NATIONAL TOXICOLOGY PROGRAM
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No. 282

TOXICOLOGY AND CARCINOGENESIS STUDIES OF CHLORODIBROMOMETHANE

(CAS NO. 124-48-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

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

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

NTP TECHNICAL REPORT

ON THE

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

August 1985

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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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 in June 1983 for use in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

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

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

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

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

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

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

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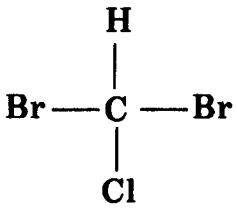


CHLORODIBROMOMETHANE

CAS NO. 124-48-1

Molecular Weight 208.29

Synonym: Dibromochloromethane

ABSTRACT

Toxicology and carcinogenesis studies of chlorodibromomethane (greater than 98% pure), a trihalomethane formed after chlorination of water supplies, were conducted by administering this test chemical in corn oil by gavage five times per week for 104 weeks to groups of 50 male and 50 female F344/N rats at 0, 40, or 80 mg/kg per day and to groups of 50 male and 50 female B6C3F$_1$ mice for 105 weeks at doses of 0, 50, or 100 mg/kg per day. Survival of dosed male and female rats and female mice was comparable to that of the corresponding vehicle control groups. An overdose of chemical was given to low dose male and female mice at week 58; this overdose killed 35 male mice, whereas the female mice were apparently not affected. Because this mortality significantly reduced the number of survivors, the low dose male mouse group was considered to be inadequate for analysis of neoplasms. High dose male mice had lower survival than the vehicle controls (44/50 vs 29/50; $P < 0.001$). At week 82, nine high dose male mice died; the cause remains unknown. High dose male rats and dosed male and female mice had lower body weights compared with those of the vehicle controls.

Compound-related nonneoplastic lesions were found in the liver and kidney in male and female rats and in male mice in the 13-week studies at the highest dose (250 mg/kg). In the 2-year studies, compound-related toxicity was seen primarily in the livers of male and female rats (fatty metamorphosis and ground-glass cytoplasmic changes) and in male mice (hepatocytomegaly, necrosis, fatty metamorphosis) and female mice (calcification and fatty metamorphosis). Toxicity was also seen in the kidneys (nephrosis) of male mice and female rats.

Administration of chlorodibromomethane significantly increased the incidence of hepatocellular adenomas (vehicle control, 2/50; low dose, 4/49; high dose, 11/50) and the combined incidences of hepatocellular adenomas or carcinomas (6/50; 10/49; 19/50) in high dose female mice. The incidence of hepatocellular carcinomas (vehicle control, 10/50; high dose, 19/50) was significantly increased in high dose male mice, although the combined incidence of hepatocellular adenomas or carcinomas (vehicle control, 23/50; high dose, 27/50) was marginally significant by the life table test but not by the incidental tumor test.

Negative trends in several common rodent tumors were found in dosed animals in the 2-year studies. These neoplasms included fibroadenomas of the mammary gland in female rats, endometrial stromal polyps of the uterus in female rats, and malignant lymphomas in male mice.

Chlorodibromomethane was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537 in the presence or absence of Aroclor-induced male Sprague-Dawley rat or male Syrian hamster liver S9.

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

Under the conditions of these gavage studies, there was *no evidence of carcinogenicity** in male or female F344/N rats receiving chlorodibromomethane at doses of 40 or 80 mg/kg five times per week for 104 weeks. Fatty metamorphosis and ground-glass cytoplasmic changes of the liver in male and female F344/N rats were related to administration of chlorodibromomethane. There was *equivocal evidence of carcinogenicity* for male $B6C3F_1$ mice; chlorodibromomethane caused an increased incidence of hepatocellular carcinomas, whereas the combined incidence of hepatocellular adenomas or carcinomas was only marginally increased. *Some evidence of carcinogenicity* was observed for female $B6C3F_1$ mice, since chlorodibromomethane caused an increased incidence of hepatocellular adenomas and an increased combined incidence of hepatocellular adenomas or carcinomas.

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

CONTRIBUTORS

This NTP Technical Report on the Toxicology and Carcinogenesis Studies of Chlorodibromomethane is based on 13-week studies that began in February 1979 and ended in May 1979 and on 2-year studies that began in January 1980 and ended in January 1982 at EG&G Mason Research Institute.

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

June K. Dunnick, Ph.D., Chemical Manager

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

NTP Pathology Working Group
(Evaluated Pathology Report and Selected Slides on 11/16/82)

R. Sauer, V.M.D. (Chair)
Clement Associates
G. Boorman, D.V.M., Ph.D.
NTP
K. Morgan, Ph.D.
Chemical Industry Institute of Toxicology
S. Eustis, D.V.M., Ph.D.
NTP
H. Solleveld, D.V.M., Ph.D.
NTP
J. Boyce, D.V.M.
Springborn Institute for Bioresearch, Inc.

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

Herman S. Lilja, Ph.D.
Principal Investigator
Alan J. Block, Ph.D.
Assistant Principal Investigator
Miasnig Hagopian, Ph.D.
Chemist
D. Stuart Wyand, D.V.M.
Veterinary Pathologist

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

Jerry F. Hardisty, D.V.M.

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

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

PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on March 23, 1984, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

National Toxicology Program Board of Scientific Counselors Technical Reports Review Subcommittee

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

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

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

Ad Hoc Subcommittee Panel of Experts

Louis S. Beliczky, M.S., M.P.H.
Director, Department of Industrial Hygiene
United Rubber Workers International Union
Akron, Ohio

Devra L. Davis, Ph.D. (Principal Reviewer)
Science Policy Director
Environmental Law Institute
Washington, D.C.

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

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

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

David Kotelchuck, Ph.D.
Research Department
United Electrical, Radio and Machine Workers of America
New York, New York

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

Steven R. Tannenbaum, Ph.D.
(Principal Reviewer)
Professor, Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts

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

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

*Unable to attend

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

On March 23, 1984, the draft Technical Report on the toxicology and carcinogenesis studies of chlorodibromomethane 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 First Floor Auditorium, Hubert Humphrey Building, Washington, D.C.

Dr. J. Swenberg, a principal reviewer, agreed with the conclusions. He asked for more discussion on the lack of pathology in the livers and kidneys of rats exposed at 60 and 125 mg/kg in the 13-week studies as well as on the salivary gland lesions, since there was a clear dose-response relationship.

As a second principal reviewer, Dr. D. Davis agreed with the conclusions. In view of the viral infections in male and female sentinel rats that were killed at 6 and 12 months and in control rats killed at 24 months, she suggested that in future studies it might be useful to examine antibody titers in living cohorts to determine whether chronic antigenic stimulation may contribute to mortality. She said that the observed negative trends for several common rodent tumors should be compared with historical control data.

As a third principal reviewer, Dr. S. Tannenbaum said that a more appropriate route of administration would have been drinking water, since that is the likely route of human exposure. Further, the vapor pressure and other physical/chemical properties of the compound in oil or in water will differ. [A clarifying statement was added to the rationale for selecting the gavage route of exposure.] Dr. J. Dunnick, NTP, reported that a Japanese study is in progress in which chlorodibromomethane was being given in a microencapsulated form in feed. Dr. Tannenbaum noted that the decreased body weight gain in both male and female mice was a likely indication of toxicity.

Although Dr. Tannenbaum agreed with the evaluations of the studies in rats and in male mice, he thought that the conclusion for female mice should be equivocal evidence of carcinogenicity because of toxicity at the high dose and no effect at the low dose. Dr. E. McConnell, NTP, said that the high dose in NTP 2-year studies was selected to cause some minimal toxicity, yet not cause debilitation or lethality; a 10%-15% reduction in weight gain compared with vehicle controls is an example of such an effect. He further stated that the "optimal dose" is rarely reached. Dr. Swenberg said that a moderate exceeding of the estimated maximal tolerated dose, as seen here, does not invalidate tumor findings; the relatively low and nonvariable historical rate of liver tumors in female $B6C3F_1$ mice, the dose-response relationship for these neoplasms, and the statistically significant increases all support the interpretation of some evidence of carcinogenicity.

The panel discussed the possible implications of an overdosing error in low dose male and female mice at week 58, as well as the deaths of nine high dose mice at week 82 for which a cause of death was unknown. Dr. J. Haseman, NIEHS, thought that this clustering of deaths in high dose male mice was suggestive of accidental causes. Dr. R. Kociba said that histopathologic examination might indicate whether the deaths at week 82 were due to overdosing or some other reason. Dr. Dunnick stated that the dosing accidents would be footnoted in the tables of data for male and female mice and highlighted in the abstract. Dr. Hook asked for assurances from the Program that positive action was being taken to decrease the occurrence of such accidents, that the NTP was striving to insure that the conduct of experiments by the contractor laboratories was commensurate with current standards, and that poor performance would lead to remedial action. Dr. G. Boorman, NTP, replied that the number of laboratories qualified to do testing for the NTP had decreased, which was likely a reflection of more stringent standards and closer monitoring and to advice by the Board of Scientific Counselors.

Dr. Swenberg moved that the Technical Report on the toxicology and carcinogenesis studies of chlorodibromomethane be accepted with the conclusions as written and with the modifications discussed. Dr. Tannenbaum seconded the motion, and the report was approved by 10 affirmative votes. There was one negative vote (Mr. L. Beliczky).

I. INTRODUCTION

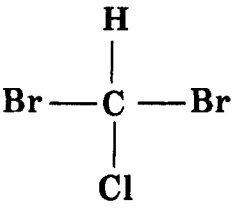
Formation and Regulation

Effects on Humans

Effects on Animals

Mutagenicity

Reason for Testing



CHLORODIBROMOMETHANE

CAS NO. 124-48-1

Molecular Weight 208.29

Synonym: Dibromochloromethane

Formation and Regulation

Chlorodibromomethane (dibromochloromethane) is a trihalomethane formed when organic substances in water are chlorinated (Hoehn et al., 1978; Rook, 1980; Stevens et al., 1976; NAS, 1980a). The Environmental Protection Agency (EPA) has established a maximum permissible contamination level of 0.1 mg/liter for total trihalomethanes in community water systems serving more than 10,000 persons (EPA, 1979, 1983). The presence of trihalomethanes in drinking water was believed to pose a risk to humans because chloroform, another trihalomethane in drinking water, was found to be a carcinogen in rats and mice (NCI, 1976; Eschenbrenner and Miller, 1945; Roe et al., 1979; IARC, 1979).

The EPA regulations for trihalomethanes in drinking water emphasize that the amounts of trihalomethane vary depending on the season, chlorine contact time, water temperature, pH, the type and chemical composition of raw water, and treatment methods. The organic precursors of trihalomethanes are more frequently found in surface water than groundwater (EPA, 1979). Trihalomethanes also have been found in swimming pools (Beech et al., 1980). The content of chlorodibromomethane in water increases with chlorination (Rook, 1974; Bellar, 1974; Brass et al., 1977; Symons et al., 1975). The mean concentration of chlorodibromomethane in U.S. chlorinated water supplies is 0.011 mg/liter (range, 0-0.25 mg/liter) (EPA, 1979).

Effects on Humans

There is no clear epidemiologic evidence for the carcinogenicity of chlorodibromomethane or other trihalomethanes in humans (IARC, 1979, 1982), although some data suggested that trihalomethanes in drinking water may be associated with an increased frequency of cancer of the bladder (NAS, 1980b). The investigation of the possible association between trihalomethanes in drinking water and urinary bladder cancer is continuing (Cantor, 1982; Cantor et al., 1978).

Effects on Animals

The following oral LD_{50} values were reported for chlorodibromomethane: 800 mg/kg, male ICR mice; 1,200 mg/kg, female ICR mice; 1,186 mg/kg, male Sprague-Dawley rats; and 848 mg/kg for female Sprague-Dawley rats (Bowman et al., 1978; Chu et al., 1980). Clinical signs included piloerection, sedation, flaccid muscle tone, ataxia, and prostration; the liver and kidneys were congested and enlarged.

Toxic effects in the liver, spleen, and immune system occurred in male and female CD-1 mice administered 0, 50, 125, or 250 mg/kg chlorodibromomethane by gavage in water for 14 consecutive days (Munson et al., 1982). Chlorodibromomethane administered to male and female Sprague-Dawley rats in the drinking water at doses of approximately 137 mg/kg per

day and 165 mg/kg per day for 90 days produced mild toxicity in the liver; the observed vacuolar changes due to fatty infiltration were reversible after a 90-day recovery period (Chu et al., 1982).

Chlorodibromomethane did not alter delayed hypersensitivity to albumin in ICR mice whereas chloroform did (Schuller et al., 1978). In a 90-day study, chlorodibromomethane caused a dose-related decrease in the vascular clearance rate of *Listeria monocytogenes* in ICR mice (Munson et al., 1978). When given to pregnant Sprague-Dawley rats at 100 mg/kg per day on the 6th-15th days of gestation, chlorodibromomethane was toxic to the fetus (Ruddick et al., 1980) but was not teratogenic at 100-200 mg/kg (Ruddick et al., 1983). (Borzelleca et al. [1980] reported in an abstract that no teratogenic effect was seen in ICR Swiss mice exposed to chlorodibromomethane; insufficient data are available to evaluate this finding.) A mixture of trihalomethanes and other organic substances concentrated from water was given by gavage to pregnant CD-1 mice at 51, 170, or 510 mg/kg per day on gestation days 7-14, and no indication of fetal toxicity was found (Kavlock et al., 1979). Chlorodibromomethane did not affect the nervous system of mice (Balster et al., 1979; Martin et al., 1977; Balster and Borzelleca, 1982). Chlorodibromomethane and other trihalomethanes including chloroform, bromoform, and bromodichloromethane were metabolized to carbon monoxide by a rat liver microsomal fraction (Ahmed et al., 1977).

Mutagenicity

Chlorodibromomethane was mutagenic in Salmonella TA100 when tested in desiccators, a procedure that was used to diminish escape of volatile compounds (Simmon et al., 1977; Simmon and Tardiff, 1977). The NTP also tested chlorodibromomethane in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 with or without Aroclor-induced Sprague-Dawley rat or Syrian hamster liver S9 (Appendix L, Table L1). These tests were not performed in desiccators, and the negative results were possibly due to the volatility of the compound. No dominant lethal effects were seen in ICR Swiss mice (Borzelleca et al., 1980).

Study Rationale

Chlorodibromomethane was tested because a related trihalomethane, chloroform, had been found to be a carcinogen in rodents and because no data were available on the carcinogenicity of the other trihalomethanes. In addition to chlorodibromomethane, bromoform (tribromomethane) and bromodichloromethane are currently being tested by the NTP in 2-year studies via gavage in F344/N rats and B6C3F$_1$ mice.

The oral route of administration was chosen for this study because human exposure is primarily oral. Chlorodibromomethane was administered by gavage in corn oil because the chemical was insoluble in water at the concentrations used in these studies and because this trihalomethane was considered too volatile to administer by feed; the gavage route was also chosen to ensure that the animals would be exposed to a sufficient amount of the test chemical. The chemical properties of chlorodibromomethane in corn oil and water were not determined or compared.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF CHLORODIBROMOMETHANE

Chlorodibromomethane was obtained in two lots from Freeman Industries, Inc. (Tuckahoe, NY). Lot no. F122277 was used for the single-administration, 14-day repeated-administration, and 13-week studies and for the first 19 months of the 2-year studies. Lot no. F810626 was used for the remainder of the 2-year studies (Table 1). Both lots were extracted with sodium carbonate to remove acid components.

Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix G). The bulk chemical was treated with sodium carbonate to remove acid contaminants. After this procedure was performed, acid components were detected at concentrations of 147 ± 18 ppm in lot no. F122277 and 118 ± 13 ppm in lot no. F810626.

Results of elemental analysis showed close agreement between actual and theoretical values. The boiling point and density were found to be 118.5° C and 2.433, respectively; these values agree with those reported in the literature (Sax, 1975). Infrared and nuclear magnetic resonance spectra were consistent with those in the literature (Sadtler Standard Spectra). No absorbance was found in the visible region (350-800 nm) of the ultraviolet spectrum. There was no absorbance maximum in the ultraviolet region (350-220 nm), but an increase in absorbance occurred between 290 nm and the solvent cutoff.

Sodium carbonate-treated chlorodibromomethane was analyzed by gas chromatography and found to be greater than 98% pure. Lot no. F122277 was found to have a major peak with an area of 98.4% of the total peak area and 10 impurities with a combined area totaling 1.6% that of the major peak, and lot no. F810626 had a major peak with an area greater than 99% of the total peak area and 4 impurities totaling less than 1% of the major peak. Five of the impurities in lot no. F122277 were further identified as bromochloromethane, dibromomethane, bromodichloromethane, bromoform, and chlorotribromomethane by gas chromatography interfaced with mass spectrometry (Appendix G).

The purity of the bulk chemical was determined by gas chromatography to be greater than 98%. Chlorodibromomethane was stored in the dark under nitrogen at 0° ± 5° C. Results of periodic reanalyses of the bulk chemical at EG&G Mason Research Institute indicated that no notable degradation occurred during the study (Appendix G).

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

The appropriate amounts of chlorodibromomethane and corn oil were mixed (w/v) to give the desired concentrations. Chlorodibromomethane (20% in corn oil) was found to be stable for 7 days at room temperature (Appendix H). Chlorodibromomethane/corn oil mixtures were stored at 0° ± 5° C for no longer than 10 days.

Results of periodic analyses of chlorodibromomethane/corn oil mixtures at EG&G Mason Research Institute and referee analyses at Midwest Research Institute indicated that all analyzed mixtures were within ± 10% of the target concentrations, except the doses mixed on February 12, 1981, and on July 27, 1981 (Appendixes I and J). Results (excluding those of February 12) are summarized below.

Target concentration (mg/ml)			
8.0	10.0	16.0	20.0
Mean (mg/ml)			
7.7	9.7	15.6	20.1
Standard deviation			
0.26	0.41	0.41	0.82
Coefficient of variation (percent)			
3.4	4.2	2.6	4.1
Range (mg/ml)			
7.2-8.1	9.0-10.2	15.1-16.4	19.0-21.6
Number of samples			
13	13	13	13

The dose prepared for week 58 for low dose male and female mice on February 12, 1981, was found to be seven times greater than the target concentration; 35 low dose male mice died after the dose was administered, whereas none of the female mice died. The deaths of nine high dose male mice at week 82 may have been the result of a mixing error on July 27, 1981; sufficient amounts of the dose preparation were not available for complete analysis.

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORODIBROMOMETHANE

Single-Administration Studies	Fourteen-Day Repeated-Administration Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Testing Laboratory			
EG&G Mason Research Institute	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Size of Test Groups			
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses			
160, 310, 630, 1,250, or 2,500 mg/kg chlorodibromomethane in corn oil by gavage; dose vol--5 ml/kg	Rats--0, 60, 125, 250, 500, or 1,000 mg/kg chlorodibromomethane in corn oil by gavage; mice--0, 30, 60, 125, 250, or 500 mg/kg; dose vol--5 ml/kg	0, 15, 30, 60, 125, or 250 mg/kg chlorodibromomethane in corn oil by gavage; dose vol--5 ml/kg	Rats--0, 40, or 80 mg/kg chlorodibromomethane in corn oil by gavage; mice--0, 50, or 100 mg/kg; dose vol--5 ml/kg
Date of First Dose			
9/26/78	11/26/78	2/26/79	Rats--1/3/80; mice--1/9/80
Date of Last Dose			
N/A	12/10/78	5/25/79	Rats--12/28/81; mice--1/12/82
Duration of Dosing			
One time only	14 consecutive days	5 d/wk for 13 wk	5 d/wk for 104 wk (rats); 5 d/wk for 105 wk (mice)
Type and Frequency of Observation			
Observed 1 × h for first 3 h, 2 × d thereafter for mortality and signs of moribundity; initial and final body weights taken	Observed 2 × d for mortality and signs of moribundity; weighed 1 × wk	Observed 2 × d for mortality and signs of moribundity; weighed on d 0, 1 × wk thereafter	Observed 2 × d for mortality or signs of moribundity; weighed 1 × wk for 12 wk, 1 × mo thereafter
Necropsy and Histologic Examination			
Necropsy performed on 1 or 2 animals of each sex and dose level; tissues examined: gross lesions; skin; mandiblar lymph node; mammary gland; salivary gland; thigh muscle; sciatic nerve; sternebrae, vertebrae, or femur including marrow; costochondral junction (rib); thymus; larynx; trachea; lungs and bronchi; heart; thyroid gland; parathyroid; esophagus; stomach; duodenum; jejunum; tissue masses; ileum; colon; cecum; rectum; mesenteric lymph node; liver; gallbladder (mice); pancreas; spleen; kidneys; adrenal glands; urinary bladder; prostate/testes/seminal vesicles or ovaries/uterus; nasal cavity; brain; pituitary; spinal cord; eyes	Necropsy performed on all animals; tissues examined same as in single-administration studies	Necropsy performed on all animals; the following tissues from all vehicle control and high dose animals were examined microscopically: gross lesions and tissue masses; mandibular lymph node; mammary gland; skin; salivary gland; sternebrae; thyroid gland; parathyroid; small intestine; colon; liver; prostate/testes or ovaries/uterus; lungs and bronchi; heart; esophagus; stomach; brain; thymus; trachea; pancreas; spleen; kidneys; adrenal glands; urinary bladder; pituitary; spinal cord (if neurologic signs present); eyes (if abnormal); livers of all male rats and of 125 mg/kg groups of female rats and male mice; kidneys and salivary glands of male and female 125 mg/kg rats; all tissues from one 125 mg/kg and one 15 mg/kg male mouse	Necropsy performed on all animals; the following tissues were examined histopathologically: tissue masses; abnormal regional lymph nodes; skin; mandibular and mesenteric lymph nodes; mammary gland; salivary gland; bone marrow; costochondral junction; thymus; larynx; trachea; lungs and bronchi; heart; thyroid gland; parathyroids; esophagus; stomach; colon duodenum; jejunum; ileum; liver; gallbladder (mice); pancreas; spleen; kidneys; adrenal glands; urinary bladder; testes/prostate/seminal vesicles or ovaries/uterus; brain; pituitary

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORODIBROMOMETHANE (Continued)

Single-Administration Studies	Fourteen-Day Repeated Administration Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE			
Species			
F344/N rats; B6C3F$_1$ mice	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animal Source			
Charles River Breeding Laboratories (Portage, MI)	Same as single-administration studies	Same as single-administrationstudies	Same as single-administration studies
Time Held Before Start of Test			
2 wk	17 d	12 d	Rats--22 d; mice--21 d
Age When Placed on Study			
Rats--6 wk; mice--not reported	Rats--7 wk; mice--8 wk	Rats--6-7 wk; mice--7 wk	8 wk
Age When Killed			
Rats--8 wk; mice--not reported	Rats--9 wk; mice--10 wk	Rats--19-20 wk; mice--20 wk	Rats--113-114 wk; mice--115-116 wk
Necropsy Dates			
10/11/78	Rats--12/12-12/14/78; mice--12/14-12/15/78	Rats--5/30-6/5/79; mice--5/29-5/30/79	Rats--1/4-1/12/82; mice--1/20-1/29/82
Method of Distribution			
Randomized by weight so that average cage weights were approximately equal	Same as single-administration studies	Same as single-administration studies	Assigned to cages according to a table of random numbers
Feed			
Ground Wayne Lab Blox® (Allied Mills, Chicago, IL); freely available	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Bedding			
Aspen Bed® (American Excelsior, Baltimore, MD)	Same as single-administration studies	Aspen Bed® or Betta Chips® (Agway, Northboro, MA)	Same as single-administration studies
Water			
Automatic watering system (Edstom Industries, Waterford, WI); freely available	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages			
Polycarbonate (Lab Products, Inc., Garfield, NJ)	Polycarbonate (Lab Products, Inc., Rochelle Pk, NJ)	Same as 14-d studies	Same as 14-d studies
Cage Filters			
Nonwoven fiber (Lab Products, Rochelle Park, NJ or Snow Filtration, Cincinnati,OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage			
5	5	5	5

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF CHLORODIBROMOMETHANE (Continued)

Single-Administration Studies	Fourteen-Day Repeated Administration Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Animal Room Environment			
10 room air changes/h; temp--23° ± 3° C; fluorescent light 12 h/d; humidity--32%-60%	10 room air changes/h; temp--21° ± 6° C; fluorescent light 12 h/d; humidity--10%-45%	10 room air changes/h; temp--19.4°-30.6° C; fluorescent light 12 h/d; humidity--14%-56%	12 room air changes/h; temp--17.8°-26.7° C (a); fluorescent light 12 h/d; humidity--15%-78%
Other Chemicals on Test in Same Room			
None	None	None	None
CHEMISTRY			
Lot Numbers Used			
F122277	F122277	F122277	F122277; F810626 from 8/10/81 to end of study
Supplier			
Freeman Industries, Inc. (Tuckahoe, NY)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
CHEMICAL/VEHICLE			
Preparation			
Compound and corn oil were mixed by inversion in ground-glass-stoppered graduated cylinders	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Maximum Storage Time			
1 d	10 d	10 d	10 d
Storage Conditions			
4° C in the dark	Same as single-administration studies	4° C	0° ± 5° C

(a) On 3 days, room temperature was 26.7°-28.9° C.

II. MATERIALS AND METHODS

SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and observed for 2 weeks before the study began. The animals were approximately 6 weeks old when placed on study.

Groups of five rats and five mice of each sex were administered a single dose of 160, 310, 630, 1,250, or 2,500 mg/kg chlorodibromomethane in corn oil by gavage. Animals were observed for mortality twice daily for 14 days. Necropsies were performed on at least one animal of each sex and dose group. Details of animal maintenance are presented in Table 1.

FOURTEEN-DAY REPEATED-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and held for 17 days before the study began. The animals were approximately 7-8 weeks old when placed on study.

Groups of five rats of each sex were administered 0, 60, 125, 250, 500, or 1,000 mg/kg chlorodibromomethane in corn oil by gavage for 14 consecutive days. Groups of five mice of each sex were administered 0, 30, 60, 125, 250, or 500 mg/kg on the same schedule.

Animals were housed five per cage. Water and feed were freely available. The rats and mice were observed twice daily for mortality and were weighed once per week. Necropsies were performed on all animals. Details of animal maintenance are presented in Table 1.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxicity of chlorodibromomethane and to determine the doses to be used in the 2-year studies. Four- to five-week-old male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 12 days, and then randomized by weight and assigned to test groups so that the average cage weights were approximately equal for all animals of the same sex and species. Animals were approximately 6-7 weeks old when placed on study.

Groups of 10 rats and 10 mice of each sex were administered 0, 15, 30, 60, 125, or 250 mg/kg chlorodibromomethane in corn oil by gavage, 5 days per week for 13 weeks. Rats and mice were housed five per cage in polycarbonate cages. Feed and water (via an automatic watering system) were freely available. Further experimental details are summarized in Table 1.

Animals were checked twice daily for signs of moribundity and mortality; moribund animals were killed. Individual animal weights were recorded weekly. At the end of the 13-week studies, survivors were killed. Necropsies were performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 1.

TWO-YEAR STUDIES

Study Design

Groups of 50 rats of each sex were administered 0, 40, or 80 mg/kg chlorodibromomethane in corn oil by gavage, 5 days per week (Monday-Friday) for 104 weeks. Groups of 50 mice of each sex were administered 0, 50, or 100 mg/kg 5 days per week (Monday-Friday) for 105 weeks.

Source and Specifications of Test Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N $\times$ C3H/HeN MTV$^-$) mice used in this study were produced under strict barrier conditions at the Charles River Breeding Laboratories (Portage, MI) under a contract to the Carcinogenesis Program. Breeding starts for the foundation colony at the production facility originated at the National Institutes of Health Repository. Animals shipped for testing were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the testing laboratory at 5 weeks of age. The animals were quarantined at the testing facility for 3 weeks. Thereafter, a complete necropsy was performed on a selected number of animals to assess their health. The rodents were placed on study at 8 weeks of age.

The health of the animals was monitored during the course of the study according to the protocols of the NTP Sentinel Animal Program (Appendix K).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ test animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoretograms that demonstrate phenotype expressions of known genetic loci.

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

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because matched concurrent controls were included in each study.

Animal Maintenance

Rats and mice were housed five per cage in polycarbonate cages. Animals were assigned to cages according to a table of random numbers. The cages then were assigned to dosed and vehicle control groups according to another table of random numbers. Cages and bedding were replaced twice per week. Feed and water (via an automatic watering system) were available ad libitum. Details of animal maintenance are summarized in Table 1.

Clinical Examinations and Pathology

All animals were observed twice daily for signs of moribundity or mortality. Clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 12 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the studies. Necropsies were 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 1.

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.

Nonneoplastic lesions are not examined routinely by the quality assurance pathologist or the PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist or the PWG if the findings 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 included 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 necropsies were performed.

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

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

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

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 three time intervals: 0-60 weeks, week 61 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 necropsies were 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--Primary survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher's 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 Data Base: The NTP Historical Control Data Base includes control tumor incidence data from the 2-year studies considered by the May 1, 1979, Peer Review Committee through those 2-year studies reviewed by the NTP Pathology Working Group and processed by the Carcinogenesis Bioassay Data System by March 16, 1983. Historical control tumor incidences for neoplasms showing evidence of chemically related effects are summarized in Appendix F for corn oil gavage control animals.

III. RESULTS

RATS

SINGLE-ADMINISTRATION STUDIES
FOURTEEN-DAY REPEATED-ADMINISTRATION STUDIES
THIRTEEN-WEEK STUDIES
TWO-YEAR STUDIES
Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION STUDIES
FOURTEEN-DAY REPEATED-ADMINISTRATION STUDIES
THIRTEEN-WEEK STUDIES
TWO-YEAR STUDIES
Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

SINGLE-ADMINISTRATION STUDIES

All rats that received 2,500 mg/kg chlorodibromomethane were dead by day 3 (Table 2). All rats that received 310 mg/kg or more were lethargic for 3 hours after dosing. Necropsies were limited to one or two animals per group; no compound-related effects were observed in those animals examined. A high dose of 1,000 mg/kg was selected for male and female rats in the 14-day repeated-administration studies because of the deaths that occurred at the 1,250 and 2,500 mg/kg dose levels.

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF CHLORODIBROMOMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)
MALE				
160	5/5	102.9 ± 4.5	186.0 ± 4.9	+ 83.1 ± 2.9
310	5/5	103.5 ± 3.7	184.4 ± 3.8	+ 80.9 ± 1.4
630	5/5	102.6 ± 4.0	165.8 ± 9.2	+ 63.2 ± 5.7
1,250	(d) 1/5	100.8 ± 3.9	171.7	+ 78.7
2,500	(e) 0/5	101.2 ± 5.9	(f)	(f)
FEMALE				
160	5/5	89.9 ± 3.2	135.1 ± 2.8	+ 45.2 ± 3.4
310	5/5	90.2 ± 2.9	130.6 ± 4.2	+ 40.4 ± 3.2
630	(g) 4/5	90.2 ± 3.6	128.5 ± 3.2	+ 40.9 ± 3.5
1,250	(h) 4/5	90.2 ± 3.0	123.4 ± 2.2	+ 33.5 ± 1.8
2,500	(i) 0/5	90.2 ± 2.5	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial mean body weight includes all animals initially in group. Subsequent calculations are based on only those animals surviving to the end of the study.
(c) Mean weight change of the survivors of the group ± standard error of the mean
(d) Days of death: 4, 4, 5, 5
(e) Days of death: 1, 2, 2, 2, 3
(f) No data are presented due to the 100% mortality in this group.
(g) Day of death: 4
(h) Day of death: 5
(i) Days of death: 2, 2, 2, 2, 2

FOURTEEN-DAY REPEATED-ADMINISTRATION STUDIES

All of the rats of each sex that received 1,000 mg/kg chlorodibromomethane and all of the female rats that received 500 mg/kg were dead by day 6 (Table 3). Lethargy, ataxia, and labored breathing were observed in rats of each sex that received 500 or 1,000 mg/kg. Mottled livers and reddened, darkened renal medullae were seen at gross necropsy in male and female rats administered 500 or 1,000 mg/kg; these effects were considered to be compound related (Table 4). Because of the liver and kidney damage and mortality at 500 and 1,000 mg/kg, a high dose of 250 mg/kg was selected for male and female rats in the 13-week studies.

TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY REPEATED-ADMINISTRATION GAVAGE STUDIES OF CHLORODIBROMOMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)
MALE				
0	5/5	163.3 ± 6.7	213.6 ± 5.8	+ 50.3 ± 7.2
60	5/5	163.0 ± 7.4	214.2 ± 5.9	+ 51.2 ± 5.5
125	5/5	163.0 ± 6.8	215.4 ± 10.3	+ 52.4 ± 5.5
250	5/5	162.6 ± 7.1	190.2 ± 10.4	+ 27.6 ± 5.6
500	(d) 2/5	163.4 ± 8.2	170.0 ± 6.0	− 4.0 ± 8.4
1,000	(e) 0/5	163.4 ± 7.9	(f)	(f)
FEMALE				
0	5/5	125.4 ± 2.5	157.0 ± 2.9	+ 31.6 ± 1.1
60	5/5	125.2 ± 2.1	152.6 ± 1.8	+ 27.4 ± 0.9
125	5/5	125.2 ± 2.2	154.2 ± 1.8	+ 29.0 ± 2.0
250	5/5	125.3 ± 2.7	149.0 ± 3.3	+ 23.7 ± 1.8
500	(g) 0/5	124.8 ± 2.2	(f)	(f)
1,000	(h) 0/5	124.6 ± 2.4	(f)	(f)

(a) Number surviving/number initially in the group
(b) Initial mean body weight includes all animals initially in group. Subsequent calculations are based on only those animals surviving to the end of the study.
(c) Mean weight change of the survivors of the group ± standard error of the mean
(d) Days of death: 5, 6, 8
(e) Days of death: 3, 4, 4, 5, 6
(f) No data are presented due to the 100% mortality in this group.
(g) Days of death: 4, 4, 4, 4, 5
(h) Days of death: 5, 5, 5, 6, 6

TABLE 4. GROSS LESIONS OBSERVED IN RATS IN THE FOURTEEN-DAY REPEATED-ADMINISTRATION GAVAGE STUDIES OF CHLORODIBROMOMETHANE

	Vehicle Control	60 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
MALE						
Liver: mottled	0/5	0/5	1/5	0/5	1/5	2/5
Kidney: medullae darkened	0/5	0/5	0/5	0/5	3/5	5/5
FEMALE						
Liver: mottled	0/5	0/5	0/5	0/5	4/5	5/5
Kidney: medullae darkened	0/5	0/5	0/5	0/5	4/5	5/5

THIRTEEN-WEEK STUDIES

Nine of 10 males and 9/10 females that received 250 mg/kg died before the end of the study (Table 5). Final mean body weights (relative to those of the vehicle controls) of rats that received 250 mg/kg were depressed 47% for males and 25% for females.

Intracytoplasmic clear vacuoles in hepatocytes (vacuolar change), interpreted as severe fatty metamorphosis, were found in the livers of 10/10 male and 9/9 female rats that received 250 mg/kg (Table 6). This change was found in other groups of dosed males and, to some extent, in control groups of male rats. Hepatocellular centrilobular necrosis was observed in high dose male (8/10) and female (7/9) rats. Toxic nephropathy in the renal cortex, characterized by tubular cell degeneration and regeneration and tubular cast formation, was found in 8/10 male and 9/9 female rats that received 250 mg/kg chlorodibromomethane.

Lesions of the salivary gland, characterized as acute inflammation and squamous metaplasia, were seen in high dose male and female rats (Table 6). These lesions have histologic features reported in rats infected with Sialodacryoadenitis virus; because these lesions were seen only in the 250 mg/kg dose groups, the effects are likely due to chlorodibromomethane exposure.

Doses selected for rats for the 2-year studies were 40 and 80 mg/kg chlorodibromomethane in corn oil by gavage, to be administered 5 days per week.

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORODIBROMOMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (c)	Change (d)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	166.8 ± 3.7	330.5 ± 6.3	+ 163.7 ± 6.3	--
15	10/10	166.8 ± 3.8	345.5 ± 6.3	+ 178.7 ± 5.1	104.5
30	10/10	167.0 ± 3.6	343.0 ± 5.9	+ 176.0 ± 5.0	103.8
60	10/10	166.5 ± 4.0	336.6 ± 5.5	+ 170.1 ± 5.6	101.8
125	10/10	166.4 ± 3.7	306.9 ± 4.1	+ 140.5 ± 4.4	92.9
250	(e) 1/10	166.6 ± 3.7	173.8	+ 23.2	52.6
FEMALE					
0	10/10	124.2 ± 1.9	201.5 ± 2.0	+ 77.3 ± 1.6	--
15	10/10	124.7 ± 2.0	203.9 ± 2.1	+ 79.2 ± 3.0	101.2
30	10/10	124.5 ± 2.1	200.2 ± 3.9	+ 75.7 ± 3.3	99.4
60	10/10	123.9 ± 2.3	205.1 ± 3.5	+ 81.2 ± 3.3	101.8
125	10/10	124.4 ± 2.2	206.1 ± 1.8	+ 81.7 ± 2.0	102.3
250	(f) 1/10	123.1 ± 2.3	152.2	+ 29.8	75.5

(a) Number surviving/number initially in the group
(b) Initial mean body weight includes all animals initially in group. Subsequent calculations are based on only those animals surviving to the end of the study.
(c) Final weights are taken from the week-12 individual body weights.
(d) Mean weight change of the survivors of the group ± standard error of the mean
(e) Week of death: 8, 8, 9, 9, 9, 9, 9, 9, 10
(f) Week of death: 5, 6, 8, 9, 9, 9, 9, 10, 10

TABLE 6. HISTOPATHOLOGIC LESIONS IN RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORODIBROMOMETHANE

	Dose (mg/kg)					
	Vehicle Control	15	30	60	125	250
MALE						
Liver						
Vacuolar change (a)	4/10	7/10	8/10	10/10	10/10	10/10
Bile duct hyperplasia	0/10	0/10	0/10	0/10	0/10	1/10
Centrilobular necrosis	0/10	(b) 1/10	0/10	0/10	0/10	8/10
Kidney						
Toxic nephropathy	0/10	(c) NE	NE	NE	0/10	8/10
Salivary Gland						
Inflammation	0/10	NE	NE	NE	0/10	5/10
Squamous metaplasia	0/10	NE	NE	NE	0/10	9/10
FEMALE						
Liver						
Vacuolar change (a)	1/10	NE	NE	NE	0/10	9/9
Bile duct hyperplasia	1/10	NE	NE	NE	0/10	6/9
Centrilobular necrosis	0/10	NE	NE	NE	0/10	7/9
Kidney						
Toxic nephropathy	0/10	NE	NE	NE	0/10	9/9
Salivary Gland						
Inflammation	0/10	NE	NE	NE	0/10	5/8
Squamous metaplasia	0/10	NE	NE	NE	0/10	6/8

(a) Interpreted as fatty metamorphosis
(b) Focal necrosis
(c) Not examined

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male rats were lower than those of the vehicle controls after week 20 (Table 7). Body weights of other dosed groups were similar to those of the vehicle controls throughout the experiment. No compound-related clinical signs were observed.

TABLE 7. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORODIBROMOMETHANE

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	154	50	157	101.9	50	155	100.6	50
1	183	50	186	101.6	50	185	101.1	50
2	202	50	210	104.0	50	209	103.5	50
3	226	50	232	102.7	50	230	101.8	50
4	242	50	250	103.3	50	245	101.2	50
5	256	50	264	103.1	50	263	102.7	50
6	267	50	275	103.0	50	271	101.5	50
7	281	50	286	101.8	50	285	101.4	50
8	288	50	296	102.8	50	289	100.3	50
9	298	50	307	103.0	50	300	100.7	50
10	305	50	313	102.6	50	306	100.3	50
11	313	50	321	102.6	50	313	100.0	50
12	313	50	322	102.9	50	315	100.6	50
16	343	50	354	103.2	50	341	99.4	50
20	366	50	370	101.1	50	354	96.7	50
24	384	50	384	100.0	50	360	93.8	50
28	399	50	396	99.2	49	374	93.7	49
32	414	50	413	99.8	49	388	93.7	49
36	409	50	416	101.7	48	394	96.3	49
40	424	50	427	100.7	47	398	93.9	49
44	427	50	436	102.1	47	413	96.7	49
48	441	50	452	102.5	47	422	95.7	49
52	457	50	454	99.3	47	427	93.4	49
56	452	50	440	97.3	47	425	94.0	48
60	470	50	465	98.9	47	430	91.5	48
64	473	50	469	99.2	47	437	92.4	48
68	478	50	474	99.2	47	438	91.6	48
72	486	46	471	96.9	46	444	91.4	48
76	489	46	475	97.1	46	445	91.0	47
80	487	46	477	97.9	44	446	91.6	47
84	485	44	490	101.0	44	449	92.6	47
88	481	44	476	99.0	43	447	92.9	47
92	479	41	472	98.5	42	444	92.7	47
96	469	40	463	98.7	42	440	93.8	47
100	462	40	460	99.6	40	438	94.8	45
105	465	34	447	96.1	38	429	92.3	43
FEMALE								
0	112	50	108	96.4	50	115	102.7	50
1	129	50	126	97.7	50	128	99.2	50
2	140	50	138	98.6	50	140	100.0	50
3	150	50	148	98.7	50	151	100.7	50
4	157	50	153	97.5	50	157	100.0	50
5	160	50	160	100.0	50	163	101.9	50
6	166	50	167	100.6	50	170	102.4	50
7	169	50	171	101.2	50	178	105.3	50
8	172	50	176	102.3	50	180	104.7	50
9	178	50	180	101.1	50	184	103.4	50
10	180	50	182	101.1	50	187	103.9	50
11	183	50	184	100.5	50	189	103.3	50
12	184	50	186	101.1	50	190	103.3	50
16	195	50	197	101.0	50	202	103.6	50
20	201	50	206	102.5	50	211	105.0	50
24	209	50	214	102.4	50	219	104.8	50
28	215	50	221	102.8	50	225	104.7	50
32	220	50	226	102.7	50	229	104.1	50
36	215	50	226	105.1	50	229	106.5	50
40	228	50	240	105.3	50	241	105.7	50
44	236	50	249	105.5	50	253	107.2	50
48	239	50	257	107.5	50	259	108.4	50
52	246	50	263	106.9	50	262	106.5	50
56	254	50	271	106.7	50	268	105.5	50
60	265	50	277	104.5	49	270	101.9	50
64	269	50	285	105.9	49	275	102.2	50
68	277	50	288	104.0	49	277	100.0	50
72	285	50	292	102.5	48	278	97.5	50
76	293	50	300	102.4	48	287	98.0	50
80	298	50	306	102.7	46	290	97.3	50
84	303	49	314	103.6	45	296	97.7	48
88	305	48	320	104.9	44	298	97.7	48
92	306	47	319	104.2	44	296	96.7	48
96	305	47	320	104.9	43	298	97.7	47
100	310	44	323	104.2	41	303	97.7	44
105	304	41	316	103.9	38	302	99.3	41

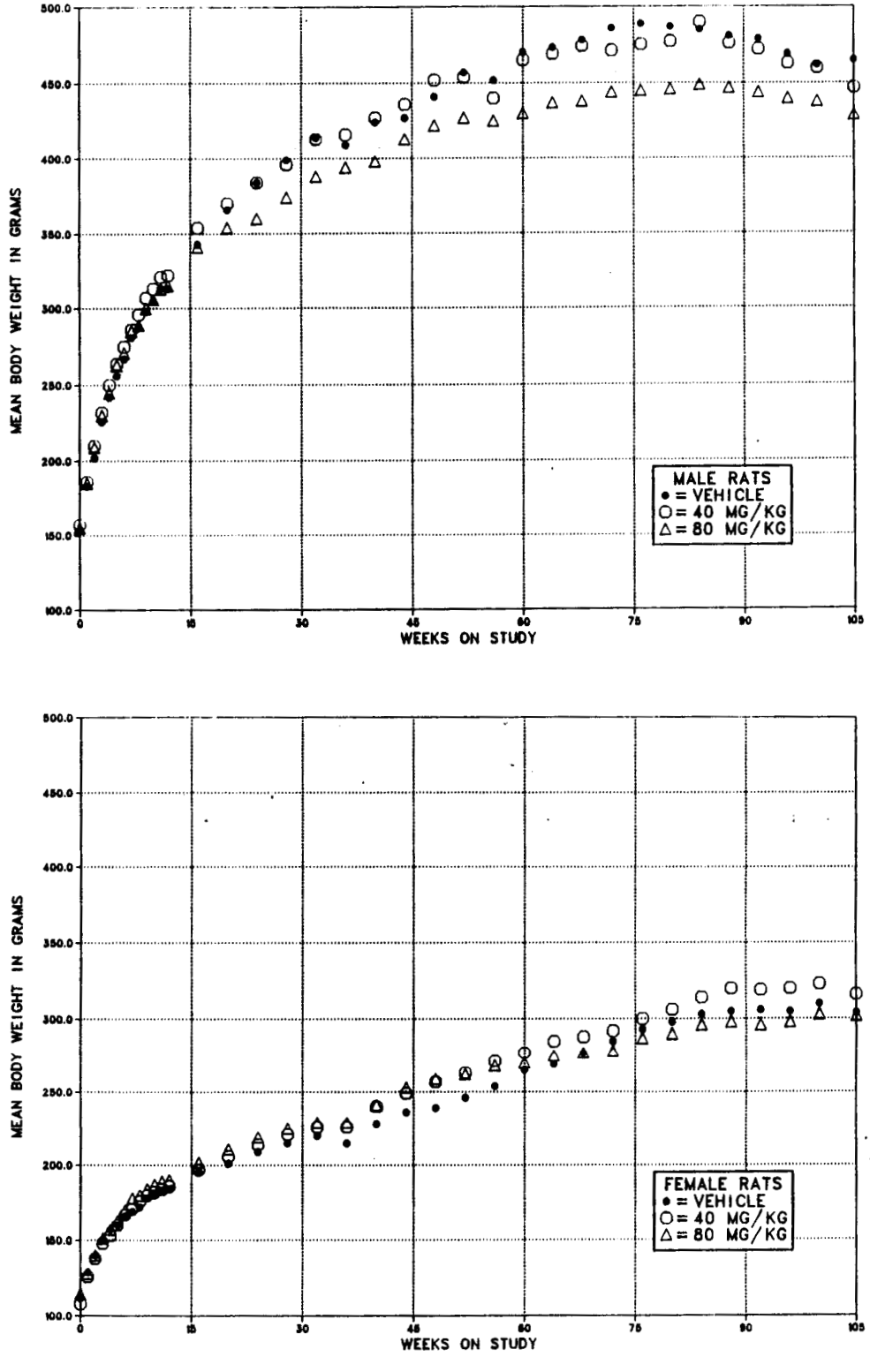


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED CHLORODIBROMOMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of the survival of male and female rats administered chlorodibromomethane by gavage at the doses used in these studies and those of the vehicle controls are shown in the Kaplan and Meier curves in Figure 2. No significant differences in survival were observed between any groups (Table 8).

Pathology and Statistical Analyses of Results

This section describes significant or noteworthy changes in the incidence of animals with neoplastic or nonneoplastic lesions. Histopathologic findings on neoplasms in rats are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 give 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, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

At no site were neoplastic lesions observed at statistically significant increased incidences in the dosed groups.

TABLE 8. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORODIBROMOMETHANE

	Vehicle Control	40 mg/kg	80 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	16	12	7
Killed at termination	34	38	43
Survival P values (c)	0.052	0.580	0.060
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	9	12	9
Killed at termination	39	37	41
Died during termination period	2	1	0
Survival P values (c)	1.00	0.552	0.992

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

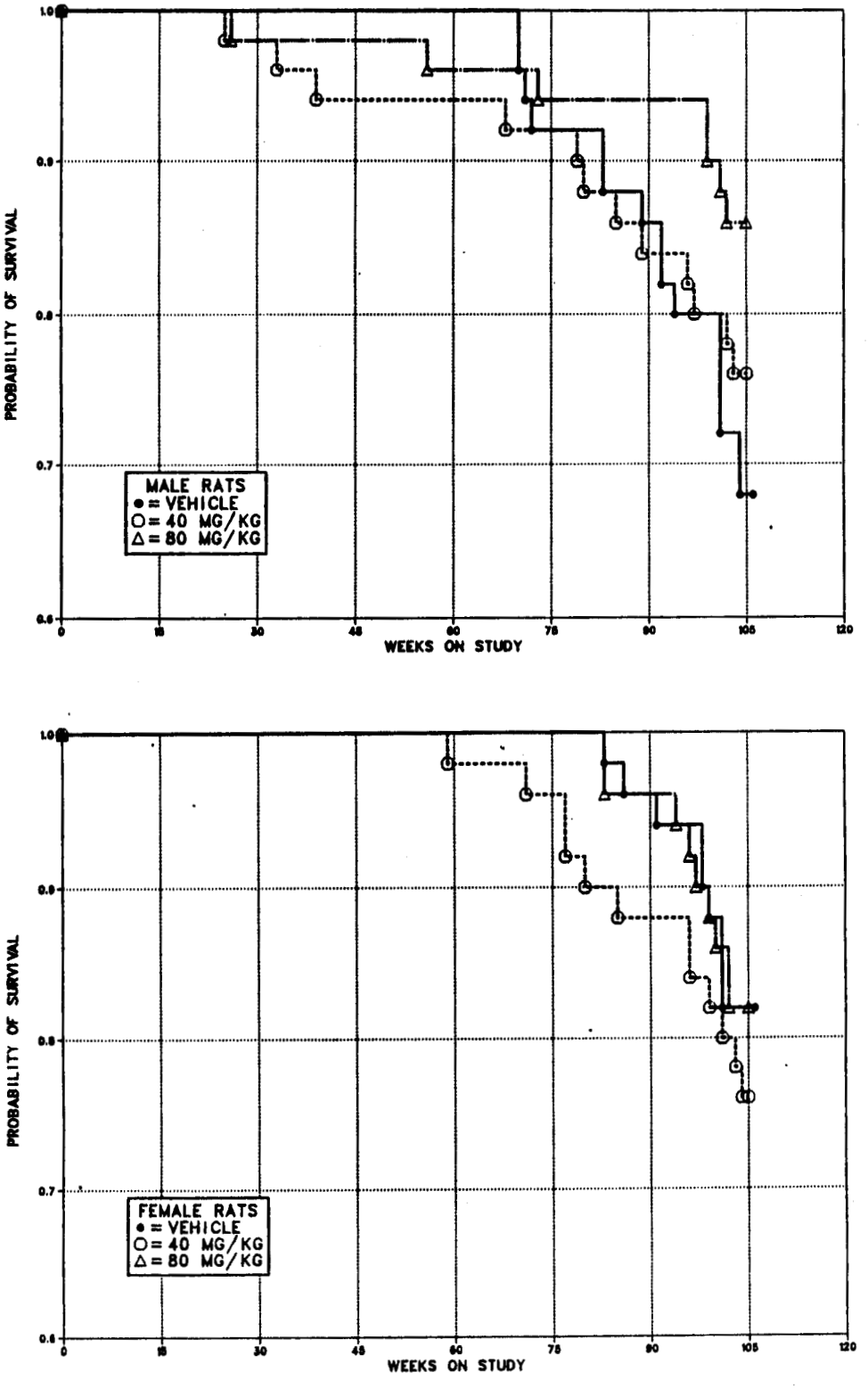


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED CHLORODIBROMOMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Liver: Livers of rats of each sex had lesions that were considered to be due to toxic effects of chlorodibromomethane. Fatty change and ground-glass cytoplasmic change occurred more frequently in dosed groups than in vehicle controls; a dose response was apparent. Ground-glass cytoplasmic change occurred in some individual hepatocytes and appeared as pink-staining homogeneous or lightly stippled cytoplasm in slightly enlarged liver cells. The nucleus was usually pushed to one side. Occasionally there was no liver cell enlargement, and the ground-glass change appeared as a pink-staining hyaline droplet in the cytoplasm. Fatty change was seen in 27/50 vehicle control, 47/50 low dose, and 49/50 high dose male rats. The incidences of fatty change in female rats were 12/50, 23/50, and 50/50. Ground-glass cytoplasmic changes occurred in 8/50, 22/50, and 34/50 male rats. The incidences of ground-glass cytoplasmic change in female rats were 0/50, 1/50, and 12/50.

The incidences of basophilic cytoplasmic changes were decreased in dosed male and female rats (males: vehicle control--29/50; low dose--7/50; high dose--8/50; females: 47/50; 26/50; 18/50).

Kidney: Nephrosis was observed at dose-related increased incidences in dosed female rats (vehicle control, 7/50; low dose, 11/50; high dose, 14/50). The incidences of nephrosis in dosed and vehicle control male rats were comparable (42/50; 44/50; 41/50).

Thyroid Gland: Statistically significant negative trends ($P < 0.05$) occurred in the incidence of follicular cell carcinomas and follicular cell adenomas or carcinomas (combined) (vehicle control, 3/49; low dose, 2/47; high dose, 0/49) in male rats and C-cell carcinomas and C-cell adenomas or carcinomas (combined) (6/49; 2/49; 1/48) in female rats. The incidence of C-cell carcinomas in high dose female rats was significantly lower than that in the vehicle controls.

Hematopoietic System: Mononuclear cell leukemia in male rats occurred with a statistically significant negative trend, and the incidence in the high dose group was significantly lower (by the life table test only) than that in the vehicle controls (vehicle control, 6/50; low dose, 3/50; high dose, 1/50). The incidence of mononuclear cell leukemia in female rats was increased in the high dose group but not significantly so: vehicle control, 6/50; low dose, 6/50; high dose, 10/50.

Mammary Gland: Fibroadenomas in female rats occurred with a significant negative trend, and the incidence in the high dose group was significantly lower than that in the vehicle controls (Table 9). The following incidences of this tumor were observed in male rats: vehicle control, 3/50; low dose, 0/50; high dose, 1/50.

Uterus: Endometrial stromal polyps occurred with a significant negative trend, and the incidence in the high dose group was significantly less than that in the vehicle controls (Table 10).

Testis: Interstitial cell tumors occurred with a significant negative trend by the life table test ($P = 0.003$) but not by the incidental tumor test, and the incidences in the dosed groups were significantly lower than that in the vehicle controls by the life table test ($P < 0.05$): vehicle control, 48/50; low dose, 43/50; high dose, 45/49.

TABLE 9. ANALYSIS OF MAMMARY GLAND LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORODIBROMOMETHANE (a)

	Vehicle Control	40 mg/kg	80 mg/kg
Cystic Hyperplasia			
Overall Rates	13/50 (26%)	3/50 (6%)	5/50 (10%)
Fibroadenoma (b)			
Overall Rates	18/50 (36%)	12/50 (24%)	4/50 (8%)
Adjusted Rates	41.6%	29.8%	9.3%
Terminal Rates	16/41 (39%)	10/38 (26%)	3/41 (7%)
Life Table Tests	P<0.001N	P=0.202N	P=0.001N
Incidental Tumor Tests	P<0.001N	P=0.168N	P<0.001N

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Mean historical incidence at this laboratory: 68/200, 34% ± 2.8%

TABLE 10. ANALYSIS OF UTERINE LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF CHLORODIBROMOMETHANE

	Vehicle Control	40 mg/kg	80 mg/kg
Endometrial Stromal Polyp (a)			
Overall Rates	(b) 14/50 (28%)	8/50 (16%)	5/50 (10%)
Adjusted Rates	32.5%	19.7%	11.0%
Terminal Rates	12/41 (29%)	6/38 (16%)	2/41 (5%)
Life Table Tests	P=0.018N	P=0.162N	P=0.025N
Incidental Tumor Tests	P=0.014N	P=0.129N	P=0.021N
Endometrial Stromal Sarcoma			
Overall Rates	2/50 (4%)	2/50 (4%)	1/50 (2%)

(a) Mean historical incidence at this laboratory: 47/200, 23.5% ± 3.4%
(b) One animal had both an endometrial stromal polyp and sarcoma.

SINGLE-ADMINISTRATION STUDIES

All the mice that received 2,500 mg/kg chlorodibromomethane and all the male and 4/5 female mice that received 1,250 mg/kg died between days 2 and 8 (Table 11). Necropsies were performed on one or two animals in each dose group. Livers with discolored foci and kidneys with dark red or pale medullae were seen more frequently in dosed than in control animals. Because of the mortality at 2,500 and 1,250 mg/kg, 500 mg/kg was selected as the highest dose for male and female mice in the 14-day repeated-administration studies.

TABLE 11. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF CHLORODIBROMOMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)
MALE				
160	5/5	24.1 ± 0.6	27.9 ± 0.9	+ 3.8 ± 0.9
310	(d) 4/5	23.8 ± 0.6	25.4 ± 0.4	+ 2.0 ± 0.3
630	(e) 2/5	23.6 ± 0.6	25.7 ± 0.1	+ 2.8 ± 1.1
1,250	(f) 0/5	24.2 ± 0.8	(g)	(g)
2,500	(h) 0/5	23.9 ± 0.6	(g)	(g)
FEMALE				
160	5/5	17.7 ± 0.3	21.3 ± 0.4	+ 3.6 ± 0.3
310	5/5	17.6 ± 0.4	20.5 ± 0.5	+ 2.9 ± 0.2
630	5/5	17.4 ± 0.4	20.7 ± 0.4	+ 3.3 ± 0.6
1,250	(i) 1/5	17.6 ± 0.4	20.3	+ 2.1
2,500	(j) 0/5	17.6 ± 0.4	(g)	(g)

(a) Number surviving/number initially in the group
(b) Initial mean body weight includes all animals initially in group. Subsequent calculations are based on only those animals surviving to the end of the study.
(c) Mean weight change of the survivors of the group ± standard error of the mean
(d) Day of death: 16
(e) Days of death: 3, 4, 4
(f) Days of death: 3, 3, 3, 3, 4
(g) No data are presented due to the 100% mortality in this group.
(h) Days of death: 2, 2, 2, 2, 4
(i) Days of death: 3, 3, 4, 8
(j) Days of death: 3, 3, 4, 4, 4

FOURTEEN-DAY REPEATED-ADMINISTRATION STUDIES

The deaths of 4/5 male and 3/5 female mice that received 500 mg/kg chlorodibromomethane were considered to be compound related (Table 12). Lethargy, ataxia, and labored breathing were observed after dosing in mice of each sex that received 500 mg/kg. Mottled livers and reddened renal medullae were seen in male and female mice administered 500 mg/kg; these changes were considered to be compound related (Table 13). Stomach lesions (white papillomatous nodules) were seen in male mice that received 125, 250, or 500 mg/kg and in female mice that received 250 or 500 mg/kg.

As a result of the deaths and pathologic changes seen in animals administered 500 mg/kg, a high dose of 250 mg/kg was selected for mice in the 13-week studies.

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY REPEATED-ADMINISTRATION GAVAGE STUDIES OF CHLORODIBROMETHANE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)
MALE				
0	5/5	25.2 ± 0.5	27.2 ± 0.6	+2.0 ± 0.1
30	4/5	25.0 ± 0.6	26.8 ± 0.6	+1.9 ± 1.1
60	5/5	26.0 ± 0.7	28.4 ± 1.7	+2.4 ± 1.1
125	5/5	25.6 ± 0.8	26.8 ± 1.1	+1.2 ± 1.5
250	5/5	25.5 ± 0.8	25.8 ± 1.0	+0.3 ± 0.7
500	(d) 1/5	25.5 ± 1.0	25.0	−1.0
FEMALE				
0	4/5	19.6 ± 0.5	21.0 ± 0.9	+1.5 ± 0.5
30	4/5	19.5 ± 0.6	20.8 ± 0.5	+0.9 ± 0.2
60	4/5	19.6 ± 0.5	22.5 ± 0.6	+2.6 ± 0.2
125	5/5	19.2 ± 0.6	21.4 ± 0.7	+2.2 ± 0.4
250	5/5	19.6 ± 0.7	21.2 ± 1.0	+1.6 ± 1.0
500	(e) 2/5	19.7 ± 1.6	21.0 ± 2.0	+0.5 ± 0.1

(a) Number surviving/number initially in the group
(b) Initial mean body weight includes all animals initially in group. Subsequent calculations are based on only those animals surviving to the end of the study.
(c) Mean weight change of the survivors of the group ± standard error of the mean
(d) Day of death: 2, 3, 3, 7
(e) Day of death: 3, 4, 4

TABLE 13. GROSS LESIONS IN MICE IN THE FOURTEEN-DAY REPEATED-ADMINISTRATION GAVAGE STUDIES OF CHLORODIBROMOMETHANE

	Vehicle Control	30 mg/kg	60 mg/kg	125mg/kg	250 mg/kg	500 mg/kg
MALE						
Liver: mottled	0/5	0/5	0/5	0/5	1/5	2/5
Kidney: medullae reddened	0/5	1/5	1/5	0/5	1/5	4/5
Stomach: white papillomatous nodules	0/5	0/5	0/5	1/5	1/5	1/5
FEMALE						
Liver: mottled	0/5	0/5	0/5	0/5	0/5	2/5
Kidney: medullae reddened	2/5	1/5	1/5	1/5	0/5	4/5
Stomach: white papillomatous nodules	0/5	0/5	0/5	0/5	1/5	2/5

THIRTEEN-WEEK STUDIES

Sporadic deaths in male mice were considered to be unrelated to dosing (Table 14). Final mean body weights relative to those of the vehicle controls were depressed 5.4%-6.3% for males that received 125 or 250 mg/kg chlorodibromomethane and 2.6%-5.9% for females that received 125 or 250 mg/kg.

Necrosis and vacuolar change (interpreted as fatty metamorphosis) of the liver were found in 5/10 male mice receiving 250 mg/kg (Table 15).

Toxic nephropathy, characterized by tubular degeneration or mineralization of the kidney, was seen in 5/10 male mice administered 250 mg/kg. Similar compound-related liver and kidney lesions were not seen in female mice.

A dose of 250 mg/kg was considered to be too high for the 2-year studies because liver and kidney lesions were produced at that dose in male mice. Doses selected for mice for the 2-year studies were 50 and 100 mg/kg chlorodibromomethane, to be administered in corn oil 5 days per week.

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

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final (c)	Change (d)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	9/10	25.1 ± 0.6	35.1 ± 0.9	+ 10.3 ± 0.6	--
15	9/10	25.2 ± 0.5	34.9 ± 0.8	+ 9.9 ± 0.5	99.4
30	10/10	24.9 ± 0.6	34.7 ± 1.0	+ 9.8 ± 0.6	98.9
60	10/10	25.0 ± 0.7	34.2 ± 1.0	+ 9.2 ± 0.6	97.4
125	9/10	24.7 ± 0.8	33.2 ± 0.8	+ 8.5 ± 0.7	94.6
250	9/10	25.1 ± 0.6	32.9 ± 0.8	+ 7.8 ± 0.6	93.7
FEMALE					
0	10/10	18.9 ± 0.3	26.9 ± 0.5	+ 8.0 ± 0.3	--
15	10/10	19.0 ± 0.4	27.6 ± 0.9	+ 8.6 ± 0.7	102.6
30	10/10	18.9 ± 0.4	29.1 ± 0.9	+ 10.2 ± 0.5	108.2
60	10/10	19.0 ± 0.4	27.2 ± 0.4	+ 8.2 ± 0.4	101.1
125	10/10	18.8 ± 0.3	26.2 ± 0.6	+ 7.4 ± 0.3	97.4
250	10/10	18.6 ± 0.3	25.3 ± 0.4	+ 6.7 ± 0.2	94.1

(a) Number surviving/number initially in the group
(b) Initial mean body weight includes all animals initially in group. Subsequent calculations are based on only those animals surviving to the end of the study.
(c) Final weights are taken from the week-12 individual body weights.
(d) Mean weight change of the survivors of the group ± standard error of the mean

TABLE 15. HISTOPATHOLOGIC LESIONS IN MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF CHLORODIBROMOMETHANE

	Dose (mg/kg)					
	Vehicle Control	15	30	60	125	250
MALE						
Liver						
Vacuolar change	0/10	(a) NE	NE	NE	0/10	5/10
Multifocal necrosis	0/10	NE	NE	NE	0/10	1/10
Kidney						
Toxic nephropathy	0/10	NE	NE	NE	0/10	5/10
Mineralization without nephropathy	0/10	NE	NE	NE	0/10	1/10
FEMALE						
Liver						
Multifocal necrosis	1/10	NE	NE	NE	NE	1/10

(a) Not examined

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose mice of each sex were lower than those of the vehicle controls throughout most of the study (Table 16 and Figure 3). Mean body weights of low dose mice were notably lower than those of the vehicle controls after week 59 (when all the low dose mice received an overdose of chlorodibromomethane). No compound-related clinical signs were observed.

