS			4 (8%)	1 (2%)
Mesothelioma, malignant		1 (2%)		3 (6%)

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(50)
Mesothelioma, NOS			1 (2%)	
Mesothelioma, malignant		1 (2%)		
Mesothelioma, invasive		1 (2%)		1 (2%)
Lower leg				
Osteosarcoma			1	
Osteosarcoma, invasive		1		
Omentum				
Mesothelioma, invasive				1
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Natural death	4	7	2	10
Moribund sacrifice	30	27	31	31
Terminal sacrifice	16	16	17	9
TUMOR SUMMARY				
Total animals with primary tumors**	50	50	50	49
Total primary tumors	120	141	148	145
Total animals with benign tumors	47	46	49	47
Total benign tumors	77	95	93	98
Total animals with malignant tumors	39	33	40	40
Total malignant tumors	43	42	48	46
Total animals with secondary tumors##		3	1	3
Total secondary tumors		4	1	4
Total animals with tumors uncertain-- benign or malignant		4	7	1
Total uncertain tumors		4	7	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
‡ Multiple occurrence of morphology in the same organ; tissue is counted once only.

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOG	50	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(50)
Papilloma, NOS	1 (2%)		1 (2%)	
Keratoacanthoma				1 (2%)
*Subcut tissue	(50)	(50)	(50)	(50)
Sarcoma, NOS				1 (2%)
Fibroma			2 (4%)	
Lipoma				1 (2%)
RESPIRATORY SYSTEM				
*Larynx	(50)	(50)	(50)	(50)
C-cell carcinoma, invasive				1 (2%)
#Trachea	(50)	(48)	(49)	(46)
C-cell carcinoma, invasive				1 (2%)
#Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	1 (2%)			
Alveolar/bronchiolar carcinoma		1 (2%)		
Follicular cell carcinoma, metas		1 (2%)		
C-cell carcinoma, metastatic				1 (2%)
Pheochromocytoma, metastatic		1 (2%)		
Endometrial stromal sarcoma, metas				1 (2%)
Osteosarcoma, metastatic				1 (2%)
HEMATOPOIETIC SYSTEM				
*Multiple organs	(50)	(50)	(50)	(50)
Malignant lymphoma, NOS				1 (2%)
Leukemia, mononuclear cell	17 (34%)	17 (34%)	23 (46%)	23 (46%)
#Bronchial lymph node	(49)	(49)	(50)	(50)
Endometrial stromal sarcoma, metas				1 (2%)
#Thymus	(31)	(39)	(34)	(31)
Thymoma, benign	1 (3%)			
CIRCULATORY SYSTEM				
*Subcut tissue	(50)	(50)	(50)	(50)
Hemangiosarcoma				1 (2%)
#Heart	(50)	(50)	(48)	(50)
Adenocarcinoma, NOS, metastatic		1 (2%)		
*Vagina	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
DIGESTIVE SYSTEM				
#Liver	(50)	(50)	(50)	(50)
Neoplastic nodule	2 (4%)	1 (2%)	3 (6%)	5 (10%)
Hepatocellular carcinoma			1 (2%)	
URINARY SYSTEM				
#Kidney	(50)	(50)	(50)	(49)
Mixed tumor, benign		1 (2%)		

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
ENDOCRINE SYSTEM				
#Pituitary	(49)	(49)	(49)	(49)
Neoplasm, NOS		1 (2%)		
Craniopharyngioma	1 (2%)			
#Anterior pituitary	(49)	(49)	(49)	(49)
Carcinoma, NOS	1 (2%)		2 (4%)	
Adenoma, NOS	24 (49%)	30 (61%)	25 (51%)	25 (51%)
#Adrenal	(50)	(50)	(49)	(49)
Cortical adenoma			1 (2%)	
Cortical carcinoma		1 (2%)		
#Adrenal medulla	(50)	(50)	(49)	(49)
Pheochromocytoma	2 (4%)	1 (2%)	4 (8%)	1 (2%)
Pheochromocytoma, malignant		2 (4%)		
#Thyroid	(47)	(46)	(48)	(42)
Follicular cell adenoma			1 (2%)	
Follicular cell carcinoma		1 (2%)	1 (2%)	
C-cell adenoma	2 (4%)		4 (8%)	2 (5%)
C-cell carcinoma	3 (6%)		2 (4%)	2 (5%)
#Pancreatic islets	(50)	(48)	(50)	(46)
Islet cell adenoma	3 (6%)			
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(50)
Carcinoma, NOS			1 (2%)	
Adenoma, NOS				1 (2%)
Adenocarcinoma, NOS	1 (2%)	2 (4%)	1 (2%)	
Mixed tumor, malignant	1 (2%)			
Fibroadenoma	5 (10%)	11 (22%)	13 (26%)	22 (44%)
*Clitoral gland	(50)	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Cystadenoma, NOS				1 (2%)
#Uterus	(50)	(49)	(50)	(47)
Endometrial stromal polyp	7 (14%)	9 (18%)	7 (14%)	6 (13%)
Endometrial stromal sarcoma		3 (6%)	1 (2%)	2 (4%)
#Ovary	(49)	(50)	(50)	(48)
Granulosa cell tumor	2 (4%)			
Sarcoma, NOS		1 (2%)		
NERVOUS SYSTEM				
#Cerebrum	(50)	(50)	(50)	(50)
Carcinoma, NOS, invasive	1 (2%)		1 (2%)	
Oligodendroglioma			1 (2%)	
SPECIAL SENSE ORGANS				
*Eye	(50)	(50)	(50)	(50)
Neurofibroma			1 (2%)	
MUSCULOSKELETAL SYSTEM				
*Skull	(50)	(50)	(50)	(50)
Osteosarcoma		1 (2%)		
*Sternum	(50)	(50)	(50)	(50)
Osteosarcoma, invasive				1 (2%)
*Rib	(50)	(50)	(50)	(50)
Osteosarcoma				1 (2%)
*Skeletal muscle	(50)	(50)	(50)	(50)
Neurofibroma			1 (2%)	

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
BODY CAVITIES				
*Peritoneum	(50)	(50)	(50)	(50)
Mesothelioma, malignant				1 (2%)
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(50)
Sarcoma, NOS, metastatic		1 (2%)		
Endometrial stromal sarcoma, invasive			1 (2%)	1 (2%)
Mesothelioma, metastatic				1 (2%)
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	50	50	50	50
Natural death	5	6	5	11
Moribund sacrifice	15	22	23	24
Terminal sacrifice	30	22	22	15
TUMOR SUMMARY				
Total animals with primary tumors**	41	46	48	48
Total primary tumors	76	85	98	99
Total animals with benign tumors	33	39	40	34
Total benign tumors	47	52	60	60
Total animals with malignant tumors	21	29	29	32
Total malignant tumors	24	31	35	34
Total animals with secondary tumors##	1	4	2	4
Total secondary tumors	1	4	2	9
Total animals with tumors uncertain-- benign or malignant	5	1	3	5
Total uncertain tumors	5	2	3	5

* 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 INHALATION STUDY OF DICHLOROMETHANE: UNTREATED CONTROL

ANIMAL NUMBER	0 2 6	0 1 4	0 3 8	0 3 5	0 3 4	0 1 9	0 4 6	0 5 0	0 4 8	0 1 1	0 3 3	0 4 2	0 4 4	0 2 7	0 0 7	0 1 3	0 0 1	0 3 9	0 3 0	0 1 8	0 4 1	0 2 9	0 0 4	0 0 9	0 1 2
WEEKS ON STUDY	0 5 7	0 6 5	0 6 7	0 7 0	0 7 3	0 7 5	0 7 5	0 7 7	0 8 1	0 8 5	0 8 5	0 8 5	0 8 5	0 8 6	0 8 7	0 9 0	0 9 1	0 9 1	0 9 2	0 9 2	0 9 2	0 9 4	0 9 5	0 9 5	0 9 6
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS																									
Trichoepithelioma																									
Sebaceous adenocarcinoma															X										
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS				X		X				X		X		X		X		X			X				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma						X																			
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma									X																
C-cell carcinoma																									
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	+	
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																	X								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS							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																							
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell	X		X		X				X	X	X	X	X	X	X	X			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
@ : Multiple Occurrence of Morphology
: : No Tissue Information Submitted
C : Necropsy, No Histology Due To Protocol
A : Autolysis
M : Animal Missing
B : No Necropsy Performed

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

ANIMAL NUMBER	015	047	031	017	021	024	025	036	040	042	003	006	008	010	016	020	022	023	028	030	032	037	043	045	049	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	096	096	098	099	101	102	102	102	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS				X		X			X										X							4
Trichoepithelioma			X																							1
Sebaceous adenocarcinoma																										1
Keratoacanthoma																			X						X	2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																					X					1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	−	−	−	−	−	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	+	+	−	+	+	31
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	−	+	+	−	+	+	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	−	43
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X					X	X		X			X	X					X		X	X	X	X	X		20
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma							X		X					X											X	5
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell adenoma																										1
C-cell carcinoma		X																								1
Parathyroid	+	+	−	+	+	+	+	+	+	+	+	−	−	+	+	−	+	+	−	+	+	−	−	−	+	29
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma																	X			X						3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	N	+	N	N	+	+	N	N	+	N	+	+	+	+	N	+	N	N	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	39
Prostate	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	−	−	+	+	+	+	+	44
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												3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										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
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X	X	X	X	X	X	X	X	X		X		X		X		X		X	X				X	X	34

* Animals Necropsied

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

ANIMAL NUMBER	022	049	008	032	037	028	001	041	045	006	048	025	002	033	050	026	035	013	021	027	031	020	030	009	011
WEEKS ON STUDY	062	062	067	068	072	075	082	082	084	086	087	088	089	089	090	091	092	092	092	092	093	094	095	096	097
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Basal cell carcinoma		X																							
Trichoepithelioma																					X				
Keratoacanthoma																				X@					
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, metastatic	X																								
Trachea	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS						X																			
Malignant lymphoma, NOS				X																					
Lymph nodes	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	–	–	–	+	–	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule													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	+	+	+	–	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	–	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS					X																				
Pheochromocytoma															X			X			X				
Thyroid	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS				X																					
Follicular cell carcinoma																									
C-cell adenoma																									
C-cell carcinoma																		X							
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
Testis	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor					X			X	X				X	X	X	X	X	X	X	X			X	X	
Prostate	+	+	+	–	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																			X						
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive		X																							
SPECIAL SENSE ORGANS																									
Ear	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N
Papilloma, NOS																									
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
Carcinoma, NOS										X									X						
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma	X																								
BODY CAVITIES																									
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
Fibrosarcoma							X																		
Tunica vaginalis	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, malignant					X																				
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, malignant								X																	
Mesothelioma, invasive					X																				
Leukemia, mononuclear cell								X	X	X		X		X	X		X		X		X				X
Lower leg NOS																									
Osteosarcoma, invasive	X																								

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

ANIMAL NUMBER	0 2 9	0 4 4	0 3 4	0 1 9	0 4 2	0 4 6	0 2 3	0 2 4	0 1 6	0 0 3	0 0 4	0 0 5	0 0 7	0 1 0	0 1 2	0 1 4	0 1 5	0 1 7	0 1 8	0 3 6	0 3 8	0 3 9	0 4 0	0 4 3	0 4 7	TOTAL:
WEEKS ON STUDY	0 9 8	0 9 8	0 9 9	1 0 1	1 0 1	1 0 1	1 0 2	1 0 2	1 0 3	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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell carcinoma																										1
Trichoepithelioma	X																									2
Keratoacanthoma															X											2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																				X						1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcinoma									X																	1
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS																										1
Malignant lymphoma, NOS																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	–	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																							X			2
Hepatocellular carcinoma																							X			1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	+	–	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	–	43
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Carcinoma, NOS																										1
Adenoma, NOS		X	X	X	X		X		X	X	X	X	X	X	X	X	X			X	X	X		X		31
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplasm, NOS																										1
Pheochromocytoma						X	X	X		X	X				X	X		X								11
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Neoplasm, NOS																										1
Follicular cell carcinoma											X															1
C cell adenoma				X								X									X					3
C cell carcinoma																										1
Parathyroid	+	+	+	+	+	–	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Islet cell adenoma	X				X		X				X							X								6
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	+	*50
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	37
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	–	+	42
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																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
SPECIAL SENSE ORGANS																										
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
Papilloma, NOS																							X			1
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	*50
Carcinoma, NOS																										2
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
BODY CAVITIES																										
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
Fibrosarcoma																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, malignant																										1
Mesothelioma, invasive																										1
Leukemia, mononuclear cell	X		X	X		X	X	X	X		X				X	X			X	X	X	X	X	X		26
Lower leg NOS																										
Osteosarcoma, invasive																										1

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE: MID DOSE

ANIMAL NUMBER	005	007	002	016	001	030	018	042	040	032	046	003	044	012	004	026	019	028	029	035	041	043	017	022	023
WEEKS ON STUDY	070	071	075	076	076	076	078	078	079	084	084	086	086	088	089	089	092	092	092	092	092	094	096	096	096
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS		X																							
Basal cell carcinoma														X											
Trichoepithelioma																									
Subcutaneous tissue	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																							X		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																		X							
Pheochromocytoma, metastatic																		X							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	–	+	+	+	–	+	–	+	+	+	+	+	+	+	–	+	–	+	+	–	+	–	+	
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	–	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
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	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum	N	N	N	N	N	N	N	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS											X														
Neurofibrosarcoma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X	X		X					X	X	X								X	X	X	X	X		X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																X									
Pheochromocytoma, malignant																		X							
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																					X				
C-cell adenoma																						X		X	
C-cell carcinoma														X											
Parathyroid	+	+	+	+	+	–	–	+	+	+	–	–	–	+	–	–	–	+	–	–	–	+	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	N	N	+	N	+	+	+	N	+	N	+	+	+	N	+	N	N	N	N	N	+
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			X	X		X	X		X	X	X		X	X	X	X	X	X		X		X	X	X	X
Prostate	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS											X														
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Ear	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																				
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
Carcinoma, NOS			X																						
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS																									
Leukemia, mononuclear cell		X					X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Lower leg NOS																									
Osteosarcoma			X																						

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

ANIMAL NUMBER	024	031	047	049	011	021	050	045	006	008	009	010	011	013	015	020	025	027	033	034	036	037	038	039	048	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	096	096	096	098	100	101	101	102	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	N	+	+	+	+	N	+	+	*50
Papilloma, NOS																										1
Basal cell carcinoma																										1
Trichoepithelioma						X																				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	N	+	+	+	+	N	+	+	*50
Fibroma																X										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma									X																	1
Alveolar/bronchiolar carcinoma																										1
Pheochromocytoma, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	–	+	–	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	35
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule					X																	X				2
Hepatocellular carcinoma		X																							X	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Carcinoma, NOS																										1
Neurofibrosarcoma						X																				1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X			X	X		X	X		X		X	X	X	X	X	X		X		X			27
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X				X	X				X		X		X	X			X		X					10
Pheochromocytoma, malignant																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma								X																		2
C-cell adenoma														X								X	X	X		6
C-cell carcinoma																										1
Parathyroid	+	+	+	–	–	+	+	–	–	–	+	+	–	+	+	–	+	+	+	+	+	+	–	+	+	30
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma													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								2
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	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	~	–	+	+	+	+	+	46
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			3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
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	*50
Carcinoma, NOS																										1
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
Carcinoma, NOS																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS		X					X							X					X							4
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS				X																						1
Leukemia, mononuclear cell		X			X		X	X				X	X		X	X		X	X	X	X			X	X	32
Lower leg NOS																										
Osteosarcoma																										1

*Animals Necropsied

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

ANIMAL NUMBER	045	025	046	018	011	032	036	048	003	013	041	019	037	004	009	010	047	014	017	035	038	027	016	031	043
WEEKS ON STUDY	062	063	075	076	078	078	079	079	080	080	082	083	083	085	085	086	086	087	089	089	089	090	092	092	092
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma																			X						
Neurilemoma, malignant																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, invasive																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	–	+	+	+	+	+	–	+	–	–	+	+	–	+	+	+	–	+	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma							X																		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, invasive																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	+	+	+	–	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, invasive																									
ENDOCRINE SYSTEM																									
Pituitary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS	X		X		X		X		X	X			X				X	X		X		X			
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma										X										X					X
Ganglioneuroma																									X
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma					X																				
C cell adenoma								X	X																
Parathyroid	+	–	+	+	–	–	+	–	–	–	–	+	+	+	+	–	+	+	–	–	–	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma					X																				
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	N	+	+	+	N	+	N	N	+	+	N	N	+	N	N	N	N	N	+	N	N	N	+
Adenoma, NOS																									
Fibroadenoma																									
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor			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																				X					
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS								X																	
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																									
Mesothelioma, malignant																									X
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, invasive																									X
Leukemia, mononuclear cell			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			X	X	X		

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

ANIMAL NUMBER	022	042	049	007	024	006	050	034	023	033	005	026	040	020	001	029	002	008	012	015	021	028	030	039	044	TOTAL TISSUES TUMORS
WEEKS ON STUDY	093	093	093	094	094	095	097	098	099	099	101	101	101	102	103	103	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma											X	X				X										3
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS			X																							1
Fibroma				X		X								X												4
Neurilemoma, malignant															X											1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma											X															1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma, invasive														X												1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	–	–	–	–	–	–	–	+	–	–	–	–	+	–	+	–	+	+	+	–	+	+	+	+	+	28
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										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
Esophagus	+	–	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma, invasive																X										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma, invasive														X												1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X	X			X	X			X		X		X		X	X		X			X	X	X		24
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma							X	X			X	X				X					X			X		10
Ganglioneuroma														X												2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
C-cell adenoma																										2
Parathyroid	–	–	+	+	–	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	–	+	–	+	32
Pancreatic islets	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	48
Islet cell adenoma													X													2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	N	N	+	N	*50
Adenoma, NOS	X																									1
Fibroadenoma												X				X		X						X		4
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	43
Prostate	+	–	+	–	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	45
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						2
Adenoma, NOS																	X	X								2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS											X															2
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS									X																	1
Mesothelioma, malignant														X		X										3
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, invasive																										1
Leukemia, mononuclear cell	X	X		X	X			X	X	X	X	X	X	X			X		X	X	X		X		X	35

*Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE *TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE: UNTREATED CONTROL*

ANIMAL NUMBER	030	004	033	024	020	011	047	050	035	023	014	016	038	008	002	015	031	043	025	009	001	003	005	006	007
WEEKS ON STUDY	050	073	074	078	079	083	083	083	086	090	092	092	092	093	096	096	096	097	099	101	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma, NOS														X											
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									X
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Thymus	–	+	+	–	+	–	+	–	–	+	+	+	+	+	–	–	–	+	–	–	+	+	+	+	+
Thymoma, benign																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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	
Craniopharyngioma																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma														X											
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																	X						X		
C-cell carcinoma																									
Parathyroid	+	–	+	+	+	–	–	+	–	–	–	–	–	+	+	+	+	–	+	+	+	+	+	+	–
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS													X												
Mixed tumor, malignant												X													
Fibroadenoma																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														
Vagina	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
Hemangioma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp		X					X								X	X	X								
Ovary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																							X		
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell		X		X	X		X		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: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	0110	0112	0113	0117	0118	0119	0121	0122	0126	0127	0128	0129	0132	0134	0136	0137	0139	0140	0141	0142	0144	0145	0146	0148	0149	TOTAL:
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Papilloma, NOS																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thymus	+	–	+	+	+	+	+	+	–	+	–	+	–	+	–	–	+	–	+	+	+	–	–	+	+	31
Thymoma, benign										X																1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																X				X						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
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS																										1
Adenoma, NOS	X	X			X		X	X		X			X	X		X	X		X	X		X			X	24
Craniopharyngioma																								X		1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma									X																	2
Thyroid	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	47
C-cell adenoma																										2
C-cell carcinoma				X	X															X						3
Parathyroid	–	–	+	+	–	–	+	–	+	–	–	–	–	+	+	+	+	+	–	–	–	–	–	+	+	26
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma												X		X											X	3
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Mixed tumor, malignant																										1
Fibroadenoma		X							X	X										X						5
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																										1
Vagina	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
Hemangioma																	X									1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp	X											X														7
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor										X										X						2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell	X	X			X				X								X				X				X	17

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE. LOW DOSE

ANIMAL NUMBER	02121	01145	01150	02205	02251	04143	04545	03232	01616	03416	03636	04747	05050	03838	04446	02293	01113	04406	04646	02234	02247	03737	02606
WEEKS ON STUDY	06101	07404	07706	07706	07708	08404	08805	08606	08808	08909	09002	09202	09202	09404	09404	09505	09707	09707	09708	09908	09908	09908	10100
RESPIRATORY SYSTEM																							
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																							
Follicular cell carcinoma, meta																							
Pheochromocytoma, metastatic																							X
Trachea	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	–	+	–	+	–	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+
CIRCULATORY SYSTEM																							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic																					X		
DIGESTIVE SYSTEM																							
Salivary gland	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule	X																						
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	–	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Large intestine	–	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																							
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mixed tumor, benign																							
Urinary bladder	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
ENDOCRINE SYSTEM																							
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Neoplasm, NOS	X																						
Adenoma, NOS			X	X			X	X		X			X	X	X	X				X		X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical carcinoma																							
Pheochromocytoma															X								
Pheochromocytoma, malignant										X													X
Thyroid	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+
Follicular cell carcinoma																							
Parathyroid	–	–	–	+	+	+	–	–	+	–	–	–	–	+	–	–	–	–	+	+	+	+	+
REPRODUCTIVE SYSTEM																							
Mammary gland	+	+	+	+	N	N	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS			X																		X		
Fibroadenoma		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
Carcinoma, NOS																							
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp			X			X											X						X
Endometrial stromal sarcoma		X		X																X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																			X				
NERVOUS SYSTEM																							
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																							
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																							
ALL OTHER SYSTEMS																							
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Sarcoma, NOS, metastatic																			X				
Leukemia, mononuclear cell					X				X	X		X		X	X		X	X	X		X	X	

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

ANIMAL NUMBER	00051	00191	00351	00401	00902	00003	00044	00066	00077	00088	00099	00111	00122	00177	00188	00221	00227	00288	00303	00311	00333	00399	00422	00488	00499	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	102	102	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma															X											1
Follicular cell carcinoma, meta			X																							1
Pheochromocytoma, metastatic																										1
Trachea	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	49
Thymus	+	+	–	+	–	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	43
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mixed tumor, benign								X																		1
Urinary bladder	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplasm, NOS																										1
Adenoma, NOS	X	X	X	X	X	X	X	X	X		X		X	X	X		X			X	X	X	X	X	X	30
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical carcinoma																					X					1
Pheochromocytoma																										1
Pheochromocytoma, malignant																										2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	46
Follicular cell carcinoma			X																							1
Parathyroid	–	–	–	–	–	–	–	–	+	–	–	+	–	+	+	–	–	+	–	–	–	+	+	–	+	19
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										2
Fibroadenoma					X		X	X									X			X	X	X			X	11
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
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	49
Endometrial stromal polyp				X	X							X			X			X								9
Endometrial stromal sarcoma																										3
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma	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
Sarcoma, NOS, metastatic																										1
Leukemia, mononuclear cell		X			X																		X	X	X	17

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE: MID DOSE

ANIMAL NUMBER	026	028	021	033	015	002	005	031	049	013	011	016	007	023	048	027	034	032	038	014	030	041	040	039	009
WEEKS ON STUDY	062	064	065	065	072	073	076	076	082	083	084	084	085	085	085	086	086	089	089	090	091	093	097	098	099
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Papilloma, NOS																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Fibroma																									
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				
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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				
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									
Pheochromocytoma																									
Thyroid	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Follicular cell carcinoma																									
C cell adenoma																									
C-cell carcinoma																	X								
Parathyroid	–	+	–	+	–	+	–	+	+	–	–	–	–	–	+	–	–	–	–	+	–	+	+	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Carcinoma, NOS																									
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																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp							X						X	X								X		X	
Endometrial stromal sarcoma	X																								
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																									X
Oligodendroglioma																					X				
SPECIAL SENSE ORGANS																									
Eye	N	N	N	N	+	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurofibroma																									
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
Neurofibroma																									
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
Endometrial stromal sarcoma, invasive	X																								
Leukemia, mononuclear cell						X			X		X	X			X	X			X	X			X	X	X

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

ANIMAL NUMBER	0 1 2	0 4 7	0 0 1	0 0 3	0 0 4	0 0 6	0 1 0	0 1 7	0 1 8	0 1 9	0 2 0	0 2 2	0 2 4	0 2 5	0 2 8	0 2 9	0 3 5	0 3 6	0 3 7	0 4 2	0 4 3	0 4 4	0 4 5	0 4 6	0 5 0	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	1 0 0	1 0 1	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	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																										
Skin	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	*50
Papilloma, NOS													X													1
Subcutaneous tissue	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	N	+	+	+	+	*50
Fibroma	X								X																	2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Thymus	+	–	–	–	+	–	+	+	+	–	+	–	+	–	–	+	+	–	+	+	+	+	+	+		34
CIRCULATORY SYSTEM																										
Heart	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+		48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Neoplastic nodule									X																	3
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		*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Esophagus	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	–	+		45
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+		49
Carcinoma, NOS													X													2
Adenoma, NOS		X	X	X	X	X	X	X	X	X				X	X	X				X	X	X		X		25
Adrenal	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Cortical adenoma																									X	1
Pheochromocytoma													X			X	X							X		4
Thyroid	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma														X												1
Follicular cell carcinoma																X										1
C-cell adenoma					X				X		X									X						4
C cell carcinoma												X														2
Parathyroid	–	–	–	–	+	+	+	+	+	–	–	+	+	+	+	–	+	+	–	+	+	–	+	+	+	26
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+		*50
Carcinoma, NOS																X										1
Adenocarcinoma, NOS																										1
Fibroadenoma			X		X	X		X								X						X	X	X		13
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
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp								X							X											7
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, NOS, invasive																										1
Oligodendroglioma																										1
SPECIAL SENSE ORGANS																										
Eye	N	N	N	N	+	+	N	N	N	N	N	+	N	N	N	N	N	+	N	N	N	N	N	N	N	*50
Neurofibroma																		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
Neurofibroma																		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
Endometrial stromal sarcoma, invasive						X						X														1
Leukemia, mononuclear cell	X					X			X			X			X	X	X	X		X	X		X			23

*Animals Necropsied

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

ANIMAL NUMBER	046	015	019	013	037	034	020	009	012	033	031	036	008	030	047	001	043	005	010	027	042	022	016	024	026
WEEKS ON STUDY	059	063	070	072	073	075	078	080	080	083	084	086	087	087	088	089	089	090	090	091	092	093	095	095	095
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma											X														
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Lipoma																									
Hemangiosarcoma																									X
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, metastatic																		X							
Endometrial stromal sarcoma, metastat	X																								
Osteosarcoma, metastatic																				X					
Trachea	+	+	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
C-cell carcinoma, invasive																		X							
Larynx	+	+	N	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+
C cell carcinoma, invasive																		X							
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	–	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal sarcoma, metastat	X																								
Thymus	–	–	–	+	–	–	+	–	–	+	+	+	+	+	–	+	+	+	+	+	+	+	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule					X											X				X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	–	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	–	+	–	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	–	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS						X		X	X		X	X	X	X		X	X								X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
C cell adenoma																				X					
C cell carcinoma																			X						
Parathyroid	+	+	–	+	–	+	–	–	–	+	+	–	+	+	–	+	+	+	+	–	–	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	N	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Fibroadenoma					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																									
Cystadenoma, NOS								X																	
Uterus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																	X								
Endometrial stromal sarcoma	X																		X						
Ovary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma																				X					
Osteosarcoma, invasive																				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
Mesothelioma, malignant				X																					
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Endometrial stromal sarcoma, invasive	X																								
Mesothelioma, metastatic				X																					
Malignant lymphoma, NOS							X																		
Leukemia, mononuclear cell		X			X			X		X	X			X	X	X	X		X	X	X	X		X	