TABLE 16. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORODIBROMOMETHANE

Weeks on Study	Vehicle Control		Low Dose			High Dose		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of veh. controls)	No. of Survivors
MALE								
0	25	50	25	100.0	50	25	100.0	50
1	27	50	26	96.3	50	26	96.3	50
2	28	50	28	100.0	50	28	100.0	50
3	30	50	29	96.7	50	28	93.3	50
4	29	50	30	103.4	50	27	93.1	50
5	31	50	31	100.0	50	28	90.3	50
6	32	50	32	100.0	50	30	93.8	50
7	32	50	32	100.0	50	30	93.8	50
8	32	50	32	100.0	50	30	93.8	50
9	33	50	32	97.0	50	30	90.9	50
10	33	50	33	100.0	50	31	93.9	50
11	34	50	34	100.0	50	32	94.1	50
12	35	50	34	97.1	50	31	88.6	50
16	37	50	35	94.6	50	33	89.2	50
20	38	50	37	97.4	50	34	89.5	50
24	39	50	39	100.0	50	36	92.3	49
28	40	50	40	100.0	50	36	90.0	49
32	41	50	40	97.6	50	36	87.8	49
36	41	50	40	97.6	50	37	90.2	49
40	43	50	42	97.7	50	38	88.4	49
44	44	50	42	95.5	50	38	86.4	49
48	46	50	44	95.7	50	40	87.0	49
52	47	50	45	95.7	50	40	85.1	49
56	48	50	44	95.7	50	41	89.1	49
60	47	50	37	78.7	(a) 15	41	87.2	48
64	47	50	39	83.0	15	42	89.4	48
68	47	50	41	87.2	15	42	89.4	47
72	47	50	41	87.2	15	42	89.4	47
76	46	50	41	89.1	14	41	89.1	46
80	46	50	40	87.0	14	39	84.8	45
84	46	50	41	89.1	13	37	80.4	35
88	46	48	40	87.0	12	38	82.6	34
92	46	47	38	82.6	12	38	82.6	34
96	45	47	40	88.9	10	37	82.2	33
100	45	46	41	91.1	8	38	84.4	31
104	44	45	37		7	35	79.5	31
106	43	44	37		7	37	86.0	29
FEMALE								
0	20	50	20	100.0	50	20	100.0	50
1	23	50	21	91.3	50	21	91.3	50
2	22	50	22	100.0	50	22	100.0	50
3	24	50	23	95.8	50		100.0	50
4	25	50	23	92.0	50		92.0	50
5	25	50	24	96.0	50	24	96.0	50
6	28	50	26	92.9	50	26	92.9	50
7	26	50	26	100.0	50	25	96.2	50
8	25	50	25	100.0	50	25	100.0	50
9	26	50	27	103.8	50	25	96.2	50
10	27	50	27	100.0	50	26	96.3	50
11	28	50	28	100.0	50	27	96.4	50
12	28	50	28	100.0	50	27	96.4	50
16	30	50	30	100.0	50	29	96.7	49
20	33	50	32	97.0	50	31	93.9	49
24	33	50	33	100.0	50	32	97.0	49
28	36	50	35	97.2	50	33	91.7	49
32	36	50	36	100.0	50	35	97.2	49
36	37	50	38	102.7	50	37	100.0	49
40	38	50	38	100.0	50	38	100.0	49
44	40	50	39	97.5	50	37	92.5	49
48	42	50	41	97.6	50	40	95.2	48
52	44	49	43	97.7	50	40	90.9	48
56	45	47	44	97.8	50	43	95.6	48
60	47	46	42	89.4	(a) 50	42	89.4	48
64	46	46	44	95.7	50	43	93.5	48
68	48	46	45	93.8	50	44	91.7	47
72	48	44	46	95.8	50	44	91.7	47
76	49	43	46	93.9	50	45	91.8	47
80	49	43	46	93.9	50	44	89.8	47
84	48	43	45	93.8	48	42	87.5	45
88	49	42	46	93.9	44	42	85.7	44
92	48	41	46	95.8	43	43	89.6	42
96	46	41	44	95.7	40	41	89.1	41
100	47	35	45	95.7	35	41	87.2	39
104	47	33	44	93.6	30	40	85.1	39
106	47	32	43	91.5	27	39	83.0	37

(a) Low dose male and female mice received a sevenfold overdose of chemical in corn oil at week 58.

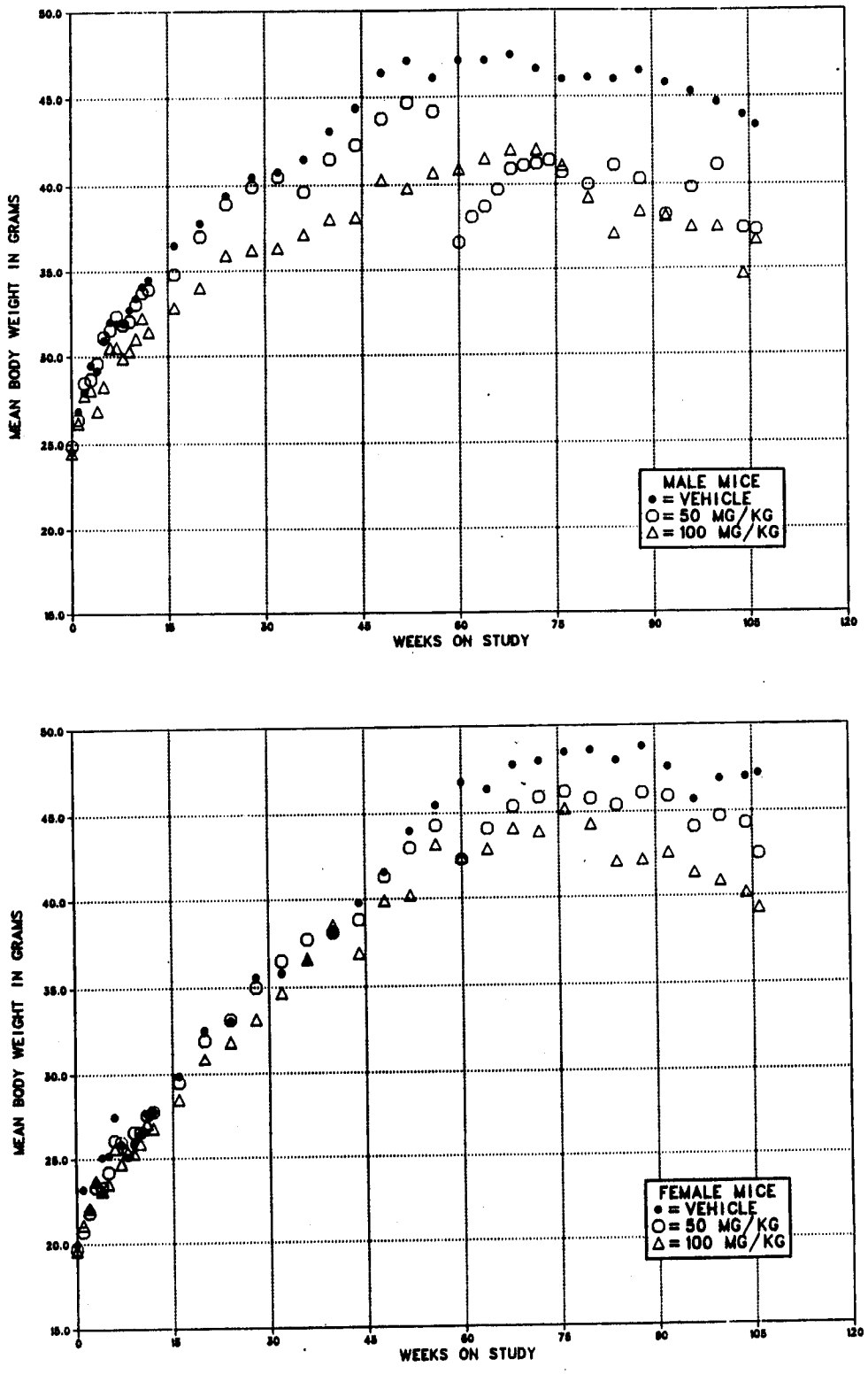


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED CHLORODIBROMOMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of the survival of male and female mice administered chlorodibromomethane at the doses of these studies and those of the vehicle controls are shown in the Kaplan and Meier curves in Figure 4. Survival of low dose and high dose male mice was significantly lower than that of the vehicle controls (Table 17). An accidental overdose caused the death of 35 low dose male mice at weeks 58-59; thus, the tumor incidence data for this group were considered inadequate for tumor analysis. Low dose female mice received the same dose preparation at week 58, but no adverse effects were noted. Nine high dose male mice died at week 82; no explanation for these deaths could be ascertained.

Pathology and Statistical Analyses of Results

This section describes significant or noteworthy changes in the incidence of animals with neoplastic or nonneoplastic lesions. Histopathologic findings on neoplasms in mice are summarized in Appendix B, Tables B1 and B2; Tables B3 and B4 give 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, contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 17. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORODIBROMOMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	6	8	21
Accidentally killed	0	35	0
Killed at termination	44	7	29
Survival P values (c)	0.001	0.001	0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	18	22	12
Animals missing	0	1	0
Killed at termination	32	27	36
Died during termination period	0	0	2
Survival P values (c)	0.271	0.650	0.310

(a) Terminal kill period: weeks 106-107
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

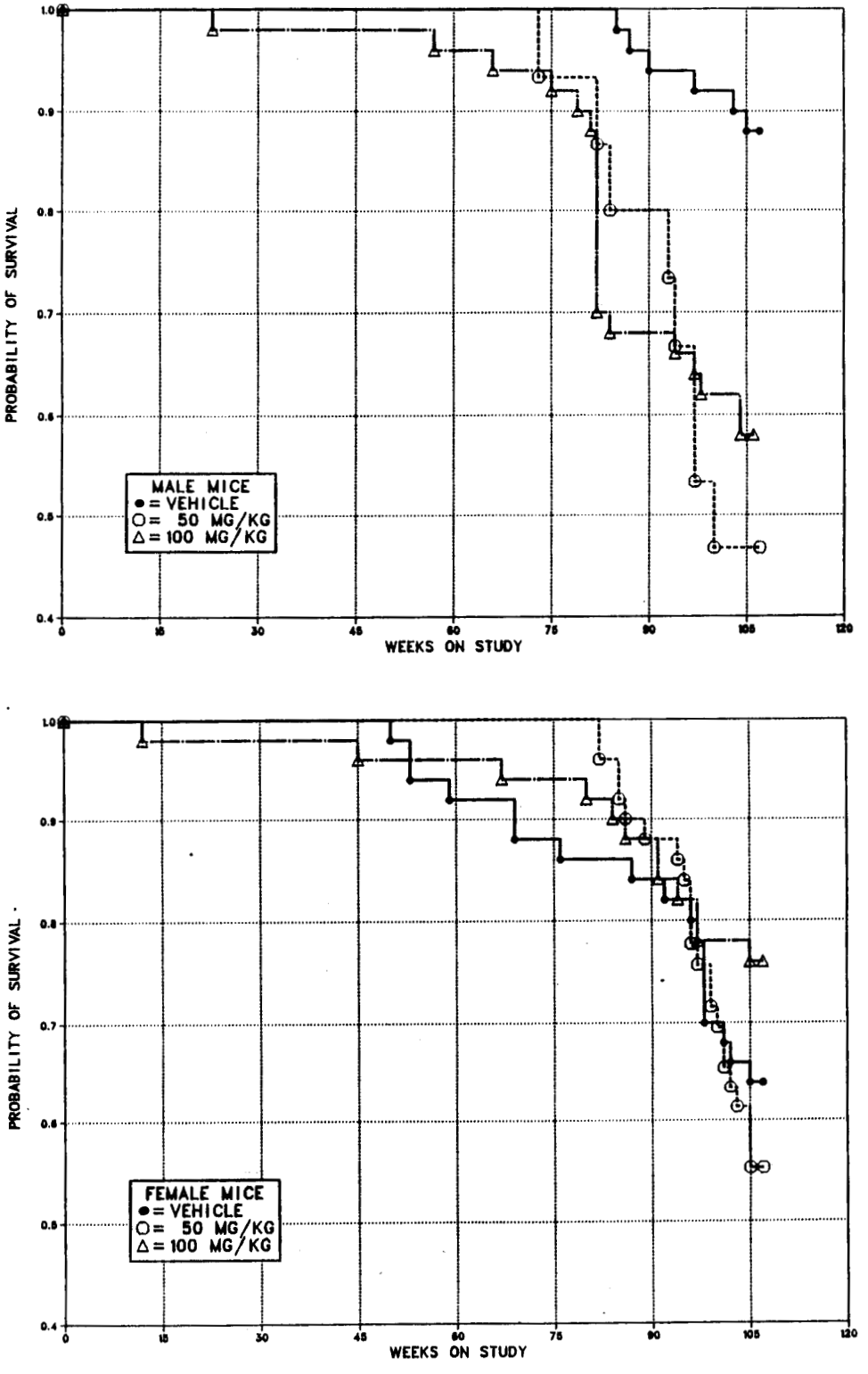


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED CHLORODIBROMOMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

Liver: Fatty metamorphosis was observed at increased incidences in dosed mice of each sex (male: vehicle control, 13/50; low dose, 32/50; high dose, 20/50; female: 7/50; 21/49; 28/50). Hepatocytomegaly was found at increased incidences in high dose male mice (0/50; 0/50; 12/50). Necrosis of the liver was observed at increased incidences in dosed male mice (2/50; 29/50; 9/50). Calcification of the liver was observed at increased incidences in high dose female mice (0/50; 0/49; 7/50).

Toxicity of chlorodibromomethane to the liver of low dose male mice was seen in the group that died at weeks 58-59; centrilobular necrosis was observed in 28/35 animals and fatty metamorphosis was observed in 32/35 animals (Table 18).

The tumor incidence data for low dose male mice were considered inadequate for tumor analysis.

The incidence of hepatocellular carcinomas in high dose male mice was significantly greater than that in the vehicle control group; the combined incidence of hepatocellular adenomas or carcinomas was increased by the life table test but not by the incidental tumor test (Table 19).

Hepatocellular adenomas and hepatocellular adenomas or carcinomas (combined) in female mice occurred with significant positive trends, and the incidences in the high dose group were significantly greater than those in the vehicle control group (Table 20). Although the incidence of fatty metamorphosis and calcification of the liver increased in high dose female mice, these nonneoplastic lesions were not seen in all animals with tumors; 2/19 high dose female mice with adenomas or carcinomas also had calcification of the liver, and 9/19 high dose female mice with adenomas or carcinomas also had fatty metamorphosis of the liver.

TABLE 18. NUMBERS OF MALE MICE WITH LIVER AND KIDNEY LESIONS IN THE TWO-YEAR GAVAGE STUDY OF CHLORODIBROMOMETHANE

	Vehicle Control	Low Dose		High Dose
		Animals Dying at Weeks 58-59	Animals Living to Terminal Kill (longer than 73 wk)	
Number examined	50	35	(a) 15	50
Liver				
Necrosis	2	28	1	9
Fatty metamorphosis	13	32	0	20
Hepatocytomegaly	0	0	0	12
Adenoma	14	3	2	10
Carcinoma	10	2	7	19
Adenoma or carcinoma	23	5	9	27
Kidney				
Nephrosis (b)	0	35	10	37
Calcification (tubular)	0	12	1	0

(a) Animals died or were killed at weeks 73, 82, 84, 93, 94, 97 (2 animals) or after 100 weeks (8 animals).
(b) Kidney or kidney/tubular nephrosis

TABLE 19. ANALYSIS OF LIVER TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORODIBROMOMETHANE (a)

	Vehicle Control	100 mg/kg
MALE		
Adenoma (b)		
Overall Rates	14/50 (28%)	10/50 (20%)
Adjusted Rates	31.8%	32.6%
Terminal Rates	14/44 (32%)	9/29 (31%)
Life Table Tests		P=0.521
Incidental Tumor Tests		P=0.587
Carcinoma (c)		
Overall Rates	10/50 (20%)	19/50 (38%)
Adjusted Rates	21.6%	53.0%
Terminal Rates	8/44 (18%)	13/29 (45%)
Life Table Tests		P=0.002
Incidental Tumor Tests		P=0.030
Adenoma or Carcinoma (Combined) (d)		
Overall Rates	23/50 (46%)	27/50 (54%)
Adjusted Rates	49.9%	74.2%
Terminal Rates	21/44 (48%)	20/29 (69%)
Life Table Tests		P=0.007
Incidental Tumor Tests		P=0.065

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Mean historical incidence at this laboratory, 36/199, 18.1% ± 5.7%; historical incidence throughout the program, 134/1,084, 12.4% ± 6.7%
(c) Mean historical incidence at this laboratory, 33/199, 16.6% ± 5.5%; historical incidence throughout the program, 222/1,084, 20.5% ± 7.9%
(d) Mean historical incidence at this laboratory, 67/199, 33.7% ± 9.4%; historical incidence throughout the program, 341/1,084, 31.5% ± 10.4%

TABLE 20. ANALYSIS OF LIVER TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORODIBROMOMETHANE

	Vehicle Control	50 mg/kg	100 mg/kg
FEMALE			
Adenoma (a)			
Overall Rates	2/50 (4%)	4/49 (8%)	11/50 (22%)
Adjusted Rates	6.3%	13.7%	28.0%
Terminal Rates	2/32 (6%)	3/27 (11%)	10/38 (26%)
Life Table Tests	P=0.010	P=0.272	P=0.018
Incidental Tumor Tests	P=0.008	P=0.305	P=0.016
Carcinoma (b)			
Overall Rates	4/50 (8%)	6/49 (12%)	8/50 (16%)
Adjusted Rates	10.3%	19.7%	19.7%
Terminal Rates	1/32 (3%)	4/27 (15%)	6/38 (16%)
Life Table Tests	P=0.217	P=0.318	P=0.247
Incidental Tumor Tests	P=0.141	P=0.458	P=0.158
Adenoma or Carcinoma (Combined) (c)			
Overall Rates	6/50 (12%)	10/49 (20%)	19/50 (38%)
Adjusted Rates	16.1%	32.2%	46.1%
Terminal Rates	3/32 (9%)	7/27 (26%)	16/38 (42%)
Life Table Tests	P=0.008	P=0.151	P=0.011
Incidental Tumor Tests	P=0.003	P=0.245	P=0.004

(a) Mean historical incidence at this laboratory, 10/198, 5.1% ± 4.2%; historical incidence throughout the program, 47/1,176, 4% ± 2.6%
(b) Mean historical incidence at this laboratory, 7/198, 3.5% ± 3.4%; historical incidence throughout the program, 34/1,176, 2.9% ± 2.2%
(c) Mean historical incidence at this laboratory, 17/198, 8.6% ± 5.5%; historical incidence throughout the program, 80/1,176, 6.8% ± 3.4%

Kidney: Nephrosis was observed at increased incidence in dosed male mice (vehicle control, 0/50; low dose, 45/50; high dose, 37/50). All 35 low dose mice dying at weeks 58-59 had kidney nephrosis. Nephrosis was observed in 2/50 female vehicle control mice but not in any of the dosed female mice. Renal tubular calcification was seen in 13/50 low dose male mice (12 of which died at weeks 58-59 due to an overdose); renal calcification was seen in 1/50 high dose male mice but not in any of the other groups.

Thyroid: Follicular cell hyperplasia occurred at increased incidence in dosed female mice: vehicle control, 1/49; low dose, 13/46; high dose, 31/50. Follicular cell hyperplasia occurred in 4/49 vehicle control male mice but not in any of the dosed male mice.

Reproductive System: Suppurative inflammation of the ovary or uterus was observed in 7 vehicle control, 13 low dose, and 5 high dose female mice. Although the uterus and ovary were not examined to identify microorganisms, *Klebsiella oxytoca* was isolated from female mice that had similar lesions in other studies performed at this laboratory.

Hematopoietic System: The incidence of malignant lymphomas in high dose male mice was significantly lower than that in the vehicle controls (Table 21). The following incidences were observed in female mice: vehicle control, 10/50; low dose, 15/49; high dose, 11/50. In addition, leukemia was diagnosed in one high dose female mouse. The incidences in dosed female groups were not significantly different from that in the vehicle controls.

Circulatory System: The incidence of hemangiomas or hemangiosarcomas (combined) in low dose female mice was significantly lower than that in the vehicle controls (incidental tumor test only) (vehicle control, 4/50; low dose, 0/49; high dose, 4/50); the group incidence was within the historical range of incidences for these tumors at this laboratory (0%-8%).

Lung: The incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in low dose female mice was lower than that in the vehicle controls (vehicle control, 5/50; low dose, 0/49; high dose, 5/50). In male mice, the incidence of alveolar/bronchiolar adenomas or carcinomas (combined) was lower in the dosed groups than in the vehicle controls: vehicle control, 11/50; low dose, 5/50; high dose, 4/50.

TABLE 21. ANALYSIS OF HEMATOPOIETIC SYSTEM TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF CHLORODIBROMOMETHANE

	Vehicle Control	100 mg/kg
Lymphoma, All Malignant (a)		
Overall Rates	9/50 (18%)	0/50 (0%)
Adjusted Rates	20.0%	0.0%
Terminal Rates	8/44 (18%)	0/29 (0%)
Life Table Tests		P=0.014N
Incidental Tumor Tests		P=0.006N

(a) Mean historical incidence at this laboratory: 14.5% ± 3.0%

IV. DISCUSSION AND CONCLUSIONS

Experimental Design

Toxicity of Chlorodibromomethane in Rats

Toxicity and Carcinogenicity of Chlorodibromomethane in Mice

Toxicity of Other Trihalomethanes

IV. DISCUSSION AND CONCLUSIONS

Experimental Design

The trihalomethane chlorodibromomethane is formed after chlorination of drinking water. It was administered by gavage for 2 years to male and female F344/N rats at doses of 0, 40, or 80 mg/kg and to male and female $B6C3F_1$ mice at doses of 0, 50, or 100 mg/kg. The survival of high dose male and female rats and female mice was as good as or better than the survival in the vehicle control groups, with over 72% of the animals in these high dose groups living until the end of the 2-year studies. Analyses of the survival of male mice were complicated by an overdosing accident at week 58 that killed 35 low dose male mice; for this reason, tumor incidence data for the low dose male mice were considered inadequate for analyses. High dose male rats and high dose male and female mice had lower total weight gains than did vehicle control groups. Survival of high dose male mice was lower than in the vehicle controls, partly because of nine unexplained deaths on week 82.

Toxicity of Chlorodibromomethane in Rats

Toxicity to the liver and kidney was seen in male and female rats administered chlorodibromomethane (250 mg/kg, the highest dose) for 13 weeks. In the 2-year studies, liver toxicity was also seen, with an increased incidence of fatty metamorphosis and ground-glass cytoplasmic changes in dosed male and female rats (Table 22). Chemically induced liver neoplasms were not seen in rats.

TABLE 22. DOSE-RELATED LIVER TOXICITY IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORODIBROMOMETHANE

	Vehicle Control	Low Dose	High Dose
RATS		**40 mg/kg**	**80 mg/kg**
MALE			
Fatty metamorphosis	27/50 (54%)	47/50 (94%)	49/50 (98%)
Ground-glass cytoplasmic changes	8/50 (16%)	22/50 (44%)	34/50 (68%)
FEMALE			
Fatty metamorphosis	12/50 (24%)	23/50 (46%)	50/50 (100%)
Ground-glass cytoplasmic changes	0/50 (0%)	1/50 (2%)	12/50 (24%)
MICE		**50 mg/kg**	**100 mg/kg**
MALE			
Adenoma	14/50 (28%)		10/50 (20%)
Carcinoma	10/50 (20%)		19/50 (38%)
Adenoma or carcinoma	23/50 (46%)		27/50 (54%)
Hepatocytomegaly	0/50 (0%)		12/50 (24%)
Necrosis	2/50 (4%)		9/50 (18%)
Fatty metamorphosis	13/50 (26%)		20/50 (40%)
FEMALE			
Adenoma	2/50 (4%)	4/49 (8%)	11/50 (22%)
Carcinoma	4/50 (8%)	6/49 (12%)	8/50 (16%)
Adenoma or carcinoma	6/50 (12%)	10/49 (20%)	19/50 (38%)
Calcification	0/50 (0%)	0/49 (0%)	7/50 (14%)
Fatty metamorphosis	7/50 (14%)	21/49 (43%)	28/50 (56%)

Toxic nephrosis was observed in the kidneys of both male and female rats after 13 weeks of dosing at 250 mg/kg. Kidney nephrosis was observed at increased incidences in dosed female rats (vehicle control, 7/50; low dose, 11/50; high dose, 14/50) but not in male rats in the 2-year studies. Kidney nephropathy frequently occurs in aging male rats and may obscure the detection of chemically induced kidney toxicity.

Dose-related decreases in neoplasms were observed in the mammary gland (fibroadenomas) and in the uterus (endometrial stromal polyps) in female rats. Haseman (1983) reported an association between decreases in mammary gland tumors in female rats and a decrease in body weight gain; this association was not seen in this study. Although other negative trends in tumor incidences (thyroid gland of male and female rats, the hematopoietic system of male rats, and the testis of male rats) were observed, the incidences in dosed groups were not different from the historical rates seen at this laboratory for these tumors and were not considered to be chemically related.

Toxicity and Carcinogenicity of Chlorodibromomethane in Mice

Liver and kidney toxicity were observed in male mice administered 250 mg chlorodibromomethane/kg body weight for 13 weeks. In the 2-year studies, fatty metamorphosis of the liver, hepatocytomegaly, and hepatocellular necrosis were observed at increased incidences in dosed male mice (Table 22). The incidence of hepatocellular carcinomas in high dose male mice was significantly increased; the number of high dose male mice with hepatocellular adenomas was not increased. The increased incidence of hepatocellular adenomas or hepatocellular carcinomas (combined) was significant by the life table test but not by the incidental tumor test.

In female mice, chlorodibromomethane increased the incidence of hepatocellular adenomas and the combined incidence of hepatocellular adenomas or carcinomas in the high dose group. Fatty metamorphosis and calcification of the liver occurred at increased incidences in dosed female mice (Table 22).

In the 13-week studies, the kidneys of the high dose male mice (250 mg/kg) showed histopathologic signs of toxicity, whereas similar evidence for kidney toxicity was not seen in female mice at this dose. In the 2-year studies, kidney toxicity characterized by tubular nephrosis was observed in male mice (vehicle control, 0/50; low dose, 45/50; high dose, 37/50) but not in female mice.

Dosed female mice showed an increased incidence of follicular cell hyperplasia of the thyroid gland (vehicle control, 1/49; low dose, 13/46; high dose, 31/50). Thyroid gland toxicity was not seen in male mice. Dose-related decreases of malignant lymphomas occurred in the hematopoietic system of male mice.

Toxicity of Other Trihalomethanes

Three other trihalomethanes have been or are being studied in the NCI/NTP Carcinogenesis Program: bromoform (tribromomethane), bromodichloromethane, and chloroform. Bromoform and bromodichloromethane are still being studied. In the 13-week bromodichloromethane studies, the liver and kidney were organs affected in male rats, the liver was affected in female rats and female mice, and the kidney was affected in male mice. In the 13-week bromoform studies, the liver was affected in male rats and male mice.

Chloroform is a well-recognized liver and kidney toxin (NCI, 1976; Kluwe, 1981). In the NCI (1976) study, chloroform was administered by gavage for 78 weeks to Osborne-Mendel rats and $B6C3F_1$ mice, followed by an observation period. Necropsies were performed on rats at 111 weeks and on mice at 92-93 weeks. The male rats received chloroform at 0, 90, or 180 mg/kg per day; female rats received an average dose of 0, 100, or 200 mg/kg per day; male mice received an average dose of 0, 138, or 277 mg/kg per day; and female mice received an average dose of 0, 238, or 477 mg/kg per day. Chloroform produced kidney epithelial neoplasms in male rats and hepatocellular carcinomas in male and female mice. In an earlier study, chloroform induced hepatomas in female strain A mice after oral doses of 600 or 1,200 mg/kg every 4th day for 4

months (Eschenbrenner and Miller, 1945). Chloroform has also been shown to produce renal neoplasms in male ICI Swiss mice following an oral dose of 60 mg/kg per day for 80 weeks (Roe et al., 1979). Chlorodibromomethane and chloroform both have been shown to produce liver neoplasms in mice.

Conclusions: Under the conditions of these gavage studies, there was *no evidence of carcinogenicity** in male or female F344/N rats receiving chlorodibromomethane at doses of 40 or 80 mg/kg five times per week for 104 weeks. Fatty metamorphosis and ground-glass cytoplasmic changes of the liver in male and female F344/N rats were related to administration of chlorodibromomethane. There was *equivocal evidence of carcinogenicity* for male $B6C3F_1$ mice; chlorodibromomethane caused an increased incidence of hepatocellular carcinomas, whereas the combined incidence of hepatocellular adenomas or carcinomas was only marginally increased. *Some evidence of carcinogenicity* was observed for female $B6C3F_1$ mice, since chlorodibromomethane caused an increased incidence of hepatocellular adenomas and an increased combined incidence of hepatocellular adenomas or carcinomas.

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

V. REFERENCES

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1. Ahmed, A.; Kubic, V.; Anders, M. (1977) Metabolism of haloforms to carbon monoxide. Drug Metab. Dispos. 5:198-204.

2. Ames, B.; McCann, J.; Yamasaki, E. (1975) Methods for detecting carcinogens and mutagens with the *Salmonella*/mammalian-microsome mutagenicity test. Mutat. Res. 31:347-364.

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

4. Balster, R.; Borzelleca, J. (1982) Behavioral toxicity of trihalomethane contaminants of drinking water in mice. Environ. Health Perspect. 46:127-136.

5. Balster, R.; Burkhalter, J.; Borzelleca, J. (1979) Behavioral toxicity evaluation of four halomethane contaminants of drinking water in adult mice. Fed. Proc. 38:846.

6. Beech, J.; Diaz, R.; Ordaz, C.; Palomeque, B. (1980) Nitrates, chlorates, and trihalomethanes in swimming pool water. Am. J. Public Health 70:79-82.

7. Bellar, T.; Lichtenberg, J.; Kroner, R. (1974) Occurrence of organohalides in chlorinated drinking waters. J. Am. Water Works Assoc. 66:703-706.

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

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

10. Borzelleca, J.; Skalsky, H.; Riddle, B. (1980) Effects of dibromochloromethane and trichloromethane in drinking water on reproduction and development in mice. Abstr. No. 3849. Fed. Proc. 39:999.

11. Bowman, F.; Borzelleca, J.; Munson, A. (1978) Toxicity of some halomethanes in mice. Toxicol. Appl. Pharmacol. 44:213-215.

12. Brass, J.; Feige, M.; Halloran, T.; Mello, J.; Munch, D.; Thomas, R. (1977) National organic monitoring survey: samplings and analyses for purgeable organic compounds. Pojasek, R., Ed.: Drinking Water Quality Enhancement Through Source Protection. Ann Arbor, MI: Ann Arbor Science Publishers, Inc..

13. Cantor, K. (1982) Epidemiology evidence of carcinogenicity of chlorinated organics in drinking water. Environ. Health Perspect. 46:187-195.

14. Cantor, K.; Hoover, R.; Mason, T.; McCabe, L. (1978) Associations of cancer mortality with halomethanes in drinking water. J. Natl. Cancer Inst. 61:979-985.

15. Chu, I.; Secours, V.; Marino, I.; Villeneuve, D. (1980) Acute toxicity of four trihalomethanes in male and female rats. Toxicol. Appl. Pharmacol. 52:351-353.

16. Chu, I.; Villeneuve, D.; Secours, V.; Becking, G. (1982) Trihalomethanes: II. Reversibility of toxicological changes produced by chloroform, bromodichloromethane and bromoform in rats. J. Environ. Sci. Health. B17(3):225-240.

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

18. Eschenbrenner, A.; Miller, E. (1945) Induction of hepatomas in mice by repeated oral administration of chloroform, with observations on sex differences. J. Natl. Cancer Inst. 5:251.

19. Federal Register (Fed. Reg.) (1978) Nonclinical Laboratory Studies: Good Laboratory Practice Regulations. Vol. 43, No. 247, Friday, December 22.

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

21. Haseman, J. (1983) Patterns of tumor incidence in two-year cancer bioassay feeding studies in Fisher 344 rats. Fundam. Appl. Toxicol. 3:1-9.

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

23. Hoehn, R.; Goode, R.; Randall, C.; Shaffer, P. (1978) Chlorination and water treatment for minimizing trihalomethanes in drinking water. Jolley, R.; Gorchrv, H.; Hamilton, D., Eds.: Water Chlorination: Environmental Impact and Health Effects, Vol 2. Ann Arbor, MI: Ann Arbor Science Publishers, Inc., pp. 519-535.

24. International Agency for Research on Cancer (IARC) (1979) Evaluation of the carcinogenic risk of chemicals to humans, Vol. 20, pp. 401-427.

25. International Agency for Research on Cancer (IARC) (1982) Evaluation of the carcinogenic risk of chemicals to humans, Supplement 4, pp. 87-93.

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

27. Kavlock, R.; Chernoff, N.; Carver, B.; Kopfler, F. (1979) Teratology studies in mice exposed to municipal drinking-water concentrates during organogenesis. Food Cosmet. Toxicol. 17:343-347.

28. Kluwe, W. (1981) The nephrotoxicity of low molecular weight halogenated alkane solvents, pesticides, and chemical intermediates. Dixon, R.; Hook, J., Eds.: Toxicology of the Kidney. New York: Raven Press, pp. 179-226.

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

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

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

32. Martin, B.; Marston, A.; Montgomery, J.; Ritter, K.; Dewey, W. (1977) Effects of halogenated organic water contaminants on the uptake of neurotransmitters and their precursors in brain synaptosomes. Pharmacologist 19:200.

33. Mass Spectrometry Data Centre (1970) Eight Peak Index of Mass Spectra--Spectrum A0114, Vol. II, 1st ed. Aldermaston, United Kingdom: Mass Spectrometry Data Centre, p. 776.

34. Munson, A.; Sanders, V.; Borzelleca, J.; Tardiff, R.; Barrett, B. (1978) Reticuloendothelial system function in mice exposed to four haloalkanes: Drinking water contaminants. Toxicol. Appl. Pharmacol. 45:329-330.

35. Munson, A.; Sain, L.; Sanders, V.; Kauffman, B.; White, K.; Page, D.; Barnes, D.; Borzelleca, J. (1982) Toxicology of organic drinking water contaminants: trichloromethane, bromodichloromethane, dibromochloromethane, and tribromomethane. Environ. Health Perspect. 46:117-126.

36. NBS Mass Spectrometry Library: Spectrum Nos. NB261, NB279, NB277. Sunnyvale, CA: Finnigan, Inc.

37. National Academy of Sciences (NAS) (1980a) Drinking water and health, Vol 2. Washington, DC: National Academy Press, pp. 139-249.

38. National Academy of Sciences (NAS) (1980b) Drinking water and health, Vol. 3. Washington, DC: National Academy Press, pp. 1-21.

39. National Cancer Institute (NCI) (1976) Report on the Carcinogenesis Bioassay of Chloroform. Bethesda, MD: National Institutes of Health.

V. REFERENCES

40. Roe, F.; Palmer, A.; Worden, A.; Van Abbe, N. (1979) Safety evaluation of toothpaste containing chloroform. I. Long-term studies in mice. J. Environ. Path. Toxicol. 2:799-819.

41. Rook, J. (1974) Formation of haloforms during chlorination of natural waters. Water Treat. Exam. 23:234-243.

42. Rook, J. (1980) Possible pathways for the formation of chlorinated degradation products during chlorination of humic acids and resorcinol in water chlorination. Jolley, R.; Brungs, W.; Cumming, R., Eds.: Environmental Impact and Health Effects, Vol. 3. Ann Arbor, MI: Ann Arbor Science Publishers, Inc., pp. 85-98.

43. Ruddick, J.; Villeneuve, D.; Chu, I.; Valli, V. (1980) Teratogenicity assessment of four trihalomethanes. Teratology 21:66A.

44. Ruddick, J.; Villeneuve, D.; Chu, I. (1983) A teratogenic assessment of four trihalomethanes in the rat. J. Environ. Health Sci. B18(3):333-349.

45. Sadtler Research Laboratories: Sadtler Standard Spectra, IR No. 1896, NMR No. 6708M. Philadelphia, PA: Sadtler Research Laboratories.

46. Sax, N. (1975) Dangerous Properties of Industrial Materials, 4th ed. New York: Van Nostrand Reinhold Co., p. 613.

47. Schuller, G.; Kaufman, B.; Borzelleca, J.; Sanders, V.; Munson, A. (1978) Effect of four haloalkanes on humoral and cell-mediated immunity in mice. Toxicol. Appl. Pharmacol. 45:329.

48. Simmon, V.; Tardiff, R. (1977) Mutagenic activity of halogenated compounds found in chlorinated drinking water. Jolley, W.; Gorchev, H.; Hamilton, D., Eds.: Water Chlorination: Environmental Impact and Health Effects, Vol. 2. Ann Arbor, MI: Ann Arbor Science Publishers, Inc., pp. 417-461.

49. Simmon, V.; Kauhanen, K.; Tardiff, R. (1977) Mutagenic activity of chemicals identified in drinking water. Dev. Toxicol. Environ. Sci. 2:249-258.

50. Stevens, A.; Slocum, C.; Seeger, D.; Robeck, G. (1976): Chlorination of organics in drinking water. J. Am. Water Works Assoc. 68:615-620.

51. Symons, J.; Bellar, T.; Carswell, J.; DeMarco, J.; Kropp, K.; Robeck, G.; Seeger, D.; Slocum, C.; Smith, B.; Stevens, A. (1975) National organics reconnaissance survey for halogenated organics. J. Am. Water Works Assoc. 67:634-646.

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

53. U.S. Environmental Protection Agency (EPA) (1979) National interim primary drinking water regulations; control of trihalomethanes in drinking water; final rule. Fed. Reg. 44(231):68624-68705 (Nov. 29).

54. U.S. Environmental Protection Agency (EPA) (1983) National interim primary drinking water regulations; trihalomethanes. Fed. Reg. 48(40):8406-8414 (Feb. 28).

55. Yahagi, T.; Degawa, M.; Seino, Y.; Matsushima, T.; Nagao, M.; Sugimura, T.; Hashimoto, Y. (1975) Mutagenicity of carcinogenic azo dyes and their derivatives. Cancer Lett. 1:91-96.

APPENDIX A

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

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
SQUAMOUS CELL CARCINOMA		1 (2%)	
BASAL-CELL TUMOR		1 (2%)	
SEBACEOUS ADENOCARCINOMA			1 (2%)
KERATOACANTHOMA	2 (4%)	1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS		1 (2%)	
FIBROMA	3 (6%)	1 (2%)	1 (2%)
LIPOMA	2 (4%)	1 (2%)	1 (2%)
RHABDOMYOSARCOMA	1 (2%)		
FIBROADENOMA			1 (2%)
RESPIRATORY SYSTEM			
*NOSE	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
*NARES	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
#LUNG	(50)	(50)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	3 (6%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)	1 (2%)	
SARCOMA, NOS, METASTATIC		1 (2%)	
OSTEOSARCOMA	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIG. LYMPHOMA, LYMPHOCYTIC TYPE			1 (2%)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	2 (4%)		1 (2%)
LEUKEMIA, MONONUCLEAR CELL	6 (12%)	3 (6%)	1 (2%)
#LIVER	(50)	(50)	(50)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)
CIRCULATORY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
HEMANGIOPERICYTOMA, BENIGN		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE	3 (6%)	5 (10%)	3 (6%)
HEPATOCELLULAR CARCINOMA		3 (6%)	
#PANCREAS	(50)	(49)	(49)
ACINAR-CELL ADENOMA	1 (2%)		2 (4%)
#PERIPANCREATIC TISSUE	(50)	(49)	(49)
MESOTHELIOMA, NOS		1 (2%)	
#COLON	(48)	(47)	(47)
ADENOMATOUS POLYP, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
LIPOSARCOMA	1 (2%)		
OSTEOSARCOMA, METASTATIC	1 (2%)		

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(48)	(48)
CARCINOMA, NOS	3 (6%)		1 (2%)
ADENOMA, NOS	12 (24%)	13 (27%)	13 (27%)
#ADRENAL	(50)	(50)	(50)
CORTICAL ADENOMA	1 (2%)	2 (4%)	
PHEOCHROMOCYTOMA	7 (14%)	8 (16%)	4 (8%)
PHEOCHROMOCYTOMA, MALIGNANT	1 (2%)		
#THYROID	(49)	(47)	(49)
FOLLICULAR-CELL ADENOMA		1 (2%)	
FOLLICULAR-CELL CARCINOMA	3 (6%)	1 (2%)	
C-CELL ADENOMA	2 (4%)	1 (2%)	2 (4%)
C-CELL CARCINOMA	2 (4%)	4 (9%)	3 (6%)
#PANCREATIC ISLETS	(50)	(49)	(49)
ISLET-CELL ADENOMA	2 (4%)	1 (2%)	1 (2%)
ISLET-CELL CARCINOMA		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
FIBROADENOMA	3 (6%)		1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS		1 (2%)	
ADENOMA, NOS	1 (2%)		
#TESTIS	(50)	(50)	(49)
INTERSTITIAL-CELL TUMOR	48 (96%)	43 (86%)	45 (92%)
#TUNICA ALBUGINEA	(50)	(50)	(49)
MESOTHELIOMA, NOS		1 (2%)	1 (2%)
*SCROTUM	(50)	(50)	(50)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
NERVOUS SYSTEM			
#CEREBRUM	(50)	(50)	(50)
ASTROCYTOMA	1 (2%)		
SPECIAL SENSE ORGANS			
*EAR CANAL	(50)	(50)	(50)
SEBACEOUS ADENOCARCINOMA	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
MESOTHELIOMA, NOS	2 (4%)	1 (2%)	
LEG			
FIBROSARCOMA	1		

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

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	9	7	2
MORIBUND SACRIFICE	7	5	5
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	34	38	43
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	50	46	48
TOTAL PRIMARY TUMORS	117	103	85
TOTAL ANIMALS WITH BENIGN TUMORS	48	46	46
TOTAL BENIGN TUMORS	86	79	72
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	14	8
TOTAL MALIGNANT TUMORS	26	16	9
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	1	
TOTAL SECONDARY TUMORS	1	1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	5	7	4
TOTAL UNCERTAIN TUMORS	5	8	4
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
KERATOACANTHOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
BASAL-CELL TUMOR	2 (4%)		
SARCOMA, NOS		2 (4%)	
FIBROMA			1 (2%)
LIPOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
CARCINOMA, NOS, METASTATIC		1 (2%)	
ALVEOLAR/BRONCHIOLAR ADENOMA			2 (4%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
LEUKEMIA, MONONUCLEAR CELL	4 (8%)	6 (12%)	10 (20%)
#LUMBAR LYMPH NODE	(49)	(49)	(50)
ENDOMETRIAL STROMAL SARCOMA, MET			1 (2%)
#LIVER	(50)	(50)	(50)
LEUKEMIA, MONONUCLEAR CELL	2 (4%)		
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
NEOPLASTIC NODULE		2 (4%)	2 (4%)
#COLON	(46)	(49)	(48)
ADENOMATOUS POLYP, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	
#URINARY BLADDER	(50)	(50)	(50)
LEIOMYOSARCOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(49)	(50)
CARCINOMA, NOS	5 (11%)	3 (6%)	2 (4%)
ADENOMA, NOS	11 (23%)	19 (39%)	10 (20%)
#ADRENAL	(50)	(50)	(49)
PHEOCHROMOCYTOMA	3 (6%)	5 (10%)	1 (2%)
#THYROID	(49)	(49)	(48)
FOLLICULAR-CELL CARCINOMA	1 (2%)		3 (6%)
C-CELL ADENOMA	1 (2%)	1 (2%)	1 (2%)
C-CELL CARCINOMA	5 (10%)	1 (2%)	
#PANCREATIC ISLETS	(48)	(50)	(50)
ISLET-CELL ADENOMA			2 (4%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
ADENOCARCINOMA, NOS	1 (2%)	1 (2%)	1 (2%)
FIBROADENOMA	18 (36%)	12 (24%)	4 (8%)
*CLITORAL GLAND	(50)	(50)	(50)
CARCINOMA, NOS	2 (4%)		1 (2%)
SQUAMOUS CELL CARCINOMA		1 (2%)	
*VAGINA	(50)	(50)	(50)
LEIOMYOSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL SARCOMA	1 (2%)		1 (2%)
#UTERUS	(50)	(50)	(50)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS	2 (4%)	2 (4%)	
ENDOMETRIAL STROMAL POLYP	14 (28%)	8 (16%)	5 (10%)
ENDOMETRIAL STROMAL SARCOMA	2 (4%)	2 (4%)	1 (2%)
#OVARY	(50)	(50)	(50)
GRANULOSA-CELL TUMOR			1 (2%)
SERTOLI-CELL TUMOR	1 (2%)		
TUBULAR ADENOMA	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
ASTROCYTOMA		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
CARCINOMA, NOS		1 (2%)	
ADENOMA, NOS		1 (2%)	
*EXTERNAL EAR	(50)	(50)	(50)
FIBROMA			1 (2%)
*EAR CANAL	(50)	(50)	(50)
SEBACEOUS ADENOCARCINOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
ADENOCARCINOMA, NOS, METASTATIC	1 (2%)		
OSTEOSARCOMA, METASTATIC		1 (2%)	
LEG			
OSTEOSARCOMA		1	

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

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	4	5	1
MORIBUND SACRIFICE	7	8	8
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	39	37	41
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	43	38	32
TOTAL PRIMARY TUMORS	78	73	54
TOTAL ANIMALS WITH BENIGN TUMORS	38	27	24
TOTAL BENIGN TUMORS	53	47	29
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	18	18
TOTAL MALIGNANT TUMORS	25	24	22
TOTAL ANIMALS WITH SECONDARY TUMORS##	1	2	1
TOTAL SECONDARY TUMORS	1	2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		2	3
TOTAL UNCERTAIN TUMORS		2	3
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

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

ANIMAL NUMBER	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 6	0 0 7	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5
WEEKS ON STUDY	0 9 2	1 0 5	1 0 1	1 0 5	1 0 5	1 1 1	1 1 5	1 1 5	1 1 5	1 1 5	1 2 5	1 3 5	1 3 5	1 4 5	1 4 5	1 4 5	1 4 5	1 4 5	1 4 5	1 4 5	1 4 5	1 4 5	1 4 5	1 4 5	1 4 5
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
KERATOACANTHOMA				X																					
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA			X												X										
LIPOMA									X																
RHABDOMYOSARCOMA											X														
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																			X	X					
ALVEOLAR/BRONCHIOLAR CARCINOMA																			X						
OSTEOSARCOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NASAL CAVITY	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SQUAMOUS CELL PAPILLOMA																									
SQUAMOUS CELL CARCINOMA																									
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	+	+	+	+	+	+	-	+	+	-	-	-	-	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE				X															X						
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA																									
ESOPHAGUS	+	+	+	+	+	+	+	+	-	-	-	+	-	-	-	-	+	+	+	-	+	+	+	+	-
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIPOSARCOMA																									
OSTEOSARCOMA, METASTATIC																									
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS																									
ADENOMA, NOS				X				X											X	X		X		X	X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA														X											
PHEOCHROMOCYTOMA		X					X								X										
PHEOCHROMOCYTOMA, MALIGNANT									X																
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA			X	X																X					
C-CELL CARCINOMA																									
PARATHYROID	-	-	+	+	-	-	-	+	+	-	+	+	+	+	+	+	-	+	-	-	-	+	-	+	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA					X	X																			
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	+	+	+	+	+	+	+	N	N	+	+	N	N	N	+	N	N	N	+	+	+	N	+	N
FIBROADENOMA			X			X																			
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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
ADENOMA, NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA																									
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
SEBACEOUS ADENOCARCINOMA																	X								
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS																							X		
MALIG.LYMPHOMA, HISTIOCYTIC TYPE								X																	
LEUKEMIA,MONONUCLEAR CELL	X									X				X											
LEG NOS																									
FIBROSARCOMA																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

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

ANIMAL NUMBER	0256	0271	0291	0321	0331	0341	0351	0361	0365	0366	0367	0368	0369	0370	0371	0372	0373	0374	0375	0376	0377	0378	0379	0380	TOTAL
WEEKS ON STUDY	106	106	094	075	072	081	041	045	070	071	076	079	086	086	086	086	088	111	061	061	061	081	092	071	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	50M
KERATOACANTHOMA		X																							2
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROMA																X									3
LIPOMA									X																2
RHABDOMYOSARCOMA																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																									1
ALVEOLAR/BRONCHIOLAR CARCINOMA														X											2
OSTEOSARCOMA																							X		1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NASAL CAVITY	M	M	M	M	M	M	M	M	+	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
SQUAMOUS CELL PAPILLOMA									X																1
SQUAMOUS CELL CARCINOMA										X															1
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	49
THYMUS	+	-	-	+	-	+	+	+	+	+	-	+	-	+	+	-	-	-	-	+	+	+	-	-	34
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE														X											1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ACINAR-CELL ADENOMA											X														1
ESOPHAGUS	+	-	-	+	+	+	+	-	+	+	+	+	+	-	+	+	-	-	+	+	+	+	+	-	34
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	48
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIPOSARCOMA				X																					1
OSTEOSARCOMA, METASTATIC																							X		1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA,NOS														X	X			X							3
ADENOMA, NOS		X										X					X		X		X				12
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																									1
PHEOCHROMOCYTOMA							X					X			X							X			7
PHEOCHROMOCYTOMA, MALIGNANT																									1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL CARCINOMA																				X	X			X	3
C-CELL ADENOMA																									2
C-CELL CARCINOMA														X											2
PARATHYROID	+	-	-	-	-	-	+	-	-	-	+	+	+	-	-	+	-	-	-	+	+	-	+	-	23
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA																									2
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	M	M	M	M	M	+	+	+	M	M	+	+	M	+	M	M	M	M	M	+	+	+	M	M	50M
FIBROADENOMA																				X					1
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	48
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	48
PREPUTIAL/CLITORAL GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
ADENOMA, NOS																		X							1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA					X																				1
SPECIAL SENSE ORGANS																									
EAR	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
SEBACEOUS ADENOCARCINOMA																									1
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	X	M	M	M	M	M	M	M	M	M	M	M	M	50M
MESOTHELIOMA, NOS																									2
MALIG.LYMPHOMA, HISTIOCYTTIC TYPE																							X		2
LEUKEMIA,MONONUCLEAR CELL	X		X				X																		4
LEO NOS																									
FIBROSARCOMA													X												1

M ANIMALS NECROPSIED

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

ANIMAL NUMBER	0301	0302	0303	0304	0305	0306	0307	0308	0309	0310	0311	0312	0313	0314	0315	0316	0317	0318	0319	0320	0321	0322	0323	0324	0325
WEEKS ON STUDY	0051	0094	0089	0251	0051	0051	0121	0051	0351	0791	0351	0351	0351	0351	0051	0051	0051	0051	0797	0051	0391	0351	0051	0051	0351
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA																									
SQUAMOUS CELL CARCINOMA																									
BASAL-CELL TUMOR																									
KERATOACANTHOMA												X													
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS			X																						
FIBROMA																									X
LIPOMA	X																								
HEMANGIOPERICYTOMA, BENIGN	X																								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																						X			
ALVEOLAR/BRONCHIOLAR CARCINOMA																				X					
SARCOMA, NOS, METASTATIC			X																						
TRACHEA	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	-	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE		X													X		X								
HEPATOCELLULAR CARCINOMA	X					X																			
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MESOTHELIOMA, NOS			X																						
ESOPHAGUS	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	-	+	-	-	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMA, NOS		X				X		X	X											X					
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																				X					
PHEOCHROMOCYTOMA	X					X	X																X	X	
THYROID	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
FOLLICULAR-CELL ADENOMA																									X
FOLLICULAR-CELL CARCINOMA																									
C-CELL ADENOMA																									
C-CELL CARCINOMA															X								X		
PARATHYROID	+	+	+	-	-	+	-	+	-	-	-	-	-	-	-	+	-	-	+	-	+	-	+	-	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
ISLET-CELL CARCINOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	+	N	N	N	N	N	+	+	N	N	+	+	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR	X		X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		X	X	X	X
MESOTHELIOMA, NOS			X																						
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																									
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MESOTHELIOMA, NOS																									
LEUKEMIA,MONONUCLEAR CELL																									
SCROTUM NOS																									
SQUAMOUS CELL PAPILLOMA																									

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

ANIMAL NUMBER	032	037	028	029	031	051	032	033	034	035	036	037	038	039	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	095	095	095	083	095	086	095	095	095	095	095	095	095	061	095	095	095	095	095	095	095	095	095	095	TISSUES TUMORS
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA								X																	1
SQUAMOUS CELL CARCINOMA							X																		1
BASAL-CELL TUMOR																						X			1
KERATOACANTHOMA																									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SARCOMA, NOS																									1
FIBROMA																									1
LIPOMA																									1
HEMANGIOPERICYTOMA, BENIGN																									1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA															X									X	3
ALVEOLAR/BRONCHIOLAR CARCINOMA																									1
SARCOMA, NOS, METASTATIC																									1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	49
THYMUS	-	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	-	+	-	+	-	+	+	38
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE													X					X			X				5
HEPATOCELLULAR CARCINOMA																									3
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
MESOTHELIOMA, NOS																									1
ESOPHAGUS	-	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	-	+	-	-	+	-	38
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	49
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	48
ADENOMA, NOS		X		X	X				X		X	X	X					X							13
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CORTICAL ADENOMA																X									2
PHEOCHROMOCYTOMA						X					X		X												8
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
FOLLICULAR-CELL ADENOMA																	X								1
FOLLICULAR-CELL CARCINOMA																									1
C-CELL ADENOMA							X										X								1
C-CELL CARCINOMA											X														4
PARATHYROID	+	+	-	+	+	+	-	+	-	-	-	-	-	-	-	-	-	+	-	-	+	+	-	+	20
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA																	X								1
ISLET-CELL CARCINOMA			X																						1
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	+	+	+	+	N	N	N	N	N	+	+	+	N	+	+	N	N	+	50N
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	43
MESOTHELIOMA, NOS																									1
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	49
PREPUTIAL/CLITORAL GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50N
CARCINOMA, NOS										X															1
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N	N	50N
MESOTHELIOMA, NOS		X					X	X																	1
LEUKEMIA, MONONUCLEAR CELL																									3
SCROTUM, NOS																									
SQUAMOUS CELL PAPILLOMA												X													1

* ANIMALS NECROPSIED

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

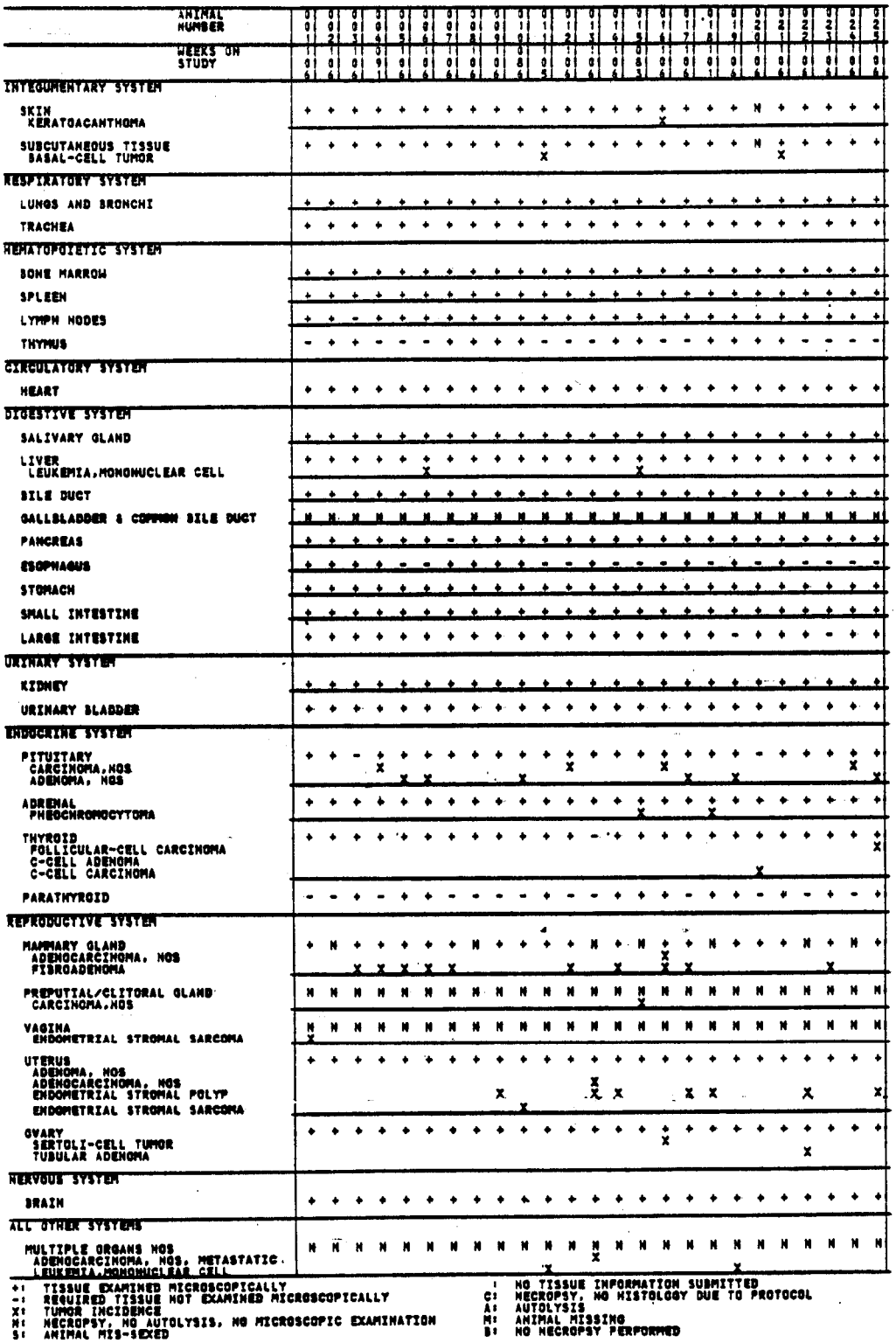
ANIMAL NUMBER	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	054	099	105	105	105	105	105	105	105	073	101	105	101	105
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SEBACEOUS ADENOCARCINOMA				X																					
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA	X																								
LIPOMA																									
FIBROADENOMA																									
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																							
MALIG.LYMPHOMA, HISTIOCYTIC TYPE													X												
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ACINAR-CELL ADENOMA		X																		X					
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	-	-	-	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ADENOMATOUS POLYP, NOS																									
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS				X																					
ADENOMA, NOS	X										X		X				X			X		X	X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA										X							X								
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
C-CELL ADENOMA																									
C-CELL CARCINOMA																									
PARATHYROID	-	-	-	-	-	-	+	-	-	-	-	-	+	-	+	+	-	-	-	-	-	+	-	-	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	+	N	N	N	+	+	+	+	N	N	N	N	N	N	N	N	+	N	N	+	+	+
FIBROADENOMA																								X	
TESTIS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR		X	X		X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
MESOTHELIOMA, NOS																			X						
PROSTATE	+	+	+	+	+	-	+	+	+	+	+	-	+	+	-	+	+	-	+	+	+	-	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE																									
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									
LEUKEMIA,MONONUCLEAR CELL								X																	

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

ANIMAL NUMBER	0026	0027	0028	0029	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040	0041	0042	0043	0044	0045	0046	0047	0048	0049	0050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	105	126	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	102	105	105	
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SEBACEOUS ADENOCARCINOMA																									1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FIBROMA																								X	1
LIPOMA																									1
FIBROADENOMA																								X	1
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	+	-	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	-	-	-	+	+	39
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE				X																					3
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																									1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ACINAR-CELL ADENOMA																									2
ESOPHAGUS	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	42
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	47
ADENOMATOUS POLYP, NOS					X																				1
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	48
CARCINOMA,NOS																									1
ADENOMA, NOS								X	X							X				X	X			X	13
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
PHEOCHROMOCYTOMA						X												X							4
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-CELL ADENOMA																	X			X					2
C-CELL CARCINOMA				X								X							X						3
PARATHYROID	+	+	-	+	-	-	-	-	+	+	+	+	-	-	-	-	+	+	+	-	-	-	+	+	18
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ISLET-CELL ADENOMA									X																1
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	M	M	M	+	M	M	M	M	M	+	M	M	+	M	+	+	M	M	M	M	M	M	+	+	50M
FIBROADENOMA																									1
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	45
MESOTHELIOMA, NOS																									1
PROSTATE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	43
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE		X																							1
MALIG.LYMPHOMA, HISTIOCYTIC TYPE											X														1
LEUKEMIA,MONONUCLEAR CELL																									1

* ANIMALS NECROPSIED

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



+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
I: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

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

ANIMAL NUMBER	0 2 6	0 2 7	0 2 8	0 2 9	0 3 0	0 3 1	0 3 2	0 3 3	0 3 4	0 3 5	0 3 6	0 3 7	0 3 8	0 3 9	0 4 0	0 4 1	0 4 2	0 4 3	0 4 4	0 4 5	0 4 6	0 4 7	0 4 8	0 4 9	0 5 0	TOTAL TISSUES TUMORS
WEEKS ON STUDY	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	0 6	
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
KERATOACANTHOMA																										1
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
BASAL-CELL TUMOR																										2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	-	-	-	+	+	-	+	-	+	+	+	-	-	-	-	-	-	+	+	+	+	+	-	+	-	24
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LEUKEMIA, MONONUCLEAR CELL																										2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	-	-	+	+	+	-	-	-	-	-	+	-	-	-	-	-	-	-	+	+	-	+	+	+	+	22
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
CARCINOMA, NOS																								X		1
ADENOMA, NOS																	X		X	X	X				X	11
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	50
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL CARCINOMA																		X								1
C-CELL ADENOMA															X	X										1
C-CELL CARCINOMA																			X	X						3
PARATHYROID	-	-	-	-	+	-	-	+	-	-	+	+	+	-	+	+	+	-	+	-	-	-	-	+	-	22
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	M	M	+	M	M	M	+	M	M	M	M	+	+	M	M	+	M	+	+	+	M	+	+	+	+	50M
ADENOCARCINOMA, NOS			X				X					X	X			X				X			X		X	1
FIBROADENOMA																										18
PREPUTIAL/CLITORAL GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
CARCINOMA, NOS																	X									2
VAGINA	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
ENDOMETRIAL STROMAL SARCOMA																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+	+	+	+	+	50
ADENOMA, NOS												X														1
ADENOCARCINOMA, NOS																										2
ENDOMETRIAL STROMAL POLYP	X	X		X	X				X												X			X		14
ENDOMETRIAL STROMAL SARCOMA	X																									2
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SERTOLI-CELL TUMOR																										1
TUBULAR ADENOMA																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
ADENOCARCINOMA, NOS, METASTATIC																										1
LEUKEMIA, MONONUCLEAR CELL			X																						X	4

M ANIMALS NECROPSIED

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

ANIMAL NUMBER	00101	00201	00301	00401	00501	00601	00701	00801	00901	01001	01101	01201	01301	01401	01501	01601	01701	01801	01901	02001	02101	02201	02301	02401
WEEKS ON STUDY	105	105	105	105	105	105	105	071	105	105	105	105	105	104	105	105	105	105	105	105	105	105	091	105
INTEGUMENTARY SYSTEM																								
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
SARCOMA, NOS				X																				
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS, METASTATIC								X																
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	+	+	-	+	+	-	+	-	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE															X			X						
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	-	-	-	+	+	+	+	+	+	-	+	-	-	-	+	+	+	+	+	+	-
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOCARCINOMA										X														
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LEIOMYOSARCOMA																								
ENDOCRINE SYSTEM																								
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA,NOS			X																				+	
ADENOMA, NOS	X							X		X		X	X		X			X						X
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA												X											X	X
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-CELL ADENOMA												X												
C-CELL CARCINOMA																								
PARATHYROID	+	-	+	-	+	+	+	-	-	+	-	+	+	-	-	+	-	+	+	-	-	-	+	-
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND	N	+	N	N	+	N	+	N	N	+	N	N	+	N	N	+	+	+	N	+	+	N	N	+
ADENOCARCINOMA, 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
SQUAMOUS CELL CARCINOMA																								
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
LEIOMYOSARCOMA																								
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS		X																			X			
ENDOMETRIAL STROMAL POLYP												X					X							
ENDOMETRIAL STROMAL SARCOMA																							X	
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR ADENOMA																								
NERVOUS SYSTEM																								
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA		X																						
SPECIAL SENSE ORGANS																								
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS								X																
ADENOMA, NOS																								
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
OSTEOSARCOMA, METASTATIC									X															
LEUKEMIA,MONONUCLEAR CELL										X													X	X
LEG NOS																								
OSTEOSARCOMA									X															

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

ANIMAL NUMBER	0241	0271	0281	0291	0311	0312	0313	0314	0315	0316	0317	0318	0319	0411	0412	0413	0414	0415	0416	0417	0418	0419	0510	TOTAL
WEEKS ON STUDY	105	105	091	105	105	105	101	105	105	077	071	105	059	105	085	105	105	051	105	105	086	094	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																								
SUBCUTANEOUS TISSUE SARCOMA, NOS	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+	50M 2
RESPIRATORY SYSTEM																								
LUNGS AND BRONCHI CARCINOMA, NOS, METASTATIC	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																								
BONE MARROW	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYMUS	-	+	-	+	+	+	+	+	-	+	-	-	-	+	+	+	+	-	+	-	-	+	-	+ - 34
CIRCULATORY SYSTEM																								
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																								
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LIVER HEOPLASTIC NODULE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 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	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	-	-	-	-	+	-	-	+	+	+	-	-	-	-	-	+	+	+ 31
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+ 49
URINARY SYSTEM																								
KIDNEY TUBULAR-CELL ADENOCARCINOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50 1
URINARY BLADDER LEIOMYOSARCOMA	+	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ 50 1
ENDOCRINE SYSTEM																								
PITUITARY CARCINOMA,NOS ADENOMA, NOS	+ X	+	+	+ X	+	+	+ X	+	+	+	+ X	+ X	+	+ X	+ X	+	+ X	+	+ X	+	+ X	+ X	+ - X	+ 0 49 3 19
ADRENAL PHEOCHROMOCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+ X	+	+	+	+	+ X	+	+	+	+	+ 50 5
THYROID C-CELL ADENOMA C-CELL CARCINOMA	+	+	+	+	+	-	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ 49 1 1
PARATHYROID	-	-	-	-	+	-	+	+	-	-	-	+	+	-	+	-	-	-	+	+	+	-	+	- + 23
REPRODUCTIVE SYSTEM																								
MAMMARY GLAND ADENOCARCINOMA, NOS FIBROADENOMA	+ X X	+	+	+	+	+ X	+	N	N	N	N	N	N	+	+ X	+	+	N	+	+ X	N	N X	+	N + X	+ 50M 1 12
PREPUTIAL/CLITORAL GLAND SQUAMOUS CELL CARCINOMA	N	N	N	N	N	N	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N N	N 50M 1
VAGINA LEIOMYOSARCOMA	N	N	N X	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N N	N 50M 1
UTERUS ADENOCARCINOMA, NOS ENDOMETRIAL STROMAL POLYP ENDOMETRIAL STROMAL SARCOMA	+	+	+	+	+ X	+	+	+ X	+ X	+	+	+	+ X	+	+ X	+	+	+	+ X	+	+ X	+	+	+ +	+ 50 2 6 2
OVARY TUBULAR ADENOMA	+	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +	+ 50 1
NERVOUS SYSTEM																								
BRAIN ASTROCYTOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+ +	+ 50 1
SPECIAL SENSE ORGANS																								
HARDERIAN GLAND CARCINOMA,NOS ADENOMA, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N X	N	N	N N	N 50M 1 1
ALL OTHER SYSTEMS																								
MULTIPLE ORGANS NOS OSTEOSARCOMA, METASTATIC LEUKEMIA,MONONUCLEAR CELL	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N X	N	N X	N	N	N N X	N 50M 1 6
LEG NOS OSTEOSARCOMA																								+ 1