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

ANIMAL NUMBER	035	040	045	041	039	049	004	038	029	025	002	003	006	007	011	014	017	018	021	023	028	032	044	048	050	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	095	096	096	097	100	100	101	101	102	103	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skinvas	N	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																										
Subcutaneous tissue	N	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																			X							
Lipoma															X											
Hemangiosarcoma																										
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, metastatic																										
Endometrial stromal sarcoma, metas																										
Osteosarcoma, metastatic																										
Trachea	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
C-cell carcinoma, invasive																										
Larynx	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
C-cell carcinoma, invasive																										
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	46
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal sarcoma, metas																										
Thymus	–	–	–	+	+	–	–	–	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	31
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule										X						X										5
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	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Esophagus	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS		X			X		X		X	X	X		X		X	X		X	X	X	X	X		X		25
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																			X							1
Thyroid	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	–	–	42
C-cell adenoma				X																						2
C-cell carcinoma											X															2
Parathyroid	+	+	–	–	+	–	–	–	–	–	+	+	+	–	–	–	–	–	–	+	+	+	+	–	–	26
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																				X						1
Fibroadenoma		X		X		X		X	X	X	X	X	X	X		X	X	X				X	X		X	22
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
Cystadenoma, NOS																										1
Uterus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Endometrial stromal polyp										X			X						X				X		X	6
Endometrial stromal sarcoma																										2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brainvas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																										1
Osteosarcoma, invasive																										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
Mesothelioma, malignant																										1
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Endometrial stromal sarcoma, invasive																										1
Mesothelioma, metastatic																										1
Malignant lymphoma, NOS																										1
Leukemia, mononuclear cell	X		X	X	X	X	X	X		X											X					23

*Animals Necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
None			
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Undifferentiated carcinoma			1 (2%)
#Lung	(50)	(50)	(50)
Undiff. carcinoma, metastatic			1 (2%)
Adenocarcinoma, NOS, metastatic			1 (2%)
Hepatocellular carcinoma, metastatic	1 (2%)	3 (6%)	4 (8%)
Alveolar/bronchiolar adenoma	3 (6%)	19 (38%)	24 (48%)
Alveolar/bronchiolar carcinoma	2 (4%)	10 (20%)	28 (56%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, NOS	2 (4%)	1 (2%)	1 (2%)
Malig. lymphoma, lymphocytic type	1 (2%)		1 (2%)
Malignant lymphoma, mixed type		1 (2%)	
#Spleen	(49)	(49)	(48)
Malignant lymphoma, mixed type	1 (2%)		
#Mesenteric l. node	(42)	(45)	(40)
Malignant lymphoma, mixed type	1 (2%)	1 (2%)	
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hemangiosarcoma			1 (2%)
#Heart	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metas		1 (2%)	
Hemangiosarcoma	1 (2%)		
#Liver	(50)	(49)	(49)
Hemangioma	1 (2%)		1 (2%)
Hemangiosarcoma		1 (2%)	4 (8%)
#Prostate	(50)	(50)	(47)
Hemangiosarcoma		1 (2%)	
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(49)
Hepatocellular adenoma	10 (20%)	14 (29%)	14 (29%)
Hepatocellular carcinoma	13 (26%)	15 (31%)	26 (53%)
Alveolar/bronchiolar carcinoma, metas		1 (2%)	1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Alveolar/bronchiolar carcinoma, metas			1 (2%)
Tubular cell adenoma			1 (2%)
Papillary cystadenoma, NOS		1 (2%)	

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Adrenal	(50)	(46)	(50)
Hepatocellular carcinoma, metastatic			2 (4%)
Alveolar/bronchiolar carcinoma, metas			1 (2%)
#Adrenal/capsule	(50)	(46)	(50)
Adenoma, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
#Testis	(50)	(50)	(50)
Interstitial cell tumor	3 (6%)		
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Vertebral column	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metas			1 (2%)
*Rib	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metas		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, metas			1 (2%)
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	12	16
Moribund sacrifice	6	12	24
Terminal sacrifice	39	24	9
Accidentally killed, nda		1	
Accidentally killed, NOS		1	1
TUMOR SUMMARY			
Total animals with primary tumors**	34	37	46
Total primary tumors	39	64	102
Total animals with benign tumors	18	24	30
Total benign tumors	18	34	40
Total animals with malignant tumors	21	26	43
Total malignant tumors	21	30	62
Total animals with secondary tumors##	1	5	9
Total secondary tumors	1	6	13

* Number of animals necropsied
** Primary tumors: all tumors except secondary tumors
# Number of animals with tissue examined microscopically
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	49
INTEGUMENTARY SYSTEM			
*Subcut tissue	(50)	(49)	(49)
Fibrosarcoma		2 (4%)	1 (2%)
RESPIRATORY SYSTEM			
#Lung	(50)	(48)	(48)
Adenocarcinoma, NOS, metastatic		1 (2%)	
Hepatocellular carcinoma, metastatic		4 (8%)	3 (6%)
Alveolar/bronchiolar adenoma	2 (4%)	23 (48%)	28 (58%)
Alveolar/bronchiolar carcinoma	1 (2%)	13 (27%)	29 (60%)
Osteosarcoma, metastatic	1 (2%)	1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(49)
Malignant lymphoma, NOS	2 (4%)		1 (2%)
Malig. lymphoma, lymphocytic type	2 (4%)		
Malig. lymphoma, histiocytic type		1 (2%)	3 (6%)
Malignant lymphoma, mixed type		4 (8%)	
#Spleen	(49)	(48)	(47)
Malig. lymphoma, histiocytic type	1 (2%)		1 (2%)
#Bronchial lymph node	(49)	(47)	(43)
Alveolar/bronchiolar carcinoma, metas			1 (2%)
#Mediastinal l. node	(49)	(47)	(43)
Alveolar/bronchiolar carcinoma, metas			1 (2%)
#Mesenteric l. node	(49)	(47)	(43)
Malignant lymphoma, NOS	1 (2%)		
*Pleural cavity	(50)	(49)	(49)
Malignant lymphoma, NOS		1 (2%)	
#Liver	(50)	(48)	(48)
Malignant lymphoma, NOS	1 (2%)		1 (2%)
#Kidney	(49)	(48)	(47)
Malignant lymphoma, mixed type			1 (2%)
#Uterus	(50)	(48)	(47)
Malig. lymphoma, histiocytic type		1 (2%)	
CIRCULATORY SYSTEM			
#Spleen	(49)	(48)	(47)
Hemangiosarcoma			1 (2%)
#Heart	(49)	(48)	(49)
Alveolar/bronchiolar carcinoma, metas			2 (4%)
#Liver	(50)	(48)	(48)
Hemangiosarcoma		2 (4%)	1 (2%)
Hemangiosarcoma, metastatic			1 (2%)
#Thymus	(30)	(20)	(9)
Hemangiosarcoma, metastatic			1 (11%)
DIGESTIVE SYSTEM			
#Liver	(50)	(48)	(48)
Hepatocellular adenoma	2 (4%)	6 (13%)	22 (46%)
Hepatocellular carcinoma	1 (2%)	11 (23%)	32 (67%)
Alveolar/bronchiolar carcinoma, metas			1 (2%)
Hepatoblastoma			1 (2%)

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Duodenum	(46)	(47)	(47)
Adenocarcinoma in adenomatous polyp	1 (2%)		
URINARY SYSTEM			
#Kidney	(49)	(48)	(47)
Papillary cystadenoma, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary	(46)	(44)	(44)
Adenoma, NOS		2 (5%)	1 (2%)
#Anterior pituitary	(46)	(44)	(44)
Adenoma, NOS	4 (9%)		
#Adrenal	(50)	(48)	(48)
Cortical adenoma			1 (2%)
#Thyroid	(48)	(47)	(46)
Follicular cell adenoma	1 (2%)	1 (2%)	4 (9%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(49)	(49)
Adenocarcinoma, NOS	2 (4%)	3 (6%)	
#Uterus	(50)	(48)	(47)
Adenocarcinoma, NOS	1 (2%)		
Leiomyosarcoma			1 (2%)
Endometrial stromal polyp	1 (2%)	1 (2%)	
#Ovary	(50)	(47)	(43)
Cystadenoma, NOS		1 (2%)	
Papillary cystadenoma, NOS	1 (2%)		
Teratoma, NOS			1 (2%)
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(49)	(49)
Adenocarcinoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Rib	(50)	(49)	(49)
Osteosarcoma		1 (2%)	
BODY CAVITIES			
*Pelvis	(50)	(49)	(49)
Osteosarcoma	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(49)
Alveolar/bronchiolar carcinoma, metas			1 (2%)
Adipose tissue			
Hepatocellular carcinoma, metastatic		1	

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	16	8	9
Moribund sacrifice	8	14	31
Terminal sacrifice	25	25	8
Accidentally killed, nda	1	1	1
Accidentally killed, NOS		1	
Animal missing		1	1
TUMOR SUMMARY			
Total animals with primary tumors**	18	41	47
Total primary tumors	26	74	130
Total animals with benign tumors	9	26	39
Total benign tumors	11	35	56
Total animals with malignant tumors	13	30	46
Total malignant tumors	15	39	73
Total animals with secondary tumors##	1	6	9
Total secondary tumors	1	7	11
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
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE: UNTREATED CONTROL

ANIMAL NUMBER	02 23	03 39	04 02	04 24	02 28	00 02	01 13	03 36	00 04	03 11	00 01	00 03	00 05	00 06	00 07	00 08	00 09	01 10	01 11	01 12	01 14	01 15	01 16	01 17
WEEKS ON STUDY	07 11	07 13	07 34	07 44	08 01	08 14	08 47	09 44	09 55	09 96	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44	10 44
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																X				X				
Alveolar/bronchiolar adenoma								X							X								
Alveolar/bronchiolar carcinoma																								
Trachea	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																								
Lymph nodes	+	+	+	–	+	+	–	–	+	+	+	+	–	+	+	+	+	–	+	+	+	–	–	+
Malignant lymphoma, mixed type																								
Thymus	–	+	–	+	–	–	+	–	–	–	–	–	–	–	+	+	+	–	–	+	+	+	+	–
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																								
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma		X		X	X						X							X	X	X				
Hepatocellular carcinoma			X		X	X			X															X
Hemangioma							X																	
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	+	N	+	+	N	+	+	+	N	+	N	+	+	N	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	–	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																								
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Malignant lymphoma, NOS	X																	X						
Malig. lymphoma, lymphocytic 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 B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: UNTREATED CONTROL (Continued)

ANIMAL NUMBER	0118	0119	0220	0221	0224	0225	0226	0227	0229	0230	0232	0233	0234	0235	0237	0238	0241	0242	0243	0245	0246	0247	0248	0249	0250	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	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic	X																									1
Alveolar/bronchiolar adenoma																		X								3
Alveolar/bronchiolar carcinoma																										2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type			X																							1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	42
Malignant lymphoma, mixed type											X															1
Thymus	–	–	+	+	+	+	+	+	+	+	+	+	–	–	–	–	–	+	–	+	+	–	–	+	+	26
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma						X																				1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+		48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Hepatocellular adenoma									Y		X					X										10
Hepatocellular carcinoma	X	X											X	X			X		X		X		X			13
Hemangioma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder & common bile duct	+	N	+	+	N	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	+	+	+		*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+		47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+		46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
ENDOCRINE SYSTEM																										
Pituitary	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+		48
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma, NOS																							X			1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+		45
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Interstitial cell tumor			X										X													3
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
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		*50
Malignant lymphoma, NOS																										2
Malig lymphoma, lymphocytic type															X											1

* Animals Necropsied

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

ANIMAL NUMBER	0 1 0	0 3 6	0 4 2	0 1 6	0 1 8	0 3 5	0 1 5	0 2 6	0 3 8	0 4 8	0 2 9	0 3 2	0 0 5	0 3 3	0 1 4	0 1 9	0 3 4	0 3 0	0 0 2	0 0 9	0 3 1	0 2 0	0 2 4	0 3 7	0 4 4
WEEKS ON STUDY	0 3 1	0 3 1	0 3 1	0 6 0	0 7 1	0 7 2	0 7 6	0 7 6	0 7 8	0 7 8	0 8 1	0 8 3	0 8 4	0 8 7	0 8 9	0 8 9	0 8 9	0 9 0	0 9 4	0 9 4	0 9 7	0 9 8	1 0 1	1 0 1	1 0 1
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic									X							X						X			
Alveolar/bronchiolar adenoma					X					X				X			X		X	X			X		X
Alveolar/bronchiolar carcinoma									X								X					X			
Trachea	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	–	+	+	+	+
Malignant lymphoma, mixed type																									
Thymus	–	–	–	–	+	+	–	–	–	+	–	–	–	+	+	–	–	–	+	+	–	–	–	–	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar ca, metastatic									X																
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X														X			X	X		X
Hepatocellular carcinoma						X				X		X	X		X			X				X	X		
Alveolar/bronchiolar ca, metastatic																									
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	+	+	+	+	N	+	+	+	N	N	+	+	+	N	+	+	+	+	N	N	+
Pancreas	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	–	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	+	–	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	–	+	–	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																									
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	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N
Alveolar/bronchiolar ca, metastatic																									
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																		
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	0 2 3	0 0 1	0 0 3	0 0 4	0 0 6	0 0 7	0 0 8	0 1 1	0 1 2	0 1 3	0 1 7	0 2 1	0 2 2	0 2 5	0 2 7	0 2 8	0 3 9	0 4 0	0 4 1	0 4 3	0 4 5	0 4 6	0 4 7	0 4 9	0 5 0	TOTAL. TISSUES TUMORS
WEEKS ON STUDY	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	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	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																										3
Alveolar/bronchiolar adenoma			X			X		X			X	X	X	X			X	X					X			19
Alveolar/bronchiolar carcinoma	X	X				X			X										X			X		X		10
Trachea	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Malignant lymphoma, mixed type																X										1
Thymus	–	+	–	–	–	–	–	+	+	–	+	+	+	–	+	+	–	+	+	+	+	+	+	–	+	23
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar ca, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma		X			X					X	X		X	X		X							X	X		14
Hepatocellular carcinoma					X		X		X				X	X	X						X					15
Alveolar/bronchiolar ca, metastatic	X																									1
Hemangiosarcoma																					X					1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	N	N	+	+	+	+	+	+	N	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	46
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary cystadenoma, NOS																								X		1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	+	–	–	+	–	+	+	–	–	–	+	–	+	–	+	–	–	–	–	+	+	–	–	–	–	19
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar ca, 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
Malignant lymphoma, NOS							X																			1
Malignant lymphoma, mixed type																										1

* Animals Necropsied

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

ANIMAL NUMBER	042	041	050	014	038	024	037	030	045	013	018	021	048	005	026	031	029	015	033	025	046	008	035	040	044
WEEKS ON STUDY	000	036	043	061	066	065	070	072	074	076	076	076	076	077	080	083	083	089	089	090	090	093	093	093	093
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Undiff. carcinoma, metastatic																									
Adenocarcinoma, NOS, metastatic																									
Hepatocellular carcinoma, metastatic				X									X												
Alveolar/bronchiolar adenoma							X	X		X	X	X			X	X			X		X		X		X
Alveolar/bronchiolar carcinoma								X							X			X		X		X	X		X
Trachea	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Undifferentiated carcinoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+
Lymph nodes	–	–	+	–	–	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+
Thymus	–	–	+	–	–	–	+	–	+	–	+	–	–	+	–	–	+	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Liver	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma															X			X			X		X		
Hepatocellular carcinoma				X	X				X			X	X	X	X	X		X	X	X		X	X	X	
Alveolar/bronchiolar ca, metastatic																									
Hemangioma																									
Hemangiosarcoma							X				X														
Bile duct	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	+	+	N	+	N	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+
Pancreas	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar ca, metastatic																									
Tubular cell adenoma																									
Urinary bladder	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic																X									
Alveolar/bronchiolar ca, metastatic																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar ca, metastatic																									
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																									
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					
Malig. lymphoma, lymphocytic type																					X				

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

ANIMAL NUMBER	0 3 1	0 1 6	0 2 8	0 1 2	0 2 0	0 3 2	0 3 9	0 0 9	0 3 6	0 4 9	0 0 4	0 1 1	0 3 4	0 0 6	0 0 1	0 0 2	0 0 4	0 1 0	0 1 7	0 1 9	0 2 2	0 2 3	0 2 7	0 4 3	0 4 7	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	0 9 6	0 9 7	0 9 7	0 9 8	1 0 0	1 0 0	1 0 0	1 0 1	1 0 1	1 0 1	1 0 2	1 0 2	1 0 2	1 0 3	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	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Undiff. carcinoma, metastatic							X																			1
Adenocarcinoma, NOS, metastatic							X																			1
Hepatocellular carcinoma, metastatic															X									X		4
Alveolar/bronchiolar adenoma				X	X			X	X	X			X	X		X		X		X		X	X	X		24
Alveolar/bronchiolar carcinoma	X	X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X		X	X	X			X	28
Trachea	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Undifferentiated carcinoma							X																			1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	–	+	+	+	+	40
Thymus	+	–	–	–	–	+	–	–	–	–	–	–	–	–	–	+	–	+	–	+	+	–	–	–	+	13
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma		X		X						X				X	X		X		X	X		X	X			14
Hepatocellular carcinoma			X		X			X	X	X	X			X	X	X			X		X			X		26
Alveolar/bronchiolar ca, metastatic																			X							1
Hemangioma									X																	1
Hemangiosarcoma													X									X				4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar ca, metastatic													X													1
Tubular cell adenoma		X																								1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+		45
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metastatic																								X		2
Alveolar/bronchiolar ca, metastatic											X															1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	–	–	–	–	–	–	–	–	–	–	+	+	–	+	–	+	+	–	–	+	–	+	–	–	+	17
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
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar ca, metastatic																			X							1
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/bronchiolar ca, metastatic																			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
Hemangiosarcoma																										1
Malignant lymphoma, NOS																										1
Malig. lymphoma, lymphocytic type																										1

*Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE: UNTREATED CONTROL

ANIMAL NUMBER	03392	02717	01818	04545	01199	01116	04646	03070	04422	04434	03802	04047	03232	00971	00868	04909	00101	01222	03131	04400	00802	02626	02525	05050	03535
WEEKS ON STUDY	00022	01199	03838	05858	06611	07722	07726	07778	07780	08082	08084	08085	08086	08087	08087	08879	08899	09093	09393	09395	09595	09596	09597	09597	09599
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																X									
Alveolar/bronchiolar carcinoma																									
Osteosarcoma, metastatic												X													
Trachea	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Spleen	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig lymphoma, histiocytic type																									
Lymph nodes	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, NOS																X									
Thymus	+	+	–	–	+	–	–	–	–	–	–	–	–	+	–	–	–	+	+	+	–	–	–	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma												X													
Hepatocellular carcinoma																									
Malignant lymphoma, NOS																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	N	N	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	N	+
Pancreas	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoca in adenomatous polyp																									
Large intestine	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	–	+	+
Adenoma, NOS																									X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	–	+	+	–	–	–	+	–	+	–	+	+	–	–	–	–	–	+	+	+	–	+	+	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	N	N	N	+	+	N	+	+	+	+	+	N	N	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Endometrial stromal polyp																					X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																									
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
Adenocarcinoma, NOS																									
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma												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
Malignant lymphoma, NOS								X											X						
Malig lymphoma, lymphocytic type																									

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

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

ANIMAL NUMBER	00202	00203	00404	00505	00909	01010	01113	01414	01515	01616	01717	02001	02121	02202	02304	02404	02809	03033	03404	03606	03707	04011	04313	04408	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	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																						2
Alveolar/bronchiolar carcinoma																			X						1
Osteosarcoma, metastatic																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	45
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malig. lymphoma, histiocytic type								X																	1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, NOS																									1
Thymus	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	30
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																							X		2
Hepatocellular carcinoma																			X						1
Malignant lymphoma, NOS										X															1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoca in adenomatous polyp				X																					1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	45
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																									
Pituitary	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS						X							X		X										4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma			X																						1
Parathyroid	+	–	–	+	–	–	–	+	+	+	+	+	+	–	–	+	+	–	+	+	+	–	–	+	26
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS			X			X																			2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS													X												1
Endometrial stromal polyp																									1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papillary cystadenoma, NOS																							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	*50
Adenocarcinoma, NOS					X																				1
BODY CAVITIES																									
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteosarcoma																									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
Malignant lymphoma, NOS																									2
Malig. lymphoma, lymphocytic type					X																	X			2

* Animals Necropsied

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

ANIMAL NUMBER	04838	05040	00643	04431	04491	00808	01100	04606	00545	03232	03331	04747	04545	01313	03834	03434	01414	03636	01228	03080	03391	00331	02939
WEEKS ON STUDY	00022	00022	00055	01108	06676	07660	08001	08811	08836	08888	08899	08909	09901	09911	09921	09931	09936	09917	09988	09898	09898	09909	10303
INTEGUMENTARY SYSTEM																							
Subcutaneous tissue	+	N	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																			X				X
RESPIRATORY SYSTEM																							
Lungs and bronchi	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic										X													
Hepatocellular carcinoma, metastatic								X						X									
Alveolar/bronchiolar adenoma								X			X		X	X	X		X			X	X	X	
Alveolar/bronchiolar carcinoma												X										X	X
Osteosarcoma, metastatic						X																	
Trachea	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	–	+	+
HEMATOPOIETIC SYSTEM																							
Bone marrow	+	A	M	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	A	M	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	A	M	+	–	–	–	–	–	–	+	+	–	+	–	–	–	–	–	–	–	–	–
CIRCULATORY SYSTEM																							
Heart	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																							
Salivary gland	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Liver	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																		X		X			
Hepatocellular carcinoma								X	X					X		X					X		
Hemangiosarcoma																			X				
Bile duct	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	M	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Pancreas	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	A	M	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
URINARY SYSTEM																							
Kidney	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																							
Urinary bladder	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																							
Pituitary	–	A	M	–	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Adenoma, NOS																							
Adrenal	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	A	M	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																							
Parathyroid	–	A	M	–	–	+	–	–	+	–	+	–	+	+	+	+	–	–	–	+	–	+	+
REPRODUCTIVE SYSTEM																							
Mammary gland	+	N	M	+	+	+	+	N	N	N	+	+	+	N	+	+	+	N	+	N	+	+	+	+
Adenocarcinoma, NOS											X										X		
Uterus	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																							
Malig. lymphoma, histiocytic type																			X				
Ovary	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+
Cystadenoma, NOS																							
NERVOUS SYSTEM																							
Brain	+	A	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																							
Bone	N	N	M	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteosarcoma						X																	
BODY CAVITIES																							
Pleura	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malignant lymphoma, NOS																						X	
ALL OTHER SYSTEMS																							
Multiple organs NOS	N	N	M	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																
Malignant lymphoma, mixed type													X										A
Adipose tissue			M																				
Hepatocellular carcinoma, metastatic																							

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

ANIMAL NUMBER	0012	0021	0041	0071	0091	0111	0151	0161	0171	0181	0191	0201	0211	0221	0231	0241	0251	0261	0271	0311	0351	0371	0401	0421	0441	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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS, metastatic																										1
Hepatocellular carcinoma, metastatic															X										X	4
Alveolar/bronchiolar adenoma	X		X		X	X				X	X	X	X	X		X		X			X	X		X		23
Alveolar/bronchiolar carcinoma		X		X	X			X		X	X					X				X		X	X			13
Osteosarcoma, metastatic																										1
Trachea	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	43
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	–	–	+	+	–	–	–	+	–	+	+	+	+	–	–	–	–	+	+	+	+	+	+	+	–	20
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma									X	X	X												X			6
Hepatocellular carcinoma					X			X		X				X	X										X	11
Hemangiosarcoma																								X		2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papillary cystadenoma, NOS										X																1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	44
Adenoma, NOS																					X	X				2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																						X				1
Parathyroid	+	+	–	+	–	–	+	–	–	+	+	–	+	+	–	+	–	+	+	+	+	–	+	–	–	25
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*49
Adenocarcinoma, NOS																						X				3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Endometrial stromal polyp																					X					1
Malig. lymphoma, histiocytic type																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Cystadenoma, NOS																					X					1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Osteosarcoma																										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*49
Malignant lymphoma, 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	*49
Malig. lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type					X																X					4
Adipose tissue																										
Hepatocellular carcinoma, metastatic															X											1

* Animals Necropsied

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

ANIMAL NUMBER	03 09	00 02	03 03	01 14	13 32	12 05	15 01	00 15	05 07	07 17	07 18	08 04	08 07	26 08	30 03	10 08	49 08	36 08	41 08	49 08	32 08	41 08	06 08	08 09	24 09
WEEKS ON STUDY	01	04	06	09	08	09	00	75	76	77	77	78	78	80	83	84	84	85	85	86	87	88	89	89	89
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	M	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metastatic						X																			
Alveolar/bronchiolar adenoma					X				X		X			X		X	X			X	X	X	X	X	
Alveolar/bronchiolar carcinoma					X		X		X	X				X	X			X	X	X		X		X	
Trachea	M	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	M	+	–	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+
Spleen	M	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																	X								
Malig. lymphoma, histiocytic type																			X						
Lymph nodes	M	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–
Alveolar/bronchiolar ca, metastatic					X														X						
Thymus	M	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	+	–	+	–	–	–	–	–	+
Hemangiosarcoma, metastatic																	X								
CIRCULATORY SYSTEM																									
Heart	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar ca, metastatic														X					X						
DIGESTIVE SYSTEM																									
Salivary gland	M	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	M	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma					X			X		X	X	X		X			X		X					X	
Hepatocellular carcinoma					X	X		X	X		X	X			X	X							X	X	X
Alveolar/bronchiolar ca, metastatic																									
Hepatoblastoma																									
Hemangiosarcoma																				X					
Hemangiosarcoma, metastatic																	X								
Malignant lymphoma, NOS													X												
Bile duct	M	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	M	+	N	N	+	+	+	N	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	N
Pancreas	M	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	M	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	M	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	M	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	M	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Urinary bladder	M	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	M	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	–	+	+
Adenoma, NOS										X															
Adrenal	M	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma											X														
Thyroid	M	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma										X															
Parathyroid	M	–	–	–	+	+	+	+	+	+	–	+	+	+	+	+	–	–	+	–	+	+	+	–	+
REPRODUCTIVE SYSTEM																									
Mammary gland	M	+	+	N	+	N	N	N	N	+	+	+	N	N	+	+	N	N	+	N	+	+	+	+	+
Uterus	M	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Ovary	M	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Teratoma, NOS			X																						
NERVOUS SYSTEM																									
Brain	M	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs NOS	M	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																		
Malignant lymphoma, NOS																									
Malig. lymphoma, histiocytic type										X										X					

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

ANIMAL NUMBER	02551	02741	04591	02707	04433	03101	04407	04408	04411	02202	02202	02203	01108	01107	03303	03505	05004	04909	01606	02201	02208	02904	03404	04606	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	08909	08909	08909	09001	09903	09906	09906	09907	09908	09908	09908	09908	09909	10011	10011	10011	10102	10104	10104	10104	10104	10104	10104	10104	10104	
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibrosarcoma																						X			1
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular carcinoma, metastatic				X													X								3
Alveolar/bronchiolar adenoma	X	X	X		X				X			X	X	X	X		X	X			X	X	X	X	X	28
Alveolar/bronchiolar carcinoma		X			X	X	X	X		X	X	X		X	X	X	X	X	X	X		X	X	X		29
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	47
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Hemangiosarcoma																									1
Malig lymphoma, histiocytic type																									1
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	43
Alveolar/bronchiolar ca, metastatic																									2
Thymus	–	–	–	–	–	–	–	–	–	–	–	–	+	–	+	–	–	–	+	+	–	–	–	+	9
Hemangiosarcoma, metastatic																									1
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar ca, metastatic																									2
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma		X					X	X		X	X	X				X	X	X	X	X				X	22
Hepatocellular carcinoma	X	X	X	X	X	X			X		X	X	X	X	X	X	X	X	X		X	X	X	X	32
Alveolar/bronchiolar ca, metastatic										X															1
Hepatoblastoma																				X					1
Hemangiosarcoma																									1
Hemangiosarcoma metastatic																									1
Malignant lymphoma NOS																									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	N	+	N	+	N	N	+	+	+	+	+	+	+	+	N	N	N	+	+	+	+	N	N	N	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malignant lymphoma, mixed type				X																					1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma, NOS																									1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Cortical adenoma																									1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	46
Follicular cell adenoma																	X			X	X				4
Parathyroid	+	+	+	+	–	+	–	–	–	–	–	–	–	–	+	+	–	–	+	–	–	–	–	–	24
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	N	+	+	*49
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leiomyosarcoma															X										1
Ovary	+	+	+	–	+	+	+	–	–	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	43
Teratoma, NOS																									1
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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	*49
Alveolar/bronchiolar ca, metastatic																									1
Malignant lymphoma, NOS													X												1
Malig lymphoma, histiocytic type																X									3

* Animals Necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOG	50	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(50)
Epidermal inclusion cyst		1 (2%)		
Inflammation, suppurative	2 (4%)	1 (2%)		
Inflammation, chronic		2 (4%)		
Hyperkeratosis				1 (2%)
Acanthosis	1 (2%)	3 (6%)		2 (4%)
*Subcut tissue	(50)	(50)	(50)	(50)
Inflammation, suppurative				1 (2%)
Inflammation granulomatous focal		1 (2%)		
RESPIRATORY SYSTEM				
*Nasal cavity	(50)	(50)	(50)	(50)
Foreign body, NOS	3 (6%)	6 (12%)		2 (4%)
Hemorrhage		2 (4%)		1 (2%)
Inflammation, suppurative	8 (16%)	10 (20%)	6 (12%)	14 (28%)
Inflammation, chronic focal	1 (2%)	1 (2%)		
Infection, bacterial		1 (2%)		
Hyperplasia, epithelial		5 (10%)	3 (6%)	3 (6%)
Metaplasia, squamous	4 (8%)	5 (10%)	3 (6%)	3 (6%)
*Larynx	(50)	(50)	(50)	(50)
Foreign body, NOS		1 (2%)		3 (6%)
Hemorrhage				1 (2%)
Inflammation, focal	1 (2%)			
Inflammation, suppurative	5 (10%)	6 (12%)	3 (6%)	6 (12%)
Inflammation, chronic focal		1 (2%)		
Infection, bacterial		1 (2%)		
Hyperplasia, epithelial				1 (2%)
#Trachea	(50)	(48)	(50)	(47)
Foreign body, NOS				1 (2%)
Inflammation, suppurative	1 (2%)	1 (2%)		2 (4%)
Infection, bacterial		1 (2%)		
Hyperplasia, epithelial		1 (2%)		
Dysplasia, epithelial		1 (2%)		
#Lung/bronchiole	(50)	(49)	(50)	(50)
Hyperplasia, epithelial			1 (2%)	
#Lung	(50)	(49)	(50)	(50)
Foreign body, NOS	1 (2%)			1 (2%)
Congestion, NOS				1 (2%)
Edema, NOS	2 (4%)			1 (2%)
Bronchopneumonia, NOS				1 (2%)
Pneumonia, aspiration				1 (2%)
Inflammation, granulomatous focal	1 (2%)			
Proteinosis, alveolar				1 (2%)
Alveolar macrophages	11 (22%)	12 (24%)	10 (20%)	4 (8%)
Hyperplasia, alveolar epithelium		5 (10%)	1 (2%)	2 (4%)
#Lung/alveoli	(50)	(49)	(50)	(50)
Hemorrhage	2 (4%)	5 (10%)	1 (2%)	7 (14%)
Inflammation, interstitial			1 (2%)	1 (2%)
Inflammation, suppurative		2 (4%)	3 (6%)	3 (6%)
Fibrosis, focal	2 (4%)		1 (2%)	1 (2%)
Fibrosis, multifocal	2 (4%)	3 (6%)	1 (2%)	1 (2%)
Fibrosis, diffuse	1 (2%)		1 (2%)	
Necrosis, focal			1 (2%)	1 (2%)
Metaplasia, osseous		1 (2%)		

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM				
#Bone marrow	(50)	(49)	(49)	(49)
Atrophy, NOS	1 (2%)	2 (4%)	1 (2%)	2 (4%)
#Spleen	(50)	(49)	(50)	(50)
Hemorrhage	1 (2%)			
Fibrosis, focal	1 (2%)	5 (10%)	10 (20%)	7 (14%)
Fibrosis, multifocal			1 (2%)	
Fibrosis, diffuse	1 (2%)	1 (2%)		1 (2%)
Necrosis, focal	2 (4%)	1 (2%)	3 (6%)	2 (4%)
Necrosis, diffuse	1 (2%)			
Hemosiderosis		1 (2%)		
Hyperplasia, lymphoid	1 (2%)			
#Splenic capsule	(50)	(49)	(50)	(50)
Cyst, NOS		1 (2%)		
#Mandibular l. node	(50)	(48)	(50)	(50)
Inflammation, suppurative	1 (2%)			
Necrosis, focal	1 (2%)			
Hyperplasia, lymphoid				1 (2%)
#Bronchial lymph node	(50)	(48)	(50)	(50)
Hyperplasia, lymphoid	1 (2%)			
CIRCULATORY SYSTEM				
*Multiple organs	(50)	(50)	(50)	(50)
Periarteritis		1 (2%)		
*Mediastinum	(50)	(50)	(50)	(50)
Periarteritis				1 (2%)
#Heart	(50)	(50)	(50)	(50)
Mineralization				1 (2%)
#Heart/atrium	(50)	(50)	(50)	(50)
Thrombosis, NOS	2 (4%)	1 (2%)	2 (4%)	4 (8%)
Fibrosis, focal			1 (2%)	1 (2%)
#Heart/ventricle	(50)	(50)	(50)	(50)
Dilatation, NOS			1 (2%)	
#Myocardium	(50)	(50)	(50)	(50)
Mineralization				1 (2%)
Hemorrhage	1 (2%)			
Inflammation, chronic focal	1 (2%)	1 (2%)	1 (2%)	
Fibrosis, focal		6 (12%)	3 (6%)	1 (2%)
Fibrosis, multifocal		1 (2%)	1 (2%)	1 (2%)
Fibrosis, diffuse	6 (12%)	4 (8%)	1 (2%)	12 (24%)
Necrosis, focal	1 (2%)			
Calcification, focal				1 (2%)
#Cardiac valve	(50)	(50)	(50)	(50)
Metaplasia, cartilaginous	8 (16%)	12 (24%)	10 (20%)	8 (16%)
*Aorta	(50)	(50)	(50)	(50)
Mineralization	1 (2%)			
*Coronary artery	(50)	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)			
*Pulmonary artery	(50)	(50)	(50)	(50)
Mineralization		1 (2%)	1 (2%)	2 (4%)
Calcification, focal				1 (2%)
*Sup. panc-duod. artery	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)			
#Liver	(50)	(49)	(50)	(50)
Thrombosis, NOS	1 (2%)	1 (2%)		
#Pancreas	(48)	(46)	(48)	(48)
Periarteritis	1 (2%)	2 (4%)		
#Testis	(50)	(49)	(50)	(50)
Periarteritis		3 (6%)	1 (2%)	1 (2%)

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM				
*Hard palate	(50)	(50)	(50)	(50)
Acanthosis				1 (2%)
*Soft palate	(50)	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)	
*Tooth	(50)	(50)	(50)	(50)
Malocclusion				1 (2%)
#Salivary gland	(49)	(47)	(47)	(49)
Inflammation, chronic				1 (2%)
Inflammation, chronic focal	1 (2%)		1 (2%)	
Inflammation, chronic diffuse		1 (2%)		
#Liver	(50)	(49)	(50)	(50)
Hemorrhage				1 (2%)
Inflammation, granulomatous				3 (6%)
Inflammation granulomatous focal	1 (2%)	7 (14%)	2 (4%)	2 (4%)
Inflammation, pyogranulomatous		1 (2%)		1 (2%)
Pigmentation, NOS			2 (4%)	
Hemosiderosis	8 (16%)	29 (59%)	37 (74%)	42 (84%)
Hepatocytomegaly	2 (4%)	10 (20%)	6 (12%)	5 (10%)
Angiectasis	1 (2%)	5 (10%)	2 (4%)	1 (2%)
#Liver/hepatocytes	(50)	(49)	(50)	(50)
Necrosis, focal	7 (14%)	23 (47%)	6 (12%)	16 (32%)
Cytoplasmic vacuolization	8 (16%)	26 (53%)	22 (44%)	25 (50%)
Basophilic cyto change	15 (30%)	22 (45%)	13 (26%)	6 (12%)
Eosinophilic cyto change	1 (2%)			1 (2%)
#Bile duct	(50)	(49)	(50)	(50)
Inflammation, suppurative			1 (2%)	
Inflammation granulomatous focal			1 (2%)	
Fibrosis	8 (16%)	10 (20%)	17 (34%)	23 (46%)
Hyperplasia, NOS	42 (84%)	37 (76%)	41 (82%)	33 (66%)
#Pancreas	(48)	(46)	(48)	(48)
Inflammation, suppurative			1 (2%)	
Inflammation, chronic focal		1 (2%)		
#Pancreatic acinus	(48)	(46)	(48)	(48)
Basophilic cyto change				1 (2%)
Atrophy, focal	11 (23%)	15 (33%)	17 (35%)	10 (21%)
Atrophy, diffuse		1 (2%)	3 (6%)	1 (2%)
*Pharyngeal mucosa	(50)	(50)	(50)	(50)
Acanthosis				1 (2%)
#Glandular stomach	(50)	(49)	(50)	(50)
Mineralization	1 (2%)			2 (4%)
Inflammation, acute		1 (2%)		
#Forestomach	(50)	(49)	(50)	(50)
Hernia, NOS	1 (2%)			
Ulcer, NOS		3 (6%)		
Inflammation, focal		1 (2%)		
Inflammation, acute	1 (2%)	2 (4%)	1 (2%)	2 (4%)
Hyperkeratosis		1 (2%)		
Acanthosis	2 (4%)		2 (4%)	2 (4%)
#Ileum	(49)	(47)	(49)	(50)
Meckel's diverticulum	1 (2%)			
#Colon	(49)	(47)	(50)	(46)
Parasitism	9 (18%)	15 (32%)	11 (22%)	9 (20%)
*Rectum	(50)	(50)	(50)	(50)
Prolapse			1 (2%)	
Parasitism	2 (4%)		5 (10%)	1 (2%)

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM				
#Kidney	(50)	(50)	(50)	(50)
Nephropathy	47 (94%)	47 (94%)	48 (96%)	45 (90%)
#Kidney/cortex	(50)	(50)	(50)	(50)
Mineralization				3 (6%)
Inflammation, suppurative		1 (2%)		
Infarct, focal			1 (2%)	
#Kidney/tubule	(50)	(50)	(50)	(50)
Degeneration, NOS	11 (22%)	13 (26%)	23 (46%)	10 (20%)
#Kidney/pelvis	(50)	(50)	(50)	(50)
Mineralization		1 (2%)		
Inflammation, suppurative		1 (2%)		
Hyperplasia, epithelial		1 (2%)		
#Urinary bladder	(50)	(47)	(50)	(48)
Calculus, unkn gross or micro			1 (2%)	
Hemorrhage			1 (2%)	
Inflammation, suppurative			1 (2%)	
Hyperplasia, epithelial		1 (2%)	2 (4%)	2 (4%)
#U. bladder/submucosa	(50)	(47)	(50)	(48)
Hemorrhage	1 (2%)			
ENDOCRINE SYSTEM				
#Anterior pituitary	(50)	(47)	(49)	(49)
Cyst, NOS	4 (8%)	2 (4%)	2 (4%)	
Hemorrhage	1 (2%)	1 (2%)	2 (4%)	
Necrosis, focal				1 (2%)
Hyperplasia, NOS	7 (14%)	2 (4%)	3 (6%)	7 (14%)
#Adrenal	(50)	(50)	(50)	(50)
Atrophy, NOS				1 (2%)
#Adrenal cortex	(50)	(50)	(50)	(50)
Cyst, NOS		1 (2%)		
Cytoplasmic vacuolization	7 (14%)	17 (34%)	6 (12%)	11 (22%)
Cytomegaly		1 (2%)		
Hyperplasia, focal		1 (2%)		
#Adrenal medulla	(50)	(50)	(50)	(50)
Cyst, NOS		1 (2%)		
Hemorrhage			1 (2%)	
Hyperplasia, NOS	3 (6%)	1 (2%)	3 (6%)	1 (2%)
Hyperplasia, focal	6 (12%)	16 (32%)	11 (22%)	9 (18%)
#Thyroid	(49)	(48)	(49)	(50)
Ultimobranchial cyst				1 (2%)
Cystic follicles		1 (2%)		2 (4%)
Hyperplasia, C-cell	5 (10%)	4 (8%)	8 (16%)	9 (18%)
#Parathyroid	(29)	(35)	(30)	(32)
Hyperplasia, NOS		6 (17%)	2 (7%)	4 (13%)
#Pancreatic islets	(48)	(46)	(48)	(48)
Hyperplasia, NOS	1 (2%)		2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(50)
Galactocele			1 (2%)	
*Preputial gland	(50)	(50)	(50)	(50)
Cyst, NOS	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Inflammation, suppurative	6 (12%)	8 (16%)	11 (22%)	9 (18%)
Inflammation, chronic	1 (2%)	1 (2%)		1 (2%)
Inflammation, chronic suppurative	1 (2%)			
Hyperplasia, epithelial	2 (4%)		1 (2%)	1 (2%)
Hyperkeratosis	1 (2%)		1 (2%)	
Acanthosis			1 (2%)	1 (2%)
Metaplasia, squamous	1 (2%)			

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)				
#Prostate	(44)	(42)	(46)	(45)
Inflammation, suppurative	1 (2%)	4 (10%)	10 (22%)	5 (11%)
Inflammation, chronic	1 (2%)			
Hyperplasia, epithelial		1 (2%)	1 (2%)	1 (2%)
*Seminal vesicle	(50)	(50)	(50)	(50)
Inflammation, suppurative	21 (42%)	22 (44%)	8 (16%)	20 (40%)
Inflammation, chronic			1 (2%)	
Hyperplasia, epithelial	2 (4%)	1 (2%)		1 (2%)
#Testis	(50)	(49)	(50)	(50)
Hemorrhage				1 (2%)
Necrosis, focal				1 (2%)
Atrophy, NOS	31 (62%)	31 (63%)	31 (62%)	38 (76%)
Hyperplasia, interstitial cell	4 (8%)	3 (6%)	2 (4%)	2 (4%)
*Epididymis	(50)	(50)	(50)	(50)
Inflammation, granulomatous focal		1 (2%)		
NERVOUS SYSTEM				
#Brain/meninges	(50)	(50)	(50)	(49)
Fibrosis		1 (2%)		
#Cerebrum	(50)	(50)	(50)	(49)
Hemorrhage	1 (2%)			1 (2%)
Malacia				1 (2%)
Atrophy, pressure				1 (2%)
#Brain	(50)	(50)	(50)	(49)
Hemorrhage	5 (10%)	7 (14%)	3 (6%)	5 (10%)
Atrophy, pressure	2 (4%)	2 (4%)	2 (4%)	
#Medulla oblongata	(50)	(50)	(50)	(49)
Hemorrhage	1 (2%)			1 (2%)
SPECIAL SENSE ORGANS				
*Eye/anterior chamber	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)			
*Eye/cornea	(50)	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)			
*Eye/lacrimal gland	(50)	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)	1 (2%)	1 (2%)	
*Nasolacrimal duct	(50)	(50)	(50)	(50)
Inflammation, suppurative	6 (12%)	3 (6%)	8 (16%)	2 (4%)
Acanthosis			1 (2%)	1 (2%)
*Zymbal gland	(50)	(50)	(50)	(50)
Metaplasia, squamous		1 (2%)		
MUSCULOSKELETAL SYSTEM				
*Bone	(50)	(50)	(50)	(50)
Pathologic fracture				1 (2%)
Healed fracture				1 (2%)
*Skull	(50)	(50)	(50)	(50)
Osteoporosis		1 (2%)		
*Maxilla	(50)	(50)	(50)	(50)
Hyperplasia, focal				1 (2%)
*Sternum	(50)	(50)	(50)	(50)
Hyperplasia, focal		1 (2%)		

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
BODY CAVITIES				
*Peritoneum	(50)	(50)	(50)	(50)
Inflammation, chronic focal	1 (2%)			
Necrosis, fat	1 (2%)			
*Pleura	(50)	(50)	(50)	(50)
Fibrosis, multifocal			1 (2%)	
*Mesentery	(50)	(50)	(50)	(50)
Ectopia		1 (2%)		
Inflammation, chronic focal			1 (2%)	
*Tunica vaginalis	(50)	(50)	(50)	(50)
Hyperplasia, mesothelial		1 (2%)		
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(50)
Mineralization		4 (8%)		
Inflammation, suppurative		3 (6%)		1 (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 INHALATION STUDY OF DICHLOROMETHANE

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50	50
ANIMALS NECROPSIED	50	50	50	50
ANIMALS EXAMINED HISTOPATHOLOG	50	50	50	50
INTEGUMENTARY SYSTEM				
*Skin	(50)	(50)	(50)	(50)
Hyperkeratosis	1 (2%)			
Acanthosis	1 (2%)			1 (2%)
RESPIRATORY SYSTEM				
*Nasal cavity	(50)	(50)	(50)	(50)
Foreign body, NOS	3 (6%)	3 (6%)	2 (4%)	1 (2%)
Hemorrhage			1 (2%)	
Inflammation, suppurative	5 (10%)	3 (6%)	11 (22%)	4 (8%)
Inflammation, chronic focal				2 (4%)
Hyperplasia, epithelial	1 (2%)	1 (2%)	2 (4%)	
Hyperplasia, focal	1 (2%)			
Metaplasia, squamous	1 (2%)	2 (4%)	3 (6%)	9 (18%)
*Larynx	(50)	(50)	(50)	(50)
Foreign body, NOS	1 (2%)			4 (8%)
Inflammation, suppurative	1 (2%)	4 (8%)	5 (10%)	7 (14%)
Inflammation, chronic focal	2 (4%)	4 (8%)	4 (8%)	1 (2%)
Hyperplasia, epithelial	1 (2%)			
Acanthosis			1 (2%)	1 (2%)
Metaplasia, squamous	1 (2%)			
#Trachea	(50)	(48)	(49)	(46)
Inflammation, suppurative		1 (2%)		
Inflammation, chronic		1 (2%)		
Hyperplasia, epithelial		2 (4%)		
#Lung/bronchiole	(50)	(50)	(50)	(50)
Foreign body, NOS			1 (2%)	
#Lung	(50)	(50)	(50)	(50)
Foreign body, NOS			1 (2%)	
Hemorrhage	1 (2%)			1 (2%)
Bronchopneumonia, focal				1 (2%)
Pneumonia, aspiration				1 (2%)
Inflammation, granulomatous			2 (4%)	
Granuloma, NOS	1 (2%)			
Inflammation, granulomatous focal	2 (4%)			
Granuloma, foreign body	1 (2%)			
Alveolar macrophages	9 (18%)	13 (26%)	10 (20%)	11 (22%)
Hyperplasia, alveolar epithelium	1 (2%)	1 (2%)	3 (6%)	2 (4%)
#Lung/alveoli	(50)	(50)	(50)	(50)
Mineralization	1 (2%)			
Congestion, NOS		1 (2%)		
Edema, NOS		1 (2%)		
Hemorrhage	2 (4%)	6 (12%)	4 (8%)	1 (2%)
Inflammation, interstitial	1 (2%)	2 (4%)	1 (2%)	
Inflammation, suppurative		2 (4%)		1 (2%)
Granuloma, NOS	1 (2%)			
Fibrosis, focal	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Fibrosis, multifocal	1 (2%)	2 (4%)	3 (6%)	
Necrosis, focal	1 (2%)			
HEMATOPOIETIC SYSTEM				
#Bone marrow	(50)	(50)	(48)	(46)
Fibrosis, multifocal			1 (2%)	1 (2%)
Fibrosis, diffuse	1 (2%)		1 (2%)	
Atrophy, NOS		2 (4%)		1 (2%)

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)				
#Spleen	(50)	(50)	(50)	(49)
Hemorrhage				1 (2%)
Inflammation, granulomatous		1 (2%)		
Fibrosis, focal		1 (2%)	4 (8%)	4 (8%)
Fibrosis, multifocal		1 (2%)		
Angiectasis			1 (2%)	
Hyperplasia, reticulum cell			1 (2%)	
Hyperplasia, lymphoid		1 (2%)		
Hematopoiesis	3 (6%)	2 (4%)	1 (2%)	
#Mandibular l. node	(49)	(49)	(50)	(50)
Cyst, NOS		1 (2%)		
#Bronchial lymph node	(49)	(49)	(50)	(50)
Hemorrhage	2 (4%)	1 (2%)		1 (2%)
#Pancreatic l. node	(49)	(49)	(50)	(50)
Hemorrhage			1 (2%)	
#Renal lymph node	(49)	(49)	(50)	(50)
Fibrosis		1 (2%)		
Pigmentation, NOS		1 (2%)		
#Liver	(50)	(50)	(50)	(50)
Hematopoiesis	2 (4%)	1 (2%)		
#Thymus	(31)	(39)	(34)	(31)
Cyst, NOS		1 (3%)	1 (3%)	
CIRCULATORY SYSTEM				
*Multiple organs	(50)	(50)	(50)	(50)
Periarteritis		1 (2%)		
*Nasal cavity	(50)	(50)	(50)	(50)
Thrombosis, NOS		3 (6%)		
#Heart/atrium	(50)	(50)	(48)	(50)
Thrombosis, NOS	2 (4%)	1 (2%)	3 (6%)	5 (10%)
Hemorrhage			1 (2%)	
Inflammation, suppurative			1 (2%)	
#Myocardium	(50)	(50)	(48)	(50)
Fibrosis, focal		2 (4%)	1 (2%)	
Fibrosis, multifocal			1 (2%)	
Fibrosis, diffuse	2 (4%)	1 (2%)	1 (2%)	2 (4%)
#Endocardium	(50)	(50)	(48)	(50)
Fibrosis, focal			1 (2%)	
#Cardiac valve	(50)	(50)	(48)	(50)
Metaplasia, cartilaginous	16 (32%)	9 (18%)	8 (17%)	9 (18%)
*Pulmonary artery	(50)	(50)	(50)	(50)
Mineralization				1 (2%)
Hyperplasia, focal			1 (2%)	
#Liver	(50)	(50)	(50)	(50)
Thrombosis, NOS		3 (6%)		
DIGESTIVE SYSTEM				
*Tongue	(50)	(50)	(50)	(50)
Acanthosis			1 (2%)	
#Salivary gland	(49)	(49)	(50)	(49)
Inflammation, chronic	1 (2%)	1 (2%)	1 (2%)	
#Liver	(50)	(50)	(50)	(50)
Inflammation, chronic diffuse				1 (2%)
Inflammation, granulomatous		2 (4%)	1 (2%)	2 (4%)
Inflammation, granulomatous focal	14 (28%)	30 (60%)	20 (40%)	22 (44%)
Inflammation, pyogranulomatous	1 (2%)			
Hemosiderosis	19 (38%)	29 (58%)	38 (76%)	45 (90%)
Hepatocytomegaly	3 (6%)	10 (20%)	18 (36%)	5 (10%)
Angiectasis		1 (2%)	1 (2%)	

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)				
#Hepatic capsule	(50)	(50)	(50)	(50)
Fibrosis, focal		2 (4%)	1 (2%)	
#Liver/hepatocytes	(50)	(50)	(50)	(50)
Necrosis, NOS			1 (2%)	
Necrosis, focal	2 (4%)	32 (64%)	19 (38%)	9 (18%)
Cytoplasmic vacuolization	10 (20%)	43 (86%)	44 (88%)	43 (86%)
Basophilic cyto change	23 (46%)	33 (66%)	21 (42%)	16 (32%)
Clear cell change		1 (2%)		
#Bile duct	(50)	(50)	(50)	(50)
Inflammation, suppurative				1 (2%)
Fibrosis	4 (8%)	3 (6%)	10 (20%)	3 (6%)
Hyperplasia, NOS	22 (44%)	21 (42%)	26 (52%)	21 (42%)
#Pancreatic acinus	(50)	(48)	(50)	(46)
Atrophy, focal	12 (24%)	10 (21%)	11 (22%)	5 (11%)
#Esophagus	(49)	(43)	(45)	(47)
Foreign body, NOS			1 (2%)	
Dilatation, NOS	1 (2%)			
#Glandular stomach	(50)	(50)	(50)	(48)
Mineralization			1 (2%)	
Ulcer, NOS			1 (2%)	1 (2%)
Inflammation, suppurative		1 (2%)		1 (2%)
Hyperplasia, NOS		1 (2%)	1 (2%)	
#Forestomach	(50)	(50)	(50)	(48)
Ulcer, NOS				1 (2%)
Inflammation, acute	1 (2%)		2 (4%)	
Hyperkeratosis			1 (2%)	
Acanthosis				1 (2%)
#Small intestine/mucosa	(47)	(47)	(49)	(47)
Hyperplasia, diffuse			1 (2%)	
#Duodenum	(47)	(47)	(49)	(47)
Inflammation, suppurative			1 (2%)	
Erosion			1 (2%)	
#Colon	(47)	(47)	(47)	(46)
Cyst, NOS		1 (2%)		
Parasitism	8 (17%)	12 (26%)	9 (19%)	5 (11%)
#Cecum	(47)	(47)	(47)	(46)
Hemorrhage			1 (2%)	
*Rectum	(50)	(50)	(50)	(50)
Parasitism	2 (4%)		5 (10%)	1 (2%)
URINARY SYSTEM				
#Kidney	(50)	(50)	(50)	(49)
Inflammation, chronic		1 (2%)		
Nephropathy	48 (96%)	45 (90%)	41 (82%)	41 (84%)
#Kidney/capsule	(50)	(50)	(50)	(49)
Hemorrhage		1 (2%)		
Inflammation, suppurative		1 (2%)		
#Kidney/medulla	(50)	(50)	(50)	(49)
Mineralization	1 (2%)	2 (4%)		
#Kidney/tubule	(50)	(50)	(50)	(49)
Mineralization	1 (2%)			
Degeneration, NOS	14 (28%)	20 (40%)	22 (44%)	25 (51%)
#Kidney/pelvis	(50)	(50)	(50)	(49)
Mineralization	6 (12%)			
Dilatation, NOS		1 (2%)		
Hyperplasia, epithelial		1 (2%)		
#Urinary bladder	(47)	(45)	(46)	(47)
Dilatation, NOS		1 (2%)		
Inflammation, suppurative			1 (2%)	
Hyperplasia, epithelial				1 (2%)