* ANIMALS NECROPSIED

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

ANIMAL NUMBER	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 6	0 0 7	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5
WEEKS ON STUDY	1 0 5	1 0 5	0 9 7	0 8 1	1 0 5	0 8 3	1 0 5	1 0 5	0 9 2	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	0 9 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA			X																						
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROMA																	X								
LIPOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA																			X						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL SARCOMA, META																			X						
THYMUS	+	+	+	+	+	-	+	+	+	-	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	-	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NEOPLASTIC NODULE									X											X					
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	-	-	+	+	+	+	+	+	-	-	-	-	-	+	+	-	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
ADENOMATOUS POLYP, NOS																									
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS													X	X				X	X		X				
ADENOMA, NOS			X																						
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
PHEOCHROMOCYTOMA																			X						
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA													X	X				X							
C-CELL ADENOMA																									
PARATHYROID	+	+	-	-	+	-	-	-	+	+	+	-	+	-	+	+	+	+	+	+	-	+	+	+	-
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA																									X
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	M	+	+	+	M	M	M	M	+	M	+	M	M	M	+	M	+	+	M	+	M	M	M	M	+
ADENOCARCINOMA, NOS									X																
FIBROADENOMA			X								X														
PREPUTIAL/CLITORAL GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
CARCINOMA, NOS									X																
VAGINA	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
ENDOMETRIAL STROMAL SARCOMA																			X						
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOMETRIAL STROMAL POLYP				X										X											
ENDOMETRIAL STROMAL SARCOMA																			X						
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GRANULOSA-CELL TUMOR	X																								
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ASTROCYTOMA										X															
SPECIAL SENSE ORGANS																									
EAR	M	M	M	M	M	M	M	M	M	M	M	M	+	+	M	+	M	M	M	M	M	M	M	M	M
SEBACEOUS ADENOCARCINOMA													X			X									
FIBROMA																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
LEUKEMIA, MONONUCLEAR CELL				X		X							X	X		X					X				

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

ANIMAL NUMBER	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	0321	TOTAL
WEEKS ON STUDY	0196	0151	0151	0151	0151	0151	0151	0151	0151	0151	0151	0151	0151	0991	0151	0151	0151	0151	0151	0151	0151	0151	0151	0151	0151	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	+	+	+	+	•	•	•	+	+	•	+	+	•	•	•	•	+	+	•	+	+	•	+	+	+	50M 1
SQUAMOUS CELL CARCINOMA																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROMA			X																							1
LIPOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA																	X									2
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL SARCOMA, META																										1
THYMUS	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	-	+	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NEOPLASTIC NODULE																										2
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	48
ADENOMATOUS POLYP, NOS															X											1
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
CARCINOMA,NOS				X													X									2
ADENOMA, NOS	X					X									X	X										10
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	-	+	+	+	48
FOLLICULAR-CELL CARCINOMA																			X							3
C-CELL ADENOMA																										1
PARATHYROID	-	+	-	-	+	+	+	+	-	+	-	-	-	+	-	-	+	+	-	+	-	+	-	+	+	29
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA														X												2
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	M	M	+	M	M	M	M	•	M	M	M	M	M	+	M	M	M	M	M	+	M	+	+	+	+	50M
ADENOCARCINOMA, NOS																										1
FIBROADENOMA																						X			X	4
PREPUTIAL/CLITORAL GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
CARCINOMA,NOS																										1
VAGINA	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
ENDOMETRIAL STROMAL SARCOMA																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOMETRIAL STROMAL POLYP		X												X						X						5
ENDOMETRIAL STROMAL SARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GRANULOSA-CELL TUMOR																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	•	+	+	+	+	+	+	+	+	+	50
ASTROCYTOMA																										1
SPECIAL SENSE ORGANS																										
EAR	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
SEBACEOUS ADENOCARCINOMA																										1
FIBROMA																										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	50M
LEUKEMIA,MONONUCLEAR CELL	X													X		X				X						10

M ANIMALS NECROPSIED

APPENDIX B

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

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

	CONTROL (VEH)	LOW DOSE†	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(50)	(50)
SARCOMA, NOS			1 (2%)
FIBROSARCOMA	2 (4%)		2 (4%)
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
HEPATOCELLULAR CARCINOMA, METAST	2 (4%)	2 (4%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	5 (10%)	4 (8%)	2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	6 (12%)	1 (2%)	2 (4%)
FIBROSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(50)	(50)
MALIGNANT LYMPHOMA, NOS	7 (14%)	3 (6%)	
#SPLEEN	(50)	(49)	(49)
MALIGNANT LYMPHOMA, NOS	1 (2%)	1 (2%)	
#MESENTERIC L. NODE	(48)	(34)	(40)
MALIG. LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(49)	(49)
HEMANGIOSARCOMA			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(50)	(50)
HEPATOCELLULAR ADENOMA	14 (28%)	5 (10%)	10 (20%)
HEPATOCELLULAR CARCINOMA	10 (20%)	9 (18%)	19 (38%)
ALVEOLAR/BRONCHIOLAR CA, METASTA			1 (2%)
#FORESTOMACH	(50)	(48)	(50)
SQUAMOUS CELL CARCINOMA	1 (2%)		
#SMALL INTESTINE	(50)	(49)	(47)
MUCINOUS ADENOCARCINOMA		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
TUBULAR-CELL ADENOMA		1 (2%)	
#URINARY BLADDER	(49)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA		1 (2%)	
ENDOCRINE SYSTEM			
#ADRENAL	(49)	(47)	(50)
PHEOCHROMOCYTOMA	1 (2%)		
#PANCREATIC ISLETS	(50)	(48)	(50)
ISLET-CELL ADENOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
#PROSTATE	(46)	(46)	(47)
MUCINOUS ADENOCARCINOMA, METASTA		1 (2%)	
#TESTIS	(50)	(49)	(50)
INTERSTITIAL-CELL TUMOR	1 (2%)		

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
CARCINOMA, NOS	1 (2%)		
ADENOMA, NOS	4 (8%)	2 (4%)	1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*TUNICA VAGINALIS	(50)	(50)	(50)
SARCOMA, NOS			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
TRANSITIONAL-CELL CARCINOMA, MET		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	4	8	15
MORIBUND SACRIFICE	2		6
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	44	7	29
DOSING ACCIDENT		35	
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING			
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	41	23	31
TOTAL PRIMARY TUMORS	55	28	39
TOTAL ANIMALS WITH BENIGN TUMORS	22	10	13
TOTAL BENIGN TUMORS	26	12	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	25	14	24
TOTAL MALIGNANT TUMORS	29	16	26
TOTAL ANIMALS WITH SECONDARY TUMORS##	3	4	2
TOTAL SECONDARY TUMORS	3	4	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
† LOW DOSE MALE AND FEMALE MICE RECEIVED A SEVENFOLD OVERDOSE OF CHEMICAL IN CORN OIL AT WEEK 58.

** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

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

	CONTROL (VEH)	LOW DOSE†	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
SEBACEOUS ADENOMA			1 (2%)
*SUBCUT TISSUE	(50)	(49)	(50)
SARCOMA, NOS	2 (4%)		
FIBROSARCOMA	1 (2%)		
OSTEOSARCOMA		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(50)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)		4 (8%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	2 (4%)		1 (2%)
SARCOMA, NOS, METASTATIC	1 (2%)		
RHABDOMYOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	8 (16%)	15 (31%)	11 (22%)
GRANULOCYTIC LEUKEMIA			1 (2%)
#SPLEEN	(50)	(49)	(50)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
#MEDIASTINAL L. NODE	(43)	(43)	(43)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
#MESENTERIC L. NODE	(43)	(43)	(43)
MALIGNANT LYMPHOMA, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#SPLEEN	(50)	(49)	(50)
HEMANGIOSARCOMA	2 (4%)		2 (4%)
#LIVER	(50)	(49)	(50)
HEMANGIOMA	1 (2%)		
#OVARY	(49)	(46)	(49)
HEMANGIOMA	1 (2%)		2 (4%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
HEPATOCELLULAR ADENOMA	2 (4%)	4 (8%)	11 (22%)
HEPATOCELLULAR CARCINOMA	4 (8%)	6 (12%)	8 (16%)
SARCOMA, NOS, METASTATIC	1 (2%)		
#FORESTOMACH	(50)	(49)	(50)
SQUAMOUS CELL PAPILLOMA			2 (4%)
URINARY SYSTEM			
#URINARY BLADDER	(49)	(46)	(50)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(41)	(32)
CARCINOMA, NOS	2 (4%)		
ADENOMA, NOS	12 (24%)	7 (17%)	9 (28%)
#ADRENAL	(49)	(46)	(49)
CORTICAL ADENOMA		1 (2%)	
PHEOCHROMOCYTOMA, MALIGNANT			1 (2%)
#THYROID	(49)	(46)	(50)
FOLLICULAR-CELL ADENOMA		3 (7%)	2 (4%)
FOLLICULAR-CELL CARCINOMA	2 (4%)		1 (2%)
#THYROID FOLLICLE	(49)	(46)	(50)
CYSTADENOMA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
ADENOCARCINOMA, NOS		2 (4%)	1 (2%)
ADENOSQUAMOUS CARCINOMA			1 (2%)
#UTERUS	(48)	(49)	(50)
ADENOCARCINOMA, NOS			1 (2%)
LEIOMYOSARCOMA		1 (2%)	
ENDOMETRIAL STROMAL POLYP	2 (4%)		1 (2%)
ENDOMETRIAL STROMAL SARCOMA			1 (2%)
#OVARY	(49)	(46)	(49)
LUTEOMA	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(49)	(50)
ADENOMA, NOS	1 (2%)	1 (2%)	3 (6%)
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(49)	(50)
SARCOMA, NOS	1 (2%)		
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
SARCOMA, NOS			1 (2%)
LEG			
RHABDOMYOSARCOMA		1	
BROWN FAT			
HEPATOCELLULAR CARCINOMA, METAST	1		

#NUMBER OF ANIMALS WITH TISSUES EXAMINED MICROSCOPICALLY
*NUMBER OF ANIMALS NECROPSIED
† LOW DOSE MALE AND FEMALE MICE RECEIVED A SEVENFOLD OVERDOSE OF CHEMICAL IN CORN OIL AT WEEK 58.

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH	13	20	12
MORIBUND SACRIFICE	5	2	2
SCHEDULED SACRIFICE			
TERMINAL SACRIFICE	32	27	36
DOSING ACCIDENT			
ACCIDENTALLY KILLED, NDA			
ACCIDENTALLY KILLED, NOS			
ANIMAL MISSING		1	
ANIMAL MISSEXED			
OTHER CASES			
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS**	33	32	37
TOTAL PRIMARY TUMORS	49	42	66
TOTAL ANIMALS WITH BENIGN TUMORS	18	15	26
TOTAL BENIGN TUMORS	23	16	36
TOTAL ANIMALS WITH MALIGNANT TUMORS	22	25	23
TOTAL MALIGNANT TUMORS	26	26	30
TOTAL ANIMALS WITH SECONDARY TUMORS##	2	1	1
TOTAL SECONDARY TUMORS	4	1	2
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

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

ANIMAL NUMBER	0011	0012	0015	0016	0017	0018	0019	0021	0022	0023	0024	0025	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035	0036	0037	0038	0039	0040
WEEKS ON STUDY	071	071	071	091	091	091	091	091	087	091	091	091	097	091	091	091	091	091	091	091	091	091	091	091	091	091	097
INTEGUMENTARY SYSTEM																											
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FIBROSARCOMA					X																						
RESPIRATORY SYSTEM																											
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA										X														X			
ALVEOLAR/BRONCHIOLAR ADENOMA												X			X												
ALVEOLAR/BRONCHIOLAR CARCINOMA																		X						X			
FIBROSARCOMA, METASTATIC					X																						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																											
BONE MARROW	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS																											
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MALIG.LYMPHOMA, HISTIOCYTIC TYPE							X																				
THYMUS	-	-	+	-	-	-	+	-	+	-	+	-	-	-	-	-	-	-	-	+	+	+	-	-	-	-	-
CIRCULATORY SYSTEM																											
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																											
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA			X							X			X														
HEPATOCELLULAR CARCINOMA				X			X	X			X		X	X							X		X				
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	N	N	+	+	+	+	+	+	N	+	+	+	+	+	N	N	+	+	+	+	N	N	+	N	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	-	-	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL CARCINOMA																		X									
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																											
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																											
PITUITARY	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA																	X										
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	-	-	-	-	+	+	-	+	-	-	+	+	+	+	-	+	+	+	+	-	-	+	+	-	+	+	+
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ISLET-CELL ADENOMA							X																				
REPRODUCTIVE SYSTEM																											
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
INTERSTITIAL-CELL TUMOR																											
PROSTATE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																											
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																											
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
CARCINOMA,NOS																											
ADENOMA, NOS				X		X																					
ALL OTHER SYSTEMS																											
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS		X																									

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
.: NO TISSUE INFORMATION SUBMITTED
G: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

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

ANIMAL NUMBER	0326	0327	0328	0329	0331	0311	0332	0333	0334	0335	0336	0337	0338	0339	0340	0341	0342	0343	0344	0345	0346	0347	0348	0349	0350	TOTAL TISSUES TUMORS
WEEKS ON STUDY	07	07	07	07	07	05	07	07	07	07	07	07	07	07	07	07	07	03	07	07	07	07	07	07	07	
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
FIBROSARCOMA						X																				2
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA																										2
ALVEOLAR/BRONCHIOLAR ADENOMA		X	X								X												X			5
ALVEOLAR/BRONCHIOLAR CARCINOMA	X											X														6
FIBROSARCOMA, METASTATIC																										1
TRACHEA	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MALIGNANT LYMPHOMA, NOS								X																		1
LYMPH NODES	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	48
MALIG.LYMPHOMA, HISTIOCYTIC TYPE																										1
THYMUS	-	-	-	-	+	-	-	-	-	-	-	-	-	-	+	+	+	-	-	+	+	+	+	-	-	16
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA		X	X				X		X		X	X				X		X		X					X	14
HEPATOCELLULAR CARCINOMA				X									X													18
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	M	+	+	+	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ESOPHAGUS	+	+	+	+	+	-	+	+	-	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	48
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL CARCINOMA																										1
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	-	46
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PARATHYROID	-	+	-	+	+	+	+	-	+	-	+	-	+	-	+	-	-	+	+	-	+	-	-	+	-	27
PANCREATIC ISLETS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ISLET-CELL ADENOMA																										1
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
INTERSTITIAL-CELL TUMOR																	X									1
PROSTATE	+	+	+	+	+	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+		46
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
CARCINOMA,NOS																						X				1
ADENOMA, NOS													X										X			4
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
MALIGNANT LYMPHOMA, NOS			X	X											X					X					X	7

M ANIMALS NECROPSIED

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

ANIMAL NUMBER	0311	0312	0313	0314	0315	0316	0317	0318	0319	0320	0321	0322	0323	0324	0325	0326	0327	0328	0329	0330	0331	0332	0333	0334	0335
WEEKS ON STUDY	0358	0599	3593	3598	3597	0107	1107	0358	0358	0358	3598	0358	0358	0358	0358	0358	0358	0358	0358	0358	0358	0358	0358	0358	0358
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																			X						
ALVEOLAR/BRONCHIOLAR ADENOMA														X											
ALVEOLAR/BRONCHIOLAR CARCINOMA			X																						
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
MALIGNANT LYMPHOMA, NOS																									
LYMPH NODES	+	+	+	-	-	+	+	+	+	+	+	+	+	+	-	-	-	+	-	-	-	+	+	+	+
THYMUS	+	+	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	+	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA						X		X			X						X		X						
HEPATOCELLULAR CARCINOMA							X																		
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	N	+	N	+	+	N	N	N	+	N	N	+	+	+	+	+	N	+	+	+	+	+	+	N
PANCREAS	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUCINOUS ADENOCARCINOMA																		X							
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TUBULAR-CELL ADENOMA						X																			
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
TRANSITIONAL-CELL CARCINOMA																									
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	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
MUCINOUS ADENOCARCINOMA, METASTAT																	X								
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS						X																			
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
TRANSITIONAL-CELL CARCINOMA, META																									
MALIGNANT LYMPHOMA, NOS					X																				

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

ANIMAL NUMBER	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	059	059	058	058	082	058	059	058	058	059	070	073	058	070	059	058	058	097	059	058	058	071	051	059	058	TISSUES TUMORS
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA										X																2
ALVEOLAR/BRONCHIOLAR ADENOMA							X		X			X														4
ALVEOLAR/BRONCHIOLAR CARCINOMA																										1
TRACHEA	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MALIGNANT LYMPHOMA, NOS		X																								1
LYMPH NODES	-	-	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	34
THYMUS	-	-	-	-	-	-	-	-	+	+	-	-	-	-	-	+	-	-	-	-	+	-	-	-	-	10
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA	X			X											X					X						5
HEPATOCELLULAR CARCINOMA					X	X					X								X							9
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	+	+	N	+	+	+	N	+	+	+	N	+	+	+	+	N	+	N	+	+	+	+	N	50N
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	46
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
MUCINOUS ADENOCARCINOMA																										1
LARGE INTESTINE	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	48
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TUBULAR-CELL ADENOMA																										1
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
TRANSITIONAL-CELL CARCINOMA																			X							1
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	-	-	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	-	+	-	+	43
ADRENAL	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	-	+	45
PARATHYROID	-	-	-	-	-	-	+	+	+	+	+	-	-	-	-	+	+	+	+	-	+	+	-	+	-	23
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	50N
TESTIS	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PROSTATE	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
MUCINOUS ADENOCARCINOMA, METASTAT																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50N
ADENOMA, NOS										X																2
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50N
TRANSITIONAL-CELL CARCINOMA, META																			X							1
MALIGNANT LYMPHOMA, NOS											X											X				1

N ANIMALS NECROPSIED

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

ANIMAL NUMBER	0 0 1	0 0 2	0 0 3	0 0 4	0 0 5	0 0 6	0 0 7	0 0 8	0 0 9	0 1 0	0 1 1	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6	0 1 7	0 1 8	0 1 9	0 2 0	0 2 1	0 2 2	0 2 3	0 2 4	0 2 5
WEEKS ON STUDY	0 8 1	0 8 6	0 8 6	0 8 6	0 8 6	0 8 6	1 0 2	1 0 6	1 0 7	1 0 7	1 0 7	1 0 8	1 0 8	1 0 8	1 0 9	1 0 9	1 0 9	1 1 0	1 1 0	1 1 0	1 1 0	1 1 0	1 1 0	1 1 0	1 1 0	1 1 0
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS							X																		
FIBROSARCOMA		X													X										
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA													X												
ALVEOLAR/BRONCHIOLAR ADENOMA																			X	X					
ALVEOLAR/BRONCHIOLAR CARCINOMA		X									X														
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	-	+	-	+	+	+	+	+	+	-	+	+	+	-	+	-	+	+	+	+	-	+	+	+	+
THYMUS	-	+	+	+	+	-	+	-	-	-	-	+	-	-	-	+	+	+	-	+	-	-	-	+	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA			X	X							X							X			X				
HEPATOCELLULAR CARCINOMA	X						X	X					X	X						X	X			X	X
ALVEOLAR/BRONCHIOLAR CA, METASTAT											X														
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	M	+	+	+	M	M	+	+	+	M	+	M	M	+	+	+	+	+	M	M	M	M	M	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	-	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
LARGE INTESTINE	-	+	+	+	+	-	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	-
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PARATHYROID	+	-	-	+	+	+	+	-	-	-	-	-	-	-	-	+	+	+	-	-	-	+	-	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
TESTIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
PROSTATE	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
ADENOMA, NOS																									X
BODY CAVITIES																									
TUNICA VAGINALIS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS			X																						

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

ANIMAL NUMBER	0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 2 2 2 2 2 2 2 2 2 2	TOTAL
WEEKS ON STUDY	2 2 2 2 3 3 3 3 3 3 3 3 3 3 4 4 4 4 4 4 4 4 4 4 4 4 5 5	TISSUES/ TUMORS
	4 7 8 9 1 2 3 4 5 5 6 7 8 9 0 1 1 2 3 4 5 7 7 7 8 9 0 3	
	6 0 0 1 7 8 0 3 0 0 0 8 0 9 8 0 6 0 6 6 2 1 5 1 6 6 0 2	
INTEGUMENTARY SYSTEM		
SUBCUTANEOUS TISSUE	+ +	50M
SARCOMA, NOS		1
FIBROSARCOMA		2
RESPIRATORY SYSTEM		
LUNGS AND BRONCHI	+ +	50
HEPATOCELLULAR CARCINOMA, METASTA		1
ALVEOLAR/BRONCHIOLAR ADENOMA		2
ALVEOLAR/BRONCHIOLAR CARCINOMA		2
TRACHEA	+ -	49
HEMATOPOIETIC SYSTEM		
BONE MARROW	+ +	50
SPLEEN	+ +	49
HEMANGIOSARCOMA		1
LYMPH NODES	+ + + + - + - + + + + + + + - + - + + + + + + + +	40
THYMUS	- + + + - - - + - - - - - - + + + + - - + + - + -	22
CIRCULATORY SYSTEM		
HEART	+ +	50
DIGESTIVE SYSTEM		
SALIVARY GLAND	+ + + + + + + + + + + + + + + - + + + + + + + + + +	46
LIVER	+ +	50
HEPATOCELLULAR ADENOMA		10
HEPATOCELLULAR CARCINOMA	X X X X X X X X X	19
ALVEOLAR/BRONCHIOLAR CA, METASTAT		1
BILE DUCT	+ +	50
GALLBLADDER & COMMON BILE DUCT	M + + + + + M + M M M M M + M + M + + + + M M M	38M
PANCREAS	+ +	50
ESOPHAGUS	+ + + + + + - + + + - + - + + + + + + + - + + - -	42
STOMACH	+ +	50
SMALL INTESTINE	+ +	47
LARGE INTESTINE	+ + + + + + + + + + + + + + + - + + + + + + + - + -	42
URINARY SYSTEM		
KIDNEY	+ +	50
URINARY BLADDER	+ +	50
ENDOCRINE SYSTEM		
PITUITARY	+ + + + + + + - - - - + - + + + + + + + + - - +	42
ADRENAL	+ +	50
THYROID	+ -	49
PARATHYROID	- - - - + - + - - - + + - + + - - + + - + - - - -	19
REPRODUCTIVE SYSTEM		
MAMMARY GLAND	M M M M M M M M M M M M M M M + M M M M M M M M M M	38M
TESTIS	+ +	50
PROSTATE	+ - + +	47
NERVOUS SYSTEM		
BRAIN	+ +	49
SPECIAL SENSE ORGANS		
HARDERIAN GLAND	M M M M M M M M M M M M M M M M M M M M M M M M M M	38M
ADENOMA, NOS		1
BODY CAVITIES		
TUNICA VAGINALIS	+ +	38M
SARCOMA, NOS		1

M ANIMALS NECROPSIED

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

ANIMAL NUMBER	30 11	30 12	30 13	30 14	30 15	30 16	30 17	30 18	30 19	30 20	30 21	30 22	30 23	30 24	30 25	30 26	30 27	30 28	30 29	30 30	30 31	30 32	30 33	30 34	30 35
WEEKS ON STUDY	10 07	10 07	10 07	10 07	10 07	08 71	05 31	10 71	10 71	10 71	09 71	09 78	10 70	10 70	10 71	10 71	10 71	10 71	09 84	10 85	10 71	10 71	08 61	09 71	09 81
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SARCOMA, NOS	X					X																			
FIBROSARCOMA										X															
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR CARCINOMA, METASTA																									X
ALVEOLAR/BRONCHIOLAR ADENOMA			X		X					X															
ALVEOLAR/BRONCHIOLAR CARCINOMA																	X								
SARCOMA, NOS, METASTATIC						X																			
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
MALIGNANT LYMPHOMA, NOS																									
LYMPH NODES	+	+	+	+	+	-	-	-	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
MALIGNANT LYMPHOMA, NOS													X												
THYMUS	-	-	-	-	+	-	-	+	+	+	+	-	+	+	+	+	-	-	-	-	-	-	-	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA																									
HEPATOCELLULAR CARCINOMA		X															X						X		X
SARCOMA, NOS, METASTATIC						X																			
HEMANGIOMA																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARCINOMA, NOS		X													X										
ADENOMA, NOS	X		X						X	X		X								X	X				
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYROID	+	+	+	+	+	+	-	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL CARCINOMA									X															X	
PARATHYROID	+	-	+	+	+	-	-	+	-	+	+	+	-	-	+	+	+	+	-	-	-	-	-	-	-
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	N	N	N	N	N	N	N	+	+	+	N	N	N	+	N	N	N	N	N	+	N	N	N
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
ENDOMETRIAL STROMAL POLYP	X																								
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
LUTEOMA				X																					
HEMANGIOMA										X															
NERVOUS SYSTEM																									
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS														X											
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
SARCOMA, NOS																			X						
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS													X		X	X				X		X	X	X	
BROWN FAT																									
HEPATOCELLULAR CARCINOMA, METASTA																									X

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
S: ANIMAL MIS-SEXED
: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

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

ANIMAL NUMBER	0256	0327	0258	0229	0330	0331	0332	0333	0334	0335	0336	0337	0338	0339	0340	0341	0342	0343	0344	0345	0346	0347	0348	0349	0350	TOTAL
WEEKS ON STUDY	0907	1007	1107	1107	0766	1002	1107	0859	1107	0998	1071	0961	0969	0950	1107	1107	0953	1107	1107	1092	1107	1107	1107	1107	1107	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SARCOMA, NOS																										2
FIBROSARCOMA																										1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR CARCINOMA, METASTA																										1
ALVEOLAR/BRONCHIOLAR ADENOMA																										3
ALVEOLAR/BRONCHIOLAR CARCINOMA																							X			2
SARCOMA, NOS, METASTATIC																										1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA	X											X														2
MALIGNANT LYMPHOMA, NOS																X										1
LYMPH NODES	+	+	+	+	+	+	+	+	-	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	43
MALIGNANT LYMPHOMA, NOS																										1
THYMUS	-	+	+	+	+	-	-	-	-	-	-	-	-	-	-	+	+	-	+	+	-	+	+	+	-	21
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA				X					X																	2
HEPATOCELLULAR CARCINOMA																										4
SARCOMA, NOS, METASTATIC																										1
HEMANGIOMA																					X					1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	+	N	+	+	+	+	N	+	+	+	+	N	+	+	+	N	+	+	+	N	+	+	+	+	50M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ESOPHAGUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	47
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
PITUITARY	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	49
CARCINOMA,NOS																										2
ADENOMA, NOS							X								X	X				X	X					12
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
FOLLICULAR-CELL CARCINOMA																										2
PARATHYROID	+	-	-	-	+	-	-	-	+	-	+	+	-	+	+	-	-	+	+	+	+	-	-	+	+	25
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	N	N	+	+	N	N	N	N	N	+	N	N	N	N	N	N	N	+	+	N	N	N	N	+	N	50M
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	48
ENDOMETRIAL STROMAL POLYP	X																									2
OVARY	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LUTEOMA																										1
HEMANGIOMA																										1
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
ADENOMA, 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	50M
SARCOMA, NOS																										1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	50M
MALIGNANT LYMPHOMA, NOS			X																							8
BROWN FAT																										
HEPATOCELLULAR CARCINOMA, METASTA																										1

M ANIMALS NECROPSIED

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

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0021	0022	0023	0024	0025	0026	0027	0028	0029	0030	0031	0032	0033	0034	0035
WEEKS ON STUDY	094	097	098	097	097	099	085	097	097	097	097	097	097	097	097	097	097	097	091	097	097	097	085	088	097
INTEGUMENTARY SYSTEM																									
SUBCUTANEOUS TISSUE	+	+	M	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
OSTEOSARCOMA	X																								
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+
RHABDOMYOSARCOMA, METASTATIC																									
TRACHEA	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LYMPH NODES	-	+	M	+	-	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
THYMUS	-	+	M	+	-	-	-	-	-	-	+	+	+	+	+	+	-	+	+	-	-	-	-	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	M	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA				X								X					X			X	X		X	X	X
HEPATOCELLULAR CARCINOMA																									
BILE DUCT	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	N	+	M	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	N	N	N	+
PANCREAS	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ESOPHAGUS	+	+	M	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
STOMACH	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SMALL INTESTINE	-	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	-	+	M	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-
URINARY SYSTEM																									
KIDNEY	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	M	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
PITUITARY	+	+	M	+	-	-	+	-	+	+	-	+	+	+	+	+	+	-	-	+	+	+	+	+	+
ADENOMA, NOS		X		X																	X				
ADRENAL	+	+	M	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CORTICAL ADENOMA																							X		
THYROID	+	+	M	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA																									
PARATHYROID	+	-	M	+	-	+	-	+	-	-	-	+	+	-	+	+	+	+	-	-	+	+	-	-	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	N	M	+	N	N	N	N	N	N	N	N	+	N	N	N	+	N	+	+	N	+	N	N	N
ADENOCARCINOMA, NOS																									
UTERUS	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	X	+	+	+	+	+	+
LEIOMYOSARCOMA																									
OVARY	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
NERVOUS SYSTEM																									
BRAIN	+	+	M	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
HARDERIAN GLAND	N	N	M	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N	N	N	N	N	N
ADENOMA, NOS																									
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
MALIGNANT LYMPHOMA, NOS									X				X			X			X						
LEG NOS			M																						
RHABDOMYOSARCOMA																	X								

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

ANIMAL NUMBER	0225	0227	0228	0229	0230	0231	0232	0233	0236	0235	0236	0237	0238	0239	0241	0241	0242	0243	0244	0245	0246	0247	0248	0249	0250	TOTAL
WEEKS ON STUDY	0961	0951	1007	1035	0885	0857	1027	1007	1007	1051	0861	0862	0821	0891	1071	0812	0961	0991	0991	1081	1027	1077	1077	1022	1077	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SUBCUTANEOUS TISSUE OSTEOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	49M 1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI RHABDOMYOSARCOMA, METASTATIC	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1
TRACHEA	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
LYMPH NODES	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	43
THYMUS	-	-	-	-	+	+	+	+	+	-	-	+	-	-	-	-	-	-	-	-	-	-	-	+	+	18
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA	+ X	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 4 1
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
GALLBLADDER & COMMON BILE DUCT	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	47M
PANCREAS	-	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	46
ESOPHAGUS	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SMALL INTESTINE	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
LARGE INTESTINE	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	44
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY BLADDER	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	46
ENDOCRINE SYSTEM																										
PITUITARY ADENOMA, NOS	-	+	+	+	+	+	+	+ X	+	+	+	+ X	+	+ X	+	+	+	-	+	+	+	+	+	+	+ X	41 7
ADRENAL CORTICAL ADENOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	-	+	+	+	+	+	+	+	46 1
THYROID FOLLICULAR-CELL ADENOMA	+	+	+	+	+	+	+	+ X	+	-	+	-	+	+	+	+	+	+	+	+ X	+	+	+	+	+	46 3
PARATHYROID	-	-	-	-	+	+	-	-	-	-	-	-	-	+	+	-	+	-	+	-	+	+	+	+	-	23
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND ADENOCARCINOMA, NOS	M	M	+	+ X	M	M	M	M	M	M	M	+	M	+ X	M	+	+	M	M	M	M	M	M	M	M	49M 2
UTERUS LEIOMYOSARCOMA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49 1
OVARY	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	46
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND ADENOMA, NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	49M 1
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS	M	M	M	M X	M X	M X	M X	M X	M	M	M X	M	M	M	M	M X	M	M X	M X	M	M X	M	M	M X	M	49M 15
LEG NOS RHABDOMYOSARCOMA																										1

M ANIMALS NECROPSIED

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

ANIMAL NUMBER	0011	0012	0013	0014	0015	0016	0017	0018	0019	0020	0111	0112	0113	0114	0115	0116	0117	0118	0119	0120	0121	0122	0123	0124	0125
WEEKS ON STUDY	096	105	106	107	106	107	107	107	106	106	107	107	106	094	107	107	107	105	107	107	107	107	107	107	107
INTEGUMENTARY SYSTEM																									
SKIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
SEBACEOUS ADENOMA																									
RESPIRATORY SYSTEM																									
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALVEOLAR/BRONCHIOLAR ADENOMA		X																							
ALVEOLAR/BRONCHIOLAR CARCINOMA																									
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOSARCOMA																									
LYMPH NODES	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS, METASTATIC																									
THYMUS	-	-	-	-	-	+	-	+	+	+	-	+	+	+	-	+	-	-	+	+	-	+	-	-	-
CIRCULATORY SYSTEM																									
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEPATOCELLULAR ADENOMA			X						X				X				X						X		X
HEPATOCELLULAR CARCINOMA					X														X		X				
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GALLBLADDER & COMMON BILE DUCT	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
ESOPHAGUS	+	+	-	+	-	+	+	+	-	+	-	+	+	+	+	+	+	+	-	+	+	+	+	-	+
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SQUAMOUS CELL PAPILLOMA							X		X																
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
LARGE INTESTINE	+	-	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+
URINARY SYSTEM																									
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS, METASTATIC																									
ENDOCRINE SYSTEM																									
PITUITARY	-	-	+	+	+	+	+	+	+	+	+	+	+	-	+	-	+	+	+	+	-	+	+	+	-	-
ADENOMA, NOS			X		X				X									X	X	X		X		X		
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+
PHEOCHROMOCYTOMA, MALIGNANT																					X					
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
FOLLICULAR-CELL ADENOMA							X														X					
FOLLICULAR-CELL CARCINOMA					X															X						
CYSTADENOMA, NOS																										
PARATHYROID	-	+	+	+	-	+	-	-	+	-	+	+	-	-	+	-	+	+	-	-	+	+	-	-	-	+	+
REPRODUCTIVE SYSTEM																									
MAMMARY GLAND	N	+	N	N	N	+	N	+	+	+	N	N	+	N	+	N	N	+	+	+	N	+	+	N	+	N
ADENOCARCINOMA, NOS															X											
ADENOSQUAMOUS CARCINOMA																										
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ADENOCARCINOMA, NOS																					X					
ENDOMETRIAL STROMAL POLYP																										
ENDOMETRIAL STROMAL SARCOMA																									X	
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+
HEMANGIOMA		X																								
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	N
ADENOMA, NOS						X																			X	
ALL OTHER SYSTEMS																									
MULTIPLE ORGANS NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
SARCOMA, NOS																					X					
MALIGNANT LYMPHOMA, NOS		X	X	X	X		X						X				X	X								
GRANULOCYTIC LEUKEMIA																										

ANIMAL NUMBER	0262	0272	0282	0292	0331	0311	0321	0331	0341	0351	0361	0371	0381	0391	0401	0411	0421	0431	0441	0451	0461	0471	0481	0491	0501	TOTAL
WEEKS ON STUDY	0107	0107	0107	0112	0391	0107	0161	0451	0371	0791	0107	0107	0107	0107	0107	0107	0107	0107	0809	0107	0107	0804	0107	0791	0107	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
SKIN	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50M
SEBACEOUS ADENOMA																			X							1
RESPIRATORY SYSTEM																										
LUNGS AND BRONCHI	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ALVEOLAR/BRONCHIOLAR ADENOMA	X																	X							X	4
ALVEOLAR/BRONCHIOLAR CARCINOMA												X														1
TRACHEA	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
BONE MARROW	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPLEEN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMANGIOSARCOMA		X					X																			2
LYMPH NODES	+	+	-	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	-	+	-	+	43
ADENOCARCINOMA, NOS, METASTATIC															X											1
THYMUS	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	+	+	+	-	-	-	-	-	-	-	16
CIRCULATORY SYSTEM																										
HEART	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
SALIVARY GLAND	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	-	+	+	+	+	+	+	+	+	+	47
LIVER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEPATOCELLULAR ADENOMA			X		X				X						X				X					X		11
HEPATOCELLULAR CARCINOMA						X	X							X											X	8
BILE DUCT	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GALLBLADDER & COMMON BILE DUCT	+	M	M	+	+	+	+	M	+	M	M	+	+	+	+	+	+	M	M	+	+	+	+	M	M	48M
PANCREAS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ESOPHAGUS	+	-	-	+	+	-	-	+	+	-	-	+	+	-	+	+	+	+	+	+	+	+	-	-	+	35
STOMACH	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SQUAMOUS CELL PAPILLOMA																										2
SMALL INTESTINE	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
LARGE INTESTINE	-	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	-	+	+	+	+	+	+	42
URINARY SYSTEM																										
KIDNEY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY BLADDER	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS, METASTATIC															X											1
ENDOCRINE SYSTEM																										
PITUITARY	-	-	+	+	-	-	-	-	+	-	+	+	+	+	+	-	+	+	-	+	-	-	+	+	+	32
ADENOMA, NOS																								X		9
ADRENAL	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
PHEOCHROMOCYTOMA, MALIGNANT																										1
THYROID	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
FOLLICULAR-CELL ADENOMA																										2
FOLLICULAR-CELL CARCINOMA																										1
CYSTADENOMA, NOS																										1
PARATHYROID	-	-	-	-	+	+	+	-	-	+	+	-	-	-	-	-	+	+	+	-	-	-	+	-	+	22
REPRODUCTIVE SYSTEM																										
MAMMARY GLAND	M	M	M	M	+	M	M	M	M	M	M	+	M	+	M	+	+	M	M	M	M	M	M	M	M	50M
ADENOCARCINOMA, NOS												X														1
ADENOSQUAMOUS CARCINOMA																										1
UTERUS	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ADENOCARCINOMA, NOS															X											1
ENDOMETRIAL STROMAL POLYP																										1
ENDOMETRIAL STROMAL SARCOMA																										1
OVARY	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMANGIOMA																								X		2
NERVOUS SYSTEM																										
BRAIN	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
HARDERIAN GLAND	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
ADENOMA, NOS							X																			3
ALL OTHER SYSTEMS																										
MULTIPLE ORGANS NOS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	50M
SARCOMA, NOS										X							X									1
MALIGNANT LYMPHOMA, NOS																									X	1
GRANULOCYTIC LEUKEMIA								X																		1

M ANIMALS NECROPSIED

APPENDIX C

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

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
HYPERKERATOSIS		1 (2%)	
KERATIN-PEARL FORMATION		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
HEMORRHAGIC CYST	3 (6%)	1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		1 (2%)
ABSCESS, NOS		3 (6%)	
RESPIRATORY SYSTEM			
#LUNG	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
INFLAMMATION, INTERSTITIAL			1 (2%)
INFLAMMATION, ACUTE	1 (2%)		
ABSCESS, NOS		1 (2%)	
INFLAMMATION, GRANULOMATOUS		1 (2%)	
INFLAMMATION GRANULOMATOUS FOCAL		1 (2%)	
HEMOSIDEROSIS		1 (2%)	
FOAM-CELL			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM	3 (6%)		1 (2%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(50)	(50)
CONGESTION, NOS		1 (2%)	
HEMOSIDEROSIS		2 (4%)	
HYPERPLASIA, STROMAL		1 (2%)	
ANGIECTASIS		1 (2%)	
HEMATOPOIESIS	1 (2%)	1 (2%)	3 (6%)
ERYTHROPOIESIS			1 (2%)
#SPLENIC FOLLICLES	(50)	(50)	(50)
HYPERPLASIA, NOS		1 (2%)	
#LYMPH NODE	(49)	(49)	(49)
CYST, NOS	1 (2%)		
INFLAMMATION, ACUTE		1 (2%)	
HYPERPLASIA, LYMPHOID		1 (2%)	
#MANDIBULAR L. NODE	(49)	(49)	(49)
HYPERPLASIA, PLASMA CELL			2 (4%)
#LUMBAR LYMPH NODE	(49)	(49)	(49)
CYST, NOS			1 (2%)
#MESENTERIC L. NODE	(49)	(49)	(49)
CYST, NOS			2 (4%)
INFLAMMATION, ACUTE	1 (2%)		
HYPERPLASIA, RETICULUM CELL	1 (2%)		
#RENAL LYMPH NODE	(49)	(49)	(49)
CYST, NOS		1 (2%)	
#LUNG	(50)	(50)	(50)
LEUKOCYTOSIS, NOS	1 (2%)		
#ADRENAL	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)		

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#MYOCARDIUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
DEGENERATION, NOS	38 (76%)	24 (48%)	22 (44%)
*PANCREATIC ARTERY	(50)	(50)	(50)
HYPERTROPHY, NOS	1 (2%)		
#PANCREAS	(50)	(49)	(49)
THROMBOSIS, NOS		1 (2%)	
PERIVASCULITIS		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(50)	(48)	(49)
DILATATION/DUCTS			3 (6%)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC		4 (8%)	3 (6%)
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)	
FIBROSIS		1 (2%)	
METAPLASIA, SQUAMOUS		4 (8%)	1 (2%)
#LIVER	(50)	(50)	(50)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
CHOLANGIOFIBROSIS			1 (2%)
METAMORPHOSIS FATTY	27 (54%)	47 (94%)	49 (98%)
CYTOPLASMIC CHANGE, NOS		1 (2%)	
BASOPHILIC CYTO CHANGE	29 (58%)	7 (14%)	8 (16%)
GROUND-GLASS CYTO CHANGE	8 (16%)	22 (44%)	34 (68%)
FOCAL CELLULAR CHANGE		3 (6%)	2 (4%)
CLEAR-CELL CHANGE	16 (32%)	22 (44%)	18 (36%)
ANGIECTASIS		1 (2%)	
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)	2 (4%)	1 (2%)
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	40 (80%)	37 (74%)	40 (80%)
#PANCREAS	(50)	(49)	(49)
INFLAMMATION, CHRONIC		2 (4%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)		2 (4%)
HYPERPLASIA, FOCAL	1 (2%)	1 (2%)	
#PANCREATIC ACINUS	(50)	(49)	(49)
ATROPHY, NOS		1 (2%)	1 (2%)
ATROPHY, FOCAL		2 (4%)	1 (2%)
HYPERPLASIA, NOS		1 (2%)	
HYPERPLASIA, FOCAL		3 (6%)	
#ESOPHAGUS	(34)	(38)	(42)
DIVERTICULUM	1 (3%)		
#FORESTOMACH	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	
HYPERPLASIA, BASAL CELL		2 (4%)	
HYPERKERATOSIS		3 (6%)	
ACANTHOSIS		3 (6%)	
#COLON	(48)	(47)	(47)
PARASITISM	4 (8%)	7 (15%)	4 (9%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CALCULUS, MICROSCOPIC EXAMINATION	1 (2%)		
NEPHROSIS, NOS	42 (84%)	44 (88%)	41 (82%)
INFARCT, NOS		1 (2%)	
CALCINOSIS, NOS	1 (2%)		
#RENAL PAPILLA	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#KIDNEY/TUBULE	(50)	(50)	(50)
NECROSIS, FOCAL	1 (2%)		
CYTOPLASMIC VACUOLIZATION			1 (2%)
#URINARY BLADDER	(50)	(48)	(49)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE HEMORRHAGIC	1 (2%)		
#URINARY BLADDER/MUCOSA	(50)	(48)	(49)
HYPERPLASIA, FOCAL	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(48)	(48)
CYST, NOS	1 (2%)		
HYPERPLASIA, FOCAL		1 (2%)	
ANGIECTASIS	1 (2%)		
#ADRENAL	(50)	(50)	(50)
NECROSIS, NOS	1 (2%)		
METAMORPHOSIS FATTY	1 (2%)		
#ADRENAL CORTEX	(50)	(50)	(50)
DEGENERATION, NOS	9 (18%)	6 (12%)	2 (4%)
HYPERPLASIA, FOCAL	3 (6%)	6 (12%)	2 (4%)
#ADRENAL MEDULLA	(50)	(50)	(50)
CALCIFICATION, FOCAL		1 (2%)	
HYPERPLASIA, FOCAL	2 (4%)		1 (2%)
#THYROID	(49)	(47)	(49)
CYSTIC FOLLICLES	3 (6%)		3 (6%)
HYPERPLASIA, CYSTIC			1 (2%)
HYPERPLASIA, C-CELL	11 (22%)	12 (26%)	7 (14%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	1 (2%)	
#PANCREATIC ISLETS	(50)	(49)	(49)
HYPERPLASIA, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
DILATATION/DUCTS	1 (2%)		
CYSTIC DUCTS		1 (2%)	
INFLAMMATION, ACUTE FOCAL	1 (2%)		
HYPERPLASIA, CYSTIC	2 (4%)	3 (6%)	1 (2%)
*PREPUTIAL GLAND	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	2 (4%)	1 (2%)	1 (2%)
HYPERPLASIA, NOS	1 (2%)		1 (2%)
#PROSTATE	(48)	(49)	(43)
HEMORRHAGE	1 (2%)		
INFLAMMATION, SUPPURATIVE	3 (6%)	7 (14%)	4 (9%)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC	5 (10%)		6 (14%)
HYPERPLASIA, CYSTIC	1 (2%)		
#TESTIS	(50)	(50)	(49)
HYPERPLASIA, INTERSTITIAL CELL	6 (12%)	5 (10%)	5 (10%)
#TESTIS/TUBULE	(50)	(50)	(49)
DEGENERATION, NOS	5 (10%)	6 (12%)	
*SCROTUM	(50)	(50)	(50)
NECROSIS, FAT	3 (6%)	3 (6%)	3 (6%)
HYPERKERATOSIS		1 (2%)	
NERVOUS SYSTEM			
#BRAIN	(50)	(50)	(50)
HYDROCEPHALUS, INTERNAL	1 (2%)		

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*EYE	(50)	(50)	(50)
ABSCESS, NOS			2 (4%)
*EAR	(50)	(50)	(50)
ACANTHOSIS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*MANDIBLE	(50)	(50)	(50)
INFLAMMATION, CHRONIC			2 (4%)
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT		1 (2%)	
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT			2 (4%)
ALL OTHER SYSTEMS			
ORBITAL REGION			
INFLAMMATION, SUPPURATIVE		1	
ADIPOSE TISSUE			
INFLAMMATION, GRANULOMATOUS	1		
NECROSIS, NOS	1		
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
ACANTHOSIS		1 (2%)	
*SUBCUT TISSUE	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
RESPIRATORY SYSTEM			
*NASAL MUCOSA	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
PARAKERATOSIS	1 (2%)		
#LUNG	(50)	(50)	(50)
INFLAMMATION, INTERSTITIAL			1 (2%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		2 (4%)	
#LUNG/ALVEOLI	(50)	(50)	(50)
HEMORRHAGE			1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(47)	(47)
HYPERPLASIA, HEMATOPOIETIC	1 (2%)		
#SPLEEN	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	
HEMOSIDEROSIS		1 (2%)	
HEMATOPOIESIS	2 (4%)	5 (10%)	1 (2%)
ERYTHROPOIESIS			1 (2%)
#LYMPH NODE	(49)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#MANDIBULAR L. NODE	(49)	(49)	(50)
HYPERPLASIA, PLASMA CELL			1 (2%)
#LIVER	(50)	(50)	(50)
HEMATOPOIESIS	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(50)	(50)	(50)
PERIVASCULITIS			1 (2%)
#MYOCARDIUM	(50)	(50)	(50)
DEGENERATION, NOS	14 (28%)	6 (12%)	2 (4%)
#ENDOCARDIUM	(50)	(50)	(50)
CALCIFICATION, FOCAL		1 (2%)	
DIGESTIVE SYSTEM			
*MOUTH	(50)	(50)	(50)
ABSCESS, NOS			1 (2%)
#SALIVARY GLAND	(50)	(50)	(47)
DILATATION/DUCTS			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, ACUTE/CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, FOCAL	1 (2%)		
METAPLASIA, SQUAMOUS		2 (4%)	1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#LIVER	(50)	(50)	(50)
ABSCESS, NOS	1 (2%)		
METAMORPHOSIS FATTY	12 (24%)	23 (46%)	50 (100%)
CYTOPLASMIC CHANGE, NOS			2 (4%)
BASOPHILIC CYTO CHANGE	47 (94%)	26 (52%)	18 (36%)
GROUND-GLASS CYTO CHANGE		1 (2%)	12 (24%)
FOCAL CELLULAR CHANGE		4 (8%)	5 (10%)
EOSINOPHILIC CYTO CHANGE			1 (2%)
CLEAR-CELL CHANGE	4 (8%)	4 (8%)	5 (10%)
#HEPATIC CAPSULE	(50)	(50)	(50)
INFLAMMATION, FIBRINOUS	1 (2%)		
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
NECROSIS, NOS		3 (6%)	
#BILE DUCT	(50)	(50)	(50)
HYPERPLASIA, NOS	25 (50%)	14 (28%)	14 (28%)
HYPERPLASIA, FOCAL		1 (2%)	
#PANCREAS	(48)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	1 (2%)
#PANCREATIC ACINUS	(48)	(50)	(50)
ATROPHY, FOCAL	1 (2%)		3 (6%)
HYPERPLASIA, FOCAL		1 (2%)	
#PANCREATIC INTERSTIT	(48)	(50)	(50)
INFLAMMATION, ACUTE	1 (2%)		
#GASTRIC MUCOSA	(50)	(50)	(50)
ULCER, NOS	1 (2%)		
EROSION		1 (2%)	
#FORESTOMACH	(50)	(50)	(50)
ULCER, NOS		1 (2%)	
INFLAMMATION, ACUTE		1 (2%)	1 (2%)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
HYPERPLASIA, BASAL CELL		1 (2%)	
HYPERKERATOSIS		3 (6%)	1 (2%)
ACANTHOSIS		3 (6%)	1 (2%)
#COLON	(46)	(49)	(48)
PARASITISM	3 (7%)	7 (14%)	5 (10%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CALCULUS,MICROSCOPIC EXAMINATION	15 (30%)	3 (6%)	
HYDRONEPHROSIS	1 (2%)	1 (2%)	
INFLAMMATION, CHRONIC FOCAL			1 (2%)
NEPHROSIS, NOS	7 (14%)	11 (22%)	14 (28%)
#RENAL PAPILLA	(50)	(50)	(50)
NECROSIS, NOS		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(49)	(50)
CYST, NOS		1 (2%)	1 (2%)
MULTIPLE CYSTS	1 (2%)		1 (2%)
HYPERTROPHY, FOCAL		1 (2%)	
HYPERPLASIA, FOCAL		2 (4%)	
#ADRENAL	(50)	(50)	(49)
METAMORPHOSIS FATTY		2 (4%)	
#ADRENAL CORTEX	(50)	(50)	(49)
DEGENERATION, NOS	10 (20%)	5 (10%)	1 (2%)
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY			3 (6%)
HYPERPLASIA, FOCAL	3 (6%)	3 (6%)	3 (6%)
ANGIECTASIS			1 (2%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#THYROID	(49)	(49)	(48)
CYSTIC FOLLICLES		5 (10%)	1 (2%)
HYPERPLASIA, CYSTIC			1 (2%)
HYPERPLASIA, C-CELL	11 (22%)	9 (18%)	7 (15%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)		
#PANCREATIC ISLETS	(48)	(50)	(50)
HYPERPLASIA, NOS			1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(50)	(50)
EPIDERMAL INCLUSION CYST		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, CYSTIC	13 (26%)	3 (6%)	5 (10%)
*CLITORAL GLAND	(50)	(50)	(50)
DILATATION/DUCTS			1 (2%)
INFLAMMATION, SUPPURATIVE	2 (4%)	2 (4%)	1 (2%)
INFLAMMATION, CHRONIC		1 (2%)	
HYPERPLASIA, NOS	1 (2%)		
HYPERPLASIA, EPITHELIAL			1 (2%)
#UTERUS	(50)	(50)	(50)
HYDROMETRA		1 (2%)	1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)	1 (2%)	1 (2%)
INFLAMMATION, ACUTE		1 (2%)	
HYPERPLASIA, ADENOMATOUS	1 (2%)		
#UTERUS/ENDOMETRIUM	(50)	(50)	(50)
INFLAMMATION, SUPPURATIVE	3 (6%)	1 (2%)	
INFLAMMATION, ACUTE			1 (2%)
HYPERPLASIA, CYSTIC	3 (6%)	1 (2%)	6 (12%)
#OVARY/PAROVARIAN	(50)	(50)	(50)
NECROSIS, FAT			1 (2%)
#OVARY	(50)	(50)	(50)
CYST, NOS	5 (10%)	5 (10%)	5 (10%)
INFLAMMATION, ACUTE		1 (2%)	
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(50)	(50)	(50)
INFLAMMATION, ACUTE			2 (4%)
ULCER, ACUTE		1 (2%)	
*EYE/CONJUNCTIVA	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
*HARDERIAN GLAND	(50)	(50)	(50)
INFLAMMATION, CHRONIC			1 (2%)
*EAR CANAL	(50)	(50)	(50)
ACANTHOSIS			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT			2 (4%)
*PLEURA	(50)	(50)	(50)
HYPERPLASIA, FOCAL	1 (2%)		
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT	3 (6%)		2 (4%)
ALL OTHER SYSTEMS			
SITE UNKNOWN			
NECROSIS, NOS	1		
OMENTUM			
INFLAMMATION, ACUTE		1	
INFLAMMATION, CHRONIC		1	
NECROSIS, FAT	2	3	3
SPECIAL MORPHOLOGY SUMMARY			
NONE			

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

APPENDIX D

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

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

	CONTROL (VEH)	LOW DOSE†	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(50)	(50)
FIBROSIS, FOCAL	1 (2%)		
NECROSIS, FOCAL	1 (2%)		
*SUBCUT TISSUE	(50)	(50)	(50)
CYST, NOS		1 (2%)	
INFLAMMATION, SUPPURATIVE		1 (2%)	
ABSCESS, NOS		1 (2%)	1 (2%)
FIBROSIS	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(50)	(50)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
#LUNG	(50)	(50)	(50)
HEMOSIDEROSIS	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	1 (2%)
METAPLASIA, SQUAMOUS	1 (2%)		
#LUNG/ALVEOLI	(50)	(50)	(50)
HISTIOCYTOSIS	7 (14%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#SPLEEN	(50)	(49)	(49)
LYMPHOID DEPLETION		1 (2%)	
HYPERPLASIA, LYMPHOID	2 (4%)		
HEMATOPOIESIS	3 (6%)		4 (8%)
#LYMPH NODE	(48)	(34)	(40)
CYST, NOS	1 (2%)		
#LUMBAR LYMPH NODE	(48)	(34)	(40)
HYPERPLASIA, LYMPHOID	1 (2%)		
#MESENTERIC L. NODE	(48)	(34)	(40)
CONGESTION, NOS	6 (13%)		1 (3%)
HEMORRHAGE		1 (3%)	
HYPERPLASIA, LYMPHOID	1 (2%)		
#RENAL LYMPH NODE	(48)	(34)	(40)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
HYPERPLASIA, RETICULUM CELL		1 (2%)	
CIRCULATORY SYSTEM			
#LUNG	(50)	(50)	(50)
PERIVASCULITIS	3 (6%)		
#HEART	(50)	(50)	(50)
ENDOCARDITIS, BACTERIAL		1 (2%)	1 (2%)
NECROSIS, NOS			1 (2%)
CALCIFICATION, NOS			2 (4%)
CALCIFICATION, FOCAL		2 (4%)	2 (4%)
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(49)	(48)
INFLAMMATION, CHRONIC FOCAL	25 (51%)	6 (12%)	22 (46%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#LIVER	(50)	(50)	(50)
CYST, NOS	2 (4%)		
MULTILOCULAR CYST		1 (2%)	
MULTIPLE CYSTS	1 (2%)		
HEMATOMA, ORGANIZED			1 (2%)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
NECROSIS, NOS	1 (2%)		3 (6%)
NECROSIS, FOCAL	1 (2%)	1 (2%)	2 (4%)
INFARCT, NOS	2 (4%)		2 (4%)
#LIVER	(50)	(50)	(50)
METAMORPHOSIS FATTY	13 (26%)	32 (64%)	17 (34%)
CALCIFICATION, NOS		1 (2%)	
BASOPHILIC CYTO CHANGE	1 (2%)		
EOSINOPHILIC CYTO CHANGE	1 (2%)		
HEPATOCYTOMEGALY			12 (24%)
CYTOLOGIC DEGENERATION			6 (12%)
ANGIECTASIS			1 (2%)
#LIVER/CENTRILOBULAR	(50)	(50)	(50)
NECROSIS, NOS		28 (56%)	4 (8%)
METAMORPHOSIS FATTY			3 (6%)
CALCIFICATION, NOS		1 (2%)	
#PANCREAS	(50)	(48)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
NECROSIS, FAT			1 (2%)
#GASTRIC MUCOSA	(50)	(48)	(50)
NECROSIS, FOCAL		1 (2%)	
CALCIFICATION, NOS		1 (2%)	
#FORESTOMACH	(50)	(48)	(50)
ULCER, FOCAL			1 (2%)
INFLAMMATION, CHRONIC FOCAL			1 (2%)
NECROSIS, DIFFUSE		1 (2%)	
HYPERKERATOSIS			1 (2%)
ACANTHOSIS	1 (2%)		2 (4%)
#S.INTESTINE/MUCOSA	(50)	(49)	(47)
CYTOPLASMIC VACUOLIZATION			1 (2%)
#COLONIC MUCOSA	(46)	(48)	(42)
NECROSIS, NOS			1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(50)	(50)
CAST, NOS			1 (2%)
INFLAMMATION, CHRONIC		2 (4%)	1 (2%)
INFLAMMATION, CHRONIC FOCAL	27 (54%)	7 (14%)	27 (54%)
NEPHROSIS, NOS		31 (62%)	8 (16%)
GLOMERULOSCLEROSIS, NOS	3 (6%)		1 (2%)
CALCIFICATION, NOS			1 (2%)
#KIDNEY/MEDULLA	(50)	(50)	(50)
INFLAMMATION, ACUTE		1 (2%)	
#RENAL PAPILLA	(50)	(50)	(50)
NECROSIS, NOS			1 (2%)
#KIDNEY/TUBULE	(50)	(50)	(50)
NEPHROSIS, NOS		14 (28%)	29 (58%)
NECROSIS, NOS			1 (2%)
CALCIFICATION, NOS		13 (26%)	
#U. BLADDER/SUBMUCOSA	(49)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	7 (14%)	1 (2%)	6 (12%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(47)	(43)	(42)
CYST, NOS	1 (2%)		
HYPERPLASIA, FOCAL	2 (4%)		
#ADRENAL	(49)	(47)	(50)
NECROSIS, NOS		1 (2%)	
ATROPHY, NOS			1 (2%)
#ADRENAL MEDULLA	(49)	(47)	(50)
HYPERPLASIA, FOCAL	1 (2%)		2 (4%)
#THYROID	(49)	(45)	(49)
CYSTIC FOLLICLES	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
HYPERPLASIA, FOLLICULAR-CELL	4 (8%)		
#PANCREATIC ISLETS	(50)	(48)	(50)
HYPERPLASIA, NOS	1 (2%)		
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(50)	(50)
ABSCESS, NOS		1 (2%)	
#PROSTATE	(46)	(46)	(47)
INFLAMMATION, SUPPURATIVE			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)		1 (2%)
#TESTIS/TUBULE	(50)	(49)	(50)
DEGENERATION, NOS	2 (4%)		1 (2%)
CALCIFICATION, NOS	1 (2%)		
NERVOUS SYSTEM			
*SPINAL CORD	(50)	(50)	(50)
COMPRESSION			1 (2%)
SPECIAL SENSE ORGANS			
*HARDERIAN GLAND	(50)	(50)	(50)
CYST, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*MEDIASTINUM	(50)	(50)	(50)
INFLAMMATION, CHRONIC	2 (4%)		
*ABDOMINAL CAVITY	(50)	(50)	(50)
NECROSIS, FAT			1 (2%)
*PLEURA	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	
*MESENTERY	(50)	(50)	(50)
NECROSIS, FAT	2 (4%)		

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(50)	(50)
INFLAMMATION, CHRONIC FOCAL	1 (2%)		
TAIL			
METAPLASIA, OSSEOUS	1		
FOOT			
EXOSTOSIS	2		
ADIPOSE TISSUE			
HEMORRHAGE	2		
SPECIAL MORPHOLOGY SUMMARY			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
† LOW DOSE MALE AND FEMALE MICE RECEIVED A SEVENFOLD OVERDOSE OF CHEMICAL IN CORN OIL AT WEEK 58.

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

	CONTROL (VEH)	LOW DOSE†	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SUBCUT TISSUE	(50)	(49)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG/BRONCHIOLE	(50)	(49)	(50)
INFLAMMATION, CHRONIC	2 (4%)	2 (4%)	4 (8%)
#LUNG	(50)	(49)	(50)
INFLAMMATION, INTERSTITIAL	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM	1 (2%)		
#LUNG/ALVEOLI	(50)	(49)	(50)
HISTIOCYTOSIS		1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(49)	(50)
HYPERPLASIA, HEMATOPOIETIC	2 (4%)		
#SPLEEN	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID			1 (2%)
HEMATOPOIESIS	10 (20%)	7 (14%)	1 (2%)
#SPLENIC CAPSULE	(50)	(49)	(50)
INFLAMMATION, ACUTE	1 (2%)		
#LYMPH NODE	(43)	(43)	(43)
CYST, NOS			1 (2%)
INFLAMMATION, ACUTE		1 (2%)	
HYPERPLASIA, PLASMA CELL		1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)
#MEDIASTINAL L. NODE	(43)	(43)	(43)
INFLAMMATION, ACUTE	1 (2%)		
HYPERPLASIA, PLASMA CELL	1 (2%)		
#LUMBAR LYMPH NODE	(43)	(43)	(43)
INFLAMMATION, ACUTE	1 (2%)		
HYPERPLASIA, PLASMA CELL	1 (2%)	1 (2%)	
HYPERPLASIA, LYMPHOID			1 (2%)
#MESENTERIC L. NODE	(43)	(43)	(43)
PHAGOCYTIC CELL		1 (2%)	
HYPERPLASIA, LYMPHOID	1 (2%)	1 (2%)	
#RENAL LYMPH NODE	(43)	(43)	(43)
CYST, NOS	1 (2%)		
HYPERPLASIA, PLASMA CELL	1 (2%)		
*PULMONARY VEIN	(50)	(49)	(50)
LEUKOCYTOSIS, NOS			1 (2%)
#LIVER	(50)	(49)	(50)
HEMATOPOIESIS	4 (8%)	3 (6%)	2 (4%)
CIRCULATORY SYSTEM			
#LUNG	(50)	(49)	(50)
PERIVASCULITIS	4 (8%)	4 (8%)	5 (10%)
#HEART	(50)	(49)	(50)
ENDOCARDITIS, BACTERIAL	1 (2%)		
CALCIFICATION, FOCAL			2 (4%)
#MYOCARDIUM	(50)	(49)	(50)
DEGENERATION, NOS	1 (2%)		
*PULMONARY VEIN	(50)	(49)	(50)
THROMBOSIS, NOS		1 (2%)	

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM (Continued)			
#GASTRIC MUCOSA	(50)	(49)	(50)
PERIVASCULITIS	1 (2%)		
#URINARY BLADDER	(49)	(46)	(50)
PERIVASCULITIS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(48)	(47)	(47)
INFLAMMATION, CHRONIC FOCAL	18 (38%)	16 (34%)	17 (36%)
#LIVER	(50)	(49)	(50)
INFLAMMATION, ACUTE FOCAL		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)	2 (4%)
NECROSIS, NOS			2 (4%)
NECROSIS, FOCAL		1 (2%)	
METAMORPHOSIS FATTY	7 (14%)	21 (43%)	28 (56%)
CALCIFICATION, NOS			5 (10%)
CALCIFICATION, FOCAL			2 (4%)
HEPATOCYTOMEGALY		1 (2%)	1 (2%)
ANGIECTASIS			1 (2%)
#HEPATIC CAPSULE	(50)	(49)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
#HEPATIC SEROSA	(50)	(49)	(50)
INFLAMMATION, ACUTE	2 (4%)	3 (6%)	1 (2%)
#LIVER/CENTRILOBULAR	(50)	(49)	(50)
NECROSIS, NOS	1 (2%)		
#BILE DUCT	(50)	(49)	(50)
INFLAMMATION, CHRONIC	1 (2%)	2 (4%)	
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)	1 (2%)
#PANCREAS	(48)	(46)	(49)
CYSTIC DUCTS			1 (2%)
INFLAMMATION, CHRONIC	1 (2%)		
INFLAMMATION, CHRONIC FOCAL	1 (2%)	1 (2%)	1 (2%)
NECROSIS, FAT			1 (2%)
METAMORPHOSIS FATTY	2 (4%)		
#PERIPANCREATIC TISSUE	(48)	(46)	(49)
NECROSIS, FAT	1 (2%)		
#FORESTOMACH	(50)	(49)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERKERATOSIS	2 (4%)	2 (4%)	
ACANTHOSIS	3 (6%)	3 (6%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(50)
INFLAMMATION, CHRONIC		1 (2%)	
GLOMERULONEPHRITIS, CHRONIC	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC FOCAL	22 (44%)	18 (37%)	18 (36%)
NEPHROSIS, NOS	1 (2%)		
GLOMERULOSCLEROSIS, NOS	1 (2%)	1 (2%)	1 (2%)
NECROSIS, CORTICAL	1 (2%)		
NECROSIS, MEDULLARY	1 (2%)		
#KIDNEY/CAPSULE	(50)	(49)	(50)
INFLAMMATION, CHRONIC	1 (2%)		
#KIDNEY/CORTEX	(50)	(49)	(50)
NEPHROSIS, NOS	1 (2%)		
#KIDNEY/GLOMERULUS	(50)	(49)	(50)
AMYLOIDOSIS		1 (2%)	
#KIDNEY/TUBULE	(50)	(49)	(50)
NECROSIS, CORTICAL			1 (2%)
#U. BLADDER/SUBMUCOSA	(49)	(46)	(50)
INFLAMMATION, CHRONIC FOCAL	12 (24%)	12 (26%)	15 (30%)

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#URINARY BLADDER/SEROSA	(49)	(46)	(50)
INFLAMMATION, ACUTE		2 (4%)	
ENDOCRINE SYSTEM			
#PITUITARY	(49)	(41)	(32)
CYST, NOS		1 (2%)	
CONGESTION, NOS			1 (3%)
HYPERPLASIA, FOCAL	2 (4%)		1 (3%)
#ADRENAL	(49)	(46)	(49)
AMYLOIDOSIS		1 (2%)	
#ADRENAL SEROSA	(49)	(46)	(49)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)	1 (2%)	
#ADRENAL CORTEX	(49)	(46)	(49)
METAMORPHOSIS FATTY	2 (4%)		
#PERIADRENAL TISSUE	(49)	(46)	(49)
INFLAMMATION, CHRONIC	1 (2%)		
#THYROID	(49)	(46)	(50)
CYSTIC FOLLICLES	1 (2%)	5 (11%)	1 (2%)
INFLAMMATION, ACUTE FOCAL	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	13 (28%)	27 (54%)
#THYROID FOLLICLE	(49)	(46)	(50)
HYPERPLASIA, CYSTIC			4 (8%)
#PARATHYROID	(25)	(23)	(22)
CYST, NOS	1 (4%)		
#PANCREATIC ISLETS	(48)	(46)	(49)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
MULTIPLE CYSTS			1 (2%)
#UTERUS	(48)	(49)	(50)
HYDROMETRA	2 (4%)	1 (2%)	3 (6%)
INFLAMMATION, ACUTE FOCAL	1 (2%)		
#UTERUS/ENDOMETRIUM	(48)	(49)	(50)
INFLAMMATION, SUPPURATIVE	3 (6%)	5 (10%)	5 (10%)
INFLAMMATION, ACUTE	1 (2%)		
HYPERPLASIA, CYSTIC	36 (75%)	38 (78%)	42 (84%)
#OVARY/PAROVARIAN	(49)	(46)	(49)
INFLAMMATION, CHRONIC	3 (6%)	2 (4%)	1 (2%)
NECROSIS, FAT	1 (2%)		1 (2%)
#OVARY	(49)	(46)	(49)
CYST, NOS	12 (24%)	8 (17%)	18 (37%)
HEMORRHAGIC CYST	3 (6%)	2 (4%)	
INFLAMMATION, SUPPURATIVE	6 (12%)	9 (20%)	3 (6%)
INFLAMMATION, CHRONIC	2 (4%)	2 (4%)	1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			

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

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(50)	(49)	(50)
INFLAMMATION, ACUTE	1 (2%)	1 (2%)	
ABSCESS, NOS			1 (2%)
BODY CAVITIES			
*MEDIASTINUM	(50)	(49)	(50)
INFLAMMATION, CHRONIC	2 (4%)	3 (6%)	
*ABDOMINAL CAVITY	(50)	(49)	(50)
HEMORRHAGE	1 (2%)		
NECROSIS, FAT		2 (4%)	1 (2%)
*ABDOMINAL SEROSA	(50)	(49)	(50)
INFLAMMATION, ACUTE	1 (2%)		
*PERITONEUM	(50)	(49)	(50)
INFLAMMATION, ACUTE	1 (2%)	1 (2%)	
*PLEURA	(50)	(49)	(50)
INFLAMMATION, ACUTE		1 (2%)	
INFLAMMATION, CHRONIC	1 (2%)		
*MESENTERY	(50)	(49)	(50)
INFLAMMATION, SUPPURATIVE	1 (2%)		
NECROSIS, FAT	2 (4%)	1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(50)
INFLAMMATION, ACUTE	1 (2%)	5 (10%)	
INFLAMMATION, CHRONIC			1 (2%)
INFLAMMATION, CHRONIC FOCAL		1 (2%)	6 (12%)
ADIPOSE TISSUE			
HEMATOMA, NOS	1		
INFLAMMATION, SUPPURATIVE			1
BROWN FAT			
CALCIFICATION, NOS	1		
OMENTUM			
HEMATOMA, NOS	1		
INFLAMMATION, ACUTE	1		
INFLAMMATION, CHRONIC	1		1
NECROSIS, FAT	1		1
SPECIAL MORPHOLOGY SUMMARY			
ANIMAL MISSING/NO NECROPSY		1	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
† LOW DOSE MALE AND FEMALE MICE RECEIVED A SEVENFOLD OVERDOSE OF CHEMICAL IN CORN OIL AT WEEK 58.