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
URINARY SYSTEM (Continued)				
#U bladder/submucosa	(47)	(45)	(46)	(47)
Edema, NOS	4 (9%)		1 (2%)	2 (4%)
Hemorrhage	1 (2%)		1 (2%)	
ENDOCRINE SYSTEM				
#Pituitary	(49)	(49)	(49)	(49)
Cyst, NOS	1 (2%)			
#Anterior pituitary	(49)	(49)	(49)	(49)
Cyst, NOS	2 (4%)	4 (8%)	7 (14%)	4 (8%)
Hemorrhage				1 (2%)
Necrosis, NOS		1 (2%)		
Hyperplasia, NOS	6 (12%)	2 (4%)	3 (6%)	5 (10%)
#Adrenal cortex	(50)	(50)	(49)	(49)
Cyst, NOS	1 (2%)			
Hemorrhage		1 (2%)		3 (6%)
Necrosis, NOS		1 (2%)		
Necrosis, focal			1 (2%)	
Cytoplasmic vacuolization	16 (32%)	11 (22%)	13 (27%)	23 (47%)
Cytomegaly	2 (4%)			1 (2%)
#Adrenal medulla	(50)	(50)	(49)	(49)
Hyperplasia, focal	1 (2%)	7 (14%)	8 (16%)	3 (6%)
#Thyroid	(47)	(46)	(48)	(42)
Ultimobranchial cyst			2 (4%)	
Hyperplasia, C-cell	6 (13%)	1 (2%)	9 (19%)	15 (36%)
#Thyroid follicle	(47)	(46)	(48)	(42)
Hyperplasia, cystic	1 (2%)			
#Parathyroid	(26)	(19)	(26)	(26)
Hyperplasia, NOS	2 (8%)		1 (4%)	
REPRODUCTIVE SYSTEM				
*Mammary gland	(50)	(50)	(50)	(50)
Galactocele	1 (2%)	1 (2%)	2 (4%)	
Hyperplasia, epithelial			1 (2%)	1 (2%)
*Clitoral gland	(50)	(50)	(50)	(50)
Mineralization	1 (2%)			
Cyst, NOS		1 (2%)	1 (2%)	
Ulcer, NOS				1 (2%)
Inflammation, suppurative	5 (10%)	8 (16%)	5 (10%)	1 (2%)
Inflammation, chronic focal	1 (2%)			
Hyperplasia, epithelial	1 (2%)	1 (2%)	1 (2%)	
Metaplasia, squamous				1 (2%)
*Vagina	(50)	(50)	(50)	(50)
Acanthosis			1 (2%)	
#Uterus	(50)	(49)	(50)	(47)
Hemorrhage	1 (2%)		1 (2%)	
Inflammation, suppurative	1 (2%)			
#Uterus/endometrium	(50)	(49)	(50)	(47)
Hyperplasia, NOS	7 (14%)	4 (8%)	5 (10%)	3 (6%)
Metaplasia, squamous			2 (4%)	1 (2%)
#Ovary	(49)	(50)	(50)	(48)
Cyst, NOS	2 (4%)	2 (4%)	1 (2%)	5 (10%)
#Mesovarium	(49)	(50)	(50)	(48)
Inflammation, chronic focal			1 (2%)	
NERVOUS SYSTEM				
#Brain/meninges	(50)	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)	
Inflammation granulomatous focal			1 (2%)	

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

	CONTROL (CHAMB)	LOW DOSE	MID DOSE	HIGH DOSE
NERVOUS SYSTEM (Continued)				
#Cerebrum	(50)	(50)	(50)	(50)
Hemorrhage				4 (8%)
Inflammation, chronic focal				1 (2%)
#Brain	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)	4 (8%)	2 (4%)	1 (2%)
Atrophy, pressure		1 (2%)	4 (8%)	1 (2%)
#Medulla oblongata	(50)	(50)	(50)	(50)
Hemorrhage	1 (2%)			2 (4%)
SPECIAL SENSE ORGANS				
*Eye	(50)	(50)	(50)	(50)
Atrophy, NOS				1 (2%)
*Eye/sclera	(50)	(50)	(50)	(50)
Mineralization				1 (2%)
*Eye/crystalline lens	(50)	(50)	(50)	(50)
Cataract	1 (2%)			3 (6%)
*Eye/lacrimal gland	(50)	(50)	(50)	(50)
Inflammation, chronic			1 (2%)	
Inflammation, chronic focal	1 (2%)		1 (2%)	
*Nasolacrimal duct	(50)	(50)	(50)	(50)
Inflammation, suppurative	2 (4%)	6 (12%)	3 (6%)	2 (4%)
Acanthosis			4 (8%)	
MUSCULOSKELETAL SYSTEM				
None				
BODY CAVITIES				
*Peritoneum	(50)	(50)	(50)	(50)
Necrosis, fat		1 (2%)		1 (2%)
*Pleura	(50)	(50)	(50)	(50)
Fibrosis, focal	1 (2%)			
*Mesentery	(50)	(50)	(50)	(50)
Inflammation, necrotizing			1 (2%)	
ALL OTHER SYSTEMS				
*Multiple organs	(50)	(50)	(50)	(50)
Hemorrhage			1 (2%)	
Inflammation, suppurative				2 (4%)
Hemosiderosis			1 (2%)	
Omentum				
Necrosis, focal	1			
Necrosis, fat				1
Broad ligament				
Necrosis, fat	1		2	1
SPECIAL MORPHOLOGY SUMMARY				
None				

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

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Ulcer, NOS		1 (2%)	
Inflammation, suppurative		1 (2%)	1 (2%)
*Subcut tissue	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Abscess, NOS	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, serous	2 (4%)	2 (4%)	3 (6%)
Inflammation, suppurative		2 (4%)	1 (2%)
Inflammation, chronic			1 (2%)
Hyperplasia, focal			1 (2%)
*Laryngeal submucosa	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
#Lung	(50)	(50)	(50)
Congestion, NOS	1 (2%)		1 (2%)
Hemorrhage	2 (4%)	1 (2%)	
Lymphocytic inflammatory infiltrate	3 (6%)	5 (10%)	1 (2%)
Inflammation, interstitial		1 (2%)	1 (2%)
Inflammation, acute/chronic	1 (2%)		1 (2%)
Hyperplasia, epithelial			1 (2%)
Histiocytosis			1 (2%)
#Lung/alveoli	(50)	(50)	(50)
Histiocytosis		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Hematopoiesis	3 (6%)		
#Bone marrow	(49)	(49)	(49)
Inflammation, suppurative		1 (2%)	
Hyperplasia, hematopoietic			1 (2%)
Hyperplasia, granulocytic	5 (10%)	3 (6%)	2 (4%)
#Spleen	(49)	(49)	(48)
Hemorrhage			1 (2%)
Atrophy, NOS			1 (2%)
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
Hematopoiesis		2 (4%)	4 (8%)
#Splenic follicles	(49)	(49)	(48)
Atrophy, NOS		3 (6%)	7 (15%)
#Lymph node	(42)	(45)	(40)
Hyperplasia, lymphoid		4 (9%)	
#Mandibular lymph. node	(42)	(45)	(40)
Hyperplasia, reticulum cell			1 (3%)
Mastocytosis			1 (3%)
#Bronchial lymph node	(42)	(45)	(40)
Atrophy, NOS	1 (2%)		
Atrophy, cystic			1 (3%)
Hyperplasia, lymphoid			1 (3%)
#Mesenteric lymph node	(42)	(45)	(40)
Hyperplasia, lymphoid		1 (2%)	
#Renal lymph node	(42)	(45)	(40)
Hemosiderosis		1 (2%)	
Hyperplasia, lymphoid			1 (3%)

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Axillary lymph node	(42)	(45)	(40)
Hyperplasia, lymphoid		1 (2%)	
#Liver	(50)	(49)	(49)
Hematopoiesis		1 (2%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Mineralization		1 (2%)	
Inflammation, acute/chronic	1 (2%)	1 (2%)	1 (2%)
#Cardiac valve	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Pigmentation, NOS			1 (2%)
#Hepatic sinusoid	(50)	(49)	(49)
Necrosis, NOS		1 (2%)	
DIGESTIVE SYSTEM			
*Tooth	(50)	(50)	(50)
Congenital malformation, NOS	4 (8%)	3 (6%)	
Inflammation, suppurative		1 (2%)	
#Salivary gland	(48)	(49)	(46)
Inflammation, acute/chronic	4 (8%)	1 (2%)	2 (4%)
#Liver	(50)	(49)	(49)
Mineralization			1 (2%)
Torsion		3 (6%)	
Congestion, NOS			1 (2%)
Inflammation, necrotizing	1 (2%)	2 (4%)	1 (2%)
Inflammation, acute/chronic	2 (4%)	1 (2%)	2 (4%)
Inflammation, chronic focal		1 (2%)	
Necrosis, NOS		1 (2%)	2 (4%)
Necrosis, focal			3 (6%)
Focal cellular change		1 (2%)	
Eosinophilic cyto change	2 (4%)		1 (2%)
Cytologic degeneration			22 (45%)
#Liver/hepatocytes	(50)	(49)	(49)
Necrosis, focal			2 (4%)
*Gallbladder	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
#Pancreas	(50)	(48)	(47)
Amyloidosis			1 (2%)
#Pancreatic duct	(50)	(48)	(47)
Inflammation, NOS			1 (2%)
#Pancreatic acinus	(50)	(48)	(47)
Atrophy, NOS			1 (2%)
#Gastric mucosa	(49)	(47)	(49)
Mineralization			1 (2%)
#Glandular stomach	(49)	(47)	(49)
Dilatation, NOS	3 (6%)	7 (15%)	9 (18%)
#Duodenum	(49)	(46)	(47)
Inflammation, acute/chronic			1 (2%)
#Ileum	(49)	(46)	(47)
Amyloidosis	1 (2%)		1 (2%)
*Rectum	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
*Anus	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(50)	(49)	(50)
Mineralization	2 (4%)	1 (2%)	1 (2%)
Hydronephrosis	1 (2%)		
Cyst, NOS		2 (4%)	
Inflammation, suppurative	1 (2%)		1 (2%)
Inflammation, necrotizing			1 (2%)
Pyelonephritis, acute	1 (2%)	2 (4%)	3 (6%)
Inflammation, acute/chronic	4 (8%)	2 (4%)	2 (4%)
Inflammation, chronic	1 (2%)		1 (2%)
Glomerulonephritis, chronic	3 (6%)	1 (2%)	1 (2%)
Inflammation, chronic focal		1 (2%)	
Fibrosis, focal			1 (2%)
Nephropathy		1 (2%)	
Infarct, NOS			1 (2%)
Calcinosis, NOS			1 (2%)
Metaplasia, osseous		2 (4%)	
#Kidney/tubule	(50)	(49)	(50)
Cast, NOS	6 (12%)	11 (22%)	20 (40%)
Cyst, NOS	2 (4%)	1 (2%)	
Nephrosis, NOS	2 (4%)		
Pigmentation, NOS		1 (2%)	
#Kidney/pelvis	(50)	(49)	(50)
Hemorrhage	1 (2%)		
Inflammation, suppurative	1 (2%)		
#Urinary bladder	(50)	(49)	(47)
Calculus, unkn gross or micro			1 (2%)
Distention	1 (2%)	2 (4%)	
Inflammation, NOS			1 (2%)
Inflammation, suppurative	2 (4%)	4 (8%)	3 (6%)
Inflammation, acute/chronic	1 (2%)		2 (4%)
Inflammation, chronic	1 (2%)	1 (2%)	
Hyperplasia, epithelial			3 (6%)
#Urinary bladder/submucosa	(50)	(49)	(47)
Angiectasis		1 (2%)	
*Urethra	(50)	(50)	(50)
Mucocele		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary	(48)	(48)	(45)
Congestion, NOS		1 (2%)	
#Adrenal	(50)	(46)	(50)
Inflammation, suppurative			1 (2%)
Necrosis, hemorrhagic	1 (2%)		
Hyperplasia, focal	1 (2%)		
#Adrenal/capsule	(50)	(46)	(50)
Hyperplasia, focal	1 (2%)		
#Adrenal cortex	(50)	(46)	(50)
Hyperplasia, NOS			1 (2%)
Hyperplasia, focal		3 (7%)	
#Adrenal medulla	(50)	(46)	(50)
Hyperplasia, NOS		2 (4%)	1 (2%)
#Thyroid	(45)	(47)	(48)
Inflammation, acute/chronic	1 (2%)	1 (2%)	
Hyperplasia, C-cell		1 (2%)	
#Thyroid follicle	(45)	(47)	(48)
Atrophy, focal			1 (2%)

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*Penis	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Inflammation, necrotizing	2 (4%)	1 (2%)	
*Prepuce	(50)	(50)	(50)
Inflammation, necrotizing			1 (2%)
*Preputial gland	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Dilatation/ducts		1 (2%)	1 (2%)
Cyst, NOS		1 (2%)	
Cystic ducts	1 (2%)	1 (2%)	
Inflammation, suppurative	2 (4%)	2 (4%)	
Inflammation, necrotizing		2 (4%)	
Abscess, NOS	1 (2%)	2 (4%)	
Inflammation, acute/chronic		1 (2%)	
Inflammation, chronic	1 (2%)		
Hyperkeratosis		2 (4%)	
#Prostate	(50)	(50)	(47)
Inflammation, suppurative	3 (6%)	2 (4%)	3 (6%)
*Seminal vesicle	(50)	(50)	(50)
Dilatation, NOS	1 (2%)		
Distention	3 (6%)	3 (6%)	
#Testis	(50)	(50)	(50)
Mineralization	1 (2%)	2 (4%)	2 (4%)
Granuloma, spermatic	1 (2%)		
Atrophy, NOS		4 (8%)	31 (62%)
Hyperplasia, interstitial cell			1 (2%)
*Scrotum	(50)	(50)	(50)
Inflammation, necrotizing		1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
#Brain	(50)	(50)	(50)
Mineralization	25 (50%)	24 (48%)	16 (32%)
Congestion, NOS		1 (2%)	
Hemorrhage		1 (2%)	
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy			1 (2%)
BODY CAVITIES			
None			

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Inflammation, acute/chronic	3 (6%)	5 (10%)	1 (2%)
Foot			
Inflammation, suppurative			1
Adipose tissue			
Inflammation, suppurative		1	
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1

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

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	48	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(49)	(49)
Epidermal inclusion cyst		1 (2%)	
Inflammation, suppurative		1 (2%)	
Inflammation, chronic focal	1 (2%)		
Hyperkeratosis		1 (2%)	
*Subcut tissue	(50)	(49)	(49)
Inflammation, suppurative	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(49)	(49)
Inflammation, serous	8 (16%)	4 (8%)	2 (4%)
Inflammation, suppurative	1 (2%)	2 (4%)	
Hyperplasia, epithelial		1 (2%)	2 (4%)
#Lung	(50)	(48)	(48)
Congestion, NOS		1 (2%)	
Edema, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	7 (14%)	5 (10%)	3 (6%)
Inflammation, interstitial		1 (2%)	
Inflammation, suppurative		1 (2%)	2 (4%)
Inflammation, necrotizing			2 (4%)
Inflammation, acute/chronic		1 (2%)	1 (2%)
Hyperplasia, NOS			1 (2%)
Hyperplasia, epithelial		1 (2%)	
#Lung/alveoli	(50)	(48)	(48)
Crystals, NOS			1 (2%)
Histiocytosis			2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(49)	(49)
Hyperplasia, lymphoid		1 (2%)	
Hematopoiesis	1 (2%)	1 (2%)	
#Bone marrow	(48)	(47)	(45)
Atrophy, NOS			1 (2%)
Hyperplasia, hematopoietic			1 (2%)
Hyperplasia, granulocytic	4 (8%)		
#Spleen	(49)	(48)	(47)
Inflammation, necrotizing		1 (2%)	
Amyloidosis	1 (2%)		
Hemosiderosis			1 (2%)
Hyperplasia, lymphoid	5 (10%)	1 (2%)	
Hematopoiesis	7 (14%)	3 (6%)	3 (6%)
#Splenic follicles	(49)	(48)	(47)
Atrophy, NOS			1 (2%)
#Mandibular lymph node	(49)	(47)	(43)
Hyperplasia, reticulum cell	1 (2%)		
Hyperplasia, lymphoid	1 (2%)	1 (2%)	
#Bronchial lymph node	(49)	(47)	(43)
Congestion, NOS			1 (2%)
Inflammation, serous		1 (2%)	
Inflammation, suppurative	1 (2%)		
Hyperplasia, lymphoid	3 (6%)		1 (2%)
#Mesenteric lymph node	(49)	(47)	(43)
Hemorrhage	1 (2%)		

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Lung	(50)	(48)	(48)
Leukocytosis, NOS	1 (2%)		
#Liver	(50)	(48)	(48)
Leukocytosis, NOS	1 (2%)		
Leukemoid reaction	1 (2%)	1 (2%)	
Hematopoiesis	1 (2%)	1 (2%)	
#Adrenal	(50)	(48)	(48)
Hematopoiesis			1 (2%)
#Thymus	(30)	(20)	(9)
Atrophy, NOS	1 (3%)		
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(49)	(49)
Periarteritis			1 (2%)
#Heart	(49)	(48)	(49)
Mineralization			1 (2%)
Inflammation, acute/chronic	1 (2%)		
Perivasculitis	1 (2%)		
#Cardiac valve	(49)	(48)	(49)
Inflammation, NOS		1 (2%)	
*Aorta	(50)	(49)	(49)
Inflammation, acute/chronic		1 (2%)	
DIGESTIVE SYSTEM			
*Tooth	(50)	(49)	(49)
Congenital malformation, NOS		1 (2%)	
*Pulp of tooth	(50)	(49)	(49)
Abscess, NOS	1 (2%)		1 (2%)
#Salivary gland	(50)	(45)	(47)
Inflammation, NOS	1 (2%)		
Inflammation, acute/chronic			2 (4%)
#Liver	(50)	(48)	(48)
Mineralization			1 (2%)
Torsion	1 (2%)		
Congestion, chronic passive		1 (2%)	
Inflammation, suppurative	1 (2%)		
Inflammation, acute/chronic		1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	
Degeneration, cystic			1 (2%)
Necrosis, NOS			2 (4%)
Necrosis, focal	3 (6%)	1 (2%)	2 (4%)
Metamorphosis, fatty	1 (2%)		1 (2%)
Pigmentation, NOS	1 (2%)		
Cytologic degeneration		23 (48%)	21 (44%)
#Pancreas	(48)	(48)	(47)
Inflammation, acute/chronic		1 (2%)	
#Pancreatic acinus	(48)	(48)	(47)
Atrophy, NOS		1 (2%)	
#Stomach	(49)	(47)	(48)
Ulcer, NOS	1 (2%)		
Inflammation, suppurative		1 (2%)	
Hyperkeratosis	1 (2%)	4 (9%)	1 (2%)
#Glandular stomach	(49)	(47)	(48)
Dilatation, NOS	1 (2%)	2 (4%)	10 (21%)
Inflammation, suppurative			1 (2%)
#Gastric submucosa	(49)	(47)	(48)
Inflammation, suppurative		1 (2%)	
#Duodenum	(46)	(47)	(47)
Inflammation, suppurative			1 (2%)
Amyloidosis		1 (2%)	

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Jejunum	(46)	(47)	(47)
Amyloidosis		1 (2%)	1 (2%)
#Ileum	(46)	(47)	(47)
Amyloidosis	1 (2%)	1 (2%)	
*Rectum	(50)	(49)	(49)
Inflammation, necrotizing	1 (2%)		
URINARY SYSTEM			
#Kidney	(49)	(48)	(47)
Hydronephrosis			2 (4%)
Hemorrhage		1 (2%)	
Glomerulonephritis, NOS	2 (4%)		1 (2%)
Inflammation, suppurative	1 (2%)		
Pyelonephritis, acute	1 (2%)		
Inflammation, acute/chronic	4 (8%)	1 (2%)	
Glomerulonephritis, subacute	1 (2%)		
Inflammation, chronic	1 (2%)		
Glomerulonephritis, chronic	4 (8%)	4 (8%)	
Infarct, NOS		1 (2%)	1 (2%)
#Kidney/tubule	(49)	(48)	(47)
Cast, NOS	8 (16%)	23 (48%)	23 (49%)
Multiple cysts	1 (2%)		1 (2%)
Necrosis, NOS			1 (2%)
#Urinary bladder	(48)	(48)	(47)
Distention		1 (2%)	
Lymphocytic inflammatory infiltrate		1 (2%)	
ENDOCRINE SYSTEM			
#Pituitary	(46)	(44)	(44)
Congestion, NOS	2 (4%)	1 (2%)	
Necrosis, focal			1 (2%)
Hypertrophy, focal	1 (2%)		
Hyperplasia, NOS	2 (4%)		
Hyperplasia, focal	1 (2%)	5 (11%)	1 (2%)
Angiectasis			1 (2%)
#Adrenal	(50)	(48)	(48)
Congestion, NOS			3 (6%)
Inflammation, suppurative		1 (2%)	
Inflammation, fibrinous	1 (2%)		
Amyloidosis	1 (2%)		
Angiectasis			1 (2%)
#Adrenal cortex	(50)	(48)	(48)
Cyst, NOS	1 (2%)		
#Adrenal medulla	(50)	(48)	(48)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal		1 (2%)	
#Thyroid	(48)	(47)	(46)
Inflammation, suppurative			1 (2%)
Inflammation, acute/chronic			1 (2%)
Hyperplasia, follicular cell	2 (4%)		2 (4%)
#Thyroid follicle	(48)	(47)	(46)
Hypertrophy, focal		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(49)	(49)
Dilatation/ducts	1 (2%)		
Hyperplasia, focal	1 (2%)		

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Uterus	(50)	(48)	(47)
Mineralization			1 (2%)
Inflammation, suppurative	6 (12%)	2 (4%)	
Abscess, NOS	1 (2%)		
Inflammation, chronic		1 (2%)	
Atrophy, NOS		1 (2%)	8 (17%)
#Uterus/endometrium	(50)	(48)	(47)
Hyperplasia, NOS	15 (30%)	8 (17%)	4 (9%)
#Ovary	(50)	(47)	(43)
Mineralization	3 (6%)		1 (2%)
Cyst, NOS	8 (16%)	9 (19%)	6 (14%)
Epidermal inclusion cyst		1 (2%)	
Congestion, NOS	1 (2%)		
Hematoma, NOS		1 (2%)	
Hemorrhagic cyst	2 (4%)	1 (2%)	3 (7%)
Abscess, NOS	9 (18%)	4 (9%)	
Inflammation, chronic		1 (2%)	
Inflammation necro granulomatous	1 (2%)		
Atrophy, NOS	6 (12%)	28 (60%)	32 (74%)
NERVOUS SYSTEM			
#Brain/meninges	(50)	(48)	(47)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Brain	(50)	(48)	(47)
Mineralization	21 (42%)	9 (19%)	12 (26%)
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	
Inflammation, hemorrhagic		1 (2%)	
Corpora amylacea			1 (2%)
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(49)	(49)
Inflammation, suppurative			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Maxilla	(50)	(49)	(49)
Fibrous osteodystrophy	4 (8%)		
*Sternum	(50)	(49)	(49)
Fibrous osteodystrophy	1 (2%)	3 (6%)	5 (10%)
BODY CAVITIES			
*Peritoneum	(50)	(49)	(49)
Hematoma, NOS	1 (2%)		
Inflammation, suppurative	1 (2%)	1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(49)	(49)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, suppurative	3 (6%)	1 (2%)	1 (2%)
Inflammation, acute/chronic	10 (20%)	6 (12%)	2 (4%)
Adipose tissue			
Inflammation, chronic		1	
Calcification, NOS	1		
Connective tissue			
Inflammation, chronic		1	

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

	CONTROL (CHAMB)	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported	1	2	2
Animal missing/no necropsy		1	1
Auto/necropsy/no histo		1	

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 INHALATION STUDIES OF DICHLOROMETHANE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE

	Control	1,000 ppm	2,000 ppm	4,000 ppm
Skin: Papilloma				
Overall Rates (a)	4/50 (8%)	0/50 (0%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	20.0%	0.0%	2.0%	0.0%
Terminal Rates (c)	1/16 (6%)	0/16 (0%)	0/17 (0%)	0/9 (0%)
Week of First Observation	99		71	
Life Table Tests (d)	P=0.058N	P=0.067N	P=0.187N	P=0.137N
Incidental Tumor Tests (d)	P=0.040N	P=0.054N	P=0.190N	P=0.057N
Cochran-Armitage Trend Test (d)	P=0.039N			
Fisher Exact Test (d)		P=0.059N	P=0.181N	P=0.059N
Skin: Keratoacanthoma				
Overall Rates (a)	2/50 (4%)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	12.5%	9.1%	0.0%	21.2%
Terminal Rates (c)	2/16 (13%)	1/16 (6%)	0/17 (0%)	0/9 (0%)
Week of First Observation	104	92		101
Life Table Tests (d)	P=0.268	P=0.693N	P=0.223N	P=0.303
Incidental Tumor Tests (d)	P=0.395	P=0.696	P=0.223N	P=0.453
Cochran-Armitage Trend Test (d)	P=0.423			
Fisher Exact Test (d)		P=0.691	P=0.247N	P=0.500
Subcutaneous Tissue: Fibroma				
Overall Rates (a)	1/50 (2%)	1/50 (2%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	6.3%	6.3%	9.2%	19.5%
Terminal Rates (c)	1/16 (6%)	1/16 (6%)	1/17 (6%)	0/9 (0%)
Week of First Observation	104	104	96	89
Life Table Tests (d)	P=0.024	P=0.764	P=0.523	P=0.095
Incidental Tumor Tests (d)	P=0.064	P=0.764	P=0.505	P=0.204
Cochran-Armitage Trend Test (d)	P=0.072			
Fisher Exact Test (d)		P=0 753	P=0.500	P=0.181
Subcutaneous Tissue: Fibroma or Sarcoma				
Overall Rates (a)	1/50 (2%)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	6.3%	6.3%	9.2%	22.7%
Terminal Rates (c)	1/16 (6%)	1/16 (6%)	1/17 (6%)	0/9 (0%)
Week of First Observation	104	104	96	89
Life Table Tests (d)	P=0.008	P=0.764	P=0.523	P=0.050
Incidental Tumor Tests (d)	P=0.026	P=0.764	P=0.505	P=0.125
Cochran-Armitage Trend Test (d)	P=0.029			
Fisher Exact Test (d)		P=0.753	P=0.500	P=0.102
Hematopoietic System: Mononuclear Cell Leukemia				
Overall Rates (a)	34/50 (68%)	26/50 (52%)	32/50 (64%)	35/50 (70%)
Adjusted Rates (b)	80.3%	77.0%	80.2%	89.4%
Terminal Rates (c)	8/16 (50%)	9/16 (56%)	10/17 (59%)	6/9 (67%)
Week of First Observation	57	82	71	75
Life Table Tests (d)	P=0.045	P=0.147N	P=0.400N	P=0.134
Incidental Tumor Tests (d)	P=0.399	P=0.049N	P=0.434N	P=0.487N
Cochran-Armitage Trend Test (d)	P=0.251			
Fisher Exact Test (d)		P=0.076N	P=0.417N	P=0.500
Liver: Neoplastic Nodule or Hepatocellular Carcinoma				
Overall Rates (a)	2/50 (4%)	2/49 (4%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	5.5%	8.7%	19.0%	2.3%
Terminal Rates (c)	0/16 (0%)	1/16 (6%)	2/17 (12%)	0/9 (0%)
Week of First Observation	86	88	96	79
Life Table Tests (d)	P=0.555N	P=0.677N	P=0.357	P=0.523N
Incidental Tumor Tests (d)	P=0.401N	P=0.697	P=0.336	P=0.366N
Cochran-Armitage Trend Test (d)	P=0.428N			
Fisher Exact Test (d)		P=0.684	P=0.339	P=0.500N