APPENDIX E

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

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

	Vehicle Control	40 mg/kg	80 mg/kg
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	8.2%	2.6%	2.3%
Terminal Rates (c)	2/34 (6%)	1/38 (3%)	1/43 (2%)
Life Table Tests (d)	P=0.152N	P=0.278N	P=0.237N
Incidental Tumor Tests (d)	P=0.208N	P=0.325N	P=0.332N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Tests		P=0.309N	P=0.309N
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	2.9%	7.9%	0.0%
Terminal Rates (c)	1/34 (3%)	3/38 (8%)	0/43 (0%)
Life Table Tests (d)	P=0.307N	P=0.345	P=0.453N
Incidental Tumor Tests (d)	P=0.307N	P=0.345	P=0.453N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Tests		P=0.309	P=0.500N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	8.8%	10.1%	0.0%
Terminal Rates (c)	3/34 (9%)	3/38 (8%)	0/43 (0%)
Life Table Tests (d)	P=0.077N	P=0.554	P=0.083N
Incidental Tumor Tests (d)	P=0.107N	P=0.508	P=0.083N
Cochran-Armitage Trend Test (d)	P=0.118N		
Fisher Exact Tests		P=0.500	P=0.121N
Hematopoietic System: Lymphoma			
Overall Rates (a)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	5.2%	0.0%	6.2%
Terminal Rates (c)	1/34 (3%)	0/38 (0%)	0/43 (0%)
Life Table Tests (d)	P=0.439	P=0.230N	P=0.558
Incidental Tumor Tests (d)	P=0.238	P=0.288N	P=0.396
Cochran-Armitage Trend Test (d)	P=0.390		
Fisher Exact Tests		P=0.247N	P=0.500
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	6/50 (12%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	15.3%	7.4%	2.3%
Terminal Rates (c)	2/34 (6%)	2/38 (5%)	1/43 (2%)
Life Table Tests (d)	P=0.023N	P=0.221N	P=0.038N
Incidental Tumor Tests (d)	P=0.099N	P=0.383N	P=0.165N
Cochran-Armitage Trend Test (d)	P=0.036N		
Fisher Exact Tests		P=0.243N	P=0.056N
Liver: Neoplastic Nodule			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	8.8%	12.7%	7.0%
Terminal Rates (c)	3/34 (9%)	4/38 (11%)	3/43 (7%)
Life Table Tests (d)	P=0.449N	P=0.415	P=0.551N
Incidental Tumor Tests (d)	P=0.513N	P=0.371	P=0.551N
Cochran-Armitage Trend Test (d)	P=0.576		
Fisher Exact Tests		P=0.357	P=0.661
Liver: Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	0.0%	7.9%	0.0%
Terminal Rates (c)	0/34 (0%)	3/38 (8%)	0/43 (0%)
Life Table Tests (d)	P=0.575N	P=0.141	(e)
Incidental Tumor Tests (d)	P=0.575N	P=0.141	(e)
Cochran-Armitage Trend Test (d)	P=0.640		
Fisher Exact Tests		P=0.121	(e)

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

	Vehicle Control	40 mg/kg	80 mg/kg
Liver: Neoplastic Nodule or Carcinoma			
Overall Rates (a)	3/50 (6%)	8/50 (16%)	3/50 (6%)
Adjusted Rates (b)	8.8%	20.4%	7.0%
Terminal Rates (c)	3/34 (9%)	7/38 (18%)	3/43 (7%)
Life Table Tests (d)	P=0.422N	P=0.136	P=0.551N
Incidental Tumor Tests (d)	P=0.479N	P=0.115	P=0.551N
Cochran-Armitage Trend Test (d)	P=0.568		
Fisher Exact Tests		P=0.100	P=0.661
Pituitary: Adenoma			
Overall Rates (a)	12/49 (24%)	13/48 (27%)	13/48 (27%)
Adjusted Rates (b)	33.8%	32.2%	30.0%
Terminal Rates (c)	11/34 (32%)	11/38 (29%)	11/41 (27%)
Life Table Tests (d)	P=0.435N	P=0.573N	P=0.481N
Incidental Tumor Tests (d)	P=0.477	P=0.529	P=0.552
Cochran-Armitage Trend Test (d)	P=0.430		
Fisher Exact Tests		P=0.476	P=0.476
Pituitary: Carcinoma			
Overall Rates (a)	3/49 (6%)	0/48 (0%)	1/48 (2%)
Adjusted Rates (b)	8.2%	0.0%	2.4%
Terminal Rates (c)	2/34 (6%)	0/38 (0%)	1/41 (2%)
Life Table Tests (d)	P=0.143N	P=0.110N	P=0.249N
Incidental Tumor Tests (d)	P=0.202N	P=0.143N	P=0.341N
Cochran-Armitage Trend Test (d)	P=0.181N		
Fisher Exact Tests		P=0.125N	P=0.316N
Pituitary Adenoma or Carcinoma			
Overall Rates (a)	15/49 (31%)	13/48 (27%)	14/48 (29%)
Adjusted Rates (b)	41.1%	32.2%	32.2%
Terminal Rates (c)	13/34 (38%)	11/38 (29%)	12/41 (29%)
Life Table Tests (d)	P=0.258N	P=0.302N	P=0.288N
Incidental Tumor Tests (d)	P=0.447N	P=0.400N	P=0.470N
Cochran-Armitage Trend Test (d)	P=0.481N		
Fisher Exact Tests		P=0.437N	P=0.527N
Adrenal: Pheochromocytoma			
Overall Rates (a)	7/50 (14%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	19.9%	19.8%	9.3%
Terminal Rates (c)	6/34 (18%)	6/38 (16%)	4/43 (9%)
Life Table Tests (d)	P=0.122N	P=0.582	P=0.148N
Incidental Tumor Tests (d)	P=0.210N	P=0.481	P=0.194N
Cochran-Armitage Trend Test (d)	P=0.226N		
Fisher Exact Tests		P=0.500	P=0.262N
Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant			
Overall Rates (a)	8/50 (16%)	8/50 (16%)	4/50 (8%)
Adjusted Rates (b)	22.8%	19.8%	9.3%
Terminal Rates (c)	7/34 (21%)	6/38 (16%)	4/43 (9%)
Life Table Tests (d)	P=0.073N	P=0.521N	P=0.088N
Incidental Tumor Tests (d)	P=0.133N	P=0.596	P=0.119N
Cochran-Armitage Trend Test (d)	P=0.152N		
Fisher Exact Tests		P=0.607	P=0.178N
Thyroid: Follicular Cell Carcinoma			
Overall Rates (a)	3/49 (6%)	1/47 (2%)	0/49 (0%)
Adjusted Rates (b)	9.1%	2.6%	0.0%
Terminal Rates (c)	3/33 (9%)	1/38 (3%)	0/43 (0%)
Life Table Tests (d)	P=0.038N	P=0.256N	P=0.079N
Incidental Tumor Tests (d)	P=0.038N	P=0.256N	P=0.079N
Cochran-Armitage Trend Test (d)	P=0.062N		
Fisher Exact Tests		P=0.324N	P=0.121N

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

	Vehicle Control	40 mg/kg	80 mg/kg
Thyroid: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	3/49 (6%)	2/47 (4%)	0/49 (0%)
Adjusted Rates (b)	9.1%	5.3%	0.0%
Terminal Rates (c)	3/33 (9%)	2/38 (5%)	0/43 (0%)
Life Table Tests (d)	P=0.050N	P=0.435N	P=0.079N
Incidental Tumor Tests (d)	P=0.050N	P=0.435N	P=0.079N
Cochran-Armitage Trend Test (d)	P=0.083N		
Fisher Exact Tests		P=0.520N	P=0.121N
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	2/49 (4%)	4/47 (9%)	3/49 (6%)
Adjusted Rates (b)	6.1%	10.5%	7.0%
Terminal Rates (c)	2/33 (6%)	4/38 (11%)	3/43 (7%)
Life Table Tests (d)	P=0.549	P=0.403	P=0.620
Incidental Tumor Tests (d)	P=0.549	P=0.403	P=0.620
Cochran-Armitage Trend Test (d)	P=0.417		
Fisher Exact Tests		P=0.319	P=0.500
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	4/49 (8%)	5/47 (11%)	5/49 (10%)
Adjusted Rates (b)	11.4%	13.2%	11.6%
Terminal Rates (c)	3/33 (9%)	5/38 (13%)	5/43 (12%)
Life Table Tests (d)	P=0.544N	P=0.578	P=0.622N
Incidental Tumor Tests (d)	P=0.527	P=0.524	P=0.565
Cochran-Armitage Trend Test (d)	P=0.432		
Fisher Exact Tests		P=0.473	P=0.500
Mammary Gland: Fibroadenoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	1/50 (2%)
Adjusted Rates (b)	7.8%	0.0%	2.3%
Terminal Rates (c)	1/34 (3%)	0/38 (0%)	1/43 (2%)
Life Table Tests (d)	P=0.144N	P=0.117N	P=0.247N
Incidental Tumor Tests (d)	P=0.276N	P=0.184N	P=0.459N
Cochran-Armitage Trend Test (d)	P=0.176N		
Fisher Exact Tests		P=0.121N	P=0.309N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	48/50 (96%)	43/50 (86%)	45/49 (92%)
Adjusted Rates (b)	100.0%	97.7%	93.8%
Terminal Rates (c)	34/34 (100%)	37/38 (97%)	40/43 (93%)
Life Table Tests (d)	P=0.003N	P=0.040N	P=0.006N
Incidental Tumor Tests (d)	P=0.184N	P=0.143N	P=0.368N
Cochran-Armitage Trend Test (d)	P=0.286N		
Fisher Exact Tests		P=0.080N	P=0.329N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 80 mg/kg and vehicle control groups.

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

	Vehicle Control	40 mg/kg	80 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	6/50 (12%)	6/50 (12%)	10/50 (20%)
Adjusted Rates (b)	14.0%	15.2%	21.6%
Terminal Rates (c)	5/41 (12%)	5/38 (13%)	6/41 (15%)
Life Table Tests (d)	P=0.172	P=0.564	P=0.216
Incidental Tumor Tests (d)	P=0.162	P=0.599	P=0.207
Cochran-Armitage Trend Test (d)	P=0.161		
Fisher Exact Tests		P=0.620	P=0.207
Pituitary: Adenoma			
Overall Rates (a)	11/47 (23%)	19/49 (39%)	10/50 (20%)
Adjusted Rates (b)	26.8%	43.7%	22.3%
Terminal Rates (c)	9/38 (24%)	14/38 (37%)	7/41 (17%)
Life Table Tests (d)	P=0.396N	P=0.067	P=0.446N
Incidental Tumor Tests (d)	P=0.387N	P=0.073	P=0.441N
Cochran-Armitage Trend Test (d)	P=0.382N		
Fisher Exact Tests		P=0.080	P=0.436N
Pituitary: Carcinoma			
Overall Rates (a)	5/47 (11%)	3/49 (6%)	2/50 (4%)
Adjusted Rates (b)	11.9%	7.1%	4.9%
Terminal Rates (c)	3/38 (8%)	1/38 (3%)	2/41 (5%)
Life Table Tests (d)	P=0.152N	P=0.380N	P=0.201N
Incidental Tumor Tests (d)	P=0.142N	P=0.326N	P=0.197N
Cochran-Armitage Trend Test (d)	P=0.138N		
Fisher Exact Tests		P=0.334N	P=0.193N
Pituitary: Adenoma or Carcinoma			
Overall Rates (a)	16/47 (34%)	22/49 (45%)	12/50 (24%)
Adjusted Rates (b)	37.2%	48.5%	26.8%
Terminal Rates (c)	12/38 (32%)	15/38 (39%)	9/41 (22%)
Life Table Tests (d)	P=0.197N	P=0.157	P=0.215N
Incidental Tumor Tests (d)	P=0.171N	P=0.176	P=0.199N
Cochran-Armitage Trend Test (d)	P=0.166N		
Fisher Exact Tests		P=0.190	P=0.193N
Adrenal: Pheochromocytoma			
Overall Rates (a)	3/50 (6%)	5/50 (10%)	1/49 (2%)
Adjusted Rates (b)	6.6%	12.3%	2.5%
Terminal Rates (c)	1/41 (2%)	3/38 (8%)	1/40 (3%)
Life Table Tests (d)	P=0.277N	P=0.323	P=0.314N
Incidental Tumor Tests (d)	P=0.267N	P=0.389	P=0.310N
Cochran-Armitage Trend Test (d)	P=0.272N		
Fisher Exact Tests		P=0.357	P=0.316N
Thyroid: Follicular Cell Carcinoma			
Overall Rates (a)	1/49 (2%)	0/49 (0%)	3/48 (6%)
Adjusted Rates (b)	2.5%	0.0%	7.7%
Terminal Rates (c)	1/40 (3%)	0/37 (0%)	3/39 (8%)
Life Table Tests (d)	P=0.173	P=0.516N	P=0.296
Incidental Tumor Tests (d)	P=0.173	P=0.516N	P=0.296
Cochran-Armitage Trend Test (d)	P=0.171		
Fisher Exact Tests		P=0.500N	P=0.301
Thyroid: C-Cell Carcinoma			
Overall Rates (a)	5/49 (10%)	1/49 (2%)	0/48 (0%)
Adjusted Rates (b)	12.5%	2.7%	0.0%
Terminal Rates (c)	5/40 (13%)	1/37 (3%)	0/39 (0%)
Life Table Tests (d)	P=0.012N	P=0.121N	P=0.035N
Incidental Tumor Tests (d)	P=0.012N	P=0.121N	P=0.035N
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Tests		P=0.102N	P=0.030N

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

	Vehicle Control	40 mg/kg	80 mg/kg
Thyroid: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/49 (12%)	2/49 (4%)	1/48 (2%)
Adjusted Rates (b)	14.4%	5.4%	2.6%
Terminal Rates (c)	5/40 (13%)	2/37 (5%)	1/39 (3%)
Life Table Tests (d)	P=0.033N	P=0.164N	P=0.065N
Incidental Tumor Tests (d)	P=0.032N	P=0.150N	P=0.064N
Cochran-Armitage Trend Test (d)	P=0.030N		
Fisher Exact Tests		P=0.134N	P=0.059N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	18/50 (36%)	12/50 (24%)	4/50 (8%)
Adjusted Rates (b)	41.6%	29.8%	9.3%
Terminal Rates (c)	16/41 (39%)	10/38 (26%)	3/41 (7%)
Life Table Tests (d)	P<0.001N	P=0.202N	P=0.001N
Incidental Tumor Tests (d)	P<0.001N	P=0.168N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Tests		P=0.138N	P<0.001N
Uterus: Adenoma or Adenocarcinoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	6.9%	5.3%	0.0%
Terminal Rates (c)	2/41 (5%)	2/38 (5%)	0/41 (0%)
Life Table Tests (d)	P=0.087N	P=0.538N	P=0.126N
Incidental Tumor Tests (d)	P=0.084N	P=0.509N	P=0.123N
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Tests		P=0.500N	P=0.121N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	14/50 (28%)	8/50 (16%)	5/50 (10%)
Adjusted Rates (b)	32.5%	19.7%	11.0%
Terminal Rates (c)	12/41 (29%)	6/38 (16%)	2/41 (5%)
Life Table Tests (d)	P=0.018N	P=0.162N	P=0.025N
Incidental Tumor Tests (d)	P=0.014N	P=0.129N	P=0.021N
Cochran-Armitage Trend Test (d)	P=0.013N		
Fisher Exact Tests		P=0.114N	P=0.020N

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

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

	Vehicle Control	50 mg/kg (a)	100 mg/kg
Subcutaneous Tissue: Sarcoma or Fibrosarcoma			
Overall Rates (b)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (c)	4.4%	0.0%	9.7%
Terminal Rates (d)	1/44 (2%)	0/7 (0%)	2/29 (7%)
Life Table Tests (e)	P=0.248	P=0.681N	P=0.321
Incidental Tumor Tests (e)	P=0.443	P=0.365N	P=0.582
Cochran-Armitage Trend Test (e)	P=0.390		
Fisher Exact Tests		P=0.247N	P=0.500
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (b)	5/50 (10%)	4/50 (8%)	2/50 (4%)
Adjusted Rates (c)	11.4%	14.3%	5.5%
Terminal Rates (d)	5/44 (11%)	0/7 (0%)	1/29 (3%)
Life Table Tests (e)	P=0.333N	P=0.145	P=0.385N
Incidental Tumor Tests (e)	P=0.176N	P=0.607N	P=0.301N
Cochran-Armitage Trend Test (e)	P=0.169N		
Fisher Exact Tests		P=0.500N	P=0.218N
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (b)	6/50 (12%)	1/50 (2%)	2/50 (4%)
Adjusted Rates (c)	13.2%	8.3%	6.9%
Terminal Rates (d)	5/44 (11%)	0/7 (0%)	2/29 (7%)
Life Table Tests (e)	P=0.242N	P=0.670N	P=0.301N
Incidental Tumor Tests (e)	P=0.128N	P=0.371N	P=0.214N
Cochran-Armitage Trend Test (e)	P=0.070N		
Fisher Exact Tests		P=0.056N	P=0.134N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (b)	11/50 (22%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (c)	24.3%	21.4%	12.3%
Terminal Rates (d)	10/44 (23%)	0/7 (0%)	3/29 (10%)
Life Table Tests (e)	P=0.173N	P=0.213	P=0.187N
Incidental Tumor Tests (e)	P=0.047N	P=0.321N	P=0.101N
Cochran-Armitage Trend Test (e)	P=0.028N		
Fisher Exact Tests		P=0.086N	P=0.045N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (b)	9/50 (18%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (c)	20.0%	35.4%	0.0%
Terminal Rates (d)	8/44 (18%)	1/7 (14%)	0/29 (0%)
Life Table Tests (e)	P=0.026N	P=0.111	P=0.014N
Incidental Tumor Tests (e)	P=0.003N	P=0.642	P=0.006N
Cochran-Armitage Trend Test (e)	P=0.001N		
Fisher Exact Tests		P=0.117N	P=0.001N
Liver: Adenoma			
Overall Rates (b)	14/50 (28%)	5/50 (10%)	10/50 (20%)
Adjusted Rates (c)	31.8%	36.1%	32.6%
Terminal Rates (d)	14/44 (32%)	2/7 (29%)	9/29 (31%)
Life Table Tests (e)	P=0.473	P=0.203	P=0.521
Incidental Tumor Tests (e)	P=0.542N	P=0.604N	P=0.587N
Cochran-Armitage Trend Test (e)	P=0.188N		
Fisher Exact Tests		P=0.020N	P=0.241N
Liver: Carcinoma			
Overall Rates (b)	10/50 (20%)	9/50 (18%)	19/50 (38%)
Adjusted Rates (c)	21.6%	57.3%	53.0%
Terminal Rates (d)	8/44 (18%)	2/7 (29%)	13/29 (45%)
Life Table Tests (e)	P=0.003	P=0.001	P=0.002
Incidental Tumor Tests (e)	P=0.043	P=0.206	P=0.030
Cochran-Armitage Trend Test (e)	P=0.025		
Fisher Exact Tests		P=0.500N	P=0.038

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

	Vehicle Control	50 mg/kg	100 mg/kg
Liver: Adenoma or Carcinoma			
Overall Rates (b)	23/50 (46%)	14/50 (28%)	27/50 (54%)
Adjusted Rates (c)	49.9%	77.1%	74.2%
Terminal Rates (d)	21/44 (48%)	4/7 (57%)	20/29 (69%)
Life Table Tests (e)	P=0.009	P<0.001	P=0.007
Incidental Tumor Tests (e)	P=0.064	P=0.190	P=0.065
Cochran-Armitage Trend Test (e)	P=0.240		
Fisher Exact Tests		P=0.048N	P=0.274
Harderian Gland: Adenoma			
Overall Rates (b)	4/50 (8%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (c)	9.1%	28.6%	3.2%
Terminal Rates (d)	4/44 (9%)	2/7 (29%)	0/29 (0%)
Life Table Tests (e)	P=0.308N	P=0.199	P=0.322N
Incidental Tumor Tests (e)	P=0.226N	P=0.199	P=0.209N
Cochran-Armitage Trend Test (e)	P=0.118N		
Fisher Exact Tests		P=0.339N	P=0.181N
Harderian Gland: Adenoma or Carcinoma			
Overall Rates (b)	5/50 (10%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (c)	11.4%	28.6%	3.2%
Terminal Rates (d)	5/44 (11%)	2/7 (29%)	0/29 (0%)
Life Table Tests (e)	P=0.215N	P=0.264	P=0.223N
Incidental Tumor Tests (e)	P=0.151N	P=0.264	P=0.138N
Cochran-Armitage Trend Test (e)	P=0.060N		
Fisher Exact Tests		P=0.218N	P=0.102N

(a) Because 35/50 low dose male mice died after receiving a sevenfold overdose of chemical in corn oil at week 58, tumor incidence data in this group were considered inadequate for evaluation.
(b) Number of tumor-bearing animals/number of animals examined at the site.
(c) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

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

	Vehicle Control	50 mg/kg (a)	100 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (b)	3/50 (6%)	0/49 (0%)	4/50 (8%)
Adjusted Rates (c)	9.4%	0.0%	10.5%
Terminal Rates (d)	3/32 (9%)	0/27 (0%)	4/38 (11%)
Life Table Tests (e)	P=0.488	P=0.152N	P=0.594
Incidental Tumor Tests (e)	P=0.488	P=0.152N	P=0.594
Cochran-Armitage Trend Test (e)	P=0.407		
Fisher Exact Tests		P=0.125N	P=0.500
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (b)	5/50 (10%)	0/49 (0%)	5/50 (10%)
Adjusted Rates (c)	15.6%	0.0%	13.2%
Terminal Rates (d)	5/32 (16%)	0/27 (0%)	5/38 (13%)
Life Table Tests (e)	P=0.481N	P=0.048N	P=0.519N
Incidental Tumor Tests (e)	P=0.481N	P=0.048N	P=0.519N
Cochran-Armitage Trend Test (e)	P=0.579		
Fisher Exact Tests		P=0.030N	P=0.630
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (b)	10/50 (20%)	15/49 (31%)	11/50 (22%)
Adjusted Rates (c)	28.9%	40.9%	26.5%
Terminal Rates (d)	8/32 (25%)	7/27 (26%)	8/38 (21%)
Life Table Tests (e)	P=0.472N	P=0.127	P=0.547N
Incidental Tumor Tests (e)	P=0.480	P=0.238	P=0.553
Cochran-Armitage Trend Test (e)	P=0.454		
Fisher Exact Tests		P=0.163	P=0.500
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (b)	10/50 (20%)	15/49 (31%)	12/50 (24%)
Adjusted Rates (c)	28.9%	40.9%	28.0%
Terminal Rates (d)	8/32 (25%)	7/27 (26%)	8/38 (21%)
Life Table Tests (e)	P=0.527	P=0.127	P=0.547
Incidental Tumor Tests (e)	P=0.360	P=0.238	P=0.424
Cochran-Armitage Trend Test (e)	P=0.364		
Fisher Exact Tests		P=0.163	P=0.405
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (b)	4/50 (8%)	0/49 (0%)	4/50 (8%)
Adjusted Rates (c)	10.0%	0.0%	10.0%
Terminal Rates (d)	1/32 (3%)	0/27 (0%)	3/38 (8%)
Life Table Tests (e)	P=0.539N	P=0.073N	P=0.588N
Incidental Tumor Tests (e)	P=0.573N	P=0.031N	P=0.600
Cochran-Armitage Trend Test (e)	P=0.588		
Fisher Exact Tests		P=0.061N	P=0.643
Liver: Adenoma			
Overall Rates (b)	2/50 (4%)	4/49 (8%)	11/50 (22%)
Adjusted Rates (c)	6.3%	13.7%	28.0%
Terminal Rates (d)	2/32 (6%)	3/27 (11%)	10/38 (26%)
Life Table Tests (e)	P=0.010	P=0.272	P=0.018
Incidental Tumor Tests (e)	P=0.008	P=0.305	P=0.016
Cochran-Armitage Trend Test (e)	P=0.004		
Fisher Exact Tests		P=0.329	P=0.007
Liver: Carcinoma			
Overall Rates (b)	4/50 (8%)	6/49 (12%)	8/50 (16%)
Adjusted Rates (c)	10.3%	19.7%	19.7%
Terminal Rates (d)	1/32 (3%)	4/27 (15%)	6/38 (16%)
Life Table Tests (e)	P=0.217	P=0.318	P=0.247
Incidental Tumor Tests (e)	P=0.141	P=0.458	P=0.158
Cochran-Armitage Trend Test (e)	P=0.141		
Fisher Exact Tests		P=0.357	P=0.178

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

	Vehicle Control	50 mg/kg	100 mg/kg
Liver: Adenoma or Carcinoma			
Overall Rates (b)	6/50 (12%)	10/49 (20%)	19/50 (38%)
Adjusted Rates (c)	16.1%	32.2%	46.1%
Terminal Rates (d)	3/32 (9%)	7/27 (26%)	16/38 (42%)
Life Table Tests (e)	P=0.008	P=0.151	P=0.011
Incidental Tumor Tests (e)	P=0.003	P=0.245	P=0.004
Cochran-Armitage Trend Test (e)	P=0.002		
Fisher Exact Tests		P=0.194	P=0.002
Pituitary: Adenoma			
Overall Rates (b)	12/49 (24%)	7/41 (17%)	9/32 (28%)
Adjusted Rates (c)	33.7%	25.2%	33.7%
Terminal Rates (d)	9/32 (28%)	5/23 (22%)	8/25 (32%)
Life Table Tests (e)	P=0.427N	P=0.332N	P=0.492N
Incidental Tumor Tests (e)	P=0.547	P=0.255N	P=0.545
Cochran-Armitage Trend Test (e)	P=0.457		
Fisher Exact Tests		P=0.276N	P=0.455
Pituitary: Adenoma or Carcinoma			
Overall Rates (b)	14/49 (29%)	7/41 (17%)	9/32 (28%)
Adjusted Rates (c)	39.5%	25.2%	33.7%
Terminal Rates (d)	11/32 (34%)	5/23 (22%)	8/25 (32%)
Life Table Tests (e)	P=0.262N	P=0.201N	P=0.327N
Incidental Tumor Tests (e)	P=0.370N	P=0.143N	P=0.481N
Cochran-Armitage Trend Test (e)	P=0.467N		
Fisher Exact Tests		P=0.150N	P=0.585N
Thyroid: Follicular Cell Adenoma			
Overall Rates (b)	0/49 (0%)	3/46 (7%)	2/50 (4%)
Adjusted Rates (c)	0.0%	10.9%	5.3%
Terminal Rates (d)	0/32 (0%)	2/26 (8%)	2/38 (5%)
Life Table Tests (e)	P=0.263	P=0.093	P=0.277
Incidental Tumor Tests (e)	P=0.232	P=0.117	P=0.277
Cochran-Armitage Trend Test (e)	P=0.210		
Fisher Exact Tests		P=0.110	P=0.253
Thyroid: Follicular Cell Adenoma or Cystadenoma			
Overall Rates (b)	0/49 (0%)	3/46 (7%)	3/50 (6%)
Adjusted Rates (c)	0.0%	10.9%	7.7%
Terminal Rates (d)	0/32 (0%)	2/26 (8%)	2/38 (5%)
Life Table Tests (e)	P=0.150	P=0.093	P=0.155
Incidental Tumor Tests (e)	P=0.108	P=0.117	P=0.122
Cochran-Armitage Trend Test (e)	P=0.107		
Fisher Exact Tests		P=0.110	P=0.125
Thyroid: All Follicular Cell Adenoma or Carcinoma			
Overall Rates (b)	2/49 (4%)	3/46 (7%)	4/50 (8%)
Adjusted Rates (c)	6.3%	10.9%	10.3%
Terminal Rates (d)	2/32 (6%)	2/26 (8%)	3/38 (8%)
Life Table Tests (e)	P=0.352	P=0.413	P=0.419
Incidental Tumor Tests (e)	P=0.303	P=0.456	P=0.378
Cochran-Armitage Trend Test (e)	P=0.275		
Fisher Exact Tests		P=0.470	P=0.349
Harderian Gland: Adenoma			
Overall Rates (b)	1/50 (2%)	1/49 (2%)	3/50 (6%)
Adjusted Rates (c)	3.1%	3.7%	7.9%
Terminal Rates (d)	1/32 (3%)	1/27 (4%)	3/38 (8%)
Life Table Tests (e)	P=0.260	P=0.724	P=0.368
Incidental Tumor Tests (e)	P=0.260	P=0.724	P=0.368
Cochran-Armitage Trend Test (e)	P=0.202		
Fisher Exact Tests		P=0.747	P=0.309

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

(a) Low dose female mice received a sevenfold overdose of chemical in corn oil at week 58.
(b) Number of tumor-bearing animals/number of animals examined at the site
(c) Kaplan-Meier estimated tumor incidence at the end of the study after adjusting for intercurrent mortality
(d) Observed tumor incidence at terminal kill
(e) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact test compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

APPENDIX F

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

TABLE F1. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN MALE F344/N RATS RECEIVING CORN OIL BY GAVAGE (a)

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidylresorcinol ether	3/47	1/47	4/47
Diglycidylresorcinol ether	9/50	2/50	11/50
1,2-Dichloropropane	1/49	1/49	2/49
Chlorodibromomethane	2/49	2/49	4/49
TOTAL	15/195 (7.7%)	6/195 (3.1%)	21/195 (10.8%)
SD (b)	7.14%	1.13%	7.80%
Range (c)			
High	9/50	2/49	11/50
Low	1/49	1/49	2/49
Overall Historical Incidence			
TOTAL	91/1,109 (8.2%)	48/1,109 (4.3%)	137/1,109 (12.4%)
SD (b)	6.06%	3.46%	6.37%
Range (c)			
High	10/47	6/50	12/49
Low	0/50	0/50	2/50

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

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

	Leukemia
Historical Incidence at EG&G Mason Research Institute	
Diglycidylresorcinol ether	5/50
Diglycidylresorcinol ether	6/50
1,2-Dichloropropane	8/50
Chlorodibromomethane	6/50
TOTAL	25/200 (12.5%)
SD (b)	2.52%
Range (c)	
High	8/50
Low	5/50
Overall Historical Incidence	
TOTAL	140/1,146 (12.2%)
SD (b)	7.59%
Range (c)	
High	13/50
Low	1/50

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

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

	Interstitial Cell Tumor
Historical Incidence at EG&G Mason Research Institute	
Diglycidylresorcinol ether	47/50
Diglycidylresorcinol ether	47/50
1,2-Dichloropropane	45/50
Chlorodibromomethane	48/50
TOTAL	187/200 (93.5%)
SD (b)	2.52%
Range (c)	
High	48/50
Low	45/50
Overall Historical Incidence	
TOTAL	1,029/1,142 (90.1%)
SD (b)	5.57%
Range (c)	
High	48/50
Low	37/49

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

TABLE F4. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE (a)