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

	Control	1,000 ppm	2,000 ppm	4,000 ppm
Pituitary: Adenoma				
Overall Rates (a)	20/50 (40%)	31/47 (66%)	27/49 (55%)	24/49 (49%)
Adjusted Rates (b)	67.2%	87.4%	81.9%	79.8%
Terminal Rates (c)	8/16 (50%)	12/16 (75%)	12/17 (71%)	5/9 (56%)
Week of First Observation	70	67	70	62
Life Table Tests (d)	P=0.078	P=0.057	P=0.190	P=0.063
Incidental Tumor Tests (d)	P=0.363	P=0.013	P=0.101	P=0.207
Cochran-Armitage Trend Test (d)	P=0.437			
Fisher Exact Test (d)		P=0.009	P=0.096	P=0.243
Pituitary: Adenoma or Carcinoma				
Overall Rates (a)	20/50 (40%)	32/47 (68%)	27/49 (55%)	24/49 (49%)
Adjusted Rates (b)	67.2%	87.6%	81.9%	79.8%
Terminal Rates (c)	8/16 (50%)	12/16 (75%)	12/17 (71%)	5/9 (56%)
Week of First Observation	70	62	70	62
Life Table Tests (d)	P=0.089	P=0.043	P=0.190	P=0.063
Incidental Tumor Tests (d)	P=0.383	P=0.007	P=0.101	P=0.207
Cochran-Armitage Trend Test (d)	P=0.466			
Fisher Exact Test (d)		P=0.005	P=0.096	P=0.243
Adrenal: Pheochromocytoma				
Overall Rates (a)	5/50 (10%)	11/50 (22%)	10/50 (20%)	10/50 (20%)
Adjusted Rates (b)	23.5%	46.4%	45.4%	52.9%
Terminal Rates (c)	2/16 (13%)	5/16 (31%)	6/17 (35%)	3/9 (33%)
Week of First Observation	75	89	89	80
Life Table Tests (d)	P=0.035	P=0.094	P=0.149	P=0.039
Incidental Tumor Tests (d)	P=0.131	P=0.093	P=0.131	P=0.108
Cochran-Armitage Trend Test (d)	P=0.192			
Fisher Exact Test (d)		P=0.086	P=0.131	P=0.131
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates (a)	5/50 (10%)	11/50 (22%)	11/50 (22%)	10/50 (20%)
Adjusted Rates (b)	23.5%	46.4%	47.0%	52.9%
Terminal Rates (c)	2/16 (13%)	5/16 (31%)	6/17 (35%)	3/9 (33%)
Week of First Observation	75	89	89	80
Life Table Tests (d)	P=0.034	P=0.094	P=0.104	P=0.039
Incidental Tumor Tests (d)	P=0.134	P=0.093	P=0.087	P=0.108
Cochran-Armitage Trend Test (d)	P=0.186			
Fisher Exact Test (d)		P=0.086	P=0.086	P=0.131
Thyroid: C-Cell Adenoma				
Overall Rates (a)	1/49 (2%)	3/48 (6%)	6/49 (12%)	2/50 (4%)
Adjusted Rates (b)	2.4%	16.5%	28.8%	4.6%
Terminal Rates (c)	0/16 (0%)	2/16 (13%)	4/17 (24%)	0/9 (0%)
Week of First Observation	81	101	94	79
Life Table Tests (d)	P=0.253	P=0.313	P=0.067	P=0.500
Incidental Tumor Tests (d)	P=0.388	P=0.306	P=0.061	P=0.661
Cochran-Armitage Trend Test (d)	P=0.435			
Fisher Exact Test (d)		P=0.301	P=0.056	P=0.508
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	2/49 (4%)	4/48 (8%)	7/49 (14%)	2/50 (4%)
Adjusted Rates (b)	6.1%	19.0%	30.7%	4.6%
Terminal Rates (c)	0/16 (0%)	2/16 (13%)	4/17 (24%)	0/9 (0%)
Week of First Observation	81	92	88	79
Life Table Tests (d)	P=0.413	P=0.351	P=0.098	P=0.664
Incidental Tumor Tests (d)	P=0.530N	P=0.337	P=0.082	P=0.546N
Cochran-Armitage Trend Test (d)	P=0.537N			
Fisher Exact Test (d)		P=0.329	P=0.080	P=0.684N

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

	Control	1,000 ppm	2,000 ppm	4,000 ppm
Pancreatic Islets: Islet Cell Adenoma				
Overall Rates (a)	3/48 (6%)	6/46 (13%)	2/48 (4%)	2/48 (4%)
Adjusted Rates (b)	15.2%	26.0%	11.8%	8.7%
Terminal Rates (c)	2/16 (13%)	2/16 (13%)	2/17 (12%)	0/9 (0%)
Week of First Observation	92	88	104	78
Life Table Tests (d)	P=0.398N	P=0.258	P=0.475N	P=0.635N
Incidental Tumor Tests (d)	P=0.287N	P=0.247	P=0.485N	P=0.561N
Cochran-Armitage Trend Test (d)	P=0.228N			
Fisher Exact Test (d)		P=0.222	P=0.500N	P=0.500N
Pancreatic Islets: Islet Cell Adenoma or Carcinoma				
Overall Rates (a)	3/48 (6%)	7/46 (15%)	2/48 (4%)	2/48 (4%)
Adjusted Rates (b)	15.2%	31.3%	11.8%	8.7%
Terminal Rates (c)	2/16 (13%)	3/16 (19%)	2/17 (12%)	0/9 (0%)
Week of First Observation	92	88	104	78
Life Table Tests (d)	P=0.364N	P=0.171	P=0.475N	P=0.635N
Incidental Tumor Tests (d)	P=0.261N	P=0.162	P=0.485N	P=0.561N
Cochran-Armitage Trend Test (d)	P=0.194N			
Fisher Exact Test (d)		P=0.141	P=0.500N	P=0.500N
Mammary Gland: Fibroadenoma				
Overall Rates (a)	0/50 (0%)	0/50 (0%)	2/50 (4%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	11.8%	34.0%
Terminal Rates (c)	0/16 (0%)	0/16 (0%)	2/17 (12%)	2/9 (22%)
Week of First Observation			104	101
Life Table Tests (d)	P<0.001	(e)	P=0.250	P=0.020
Incidental Tumor Tests (d)	P=0.003	(e)	P=0.250	P=0.040
Cochran-Armitage Trend Test (d)	P=0.009			
Fisher Exact Test (d)		(e)	P=0.247	P=0.059
Mammary Gland: Adenoma or Fibroadenoma				
Overall Rates (a)	0/50 (0%)	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	0.0%	0.0%	11.8%	36.6%
Terminal Rates (c)	0/16 (0%)	0/16 (0%)	2/17 (12%)	2/9 (22%)
Week of First Observation			104	93
Life Table Tests (d)	P<0.001	(e)	P=0.250	P=0.010
Incidental Tumor Tests (d)	P<0.001	(e)	P=0.250	P=0.023
Cochran-Armitage Trend Test (d)	P=0.003			
Fisher Exact Test (d)		(e)	P=0.247	P=0.028
Mammary Gland or Subcutaneous Tissue: Adenoma, Fibroadenoma, or Fibroma				
Overall Rates (a)	1/50 (2%)	1/50 (2%)	4/50 (8%)	9/50 (18%)
Adjusted Rates (b)	6.3%	6.3%	20.6%	49.0%
Terminal Rates (c)	1/16 (6%)	1/16 (6%)	3/17 (18%)	2/9 (22%)
Week of First Observation	104	104	96	89
Life Table Tests (d)	P<0.001	P=0.764	P=0.196	P=0.002
Incidental Tumor Tests (d)	P=0.003	P=0.764	P=0.186	P=0.008
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.753N	P=0.181	P=0.008
Preputial Gland: Carcinoma				
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	15.1%	3.0%	11.5%	13.9%
Terminal Rates (c)	2/16 (13%)	0/16 (0%)	1/17 (6%)	1/9 (11%)
Week of First Observation	91	92	84	89
Life Table Tests (d)	P=0.522	P=0.304N	P=0.641N	P=0.678N
Incidental Tumor Tests (d)	P=0.527N	P=0.305N	P=0.654N	P=0.588N
Cochran-Armitage Trend Test (d)	P=0.523N			
Fisher Exact Test (d)		P=0.309N	P=0.661	P=0.500N

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

	Control	1,000 ppm	2,000 ppm	4,000 ppm
Preputial Gland: Adenoma or Carcinoma				
Overall Rates (a)	3/50 (6%)	1/50 (2%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	15.1%	3.0%	11.5%	35.4%
Terminal Rates (c)	2/16 (13%)	0/16 (0%)	1/17 (6%)	3/9 (33%)
Week of First Observation	91	92	84	89
Life Table Tests (d)	P=0.139	P=0.304N	P=0.641N	P=0.262
Incidental Tumor Tests (d)	P=0.235	P=0.305N	P=0.654N	P=0.334
Cochran-Armitage Trend Test (d)	P=0.282			
Fisher Exact Test (d)		P=0.309N	P=0.661	P=0.500
Testis: Interstitial Cell Tumor				
Overall Rates (a)	39/50 (78%)	37/49 (76%)	41/50 (82%)	43/50 (86%)
Adjusted Rates (b)	94.9%	97.3%	95.2%	97.7%
Terminal Rates (c)	14/16 (88%)	15/16 (94%)	15/17 (88%)	8/9 (89%)
Week of First Observation	65	69	75	75
Life Table Tests (d)	P=0.009	P=0.420N	P=0.512	P=0.029
Incidental Tumor Tests (d)	P=0.114	P=0.385N	P=0.387	P=0.258
Cochran-Armitage Trend Test (d)	P=0.129			
Fisher Exact Test (d)		P=0.478N	P=0.401	P=0.218
Tunica Vaginalis: Malignant Mesothelioma				
Overall Rates (a)	0/50 (0%)	1/50 (2%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	2.2%	0.0%	19.6%
Terminal Rates (c)	0/16 (0%)	0/16 (0%)	0/17 (0%)	0/9 (0%)
Week of First Observation		69		92
Life Table Tests (d)	P=0.025	P=0.496	(e)	P=0.068
Incidental Tumor Tests (d)	P=0.060	P=0.473	(e)	P=0.172
Cochran-Armitage Trend Test (d)	P=0.044			
Fisher Exact Test (d)		P=0.500	(e)	P=0.121
Tunica Vaginalis: Mesothelioma (All Types)				
Overall Rates (a)	0/50 (0%)	1/50 (2%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	0.0%	2.2%	19.2%	24.4%
Terminal Rates (c)	0/16 (0%)	0/16 (0%)	2/17 (12%)	0/9 (0%)
Week of First Observation		69	96	92
Life Table Tests (d)	P=0.009	P=0.496	P=0.070	P=0.031
Incidental Tumor Tests (d)	P=0.030	P=0.473	P=0.062	P=0.097
Cochran-Armitage Trend Test (d)	P=0.029			
Fisher Exact Test (d)		P=0.500	P=0.059	P=0.059
All Sites: Malignant Mesothelioma				
Overall Rates (a)	0/50 (0%)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	4.4%	0.0%	19.6%
Terminal Rates (c)	0/16 (0%)	0/16 (0%)	0/17 (0%)	0/9 (0%)
Week of First Observation		69		92
Life Table Tests (d)	P=0.066	P=0.243	(e)	P=0.068
Incidental Tumor Tests (d)	P=0.136	P=0.225	(e)	P=0.172
Cochran-Armitage Trend Test (d)	P=0.097			
Fisher Exact Test (d)		P=0.247	(e)	P=0.121
All Sites: Mesothelioma (All Types)				
Overall Rates (a)	0/50 (0%)	2/50 (4%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	0.0%	4.4%	22.8%	24.4%
Terminal Rates (c)	0/16 (0%)	0/16 (0%)	2/17 (12%)	0/9 (0%)
Week of First Observation		69	96	92
Life Table Tests (d)	P=0.020	P=0.243	P=0.038	P=0.031
Incidental Tumor Tests (d)	P=0.063	P=0.225	P=0.030	P=0.097
Cochran-Armitage Trend Test (d)	P=0.052			
Fisher Exact Test (d)		P=0.247	P=0.028	P=0.059

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

(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 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 controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the dosed and control groups

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE

	Control	1,000 ppm	2,000 ppm	4,000 ppm
Hematopoietic System: Mononuclear Cell Leukemia				
Overall Rates (a)	17/50 (34%)	17/50 (34%)	23/50 (46%)	23/50 (46%)
Adjusted Rates (b)	41.1%	44.4%	63.6%	58.1%
Terminal Rates (c)	8/30 (27%)	4/22 (18%)	10/22 (45%)	1/15 (7%)
Week of First Observation	73	76	73	63
Life Table Tests (d)	P=0.009	P=0.402	P=0.049	P=0.028
Incidental Tumor Tests (d)	P=0.273	P=0.425N	P=0.189	P=0.579
Cochran-Armitage Trend Test (d)	P=0.086			
Fisher Exact Test (d)		P=0.584N	P=0.154	P=0.154
Liver: Neoplastic Nodule				
Overall Rates (a)	2/50 (4%)	1/50 (2%)	3/50 (6%)	5/50 (10%)
Adjusted Rates (b)	6.7%	2.0%	10.2%	19.6%
Terminal Rates (c)	2/30 (7%)	0/22 (0%)	1/22 (5%)	1/15 (7%)
Week of First Observation	104	61	85	73
Life Table Tests (d)	P=0.030	P=0.569N	P=0.382	P=0.080
Incidental Tumor Tests (d)	P=0.097	P=0.494N	P=0.482	P=0.229
Cochran-Armitage Trend Test (d)	P=0.078			
Fisher Exact Test (d)		P=0.500N	P=0.500	P=0.218
Liver: Neoplastic Nodule or Hepatocellular Carcinoma				
Overall Rates (a)	2/50 (4%)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	6.7%	2.0%	14.4%	19.6%
Terminal Rates (c)	2/30 (7%)	0/22 (0%)	2/22 (9%)	1/15 (7%)
Week of First Observation	104	61	85	73
Life Table Tests (d)	P=0.027	P=0.569N	P=0.223	P=0.080
Incidental Tumor Tests (d)	P=0.086	P=0.494N	P=0.297	P=0.229
Cochran-Armitage Trend Test (d)	P=0.079			
Fisher Exact Test (d)		P=0.500N	P=0.339	P=0.218
Pituitary: Adenoma				
Overall Rates (a)	24/49 (49%)	30/49 (61%)	25/49 (51%)	25/49 (51%)
Adjusted Rates (b)	62.1%	82.2%	76.2%	83.5%
Terminal Rates (c)	16/30 (53%)	16/22 (73%)	14/21 (67%)	11/15 (73%)
Week of First Observation	73	74	72	75
Life Table Tests (d)	P=0.027	P=0.033	P=0.104	P=0.020
Incidental Tumor Tests (d)	P=0.380	P=0.138	P=0.374	P=0.288
Cochran-Armitage Trend Test (d)	P=0.461N			
Fisher Exact Test (d)		P=0.155	P=0.500	P=0.500
Pituitary: Adenoma or Carcinoma				
Overall Rates (a)	25/49 (51%)	30/49 (61%)	27/49 (55%)	25/49 (51%)
Adjusted Rates (b)	64.8%	82.2%	80.4%	83.5%
Terminal Rates (c)	17/30 (57%)	16/22 (73%)	15/21 (71%)	11/15 (73%)
Week of First Observation	73	74	72	75
Life Table Tests (d)	P=0.030	P=0.045	P=0.065	P=0.026
Incidental Tumor Tests (d)	P=0.416	P=0.179	P=0.277	P=0.338
Cochran-Armitage Trend Test (d)	P=0.414N			
Fisher Exact Test (d)		P=0.208	P=0.420	P=0.580
Adrenal: Pheochromocytoma				
Overall Rates (a)	2/50 (4%)	1/50 (2%)	4/49 (8%)	1/49 (2%)
Adjusted Rates (b)	5.9%	2.9%	19.0%	6.7%
Terminal Rates (c)	1/30 (3%)	0/22 (0%)	4/21 (19%)	1/15 (7%)
Week of First Observation	93	94	104	104
Life Table Tests (d)	P=0.465	P=0.545N	P=0.195	P=0.683N
Incidental Tumor Tests (d)	P=0.551	P=0.393N	P=0.210	P=0.581N
Cochran-Armitage Trend Test (d)	P=0.510N			
Fisher Exact Test (d)		P=0.500N	P=0.329	P=0.508N

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

	Control	1,000 ppm	2,000 ppm	4,000 ppm
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant				
Overall Rates (a)	2/50 (4%)	3/50 (6%)	4/49 (8%)	1/49 (2%)
Adjusted Rates (b)	5.9%	8.9%	19.0%	6.7%
Terminal Rates (c)	1/30 (3%)	0/22 (0%)	4/21 (19%)	1/15 (7%)
Week of First Observation	93	89	104	104
Life Table Tests (d)	P=0.578	P=0.447	P=0.195	P=0.683N
Incidental Tumor Tests (d)	P=0.455N	P=0.639	P=0.210	P=0.581N
Cochran-Armitage Trend Test (d)	P=0.381N			
Fisher Exact Test (d)		P=0.500	P=0.329	P=0.508N
Thyroid: C-Cell Adenoma				
Overall Rates (a)	2/47 (4%)	0/46 (0%)	4/48 (8%)	2/42 (5%)
Adjusted Rates (b)	6.4%	0.0%	18.2%	7.8%
Terminal Rates (c)	1/27 (4%)	0/21 (0%)	4/22 (18%)	0/11 (0%)
Week of First Observation	96		104	91
Life Table Tests (d)	P=0.172	P=0.281N	P=0.243	P=0.512
Incidental Tumor Tests (d)	P=0.279	P=0.205N	P=0.250	P=0.633N
Cochran-Armitage Trend Test (d)	P=0.359			
Fisher Exact Test (d)		P=0.253N	P=0.349	P=0.648
Thyroid: C-Cell Carcinoma				
Overall Rates (a)	3/47 (6%)	0/46 (0%)	2/48 (4%)	2/42 (5%)
Adjusted Rates (b)	11.1%	0.0%	7.3%	11.8%
Terminal Rates (c)	3/27 (11%)	0/21 (0%)	1/22 (5%)	1/11 (9%)
Week of First Observation	104		86	90
Life Table Tests (d)	P=0.393	P=0.167N	P=0.591N	P=0.541
Incidental Tumor Tests (d)	P=0.469	P=0.167N	P=0.542N	P=0.598
Cochran-Armitage Trend Test (d)	P=0.590			
Fisher Exact Test (d)		P=0.125N	P=0.490N	P=0.554N
Thyroid: C-Cell Adenoma or Carcinoma				
Overall Rates (a)	5/47 (11%)	0/46 (0%)	6/48 (13%)	4/42 (10%)
Adjusted Rates (b)	17.2%	0.0%	24.9%	18.8%
Terminal Rates (c)	4/27 (15%)	0/21 (0%)	5/22 (23%)	1/11 (9%)
Week of First Observation	96		86	90
Life Table Tests (d)	P=0.138	P=0.056N	P=0.356	P=0.395
Incidental Tumor Tests (d)	P=0.245	P=0.040N	P=0.395	P=0.625
Cochran-Armitage Trend Test (d)	P=0.384			
Fisher Exact Test (d)		P=0.030N	P=0.515	P=0.572N
Pancreatic Islets: Islet Cell Adenoma				
Overall Rates (a)	3/50 (6%)	0/48 (0%)	0/50 (0%)	0/46 (0%)
Adjusted Rates (b)	10.0%	0.0%	0.0%	0.0%
Terminal Rates (c)	3/30 (10%)	0/22 (0%)	0/22 (0%)	0/15 (0%)
Week of First Observation	104			
Life Table Tests (d)	P=0.086N	P=0.180N	P=0.180N	P=0.265N
Incidental Tumor Tests (d)	P=0.086N	P=0.180N	P=0.180N	P=0.265N
Cochran-Armitage Trend Test (d)	P=0.050N			
Fisher Exact Test (d)		P=0.129N	P=0.121N	P=0.137N
Mammary Gland: Fibroadenoma				
Overall Rates (a)	5/50 (10%)	11/50 (22%)	13/50 (26%)	22/50 (44%)
Adjusted Rates (b)	15.7%	41.2%	43.6%	79.4%
Terminal Rates (c)	4/30 (13%)	8/22 (36%)	7/22 (32%)	10/15 (67%)
Week of First Observation	96	74	65	73
Life Table Tests (d)	P<0.001	P=0.028	P=0.009	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.049	P=0.025	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.086	P=0.033	P<0.001

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

	Control	1,000 ppm	2,000 ppm	4,000 ppm
Mammary Gland: Adenoma or Fibroadenoma				
Overall Rates (a)	5/50 (10%)	11/50 (22%)	13/50 (26%)	23/50 (46%)
Adjusted Rates (b)	15.7%	41.2%	43.6%	83.5%
Terminal Rates (c)	4/30 (13%)	8/22 (36%)	7/22 (32%)	11/15 (73%)
Week of First Observation	96	74	65	73
Life Table Tests (d)	P<0.001	P=0.028	P=0.009	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.049	P=0.025	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.086	P=0.033	P<0.001
Mammary Gland: Adenoma, Fibroadenoma, or Adenocarcinoma				
Overall Rates (a)	6/50 (12%)	13/50 (26%)	14/50 (28%)	23/50 (46%)
Adjusted Rates (b)	17.8%	44.4%	44.9%	83.5%
Terminal Rates (c)	4/30 (13%)	8/22 (36%)	7/22 (32%)	11/15 (73%)
Week of First Observation	92	74	65	73
Life Table Tests (d)	P<0.001	P=0.023	P=0.012	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.053	P=0.043	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.062	P=0.039	P<0.001
Mammary Gland: Adenoma, Fibroadenoma, Adenocarcinoma, or Mixed Tumor, Malignant				
Overall Rates (a)	7/50 (14%)	13/50 (26%)	(e) 14/50 (28%)	23/50 (46%)
Adjusted Rates (b)	20.0%	44.4%	44.9%	83.5%
Terminal Rates (c)	4/30 (13%)	8/22 (36%)	7/22 (32%)	11/15 (73%)
Week of First Observation	92	74	65	73
Life Table Tests (d)	P<0.001	P=0.045	P=0.022	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.092	P=0.083	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.105	P=0.070	P<0.001
Clitoral Gland: Cystadenoma or Carcinoma				
Overall Rates (a)	1/50 (2%)	2/50 (4%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	2.5%	9.1%	8.5%	14.2%
Terminal Rates (c)	0/30 (0%)	2/22 (9%)	1/22 (5%)	1/15 (7%)
Week of First Observation	92	104	101	80
Life Table Tests (d)	P=0.101	P=0.423	P=0.399	P=0.181
Incidental Tumor Tests (d)	P=0.212	P=0.428	P=0.507	P=0.383
Cochran-Armitage Trend Test (d)	P=0.232			
Fisher Exact Test (d)		P=0.500	P=0.500	P=0.309
Uterus: Endometrial Stromal Polyp				
Overall Rates (a)	7/50 (14%)	9/49 (18%)	7/50 (14%)	6/47 (13%)
Adjusted Rates (b)	18.1%	32.0%	21.7%	33.2%
Terminal Rates (c)	2/30 (7%)	5/21 (24%)	2/22 (9%)	4/15 (27%)
Week of First Observation	73	74	76	89
Life Table Tests (d)	P=0.413	P=0.253	P=0.455	P=0.377
Incidental Tumor Tests (d)	P=0.381N	P=0.530	P=0.519N	P=0.513N
Cochran-Armitage Trend Test (d)	P=0.399N			
Fisher Exact Test (d)		P=0.376	P=0.613	P=0.548N
Uterus: Endometrial Stromal Sarcoma				
Overall Rates (a)	0/50 (0%)	3/49 (6%)	1/50 (2%)	2/47 (4%)
Adjusted Rates (b)	0.0%	7.4%	2.0%	5.0%
Terminal Rates (c)	0/30 (0%)	0/21 (0%)	0/22 (0%)	0/15 (0%)
Week of First Observation		74	62	59
Life Table Tests (d)	P=0.296	P=0.119	P=0.504	P=0.218
Incidental Tumor Tests (d)	P=0.494	P=0.255	P=0.695	P=0.361
Cochran-Armitage Trend Test (d)	P=0.317			
Fisher Exact Test (d)		P=0.117	P=0.500	P=0.232

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

(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 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 controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) A carcinoma was also present in one of the animals that had a fibroadenoma.

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE

	Control	2,000 ppm	4,000 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/50 (6%)	19/50 (38%)	24/50 (48%)
Adjusted Rates (b)	7.7%	55.6%	78.5%
Terminal Rates (c)	3/39 (8%)	10/24 (42%)	6/11 (55%)
Week of First Observation	104	71	70
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	2/50 (4%)	10/50 (20%)	28/50 (56%)
Adjusted Rates (b)	4.9%	34.0%	92.9%
Terminal Rates (c)	1/39 (3%)	6/24 (25%)	9/11 (82%)
Week of First Observation	94	78	72
Life Table Tests (d)	P<0.001	P=0.002	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.016	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.014	P<0.001
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	27/50 (54%)	40/50 (80%)
Adjusted Rates (b)	12.4%	74.2%	100.0%
Terminal Rates (c)	4/39 (10%)	15/24 (63%)	11/11 (100%)
Week of First Observation	94	71	70
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	5/50 (10%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	12.1%	10.4%	6.5%
Terminal Rates (c)	4/39 (10%)	2/24 (8%)	0/11 (0%)
Week of First Observation	71	76	90
Life Table Tests (d)	P=0.511N	P=0.573N	P=0.604N
Incidental Tumor Tests (d)	P=0.301N	P=0.482N	P=0.365N
Cochran-Armitage Trend Test (d)	P=0.158N		
Fisher Exact Test (d)		P=0.358N	P=0.218N
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	2.6%	7.6%	21.4%
Terminal Rates (c)	1/39 (3%)	1/24 (4%)	1/11 (9%)
Week of First Observation	104	101	70
Life Table Tests (d)	P=0.007	P=0.352	P=0.017
Incidental Tumor Tests (d)	P=0.083	P=0.495	P=0.142
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.102
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	2/50 (4%)	2/50 (4%)	6/50 (12%)
Adjusted Rates (b)	4.8%	7.6%	25.8%
Terminal Rates (c)	1/39 (3%)	1/24 (4%)	1/11 (9%)
Week of First Observation	87	101	70
Life Table Tests (d)	P=0.010	P=0.558	P=0.022
Incidental Tumor Tests (d)	P=0.170	P=0.643N	P=0.301
Cochran-Armitage Trend Test (d)	P=0.080		
Fisher Exact Test (d)		P=0.691	P=0.134

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

	Control	2,000 ppm	4,000 ppm
Liver: Hepatocellular Adenoma			
Overall Rates (a)	10/50 (20%)	14/49 (29%)	14/49 (29%)
Adjusted Rates (b)	23.0%	46.9%	68.3%
Terminal Rates (c)	7/39 (18%)	9/24 (38%)	6/11 (55%)
Week of First Observation	73	71	80
Life Table Tests (d)	P<0.001	P=0.041	P=0.001
Incidental Tumor Tests (d)	P=0.075	P=0.161	P=0.095
Cochran-Armitage Trend Test (d)	P=0.194		
Fisher Exact Test (d)		P=0.224	P=0.224
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	13/50 (26%)	15/49 (31%)	26/49 (53%)
Adjusted Rates (b)	29.7%	43.7%	76.4%
Terminal Rates (c)	9/39 (23%)	7/24 (29%)	5/11 (45%)
Week of First Observation	73	72	61
Life Table Tests (d)	P<0.001	P=0.111	P<0.001
Incidental Tumor Tests (d)	P=0.016	P=0.422	P=0.042
Cochran-Armitage Trend Test (d)	P=0.004		
Fisher Exact Test (d)		P=0.387	P=0.005
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	22/50 (44%)	24/49 (49%)	33/49 (67%)
Adjusted Rates (b)	48.3%	66.8%	93.0%
Terminal Rates (c)	16/39 (41%)	13/24 (54%)	9/11 (82%)
Week of First Observation	73	71	61
Life Table Tests (d)	P<0.001	P=0.048	P<0.001
Incidental Tumor Tests (d)	P=0.010	P=0.305	P=0.020
Cochran-Armitage Trend Test (d)	P=0.013		
Fisher Exact Test (d)		P=0.384	P=0.016
Testis: Interstitial Cell Tumor			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.7%	0.0%	0.0%
Terminal Rates (c)	3/39 (8%)	0/24 (0%)	0/11 (0%)
Week of First Observation	104		
Life Table Tests (d)	P=0.137N	P=0.219N	P=0.410N
Incidental Tumor Tests (d)	P=0.137N	P=0.219N	P=0.410N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	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 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 controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR INHALATION STUDY OF DICHLOROMETHANE

	Control	2,000 ppm	4,000 ppm
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/50 (4%)	23/48 (48%)	28/48 (58%)
Adjusted Rates (b)	6.7%	66.5%	91.1%
Terminal Rates (c)	1/25 (4%)	14/25 (56%)	6/8 (75%)
Week of First Observation	87	83	68
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	1/50 (2%)	13/48 (27%)	29/48 (60%)
Adjusted Rates (b)	4.0%	45.9%	92.2%
Terminal Rates (c)	1/25 (4%)	10/25 (40%)	6/8 (75%)
Week of First Observation	104	89	68
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	30/48 (63%)	41/48 (85%)
Adjusted Rates (b)	10.6%	82.9%	100.0%
Terminal Rates (c)	2/25 (8%)	19/25 (76%)	8/8 (100%)
Week of First Observation	87	83	68
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Hematopoietic System: Lymphoma, Histiocytic			
Overall Rates (a)	1/50 (2%)	2/49 (4%)	4/49 (8%)
Adjusted Rates (b)	4.0%	5.5%	16.2%
Terminal Rates (c)	1/25 (4%)	0/25 (0%)	0/8 (0%)
Week of First Observation	104	80	77
Life Table Tests (d)	P=0.054	P=0.525	P=0.078
Incidental Tumor Tests (d)	P=0.224	P=0.538	P=0.243
Cochran-Armitage Trend Test (d)	P=0.118		
Fisher Exact Test (d)		P=0.500	P=0.181
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	0/50 (0%)	4/49 (8%)	1/49 (2%)
Adjusted Rates (b)	0.0%	13.9%	4.5%
Terminal Rates (c)	0/25 (0%)	2/25 (8%)	0/8 (0%)
Week of First Observation		90	90
Life Table Tests (d)	P=0.160	P=0.072	P=0.425
Incidental Tumor Tests (d)	P=0.388	P=0.077	P=0.615
Cochran-Armitage Trend Test (d)	P=0.390		
Fisher Exact Test (d)		P=0.059	P=0.500
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	7/50 (14%)	7/49 (14%)	7/49 (14%)
Adjusted Rates (b)	22.9%	21.7%	28.0%
Terminal Rates (c)	4/25 (16%)	2/25 (8%)	0/8 (0%)
Week of First Observation	76	80	77
Life Table Tests (d)	P=0.201	P=0.573N	P=0.242
Incidental Tumor Tests (d)	P=0.416N	P=0.607N	P=0.553N
Cochran-Armitage Trend Test (d)	P=0.557		
Fisher Exact Test (d)		P=0.613	P=0.613

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

	Control	2,000 ppm	4,000 ppm
Liver: Hepatocellular Adenoma			
Overall Rates (a)	2/50 (4%)	6/48 (13%)	22/48 (46%)
Adjusted Rates (b)	6.5%	21.3%	83.0%
Terminal Rates (c)	1/25 (4%)	4/25 (16%)	5/8 (63%)
Week of First Observation	84	96	68
Life Table Tests (d)	P<0.001	P=0.151	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.155	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.121	P<0.001
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	1/50 (2%)	11/48 (23%)	32/48 (67%)
Adjusted Rates (b)	4.0%	34.0%	96.5%
Terminal Rates (c)	1/25 (4%)	6/25 (24%)	7/8 (88%)
Week of First Observation	104	83	68
Life Table Tests (d)	P<0.001	P=0.005	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.004	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.001	P<0.001
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	16/48 (33%)	40/48 (83%)
Adjusted Rates (b)	10.4%	48.0%	100.0%
Terminal Rates (c)	2/25 (8%)	9/25 (36%)	8/8 (100%)
Week of First Observation	84	83	68
Life Table Tests (d)	P<0.001	P=0.002	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.002	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Pituitary Gland: Adenoma			
Overall Rates (a)	4/46 (9%)	2/44 (5%)	1/44 (2%)
Adjusted Rates (b)	15.9%	8.3%	2.4%
Terminal Rates (c)	3/24 (13%)	2/24 (8%)	0/8 (0%)
Week of First Observation	99	104	77
Life Table Tests (d)	P=0.321N	P=0.333N	P=0.469N
Incidental Tumor Tests (d)	P=0.214N	P=0.300N	P=0.287N
Cochran-Armitage Trend Test (d)	P=0.128N		
Fisher Exact Test (d)		P=0.360N	P=0.195N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	1/48 (2%)	1/47 (2%)	4/46 (9%)
Adjusted Rates (b)	4.2%	4.0%	35.0%
Terminal Rates (c)	1/24 (4%)	1/25 (4%)	2/8 (25%)
Week of First Observation	104	104	77
Life Table Tests (d)	P=0.012	P=0.754N	P=0.022
Incidental Tumor Tests (d)	P=0.040	P=0.754N	P=0.069
Cochran-Armitage Trend Test (d)	P=0.093		
Fisher Exact Test (d)		P=0.747	P=0.168
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	2/50 (4%)	3/49 (6%)	0/49 (0%)
Adjusted Rates (b)	8.0%	9.5%	0.0%
Terminal Rates (c)	2/25 (8%)	1/25 (4%)	0/8 (0%)
Week of First Observation	104	88	
Life Table Tests (d)	P=0.390N	P=0.530	P=0.510N
Incidental Tumor Tests (d)	P=0.266N	P=0.530	P=0.510N
Cochran-Armitage Trend Test (d)	P=0.207N		
Fisher Exact Test (d)		P=0.490	P=0.253N

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

(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 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 controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE RECEIVING NO TREATMENT

TABLE F1. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Leukemia in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
Propylene oxide	20/50
Propylene	16/50
TOTAL	36/100 (36.0%)
Overall Historical Incidence	
TOTAL	458/1,727 (26.5%)
SD (b)	8.83%
Range (c)	
High	23/50
Low	5/50

(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 F2. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	21/47	0/47	21/47
Propylene	12/46	0/46	12/46
TOTAL	33/93 (35.5%)	0/93 (0.0%)	33/93 (35.5%)
Overall Historical Incidence			
TOTAL	325/1,614 (20.1%)	38/1,614 (2.4%)	363/1,614 (22.5%)
SD (b)	11.14%	3.04%	10.98%
Range (c)			
High	24/46	5/45	25/46
Low	2/39	0/50	2/39

(a) Data as of August 3, 1984, for studies of at least 104 weeks. Data includes all diagnoses of tumors designated NOS, chromophobe, acidophil, or basophil; adenocarcinomas are grouped with carcinomas.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F3. HISTORICAL INCIDENCE OF ADRENAL GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Pheochromocytoma	Malignant Pheochromocytoma	Pheochromocytoma or Malignant Pheochromocytoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	3/48	0/48	3/48
Propylene	3/50	2/50	5/50
TOTAL	6/98 (6.1%)	2/98 (2.0%)	8/98 (8.2%)
Overall Historical Incidence			
TOTAL	338/1,702 (19.9%)	20/1,702 (1.2%)	358/1,702 (21.0%)
SD (b)	9.87%	1.49%	9.63%
Range (c)			
High	20/49	3/48	21/49
Low	2/50	0/50	3/50

(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 F4. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Fibroadenoma	Adenocarcinoma	Fibroadenoma or Adenocarcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	0/50	0/50	0/50
Propylene	0/50	1/50	1/50
TOTAL	0/100 (0.0%)	1/100 (1.0%)	1/100 (1.0%)
Overall Historical Incidence			
TOTAL	(b) 51/1,727 (3.0%)	(c) 3/1,727 (0.2%)	54/1,727 (3.1%)
SD (d)	2.98%	0.58%	3.02%
Range (e)			
High	6/49	1/50	6/49
Low	0/50	0/90	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes three diagnoses of adenoma, NOS
(c) Includes one diagnosis of carcinoma, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE F5. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM FIBROMAS OR FIBROSARCOMAS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Fibroma	Fibrosarcoma	Fibroma or Fibrosarcoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	3/50	0/50	3/50
Propylene	3/50	0/50	3/50
TOTAL	6/100 (6.0%)	0/100 (0.0%)	6/100 (6.0%)
Overall Historical Incidence			
TOTAL	(b) 91/1,727 (5.3%)	(c) 20/1,727 (1.2%)	(d) 110/1,727 (6.4%)
SD (e)	3.18%	1.40%	3.32%
Range (f)			
High	6/50	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) Includes two fibroadenomas of the mammary gland and three integumentary system neurofibromas
(c) Includes two neurofibrosarcomas
(d) Eight sarcomas, NOS, were also observed. The inclusion of these tumors would increase the high range to 7/50.
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE F6. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM PAPILLOMAS OR CARCINOMAS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	0/50	0/50	0/50
Propylene	0/50	0/50	0/50
TOTAL	0/100 (0.0%)	0/100 (0.0%)	0/100 (0.0%)
Overall Historical Incidence			
TOTAL	29/1,727 (1.7%)	15/1,727 (0.9%)	44/1,727 (2.5%)
SD (b)	1.63%	1.23%	1.82%
Range (c)			
High	2/40	2/50	3/50
Low	0/50	0/90	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 F7. HISTORICAL INCIDENCE OF TESTICULAR TUMORS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Interstitial Cell Tumors in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
Propylene oxide	29/49
Propylene	37/50
TOTAL	66/99 (66.7%)
Overall Historical Incidence	
TOTAL	(b) 1,511/1,703 (88.7%)
SD (c)	7.79%
Range (d)	
High	49/50
Low	34/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Total includes one interstitial cell tumor, malignant.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F8. HISTORICAL INCIDENCE OF MESOTHELIOMAS IN MALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Mesotheliomas in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
Propylene oxide	1/50
Propylene	3/50
TOTAL	(b) 4/100 (4.0%)
Overall Historical Incidence	
TOTAL	(c) 44/1,727 (2.5%)
SD (d)	2.35%
Range (e)	
High	5/50
Low	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) All designated NOS
(c) Includes 2 benign, 14 malignant, and 28 NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE F9. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence of Leukemia in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
Propylene oxide	14/50
Propylene	13/49
TOTAL	27/99 (27.3%)
Overall Historical Incidence	
TOTAL	307/1,772 (17.3%)
SD (b)	6.00%
Range (c)	
High	19/50
Low	3/50

(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 F10. HISTORICAL INCIDENCE OF LIVER TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Neoplastic Nodule	Hepatocellular Carcinoma	Neoplastic Nodule or Hepatocellular Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	1/50	0/50	1/50
Propylene	0/48	0/48	0/48
TOTAL	1/98 (1.0%)	0/98 (0.0%)	1/98 (1.0%)
Overall Historical Incidence			
TOTAL	46/1,766 (2.6%)	3/1,766 (0.2%)	48/1,766 (2.7%)
SD (b)	2.77%	0.75%	2.99%
Range (c)			
High	4/50	2/50	5/50
Low	0/50	0/88	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 F11. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Fibroadenoma	Adenocarcinoma	Fibroadenoma or Adenocarcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	7/50	1/50	8/50
Propylene	9/49	0/49	9/49
TOTAL	16/99 (16.2%)	1/99 (1.0%)	17/99 (17.2%)
Overall Historical Incidence			
TOTAL	(b) 492/1,772 (27.8%)	(c) 45/1,772 (2.5%)	520/1,772 (29.3%)
SD (d)	9.61%	2.45%	9.29%
Range (e)			
High	24/49	4/49	24/49
Low	5/50	0/50	6/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes 470 fibroadenomas. The remaining tumors include adenomas, NOS, cystadenomas, papillary cystadenomas, and cystfibroadenomas of the mammary gland and integumentary system fibroadenomas.
(c) Inlcudes one squamous cell carcinoma
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE F12. HISTORICAL INCIDENCE OF PITUITARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	25/48	0/48	25/48
Propylene	18/44	1/44	19/44
TOTAL	43/92 (46.7%)	1/92 (1.1%)	44/92 (47.8%)
Overall Historical Incidence			
TOTAL	743/1,704 (43.6%)	62/1,704 (3.6%)	805/1,704 (47.2%)
SD (b)	11.71%	4.24%	11.01%
Range (c)			
High	33/47	8/49	33/47
Low	7/39	0/50	9/39

(a) Data as of August 3, 1984, for studies of at least 104 weeks. Data includes all diagnoses of tumors designated NOS, chromophobe, acidophil, or basophil; adenocarcinomas are grouped with carcinomas.
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F13. HISTORICAL INCIDENCE OF THYROID GLAND C-CELL TUMORS IN FEMALE F344/N RATS RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	1/45	1/45	2/45
Propylene	5/39	1/39	6/39
TOTAL	6/84 (7.1%)	2/84 (2.4%)	8/84 (9.5%)
Overall Historical Incidence			
TOTAL	79/1,704 (4.6%)	61/1,704 (3.6%)	137/1,704 (8.0%)
SD (b)	4.08%	2.73%	4.52%
Range (c)			
High	6/49	5/50	9/50
Low	0/86	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 F14. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	14/50	2/50	15/50
Propylene	7/50	9/50	16/50
TOTAL	21/100 (21.0%)	11/100 (11.0%)	31/100 (31.0%)
Overall Historical Incidence			
TOTAL	215/1,780 (12.1%)	87/1,780 (4.9%)	296/1,780 (16.6%)
SD (b)	6.80%	4.06%	8.22%
Range (c)			
High	14/50	8/48	17/50
Low	1/50	0/50	1/49

(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.

TABLE F15. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Hemangiosarcoma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	0/50	2/50	2/50
Propylene	0/50	0/50	0/50
TOTAL	0/100 (0.0%)	2/100 (2.0%)	2/100 (2.0%)
Overall Historical Incidence			
TOTAL	23/1,791 (1.3%)	(b) 56/1,791 (3.1%)	78/1,791 (4.4%)
SD (c)	2.68%	2.53%	4.06%
Range (d)			
High	(e) 7/50	5/49	(f) 10/50
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes angiosarcoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Second highest incidence: 3/49
(f) Second highest incidence: 7/49

TABLE F16. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	8/50	6/50	14/50
Propylene	5/50	9/50	14/50
TOTAL	13/100 (13.0%)	15/100 (15.0%)	28/100 (28.0%)
Overall Historical Incidence			
TOTAL	179/1,784 (10.0%)	377/1,784 (21.1%)	540/1,784 (30.3%)
SD (b)	7.36%	6.54%	8.04%
Range (c)			
High	(d) 22/50	16/50	(e) 29/50
Low	0/49	4/50	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.
(d) Second highest incidence: 9/50
(e) Second highest incidence: 20/50

TABLE F17. HISTORICAL INCIDENCE OF TESTICULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

	Incidence of Interstitial Cell Tumors in Controls
Historical Incidence at Battelle Pacific Northwest Laboratories	
Propylene oxide	0/48
Propylene	2/50
TOTAL	2/98 (2.0%)
Overall Historical Incidence	
TOTAL	(b) 5/1,768 (0.3%)
SD (c)	0.71%
Range (d)	
High	1/48
Low	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) No malignant interstitial cell tumors were observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F18. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	4/50	0/50	4/50
Propylene	6/50	0/50	6/50
TOTAL	10/100 (10.0%)	0/100 (0.0%)	10/100 (10.0%)
Overall Historical Incidence			
TOTAL	87/1,777 (4.9%)	36/1,777 (2.0%)	122/1,777 (6.9%)
SD (b)	3.86%	1.98%	4.44%
Range (c)			
High	7/50	3/50	8/50
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 F19. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	1/50	2/50	3/50
Propylene	0/50	2/50	2/50
TOTAL	1/100 (1.0%)	4/100 (4.0%)	5/100 (5.0%)
Overall Historical Incidence			
TOTAL	68/1,781 (3.8%)	(b) 82/1,781 (4.6%)	147/1,781 (8.3%)
SD (c)	4.14%	3.08%	4.76%
Range (d)			
High	9/49	7/48	10/49
Low	0/50	0/50	0/50

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

TABLE F20. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING NO TREATMENT (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Battelle Pacific Northwest Laboratories			
Propylene oxide	1/45	0/45	1/45
Propylene	4/45	0/45	4/45
TOTAL	5/90 (5.6%)	0/90 (0.0%)	5/90 (5.6%)
Overall Historical Incidence			
TOTAL	(b) 36/1,661 (2.2%)	7/1,661 (0.4%)	43/1,661 (2.6%)
SD (c)	2.40%	1.21%	3.15%
Range (d)			
High	4/48	3/48	7/48
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes 34 follicular cell adenomas, one adenoma, NOS, and one papillary cystadenoma of the thyroid and two cystadenomas of the thyroid follicle.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

APPENDIX G

CHEMICAL CHARACTERIZATION OF DICHLOROMETHANE

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

A. Lot No. 766062

1. Physical Properties

	Determined	Literature Values
a. Boiling Point:	39° C (Dupont 900 DTA) 39.7° ± 0.1° C (at 736 mm, capillary)	39.75° C (Dreisbach, 1959)
b. Appearance:	Clear, colorless liquid	

2. Spectral Data

a. Infrared	Determined	Literature Values
Instrument:	Beckman IR-12	
Cell:	0.05 mm liquid cell, sodium chloride windows	
Results:	See Figure 5	Consistent with literature spectrum (Dreisbach, 1959)

b. Ultraviolet/Visible	Determined	Literature Values
Instrument:	Cary 118	
Solvent:	Neat liquid	
Results:	No absorbance between 350 and 800 nm. No maxima between 350 and 200 nm but a gradual increase in absorbance between 220 nm and the cutoff at 200 nm.	No literature reference found.

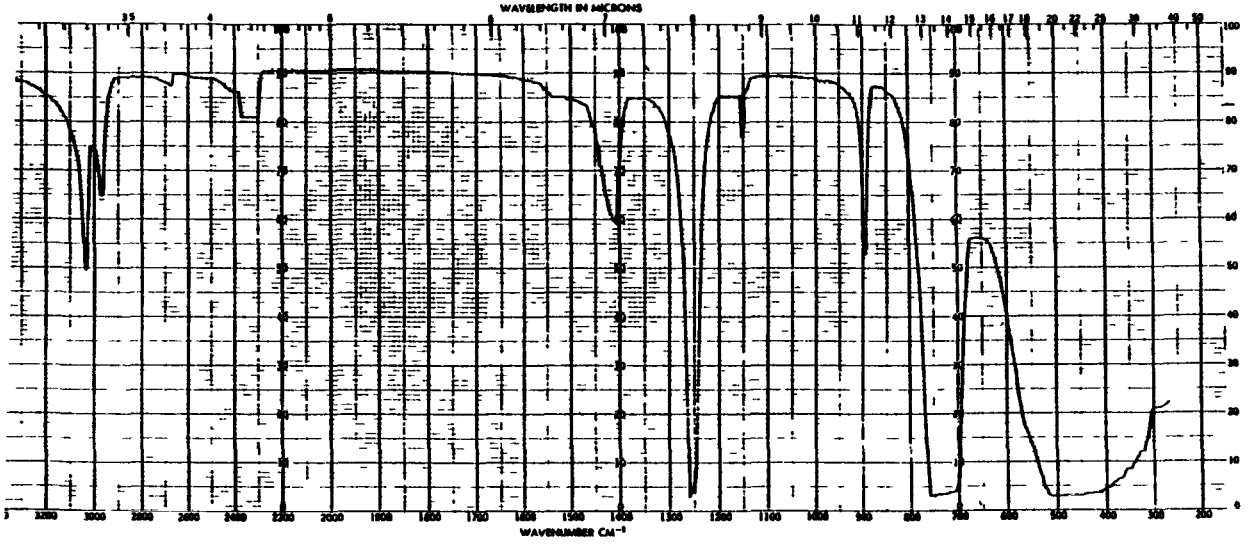

FIGURE 5. INFRARED ABSORPTION SPECTRUM OF DICHLOROMETHANE (LOT NO. 766062)

c. Nuclear Magnetic Resonance

	Determined	Literature Values
(1) Instrument:	Varian HA-100	
(2) Solvent:	Neat, tetramethyl-silane added	
(3) Assignments:	See Figure 6	Consistent with literature spectrum (Sadtler Standard Spectra)
(4) Chemical Shift (δ):	a s, 5.27 ppm	
(5) Integration Ratios:	a 2.00	

3. Water Analysis (Karl Fischer): 0.008% ± 0.002(δ)%

4. Elemental Analysis

Element	C	H	Cl
Theory	14.14	2.37	83.48
Determined	14.17	2.35	83.36
	14.19	2.40	83.40

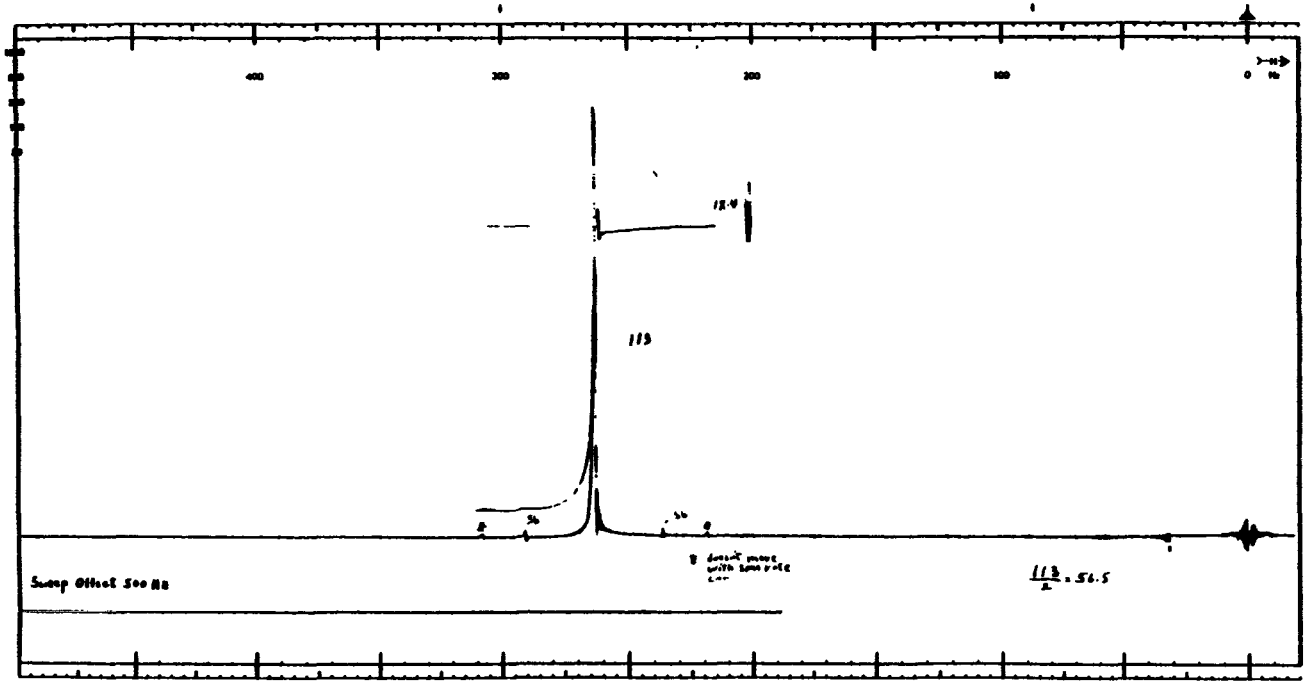

FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DICHLOROMETHANE (LOT NO. 766062)

5. Chromatographic Analysis: Gas Chromatography

Instrument: Tracor MT-220
Detector: Flame ionization
Inlet temperature: 225° C
Detector temperature: 300° C

a. Identification of Impurities

System 1

Column: Chromosorb 102, 100/120, 1.8 m × 4 mm ID, glass
Oven temperature program: 50° to 200° C at 10° C/minute

Results: Major peak only

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	11.33	1.00	100

System 2

Column: 10% Carbowax 20 M-TPA on 80/100 Chromosorb W(AW), 1.8 m × 4 mm ID, glass
Oven temperature program: 10 minutes at 50° C, then 50° to 200° C at 10° C/minute

Results: Major peak and one impurity.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.78	0.40	0.094
2	1.95	1.00	100

The sample was spiked with a small amount of vinylidene chloride, and peak no. 1 was enhanced.

b. Quantitation of Impurities

System 1

Column: 10% Carbowax 20 M-TPA on 80/100 Chromosorb W(AW), (1.8 m × 4mm ID)
Oven temperature: 50° C, isothermal

The first impurity peak was quantitated against a standard solution of vinylidene chloride, 0.05% (v/v) in *n*-butanol.

Concentration of vinylidene chloride in the sample: 0.044% ± 0.005(δ)%

During the analysis, another small impurity peak was observed just before the major peak (not detected in system 2 above because the injection volume was kept low to prevent detector overload). This impurity peak was enhanced when an aliquot of the dichloromethane sample was spiked with *trans*-1,2-dichloroethylene. It was quantitated by comparison with *trans*-dichloroethylene standard, 0.005% (v/v) in *n*-butanol.

Concentration of *trans*-1,2-dichloroethylene in the sample: 0.0016% ± 0.0002(δ)%

System 2

Column: Chromosorb 102, 100/120, 1.8 m × 4 mm, ID, glass
Oven temperature: 150° C, isothermal

A standard was injected containing 0.005% (v/v) carbon tetrachloride, 0.005% (v/v) 1,2-dichloroethane, and 0.015% (v/v) chloroform in pentane. These compounds had retention times of 9.4, 8.3, and 7.3 minutes, respectively. One microliter of the dichloromethane sample was injected under the same conditions.

The sample contained <0.005% carbon tetrachloride, <0.005% 1,2-dichloroethane, and <0.015% chloroform.

6. Conclusions: The results of elemental analysis agreed with theoretical values. Karl Fischer analysis indicated 0.008% water. Gas chromatography on Chromosorb 102 indicated only the major peak. Carbowax 20M-TPA showed one impurity in addition to the major peak; on overloading the major peak, another small impurity was found. The two impurities were identified as vinylidene chloride, 0.04%, and *trans*-1,2-dichloroethylene, 0.002%. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with those expected for the structure of dichloromethane.

B. Lot No. 767132

1. Physical Properties

a. Boiling Point:	**Determined** 40.9° C at 734 torr (visual, microboiling point); 41.5°-41.8° C (Dupont 900 DTA)	**Literature Values** 39.75° C (Dreisbach, 1959)
b. Index of Refraction:	**Determined**	**Literature Values**
	n_D^{20}: 1.424 ± 0.002(δ)	n_D^{20}: 1.4244 (Merck Index, 1976)
c. Density:	**Determined**	**Literature Values**
	d_{22}^{24}: 1.3201 ± 0.0005(δ) g/ml	d_4^{20}: 1.3255 g/ml (Merck Index, 1976)
d. Appearance:	Clear, colorless liquid	

2. Spectral Data

a. Infrared	**Determined**	**Literature Values**
Instrument:	Beckman IR-12	
Cell:	0.016 mm liquid cell, sodium chloride windows	
Results:	See Figure 7	Consistent with literature spectrum (Sadtler Standard Spectra)
b. Ultraviolet/Visible	**Determined**	**Literature Values**
Instrument:	Cary 118	
Solvent:	Methanol	
Concentration:	1%	
Results:	No absorbance between 350 and 800 nm. No maximum between 210 and 350 nm but a gradual increase in absorbance toward the solvent cutoff at 210 nm.	No literature reference found

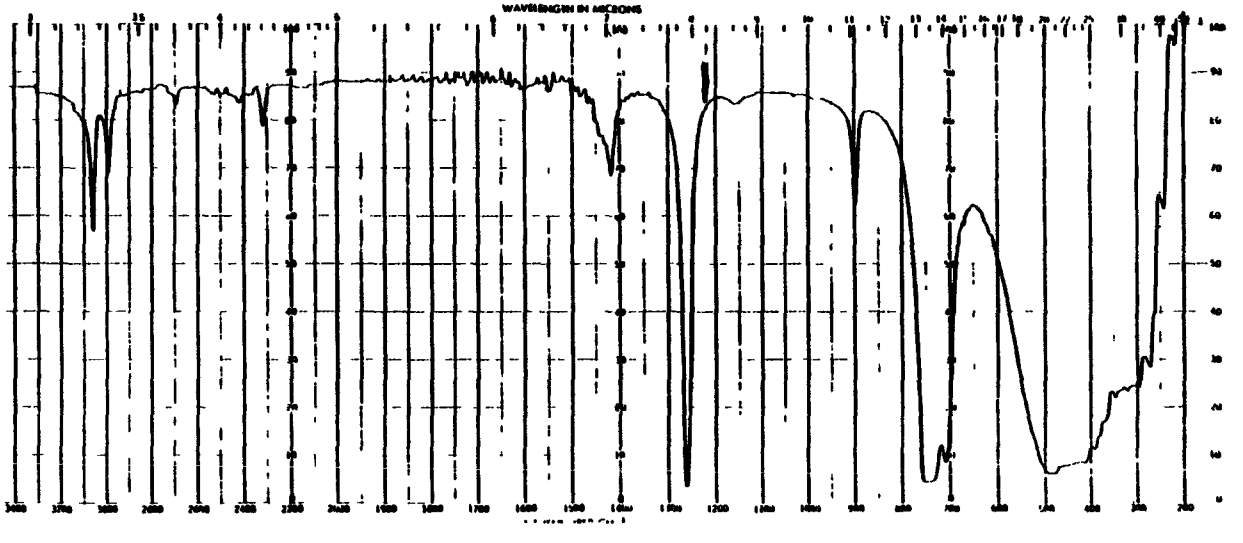

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF DICHLOROMETHANE (LOT NO. 767132)

c. Nuclear Magnetic Resonance

	Determined	Literature Values
(1) Instrument:	Varian HA-100	
(2) Solvent:	Neat, tetramethylsilane added	
(3) Assignments:	See Figure 8	Consistent with literature spectrum (Sadtler Standard Spectra)
(4) Chemical Shift (δ):	a s, 5.23 ppm	
(5) Integration Ratios:	a 2.00	

3. Water Analysis (Karl Fischer): 0.018% ± 0.002(δ)%

4. Elemental Analysis

Element	C	H	Cl
Theory	14.14	2.37	83.48
Determined	13.98 14.23	2.30 2.23	83.45 83.65

5. Titration for Acidic Components

< 1 ppm acidity (assumed to be hydrochloric acid)

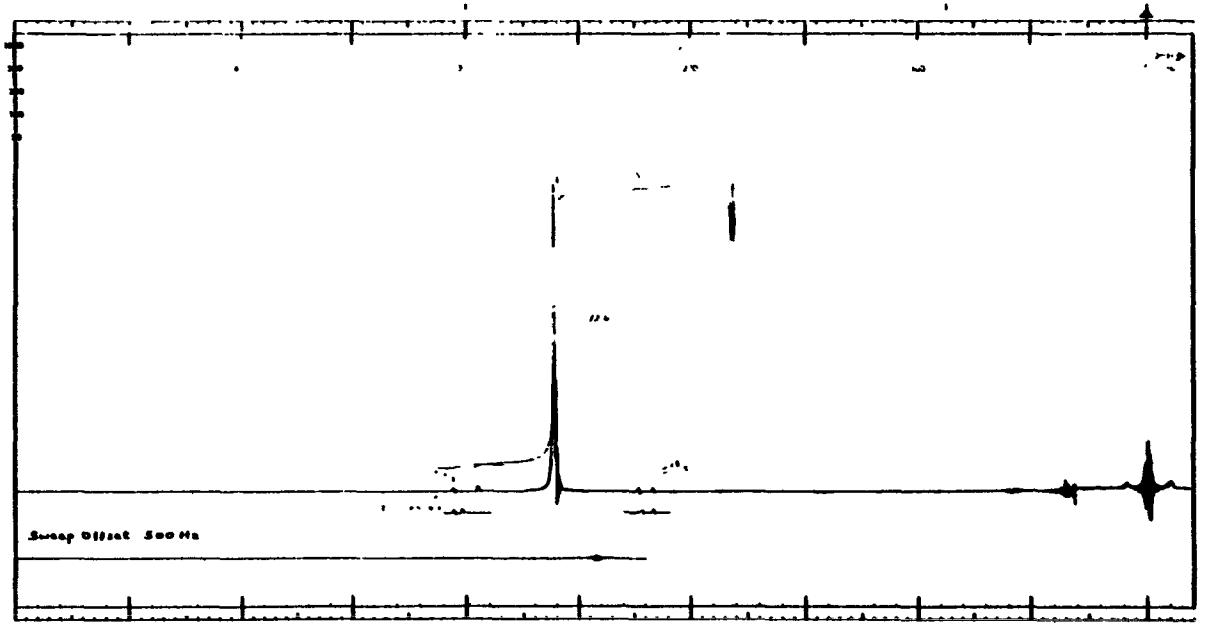

FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DICHLOROMETHANE (LOT NO. 767132)

6. Chromatographic Analysis: Gas Chromatography

Instrument: Tracor MT 220
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 215° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/minute

a. Detection of Impurities

System 1

Column: 20% SP2100/0.1% Carbowax 1500 on 80/100 Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C for 5 minutes, then 50°-170° C at 10° C/minute
Sample injected: 5 µl neat liquid, diluted to 1% and 0.5% in *o*-dichlorobenzene to quantitate the major peak and check for overloading

Results: Major peak and 12 impurities. The areas of the impurities total 0.1% or less of the area of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.3	0.2	<0.001
2	0.5	0.4	<0.001
3	0.6	0.5	<0.001
4	0.6	0.5	<0.001
5	0.7	0.5	<0.001
6	0.8	0.6	<0.001
7	0.9	0.7	<0.001
8	1.0	0.8	<0.001
9	1.1	0.8	shoulder 0.004-0.02
10	1.3	1.0	100
11	1.7	1.3	shoulder 0.03-0.1
12	2.4	1.8	0.004
13	2.9	2.2	<0.001

System 2

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C for 5 minutes, then 50°-200° C at 10° C/minute
Sample injected: 7 µl neat liquid diluted to 1% and 0.5% in *o*-dichlorobenzene to quantitate the major peak and check for overloading

Results: Major peak and six impurities. The areas of the impurities total approximately 0.1% of the area of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.3	0.2	<0.001
2	0.4	0.2	0.07
3	0.7	0.3	0.03
4	1.0	0.5	<0.001
5	1.3	0.7	0.01
6	1.9	1.0	100
7	3.7	1.9	<0.001

b. Quantitation of Vinylidene Chloride

Column: OPN/Porasil C, 80/100 mesh, 1.4 m × 4 mm ID, glass
Oven temperature: 50° C, isothermal
Sample injected: 6 µl neat dichloromethane and 6 µl 0.025% (v/v) vinylidene chloride in methanol

Results: The OPN/Porasil C system appeared to give a homogeneous peak for vinylidene chloride with a retention time of 3.2 minutes; the major peak began eluting at 3.3 minutes. The area of the peak at 3.2 minutes was compared with the area of similar-sized injections of 0.025% vinylidene chloride in methanol.

The sample contains 0.026% ± 0.005(δ)% (v/v) vinylidene chloride.

7. Conclusions: The results of elemental analysis agreed with the theoretical values. Gas chromatography indicated 12 impurities with one system and 6 impurities with a second system. With either system, the areas of the impurities totaled 0.1% or less of the major peak. Titration for acidic components indicated <1 ppm acidity (assumed to be hydrochloric acid). Gas chromatography was also used to determine that the concentration of vinylidene chloride in the sample was 0.026% ± 0.005(δ)% (v/v). The infrared and nuclear magnetic resonance spectra were consistent with those expected for the structure.

C. Lot No. 77-26-22

1. Spectral Data

a. Infrared	**Determined**	**Literature Values**
Instrument:	Perkin-Elmer Model 137 *Infracord*	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 9	Consistent with literature spectrum (Sadtler Standard Spectra)

b. Ultraviolet/Visible	**Determined**	**Literature Values**
Instrument:	Cary 118	
Solvent:	Methanol	
Concentration:	1%	
Results:	No absorbance between 350 and 800 nm. No maximum between 212 and 350 nm, but a gradual increase in absorbance toward the solvent cutoff at 212 nm.	No literature reference found.

c. Nuclear Magnetic Resonance

	Determined	**Literature Values**
Instrument:	Varian HA-100	
Solvent:	Neat, tetramethylsilane added	
Assignments:	See Figure 10	Consistent with literature spectrum (Sadtler Standard Spectra)
Chemical Shift (δ):	a s, 5.24 ppm	
Integration Ratios:	a 2.00	

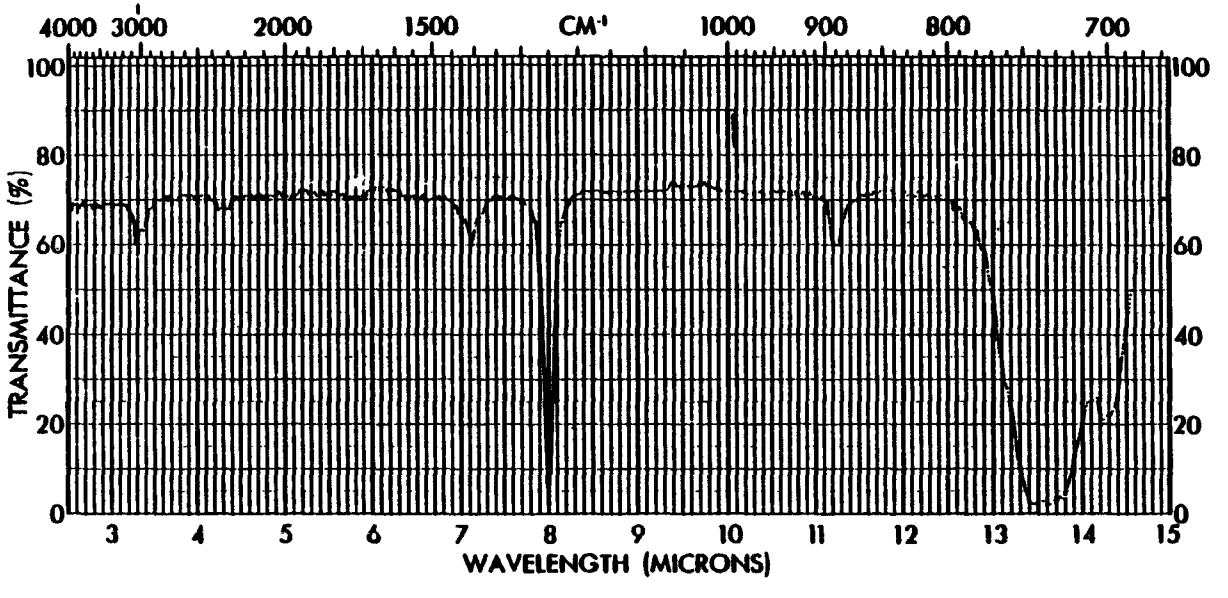

FIGURE 9. INFRARED ABSORPTION SPECTRUM OF DICHLOROMETHANE (LOT NO. 77-26-22)

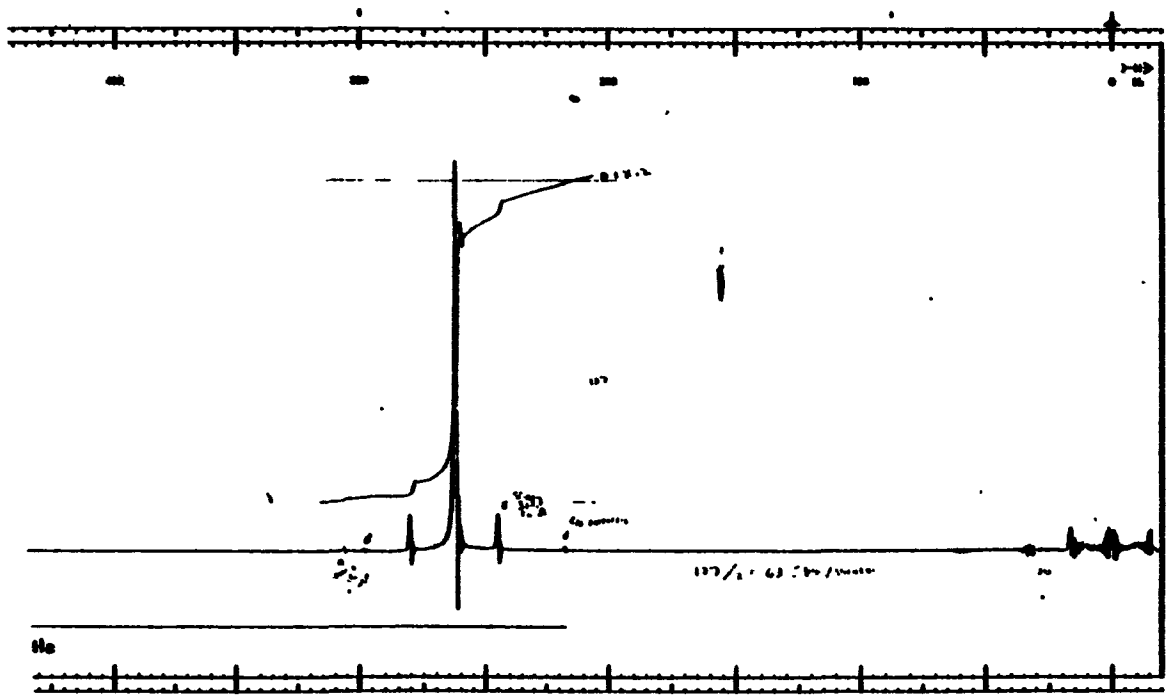

FIGURE 10. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DICHLOROMETHANE (LOT NO. 77-26-22)

2. Water Analysis (Karl Fischer): 0.012% ± 0.001(δ)%

3. Elemental Analysis

Element	C	H	Cl
Theory	14.14	2.37	83.48
Determined	14.27 14.11	2.39 2.23	83.31 83.52

4. Titration for Acidic Components: Titration with sodium hydroxide

1.75 ± 0.24(δ) ppm acidity (assumed to be hydrochloric acid)

5. Chromatographic Analysis: Gas Chromatography

Instrument: Tracor MT 220
Detector: Flame ionization
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/minute

a. Detection of Impurities

System 1

Inlet temperature: 220° C
Detector temperature: 270° C
Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C for 5 minutes, then 50°-170° C at 10° C/minute
Sample injected: 4 µl neat liquid, diluted to 1.0% and 0.5% in *o*-dichlorobenzene to quantitate the major peak and check for overloading

Results: Major peak and one impurity. The area of the impurity was 0.02% of the area of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to major peak	Area (percent of major peak)
1	1.7	1.0	100
2	2.3	1.4	0.02

System 2

Inlet temperature: 200° C
Detector temperature: 215° C
Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W (AW), 1.8 m × 4 mm ID
Oven temperature program: 50° C for 5 minutes, then 50°-200° C at 10° C/minute
Sample injected: 4 µl neat liquid in *o*-dichlorobenzene to quantitate the major peak and check for overloading

Results: Major peak and three impurities. The areas of the impurities totaled 0.18% of the area of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.55	0.20	0.10
2	0.80	0.29	0.05
3	1.46	0.53	0.03
4	2.77	1.00	100

b. Quantitation of Vinylidene Chloride

Inlet temperature: 200° C
Detector temperature: 215° C
Column: OPN/Porasil C, 80/100 mesh, 1.4 m × 4 mm ID, glass
Oven temperature: 50 ° C, isothermal

Results: Standards (6 µl) containing 0.05% (v/v) vinylidene chloride in methanol were injected. Vinylidene chloride had a retention time of 2.8 minutes. The dichloromethane sample had an impurity peak with a retention time of 2.8 minutes, appearing in front of the major peak, which began eluting at 3.0 minutes. Addition of vinylidene chloride to the neat sample enhanced the peak at 2.8 minutes. Vinylidene chloride in the sample was quantitated against similar sized injections of vinylidene chloride in methanol.

The sample contained 0.023% ± 0.003(δ)% vinylidene chloride.

6. Conclusions: The results of elemental analysis agreed with the theoretical values. Titration for acidic components indicated 2 ppm acidity (assumed to be hydrochloric acid). Gas chromatography with one system showed one impurity with an area 0.02% of the major peak. A second system indicated three impurities with total areas 0.18% of the area of the major peak. Gas chromatography also determined the concentration of vinylidene chloride in the sample to be 0.023% ± 0.003(δ)%. The infrared and nuclear magnetic resonance spectra were consistent with those expected for the structure.

D. Lot No. 775007

1. Appearance:	Colorless liquid

2. Spectral Data

a. Infrared	**Determined**	**Literature Values**
Instrument:	Beckman IR-12	
Cell:	Silver chloride, 25-micron path length	
Results:	See Figure 11	Identical to literature spectrum (Sadtler Standard Spectra)

b. Ultraviolet/Visible	**Determined**	**Literature Values**
Instrument:	Cary 118	
Solvent:	Methanol	
Results:	A 10% (v/v) solution exhibited no absorbance between 800 and 350 nm. A 1% (v/v) solution showed no absorbance maximum. However, a rapid increase in absorbance was noted below 230 nm.	No literature reference found. Spectrum consistent with the structure.

c. Nuclear Magnetic Resonance

	Determined	**Literature Values**
(1) Instrument:	Varian EM-360-A	
(2) Solvent:	Neat, tetramethyl-silane internal standard	
(3) Assignments:	See Figure 12	Identical to literature spectrum (Sadtler Standard Spectra)
(4) Chemical Shift (δ):	a s, 5.30 ppm	
(5) Integration Ratios:	a 2.00	

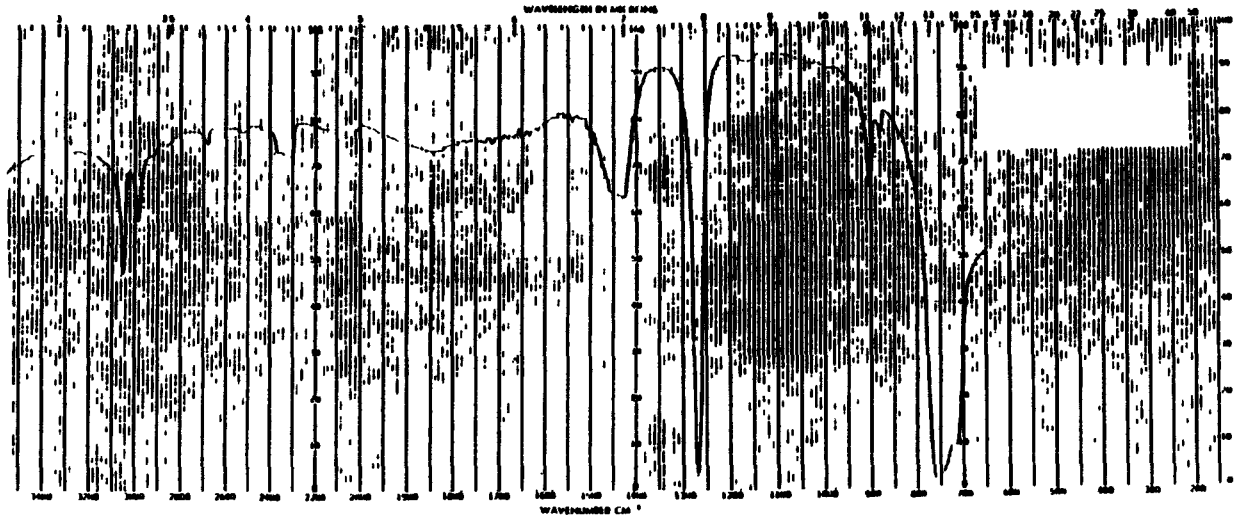

FIGURE 11. INFRARED ABSORPTION SPECTRUM OF DICHLOROMETHANE (LOT NO. 775007)

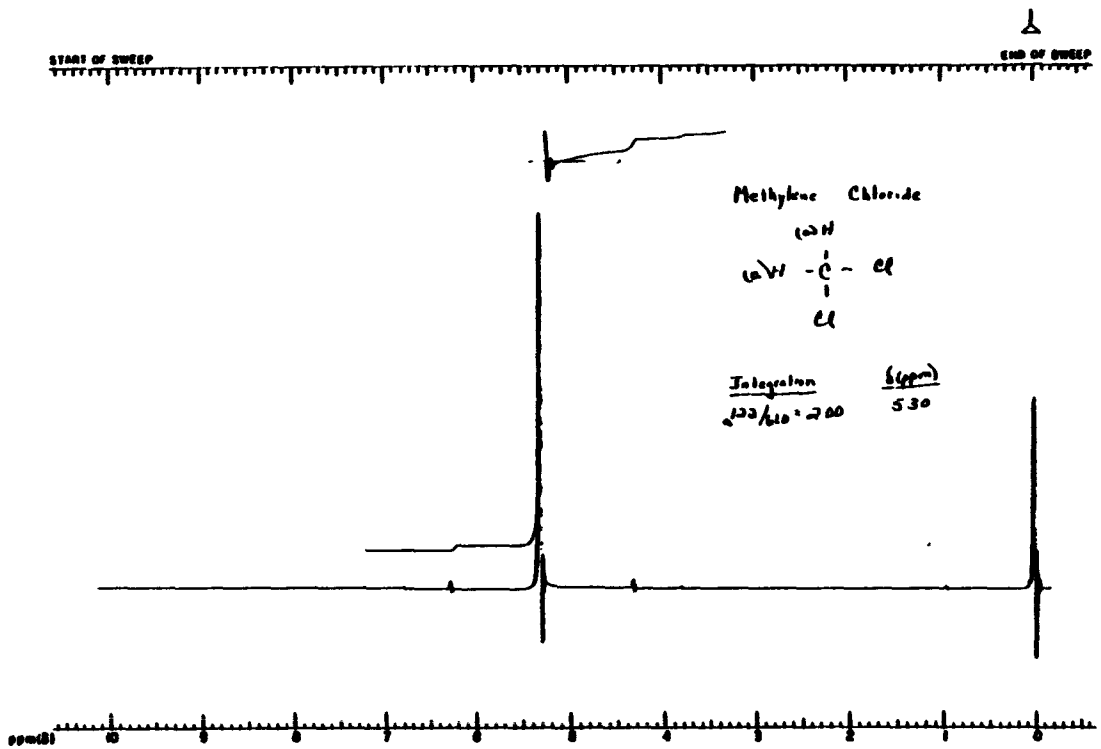

FIGURE 12. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DICHLOROMETHANE (LOT NO. 775007)

3. Water Analysis (Karl Fischer): 0.008% ± 0.001%

4. Elemental Analysis

Element	C	H	Cl
Theory	14.14	2.37	83.48
Determined	13.95 14.17	2.19 2.28	83.60 83.54

5. Titration: Free acid (as hydrochloric acid) < 3 ppm

6. Chromatographic Analysis: Gas Chromatography

Instrument: Perkin Elmer 3920
Detector: Flame ionization
Carrier gas: Nitrogen

a. System 1:

Column: Carbopack C/0.1% SP2100, 1.8 m × 4 mm ID, glass
Inlet temperature: 210° C
Detector temperature: 240° C
Carrier flow rate: 35 ml/min
Oven temperature program: 50° C for 4 minutes, then 50° to 250° C at 16° C/minute
Samples injected: 6 µl of the neat compound to detect and quantitate impurities and 5 µl of a 1.0% and 0.5% (v/v) solution in 1,2-dichloroethane to establish detector response linearity.

Results: A major peak followed by five impurity peaks.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	2.8	1.00	100
2	4.9	1.75	0.05
3	5.1	1.82	
4	6.9	2.46	0.05
5	8.0	2.96	0.01
6	9.2	3.29	0.13

b. System 2

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m × 4 mm ID, glass
Inlet temperature: 110° C
Detector temperature: 270° C
Carrier flow rate: 50 ml/minute
Oven temperature program: 30° C for 4 minutes, then 30° to 200° C at 16° C/minute
Samples injected: 0.5 µl, neat, to detect and quantitate impurities; 3.2 µl and 1.7 µl of a 1% (v/v) solution in 1,2-dichloroethane to establish linearity of detector response.

Results: A major peak preceded by three impurity peaks.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.5	0.17	0.11
2	0.7	0.23	0.06
3	1.3	0.43	0.04
4	3.0	1.00	100

7. Conclusions: The results of elemental analysis for carbon, hydrogen, and chlorine agreed, within experimental limits, with theoretical values. The water content was 0.008% ± 0.001% by Karl Fischer titration. The free acid concentration (as hydrochloric acid) by titration was less than 3 ppm. Gas chromatography detected a major peak followed by five impurity peaks with a combined relative area of 0.24% in one system and a major peak preceded by three impurities with a combined relative area of 0.21% in a second system. Infrared and nuclear magnetic resonance spectra were identical to the literature spectra. The ultraviolet/visible spectra were consistent with the structure.

E. Lot No. D112480

1. **Appearance:** Clear, colorless liquid

2. **Spectral Data**

a. Infrared	Determined	Literature Values
Instrument:	Perkin-Elmer 283	
Cell:	Thin film between silver chloride plates	
Results:	See Figure 13	Consistent with literature spectrum (Sadtler Standard Spectra)

b. Ultraviolet/Visible	Determined	Literature Values
Instrument:	Cary 118	
Solvent:	Methanol	
Results:	No absorbance from 800 to 350 nm at a concentration of 10% (v/v). No maximum from 350 to 209 nm but a gradual increase in absorbance toward 209 nm was observed at a concentration of 1% (v/v).	No literature reference found. Spectrum consistent with structure.

c. **Nuclear Magnetic Resonance**

	Determined	Literature Values
(1) Instrument:	Varian EM-360-A	
(2) Solvent:	Neat, internal standard tetramethylsilane	
(3) Assignments:	See Figure 14	Consistent with literature spectrum (Sadtler Standard Spectra)
(4) Chemical Shift (δ):	a s, 5.32 ppm	
(5) Integration Ratios:	a 2.00	

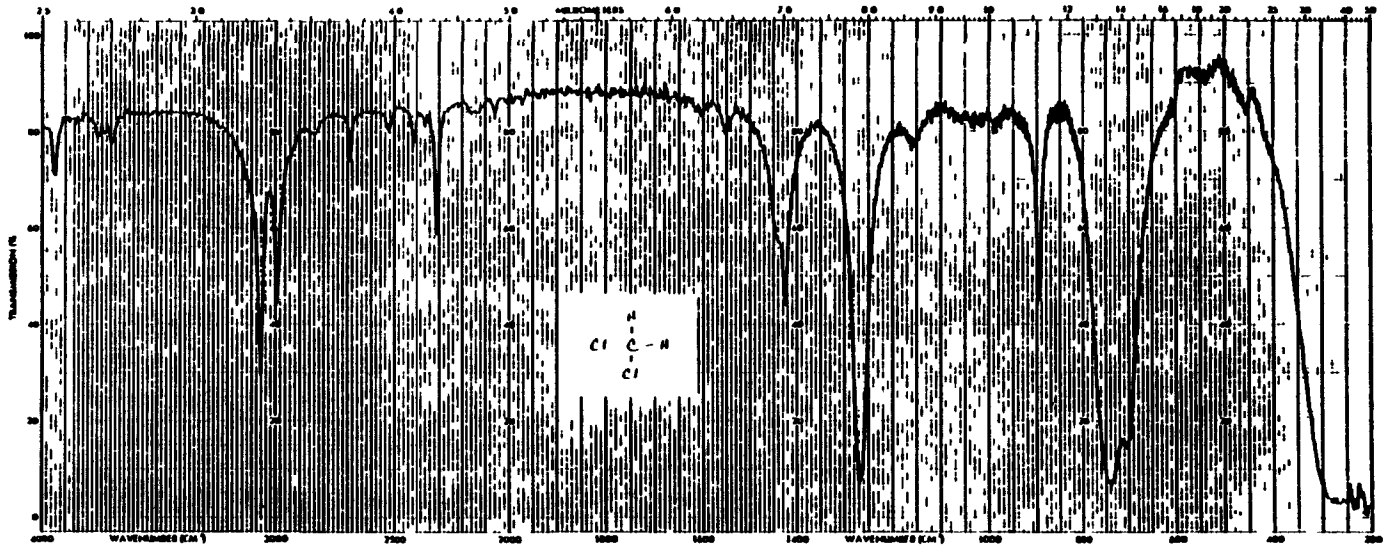

FIGURE 13. INFRARED ABSORPTION SPECTRUM OF DICHLOROMETHANE (LOT NO. D112480)

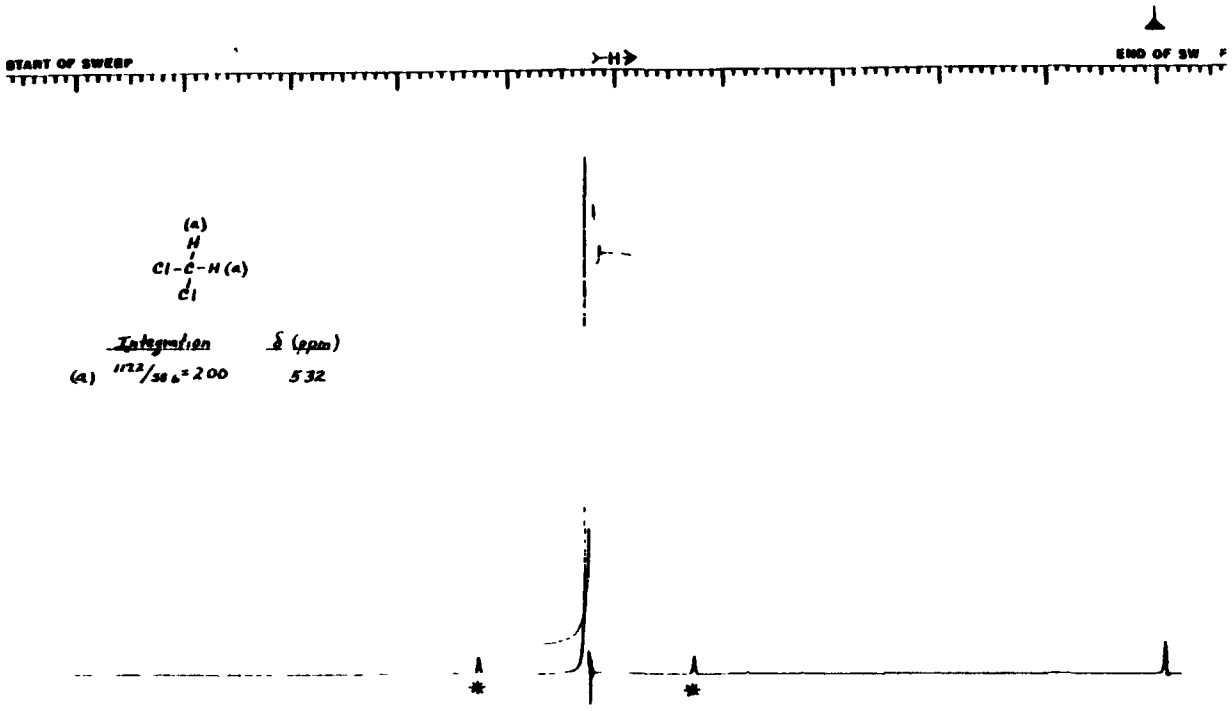

FIGURE 14. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DICHLOROMETHANE (LOT NO. D112480)

3. Water Analysis (Karl Fischer): 0.0092% ± 0.0004(δ)%

4. Elemental Analysis

Element	C	H	Cl
Theory	14.14	2.37	83.49
Determined	14.13 14.15	2.35 2.24	83.19 83.21

5. Titration for Acidic Components: Titration was done in isopropanol with 0.01 N sodium hydroxide titrant using phenolphthalein indicator.

0.26 ± 0.09(δ) ppm (as hydrochloric acid)

6. Chromatographic Analysis: Gas Chromatography

Instrument: Varian 3700
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 250° C
Carrier gas: Nitrogen
Carrier flow rate: 70 ml/minute

a. System 1

Column: 80/100 Carbopack C/0.1% SP2100, 1.8 m × 4 mm ID, glass
Oven temperature program: 50° C for five minutes, then 50° C to 220° C at 10° C/minute
Samples injected: Neat liquid (3 µl) and solutions of 1% and 0.5% dichloromethane in *o*-dichlorobenzene to quantitate the major peak and check for detector overload

Results: Major peak and one impurity after the major peak with an area of 0.09% relative to the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	1.5	1.0	100
2	8.4	5.6	0.09

b. System 2

Column: 10% Carbowax 20M-TPA on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 60° C for 6 minutes, then 60° C to 200° C at 10° C/minute
Samples injected: Neat liquid (3 µl) and solutions of 1% and 0.5% dichloromethane in *o*-dichlorobenzene to quantitate the major peak and check for detector overload

Results: Major peak and two impurity peaks before the major peak with a combined area of 0.20% relative to the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.7	0.37	0.18
2	1.2	0.63	0.02
3	1.9	1.00	100

6. Conclusions: The results of elemental analysis for carbon, hydrogen, and chlorine agreed with the theoretical values. Karl Fischer analysis indicated 0.0092% ± 0.004(δ)% water. The free acid content (as hydrochloric acid) was 0.26 ± 0.09(δ) ppm. Gas chromatography with an 80/100 Carbopack C/0.1% SP2100 column indicated a major peak and one impurity eluting after the major peak with an area of 0.09% relative to the major peak area. A second gas chromatographic system with a 10% Carbowax 20M-TPA column indicated a major peak and two impurities eluting before the major peak with a combined area totaling 0.20% of the major peak area. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with those expected for the structure of dichloromethane.

II. Test Chemical Stability Study of Lot No. 766062 Performed by the Analytical Chemistry Laboratory

A. Sample Storage: Samples of dichloromethane were stored in tightly screw-capped vials for two weeks at −20°, 5°, 25°, or 35° C. They were then analyzed by gas chromatography.

B. Analytical Method: Gas Chromatography

1. **Instrument:** Bendix 2500 with Hewlett-Packard 3380A Automatic Integrator
2. **Detector:** Flame ionization
3. **Column:** Chromosorb 102, 100/120 mesh, glass, 1.8 m × 4 mm
4. **Inlet temperature:** 200° C
5. **Detector temperature:** 250° C
6. **Oven temperature program:** 150° C, isothermal
7. **Retention time:** 6.3 minutes

C. Results

Storage Temperature	Average Percent Compound Recovered
−20° C	99.5 ± 2.6
5° C	101.3 ± 2.6
25° C	99.1 ± 2.6
35° C	99.9 ± 2.6

D. Conclusion: Dichloromethane is stable when stored for 2 weeks at temperatures up to 35° C.

III. Test Chemical Stability Study of Dichloromethane Lot No. D112480 Performed by the Testing Laboratory

A. Storage Conditions: Bulk chemical--Room temperature in steel drums

B. Analytical Methods

1. Gas Chromatography

a. Instrument: HP5840A or HP5830 gas chromatograph
b. Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.7 m × 4 mm ID, glass
c. Detector: Flame ionization
d. Detector temperature: 275° C
e. Injector temperature: 200° C
f. Oven temperature: 30° C, isothermal
g. Carrier gas: Helium
h. Concentration: Neat

2. Infrared Spectroscopy: Beckman Acculab 6 or Beckman Acculab 8; run as liquid in a cell with sodium chloride windows.

C. Results

1. Gas Chromatography

Date	Percent Purity of Bulk Chemical (a)
12/19/80	99.69
03/05/81	99.65
04/22/81	99.70
07/23/81	99.72
11/16/81	99.70
03/18/82	99.94
07/13/82	99.94
11/08/82	99.73
03/21/83	99.67
05/03/83	99.71

(a) Values are the average of three determinations

2. Infrared Spectroscopy: Spectra were consistent with the reference spectra and with the spectra provided by the analytical chemistry laboratory.

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

APPENDIX H

GENERATION AND MEASUREMENT OF CHAMBER CONCENTRATIONS AT BATTELLE PACIFIC NORTHWEST LABORATORIES

APPENDIX H. GENERATION AND MEASUREMENT

I. Vapor Generation System

The liquid to be vaporized was contained in a 5.6-liter stainless steel reservoir that was housed in a vapor hood within the exposure room. The liquid was pumped from this reservoir to a stainless steel cylinder covered with a glass fiber wick from which the liquid was vaporized (Decker et al., 1982). An 80-watt heater and a temperature-sensing element were incorporated within the cylinder. The heater maintained the vaporizer at 40° ± 2° C. The surface temperature of the vaporizer was slightly less than this temperature. Each cylindrical vaporizer was positioned in the fresh air duct leading directly into the exposure chamber to minimize material loss due to condensation on duct walls (Figure 15).

II. Vapor Concentration Monitoring

A Hewlett Packard Model 5840 gas chromatograph equipped with a flame ionization detector, a Porapak 80/100 packed column, and an automatic sampling valve was used to monitor the concentration of dichloromethane in the chambers. All chambers and the room air were sampled approximately twice during each exposure hour. Starting on the 231st exposure day, hexane in nitrogen was added to the sampling sequence to establish instrumental performance. The calibration of the monitoring gas chromatograph was confirmed and corrected as necessary by periodic assay of grab samples from the chambers analyzed on a second gas chromatograph.

Weekly concentrations are graphically presented in Figures 16-18.

III. Vapor Concentration Uniformity in Chamber

Uniformity of vapor concentration in each exposure chamber was measured periodically throughout the study with a portable photoionization detector (Model PI201, HNU Systems, Inc., Newton, MA). The standard deviations of the normalized average concentrations did not exceed ± 3.

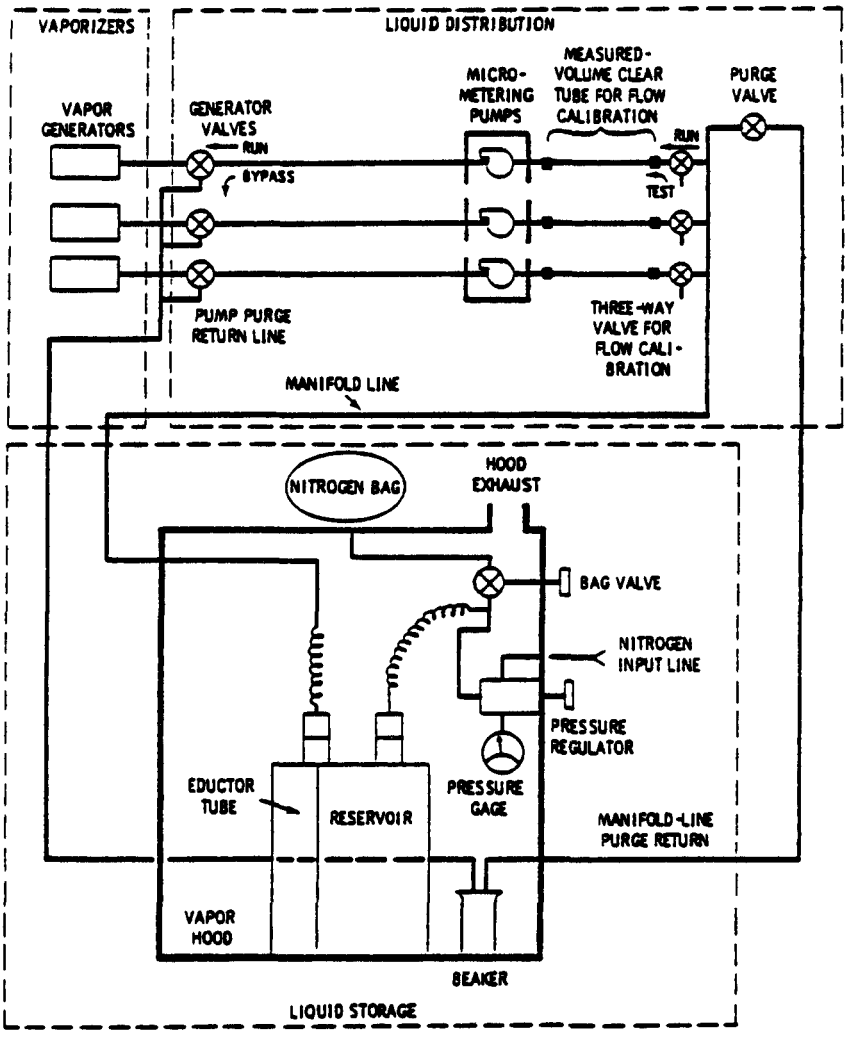

FIGURE 15. DICHLOROMETHANE VAPOR GENERATION SYSTEM

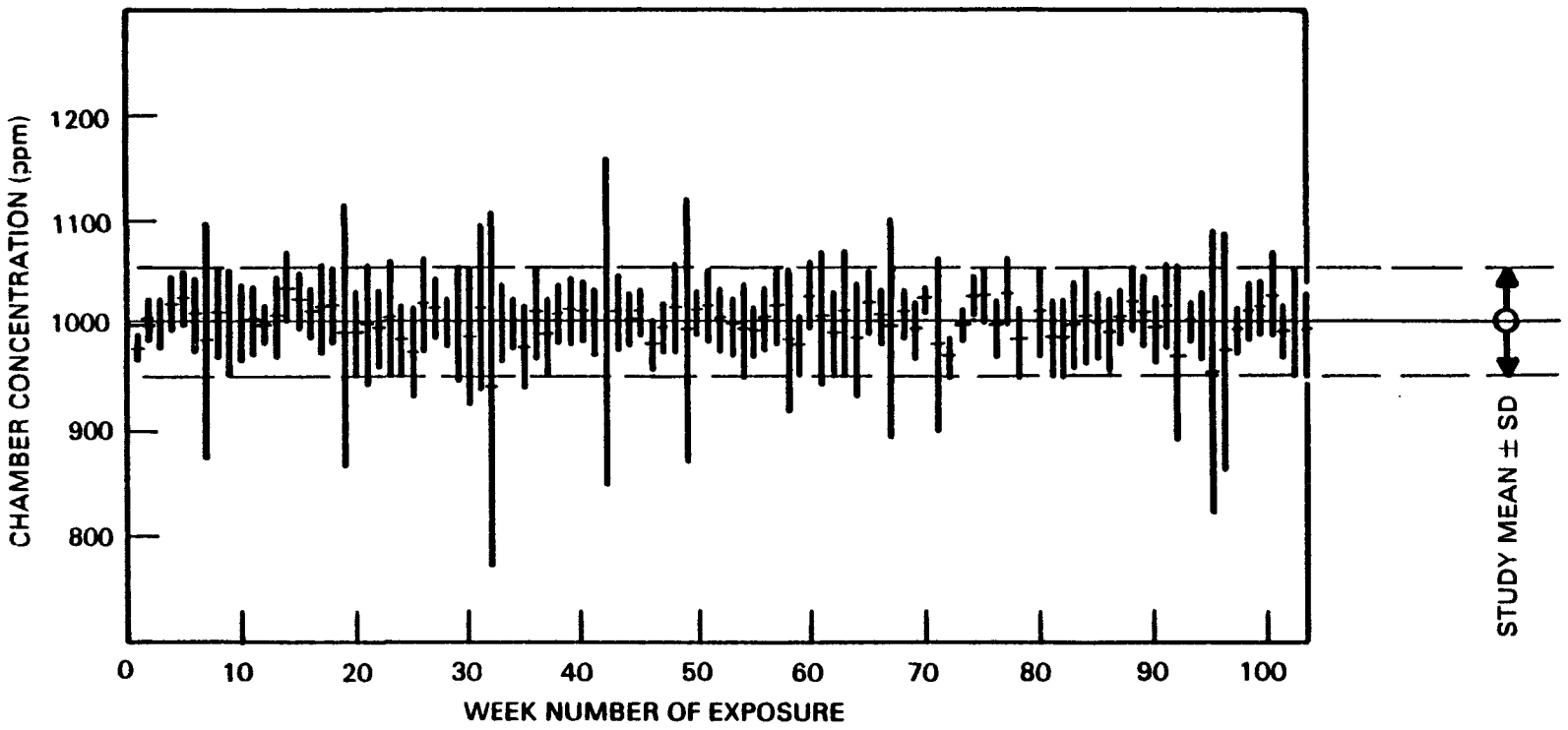

FIGURE 16. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN 1,000-PPM RAT EXPOSURE CHAMBER IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

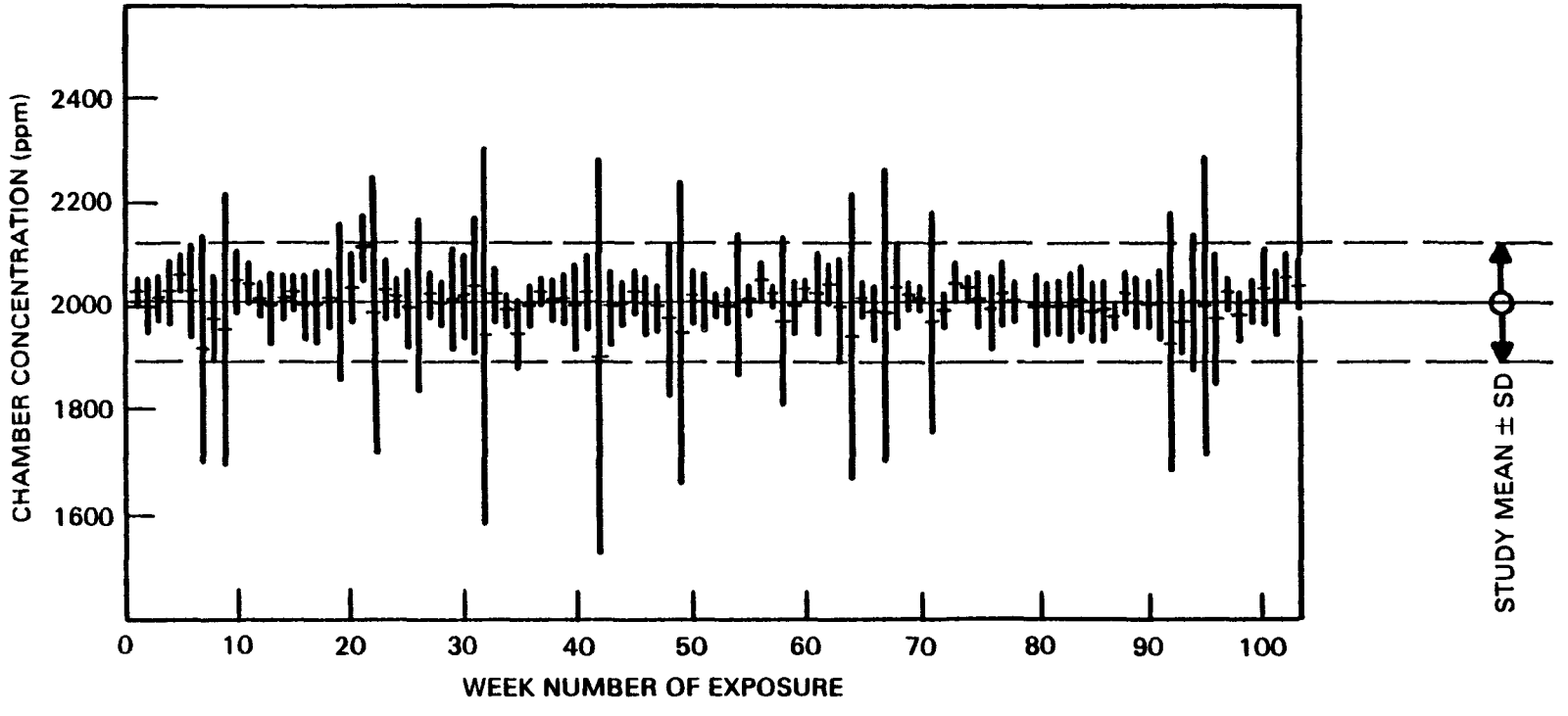

FIGURE 17. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN 2,000-PPM RAT AND MOUSE EXPOSURE CHAMBER IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

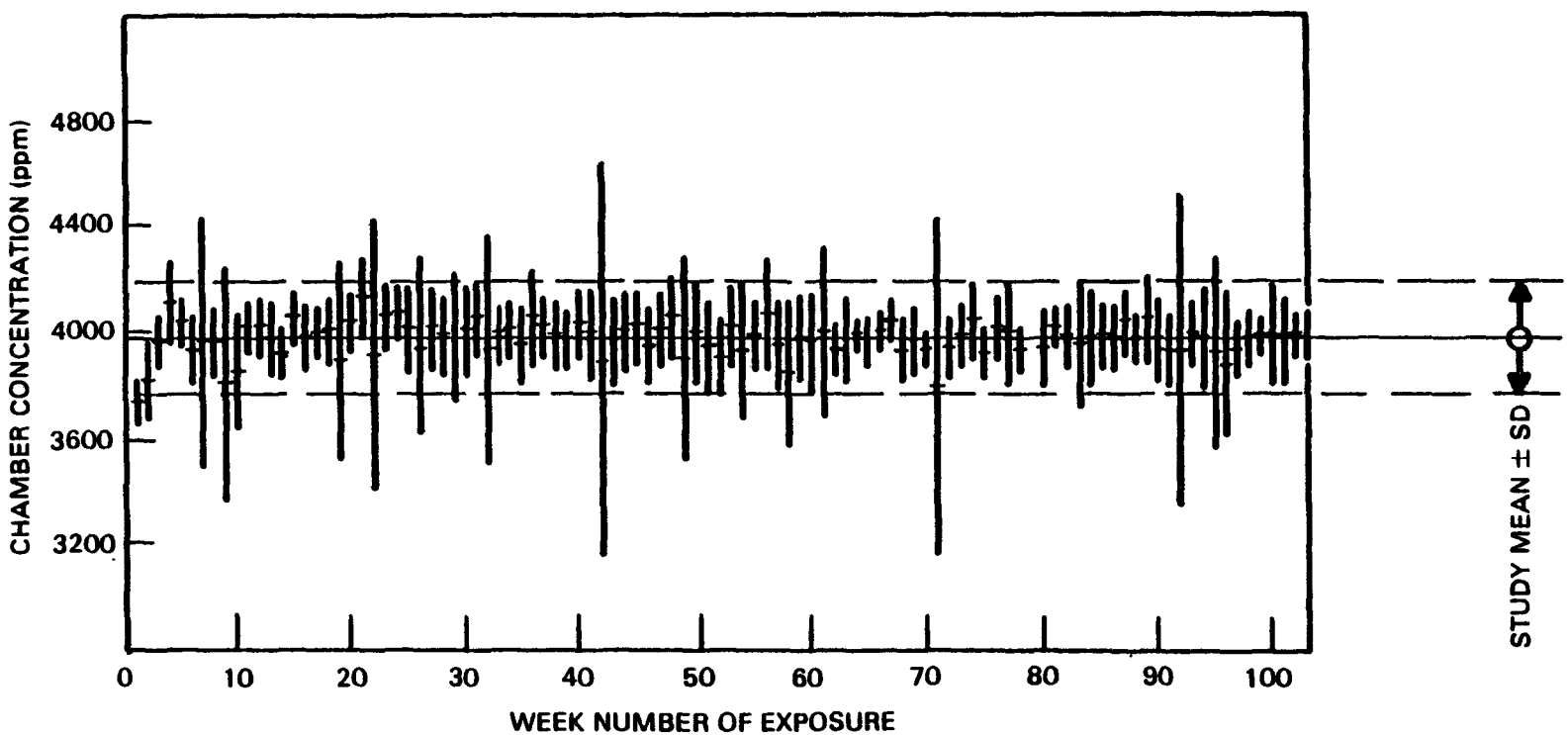

FIGURE 18. WEEKLY MEAN CONCENTRATION AND STANDARD DEVIATION IN 4,000-PPM RAT AND MOUSE EXPOSURE CHAMBER IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

APPENDIX I

RESULTS OF

SEROLOGIC ANALYSES

APPENDIX I. SEROLOGIC ANALYSES

I. Methods

Blood was drawn as described below:

Species	Male/Female	Dates Drawn	Status of Animals
Rat	8/8	01/08/82	Chronic (tested for Sendai only)
Rat	6/4	12/07-12/16/82	Chronic/moribund kill
Mouse	1/9	01/14-04/01/83	Chronic/moribund kill
Rat	5/5	04/25/83 & 04/27/83	Chronic/terminal kill
Mouse	5/5	04/26/83 & 04/27/83	Chronic/terminal kill

The blood from each animal was collected and clotted, and the serum was separated The serum was cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the antibody titers. The following tests were performed:

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

II. Results

Results are presented in Table I1.

TABLE I1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR INHALATION STUDIES OF DICHLOROMETHANE

	Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS			
	8	4/6	Sendai
	19	10/10	PVM
		5/10	Sendai
		3/10	RCV
	24	10/10	PVM
		4/10	Sendai
		4/10	KRV
		5/10	RCV
		10/10	*M. pul.*
MICE			
	23	1/7	PVM
		2/10	MHV
	24	4/10	PVM
		1/10	MHV

APPENDIX J

DATA AUDIT SUMMARY

APPENDIX J. DATA AUDIT SUMMARY

The experimental data and tables of the NTP Technical Report on the toxicology and carcinogenesis inhalation studies of dichloromethane in F344/N rats and B6C3F$_1$ mice were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements from October 29 to November 2, 1984, at Battelle Pacific Northwest Laboratories, Richland, Washington, and during the week of January 21, 1985, at the NTP Archives, Research Triangle Park, North Carolina. The audit was conducted by Argus Research Laboratories, Inc. The following people were involved in the audit: J. Goeke, Ph.D.; J. Hills,, B.A.; A. Hoberman, Ph.D.; V. Everline, V.S.; G. Knutsen, D.V.M., M.S.; C. Veigle, H.T. The 2-year studies in rats and mice were conducted between April 1981 and April 1983 at Battelle Pacific Northwest Laboratories.

The full report of the audit is on file at the NTP, NIEHS. The audit included, but was not limited to, a review of the records of the in-life portion of the studies for 10% of the animals, 100% of the records for test article administration, 10% of the daily gas chromatograph printouts, and 100% of all other chemistry data. All Individual Animal Data Records (IADR's) were examined for correspondence between necropsy observations and histologic findings. A 10% audit of randomly selected wet tissue bags was conducted for verification of unique animal identification and to examine residual tissues for untrimmed lesions. A complete slide/block match for each sex of both species in the high dose and control groups was performed.

The examination of wet tissues indicated one animal with a missing ear tag and two others with discrepancies between ear tag and IADR number. These discrepancies were resolved during the course of the audit. The IADR's contained some minor clerical errors. With few exceptions, gross observations were followed by microscopic diagnoses. There were a few incidences of lack of correlation between gross and microscopic diagnoses, some of which were resolved by examination of the slides. These discrepancies (eight in male rats, three in female mice, none in female rats or male mice) were distributed over dose groups and tissue sites. A slide/block match performed at the NTP Archives identified a few broken slides, missing slides and blocks, or blocks not cut full face or sealed properly. Untrimmed lesions were found in the wet tissues, primarily in the livers of four rats (one mid dose and two high dose males, one high dose female). These lesions were not rediagnosed because they would not have significantly affected the conclusions for that target site.

The audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies that influenced the final interpretations of the results of these studies were found. The data examined during this audit are considered adequate to support the conclusions presented in the Technical Report.

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