	Fibroadenoma
Historical Incidence at EG&G Mason Research Institute	
Diglycidylresorcinol ether	18/50
Diglycidylresorcinol ether	17/50
1,2-Dichloropropane	15/50
Chlorodibromomethane	18/50
TOTAL	68/200 (34.0%)
SD (b)	2.83%
Range (c)	
High	18/50
Low	15/50
Overall Historical Incidence	
TOTAL	269/1,147 (23.5%)
SD (b)	9.38%
Range (c)	
High	18/50
Low	1/48

(a) Data as of March 17, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F5. HISTORICAL INCIDENCE OF UTERINE ENDOMETRIAL TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE (a)

	Polyp	Sarcoma	Polyp or Sarcoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidylresorcinol ether	11/50	1/50	12/50
Diglycidylresorcinol ether	12/50	3/50	15/50
1,2-Dichloropropane	10/50	1/50	10/50
Chlorodibromomethane	14/50	2/50	15/50
TOTAL	47/200 (23.5%)	7/200 (3.5%)	52/200 (26.0%)
SD (b)	3.42%	1.91%	4.9%
Range (c)			
High	14/50	3/50	15/50
Low	10/50	1/50	10/50
Overall Historical Incidence			
TOTAL	248/1,125 (22%)	23/1,125 (2%)	263/1,125 (23.4%)
SD (b)	6.74%	1.72%	6.88%
Range (c)			
High	17/50	3/50	17/50
Low	4/49	0/50	5/49

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

TABLE F6. HISTORICAL INCIDENCE OF THYROID GLAND C-CELL TUMORS IN FEMALE F344/N RATS RECEIVING CORN OIL BY GAVAGE (a)

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidylresorcinol ether	2/50	1/50	3/50
Diglycidylresorcinol ether	5/50	0/50	5/50
1,2-Dichloropropane	0/50	1/50	1/50
Chlorodibromomethane	1/49	5/49	6/49
TOTAL	8/199 (4.0%)	7/199 (3.5%)	15/199 (7.5%)
SD (b)	4.31%	4.53%	4.52%
Range (c)			
High	5/50	5/49	6/49
Low	0/50	0/50	1/50
Overall Historical Incidence			
TOTAL	78/1,104 (7.1%)	34/1,104 (3.1%)	110/1,104 (10.0%)
SD (b)	5.31%	3.08%	5.37%
Range (c)			
High	10/50	5/49	12/50
Low	0/50	0/50	1/50

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

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

	Leukemia	Lymphoma	Leukemia or Lymphoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidylresorcinol ether	0/50	6/50	6/50
1,2-Dichloropropane	0/50	8/50	8/50
Chlorodibromomethane	0/50	9/50	9/50
Bis(2-chloro-1-methylethyl)ether	0/50	6/50	6/50
TOTAL	0/200 (0.0%)	29/200 (14.5%)	29/200 (14.5%)
SD (b)	0.00%	3.00%	3.00%
Range (c)			
High	0/50	9/50	9/50
Low	0/50	6/50	6/50
Overall Historical Incidence			
TOTAL	6/1,090 (0.6%)	126/1,090 (11.6%)	132/1,090 (12.1%)
SD (b)	2.24%	5.63%	6.35%
Range (c)			
High	5/48	11/50	13/48
Low	0/50	0/50	0/50

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

TABLE F8. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE (a)

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidylresorcinol ether	7/49	7/49	13/49
1,2-Dichloropropane	7/50	11/50	18/50
Chlorodibromomethane	(b) 14/50	10/50	(b) 23/50
Bis (2-Chloro-1-methylethyl) ether	8/50	5/50	13/50
TOTAL	36/199 (18.1%)	33/199 (16.6%)	67/199 (33.7%)
SD (c)	5.69%	5.47%	9.44%
Range (d)			
High	14/50	11/50	23/50
Low	7/50	5/50	13/50
Overall Historical Incidence			
TOTAL	134/1,084 (12.4%)	222/1,084 (20.5%)	341/1,084 (31.5%)
SD (c)	6.67%	7.90%	10.42%
Range (d)			
High	(e) 14/50	18/50	25/50
Low	0/50	4/50	5/50

(a) Data as of March 17, 1983, for studies of at least 104 weeks
(b) Given as 13/50 and 22/50 in the March 17, 1983, compilation
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Second highest incidence: 11/50 (22%)

TABLE F9. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE (a)

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidylresorcinol ether	6/50	0/50	6/50
1,2-Dichloropropane	9/50	3/50	11/50
Chlorodibromomethane	5/50	6/50	11/50
Bis(2-chloro-1-methylethyl)ether	5/50	1/50	6/50
TOTAL	25/200 (12.5%)	10/200 (5.0%)	34/200 (17.0%)
SD (b)	3.79%	5.29%	5.77%
Range (c)			
High	9/50	6/50	11/50
Low	5/50	0/50	6/50
Overall Historical Incidence			
TOTAL	99/1,082 (9.1%)	58/1,082 (5.4%)	155/1,082 (14.3%)
SD (b)	4.77%	4.13%	6.31%
Range (c)			
High	10/50	7/50	13/50
Low	0/47	0/50	1/50

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

TABLE F10. HISTORICAL INCIDENCE OF HEPATOCELLULAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE (a)

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidylresorcinol ether	3/48	0/48	3/48
1,2-Dichloropropane	0/50	1/50	1/50
Chlorodibromomethane	2/50	4/50	6/50
Bis(2-chloro-1-methylethyl) ether	5/50	2/50	7/50
TOTAL	10/198 (5.1%)	7/198 (3.5%)	17/198 (8.6%)
SD (b)	4.19%	3.42%	5.47%
Range (c)			
High	5/50	4/50	7/50
Low	0/50	0/48	1/50
Overall Historical Incidence			
TOTAL	47/1,176 (4.0%)	34/1,176 (2.9%)	80/1,176 (6.8%)
SD (b)	2.55%	2.18%	3.37%
Range (c)			
High	5/50	4/50	7/50
Low	0/50	0/50	1/50

(a) Data as of March 17, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F11. HISTORICAL INCIDENCE OF CIRCULATORY SYSTEM TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE (a)

	Hemangioma	Hemangiosarcoma	Hemangioma or Hemangiosarcoma
Historical Incidence at Mason Research Institute			
Diglycidylresorcinol ether	0/50	0/50	0/50
1,2-Dichloropropane	1/50	3/50	4/50
Chlorodibromomethane	2/50	2/50	4/50
Bis(2-chloro-1-methyl-ethyl)ether	0/50	0/50	0/50
TOTAL	3/200 (1.5%)	5/200 (2.5%)	8/200 (4.0%)
SD (b)	1.91%	3.00%	4.62%
Range (c)			
High	2/50	3/50	4/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	9/1,187 (0.8%)	33/1,187 (2.8%)	42/1,187 (3.5%)
SD (b)	1.32%	2.47%	2.90%
Range (c)			
High	2/50	3/49	4/50
Low	0/97	0/50	0/50

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

TABLE F12. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE B6C3F$_1$ MICE RECEIVING CORN OIL BY GAVAGE (a)

	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at EG&G Mason Research Institute			
Diglycidylresorcinol ether	3/49	0/49	3/49
1,2-Dichloropropane	5/50	1/50	6/50
Chlorodibromomethane	3/50	2/50	5/50
Bis(2-chloro-1-methylethyl)ether	1/50	0/50	1/50
TOTAL	12/199 (6.0%)	3/199 (1.5%)	15/199 (7.5%)
SD (b)	3.27%	1.91%	4.42%
Range (c)			
High	5/50	2/50	6/50
Low	1/50	0/50	1/50
Overall Historical Incidence			
TOTAL	36/1,103 (3.3%)	16/1,103 (1.5%)	52/1,103 (4.7%)
SD (b)	2.81%	1.61%	3.46%
Range (c)			
High	5/50	2/49	6/50
Low	0/50	0/50	0/50

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

APPENDIX G

CHEMICAL CHARACTERIZATION OF CHLORODIBROMOMETHANE

APPENDIX G. CHEMICAL CHARACTERIZATION

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

A. Lot No. F122277

1. Physical Properties

a. Boiling Point:	Determined	Literature Values
	118.5° C (visual micro boiling point) Endotherm 117°-120° C (liquid DSC, Dupont 900 DTA)	118°-122° C (Sax, 1975)

b. Density:	Determined	Literature Values
	d_{25}^{25} 2.433	d_{25}^{25} 2.440 (Sax, 1975)

c. Appearance and Cleanup Procedure: The compound, as received, contained dark colored globules floating in the liquid. It was received in two (7.2 and 2.8 kg) amber glass bottles. In order to remove the dark colored globules present in the sample, the contents were poured through a funnel, which contained a plug of glass wool and a large amount of anhydrous sodium sulfate, into a large polyethylene jug.

A solution of 1M sodium carbonate was prepared with a volume equal to that of the sample of chlorodibromomethane to be washed and decolorized. These equal volumes were combined and thoroughly agitated in a separatory funnel. The top aqueous layer was discarded after the mixture had been allowed to separate for about 10 min. The organic phase was washed two additional times with distilled water. A volume of distilled water approximately equal to the sample volume was used each time, with the aqueous layer being discarded after each wash. The sample was then placed in a light-resistant bottle. Anhydrous magnesium sulfate was added at a concentration of approximately 3% (w/v). After approximately 30 min, powdered activated charcoal was added at a concentration of approximately 0.5 g/100 ml sample followed by vigorous shaking. The sample of chlorodibromomethane was filtered under vacuum with a sintered glass funnel containing Celite 545® and transferred to a clean light-resistant container. The head space was flushed with nitrogen before the container was sealed.

2. Spectral Data

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

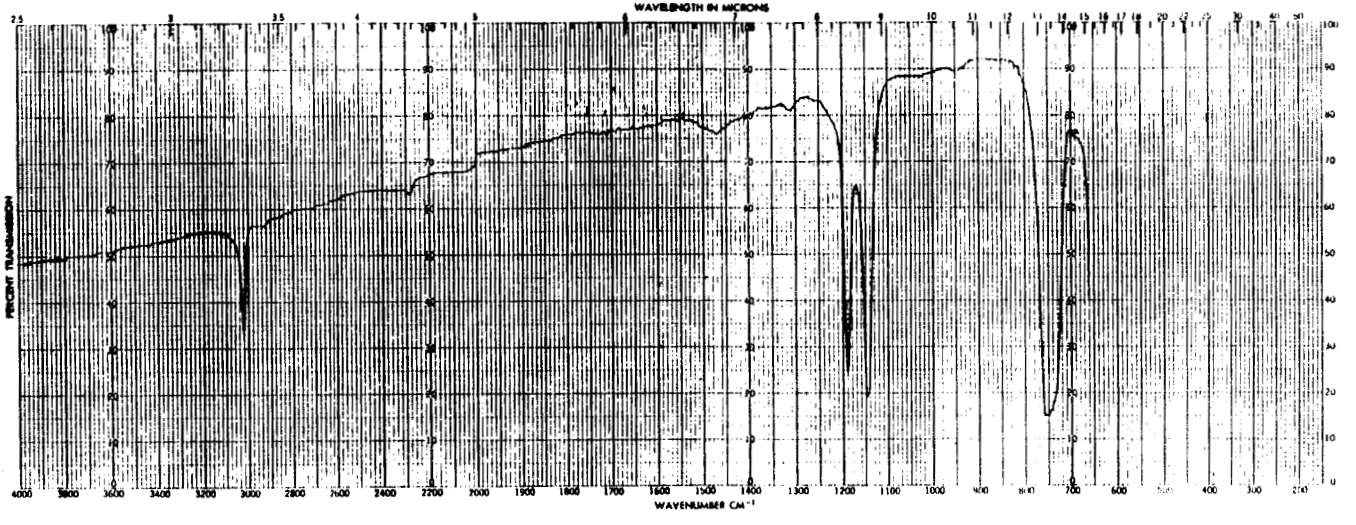


FIGURE 5. INFRARED ABSORPTION SPECTRUM OF CHLORODIBROMOMETHANE (LOT NO. F122277)

b. Ultraviolet/Visible

	Determined	Literature Values
Instrument:	Cary 118	
Solvent:	95% Ethanol	
Results:	There was no absorbance in the visible region (350-800 nm). There were no maxima in the ultraviolet region (350-220 nm) but an increase in absorbance from 290 nm toward the solvent cutoff was observed.	No literature reference found. Spectrum consistent with structure.

c. Nuclear Magnetic Resonance

	Determined	Literature Values
Instrument:	Varian EM-360A	
Solvent:	Deuterated chloroform with tetramethylsilane added	
Assignments:	See Figure 6	Consistent with literature spectrum (Sadtler Standard Spectra)
Chemical Shift (δ):	a s, 7.08 ppm b 1.44 ppm (impurity) c 8.76 ppm (impurity)	
Integration Ratios:	a 1.00 b 0.01 (impurity) c 0.01 (impurity)	

3. Titration of Acidic Components with Sodium Hydroxide

a. Before cleanup: 3,100 ± 300 (δ) ppm (as HBr)

b. After cleanup: 147 ± 18 (δ) ppm (as HBr) (Both Br_2 and HBr will react with sodium hydroxide.)

4. Water Analysis (Karl Fischer):

0.016% ± 0.006 (δ)%

5. Elemental Analysis:

Element	C	H	Br	Cl
Theory (percent)	5.77	0.48	76.73	17.02
Determined (percent)	6.04 6.11	0.55 0.58	71.39 71.16	16.01 15.90

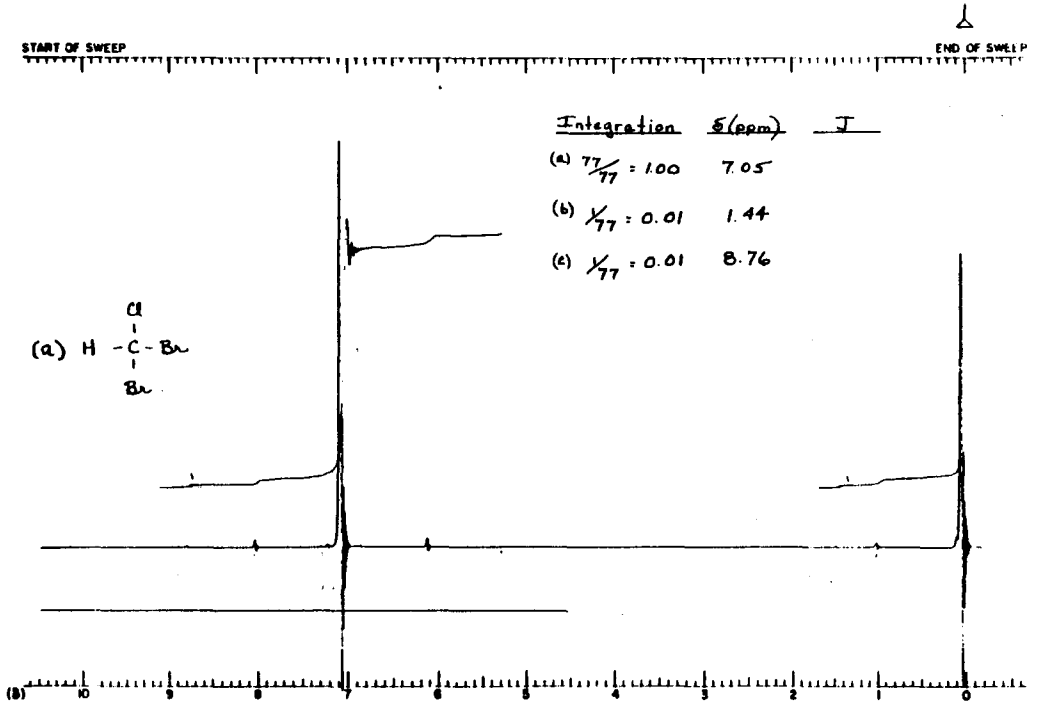


FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORODIBROMOMETHANE (LOT NO. F122277)

6. Gas Chromatographic Analyses:

Instrument: Varian 3740
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 270° C
Carrier gas: Nitrogen
Carrier flow rate: 70 cc/min

a. System 1 (Before cleanup):

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m × 4 mm ID, glass
Oven temperature program: 5 min at 50° C, then 50°-200° C at 10° C/min
Sample injected: Neat liquid (4 µl) and 1.0% and 0.5% chlorodibromomethane in pentane to quantitate the major peak and check for overloading

Results: Major peak and six impurities. Three impurities had areas 0.99%, 0.19%, and 0.43% relative to the major peak; the other three impurities had a total area of 0.15% of the major peak area. Four impurities were observed before and two after the major peak.

Peak	Retention Time (min.)	Retention Time (relative to major peak)	Area (percent of major peak)
1	1.20	0.11	0.03
2	8.45	0.75	0.99
3	9.72	0.86	0.06
4	10.27	0.91	0.06
5	11.30	1.00	100
6	13.19	1.17	0.19
7	13.43	1.19	0.43

b. System 2 (Before cleanup):

Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Oven temperature program: 5 min at 50° C, then 50°-170° C at 10° C/min
Sample injected: Neat liquid (6 µl) and 1.0% and 0.5% chlorodibromomethane in pentane to quantitate the major peak and check for overloading

Results: Major peak and 10 impurities. Three impurities had areas 0.99%, 0.47%, and 0.23% relative to the major peak; the other seven impurities had a combined area of 0.22% of the major peak. Seven impurities were observed before and three after the major peak.

Peak	Retention Time (min.)	RetentionTime (relative to major peak)	Area (percent of major peak)
1	1.22	0.13	0.03
2	1.46	0.16	0.05
3	3.08	0.33	0.02
4	5.73	0.61	0.02
5	6.12	0.66	0.99
6	6.72	0.72	0.03
7	8.53	0.92	0.02
8	9.32	1.00	100
9	10.90	1.17	0.05
10	11.30	1.21	0.47
11	13.00	1.39	0.23

c. **System 2** (After cleanup):

Sample injected: Neat liquid (5 µl) and 1.0% and 0.5% chlorodibromomethane in pentane to quantitate the major peak and check for overloading

Results: Major peak and 10 impurities with a combined area of 1.6% relative to the major peak area. There were seven impurities before and three after the major peak.

Peak	Retention Time (min.)	RetentionTime (relative to major peak)	Area (percent of major peak)
1 } unresolved	1.38	0.16	0.02
2 } unresolved	1.57	0.18	
3	3.06	0.34	0.01
4 shoulder	5.72	0.64	0.02
5	6.09	0.68	0.83
6	6.69	0.75	0.02
7	8.32	0.94	0.02
8	8.90	1.00	100
9	10.79	1.21	0.04
10	11.20	1.26	0.44
11	12.92	1.45	0.24

7. Conclusions: The carbon and hydrogen analyses were in agreement with theoretical values (within 0.3% absolute error). Bromine and chlorine analyses were low and outside the error limits.

Titration of acidic components before cleanup indicated 3,000 ppm acid, expressed as HBr (both HBr and Br_2 will react with base).

Gas chromatography by one system indicated six impurities, four before and two after the major peak. Three impurities had areas 0.99%, 0.19%, and 0.43% relative to the major peak; the other three impurities had a combined area of 0.15% of the major peak. A second gas chromatography system indicated 10 impurities, 7 before and 3 after the major peak. Three impurities had areas 0.99%, 0.47%, and 0.23% relative to the major peak; the other seven had a combined area of 0.22% of the major peak.

The procedure used to clean up the sample reduced the acid components from 3,100 ± 300 (δ) ppm to 147 ± 18 (δ) ppm (assumed to be HBr). Gas chromatography using a 20% SP 2100/0.1% Carbowax 1500 column produced very similar chromatograms for the original and the cleaned-up sample.

The infrared, ultraviolet/visible and nuclear magnetic resonance spectra were consistent with the structure.

B. Lot No. F810626

1. Physical Properties

Appearance: Clear, colorless liquid (after cleanup) (See A. 1. c. for cleanup procedure.)

2. Spectral Data

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

b. Ultraviolet/Visible	**Determined**	**Literature Values**
Instrument:	Cary 219	
Solvent:	Ethanol	
Results:	λ_{max} (nm) $\quad$ $\varepsilon \times 10^{-2}$	
	242 (shoulder) 5.03 ± 0.04 (δ) (Observed but not reported for Lot No. F122277) No absorbance maxima were observed from 800 to 290 nm with a 1% (v/v) solution of ethanol	No literature reference found; spectrum consistent with structure

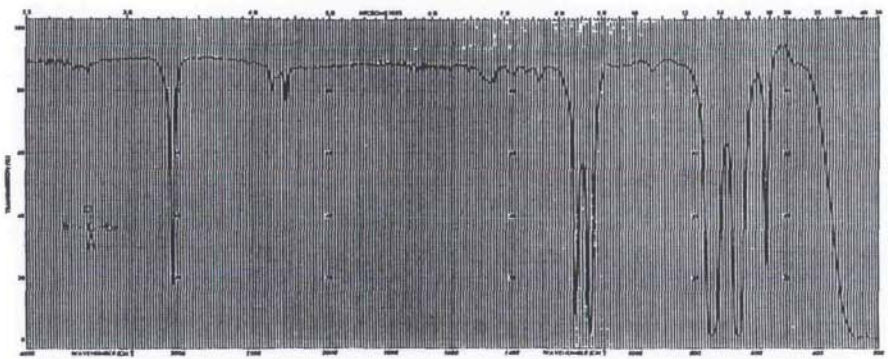


FIGURE 7. INFRARED ABSORPTION SPECTRUM OF CHLORODIBROMOMETHANE (LOT NO. F810626)

c. Nuclear Magnetic Resonance

	Determined	Literature Values
Assignments:	See Figure 8	Consistent with literature spectrum (Sadtler Standard Spectra)

Solvent: Chloroform-d_1 containing tetramethylsilane

Chemical Shift (δ): a s, 7.00
b 1.53, impurity

Integration Ratios: a 1.00
b <0.01

3. Titration of Acidic Components with 0.01N Sodium Hydroxide

118 ± 13 (δ) ppm (as HBr) (Both Br_2 and HBr will react with sodium hydroxide.)

4. Water Analysis (Karl Fischer):

<0.05%

5. Elemental Analysis:

Element	C	H	Br	Cl
Theory (percent)	5.77	0.48	76.73	17.02
Determined (percent)	5.78 5.65	0.48 0.51	73.87 73.67	16.16 16.35

6. Gas Chromatographic Analyses:

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

a. System 1:

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m × 4 mm ID, glass
Oven temperature program: 5 min at 50° C, then 50°-200° C at 10° C/min
Sample injected: Neat liquid (4 µl) and 1.0% and 0.5% chlorodibromomethane in pentane to quantitate the major peak and check linearity of detector response

Results: A major peak, two well-resolved impurities, and two groups of poorly resolved impurities were observed. The largest impurity had an area of 0.45% relative to the major peak. The cumulative area of the remaining impurities was 0.25% of the major peak. There were no additional impurities observed to elute up to 21 min after the peak.

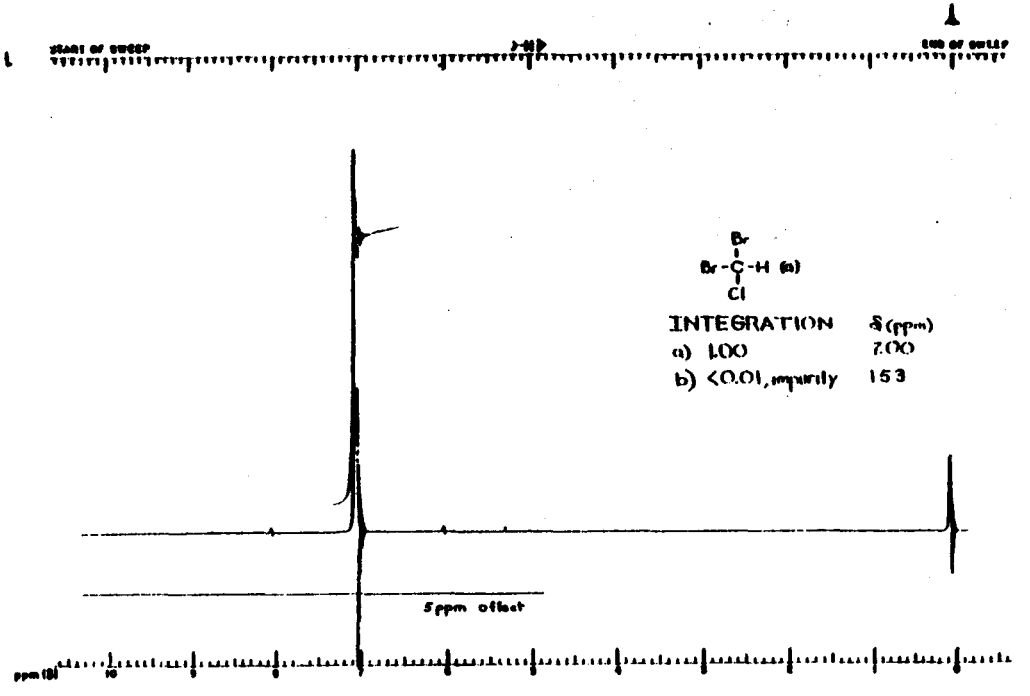


FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORODIBROMOMETHANE (LOT NO. F810626)

Peak	Retention Time (min.)	Retention Time (relative to major peak)	Area (percent of major peak)
1	1.25	0.11	0.05
2	8.85	0.77	0.45
3	10.6-10.9	0.93-0.95	0.02
4	11.45	1.00	100
5	12.8-13.7	1.12-1.20	0.18

b. System 2:

Column: 20% SP 2100 on 100/120 Supelcoport, 1.8 m x 4 mm ID, glass
Oven temperature program: 5 min at 50° C, then 50°-170° C at 10° C/min
Sample injected: Neat liquid (4 µl) and 1.0% and 0.5% chlorodibromomethane in pentane to quantitate the major peak and check linearity of detector response

Results: Major peak and four impurities with individual areas greater than 0.01% relative to the major peak. Two of these impurities eluted before the major peak, the largest of which had an area 0.36% of the major peak. Four additional impurities, one before and three after the major peak, were resolved, but their individual areas were much less than 0.01% of the major peak. No other impurities were observed to elute up to 20 min after the major peak.

Peak	Retention Time (min.)	RetentionTime (relative to major peak)	Area (percent of major peak)
1	1.2	0.15	0.04
2	5.3	0.65	0.36
3	8.2	1.00	100
4	10.6	1.29	0.01
5	12.3	1.50	0.19

7. Conclusions: The sample was identified as chlorodibromomethane by spectroscopy. Water content was less than 0.05%. Free acid (as HBr) was 118 ± 13 (δ) ppm. Gas chromatography indicated 0.70% impurities by one system and 0.60% by a second system. It is estimated from the combined data that this lot of chlorodibromomethane is slightly higher in purity (approximately 99%) than lot no. F122277. The low bromine result from the elemental analysis is attributed to the semi-quantitative results normally obtained for bromine for this type of compound.

II. Identification of Impurities in Lot F122277 by Gas Chromatography/Mass Spectrometry Analysis (performed on sample before cleanup)

Instrument: Varian MAT CH4B mass spectrometer interfaced via a Watson-Biemann helium separator to a Tracor MT-2000 MF gas chromatograph. Data processed by a Varian 620/i computer.
Column: GP 20% SP-2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Carrier gas: Helium
Carrier flow rate: 30 cc/min
Oven temperature program: 5 min at 50° C, then 50°-170° C at 10° C/min
Inlet temperature: 200° C
Transfer temperature: 285° C
Ionization voltage: 70 ev

Results:

A. Gas Chromatographic Analysis: (Ion Current Monitor)

Peak	Retention Time (min.)	Retention Time (relative to major peak)
1	9.0	0.65
2	11.8	0.86
3	13.8	1.00
4	15.5	1.12
5	17.0	1.23

B. Mass Spectral Analysis: (Tables G1 and G2)

1. Peak 1 – Bromochloromethane: The mass spectrum of peak 1 was consistent with the structure and with a literature spectrum of bromochloromethane. Relative intensities of the isotopic clusters obtained were also in agreement with theoretical values.

2. Peak 2 – Dibromomethane and Bromodichloromethane: The mass spectrum of peak 2 indicated two components, which are given as peaks 2a and 2b in Table G1. The spectra, when separated and normalized against their respective base peaks, are consistent with the structures and with literature spectra of dibromomethane and bromodichloromethane. The relative intensities of the isotopic clusters obtained are in agreement with theoretical values, although there is some overlap between the two spectra.

3. Peak 3 – Major Component

4. Peak 4 – Bromoform: The mass spectrum of peak 4 was consistent with the structure and with a literature spectrum of bromoform. Relative intensities of the isotopic clusters obtained were also in agreement with theoretical values.

5. Peak 5 – Chlorotribromomethane: The mass spectrum of peak 5 yielded fragments indicating chlorotribromomethane. The cluster m/e 205, 207, 209, and 211 ($CClBr_2^+$) was by far the most intense cluster seen; therefore, a partially saturated spectrum was used to quantitate the relative intensities of the less abundant clusters, whereas the relative intensities of the base peak cluster were taken from an unsaturated spectrum. Relative intensities of the isotopic clusters were in agreement with the theoretical values. No literature spectrum could be obtained for comparison.

The identities of dibromomethane, bromodichloromethane, and bromoform were confirmed by spiking the original mixture with authentic samples of the suspected impurities.

TABLE G1. GAS CHROMATOGRAPHY/MASS SPECTROMETRY

Peak No.	Retention Time (min)	Mass Fragments	Percent of Base Peak	Normalized Percent of Base Peak	Assignment	Literature Mass Fragments	Spectrum Percent of Base Peak
1	9.0	49	100	100	Bromochloro-methane	(a) 49	100
		130	78	97		130	97
		128	61	71		128	71
		51	34	30		51	30
		132	18	22		132	22
		93	16	21		93	21
		95	11	15		95	15
		47	6	6		(b) 47	6
2a	11.8	174	88	100	Dibromomethane	174	100
		93	64	73		93	77
		95	55	63		95	64
		172	45	51		172	53
		176	40	44		176	49
		79	8	10		79	21
		81	8	10		81	20
		91	9	10		91	11
2b	11.8	83	100	100	Bromodichloro-methane	(b) 83	100
		85	58	58		85	64
		129	14	14		129	15
		127	12	12		127	12
		79	8	8		79	11
		47	10	10		47	10
		87	10	10		87	10
		48	8	8		48	7
3	13.8 (Major component)						
4	15.5	173	68	100	Bromoform	(b) 173	100
		171	33	48		171	50
		175	34	50		175	49
		93	13	19		93	22
		91	13	20		91	22
		79	7	10		79	18
		81	6	9		81	17
		94	8	12		94	13
5	17.0	No good, unsaturated spectra obtained; see Table G2 for mass fragments with tentative assignments			Tribromo-chloromethane	No literature spectra available	

(a) Mass Spectrometry Data Centre, 1970
(b) NBS Mass Spectrometry Library

TABLE G2. MASS FRAGMENTS WITH TENTATIVE ASSIGNMENTS

Mass Fragments	Percent of Base Peak	Fragment Assignment
47	12	CCl^+
79	19	Br^+
91	14	CBr^+
128	32	$CBrCl^+$
160	4	Br_2^+
172	11	CBr_2^+
(a) 209	100	$CClBr_2^+$
251	10	CBr_3^+
(b) 288	0.4	$CClBr_3^+$

(a) Partially saturated
(b) Isotope peak of the parent peak (mw = 284) which was not observed

3. Conclusions: Gas chromatography/mass spectrometry was used to identify some of the impurities present. The gas chromatography system used for mass spectrometry indicated two impurity peaks before and two after the major peak. Identifications by mass spectra were as follows: bromochloromethane (peak 1) dibromomethane and bromodichloromethane (peak 2, components not resolved), bromoform (peak 4) and chlorotribromomethane (peak 5). Gas chromatography with the system I. A. 6. b. was used to identify, by spiking, some of the impurities which were indicated by mass spectrometry. The following compounds were identified: dibromomethane (peak 4, shoulder on peak 5), bromodichloromethane (peak 5) and bromoform (peak 10). A standard for bromochloromethane could not be obtained, but the possibilities are limited to peaks 1 through 3, all of which are less than 0.05% of the major peak in Section I. A. 6. b. A standard also could not be found for chlorotribromomethane, but comparison of mass spectral data and the original chromatogram indicates that peak 11 is chlorotribromomethane, based on retention data and relative areas.

III. Test Chemical Stability Study of Lot No. F122277 Performed by the Analytical Chemistry Laboratory

A. Sample Storage: Samples were stored in glass tubes with Teflon®-lined lids for 2 weeks at −20°, 25°, and 60° C.

B. Analytical Method: Solutions of chlorodibromomethane from each storage temperature were dissolved at 0.4% in methanol containing 0.1% tetradecane as an internal standard. The solutions were analyzed by the following gas chromatography system:

1. **Instrument:** Varian 3740 (with autoinjector)
2. **Detector:** Flame ionization
3. **Column:** 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m x 4 mm ID, glass
4. **Inlet temperature:** 200° C
5. **Detector temperature:** 300° C
6. **Carrier gas:** Nitrogen
7. **Carrier flow rate:** 70 cc/min
8. **Oven temperature program:** 120° C, isothermal
9. **Retention times:** Chlorodibromomethane, 1.8 min; tetradecane, 3.0 min

C. Results: The chlorodibromomethane peak was compared with the internal standard peak, and the recovery of chlorodibromomethane was compared with the recovery of the −20° C sample.

Storage Temperature	Percent Chlorodibromomethane
−20° C	100.0 ± 1.4
25° C	97.6 ± 1.4
60° C	99.3 ± 1.4

D. Conclusion: Chlorodibromomethane is stable as the bulk chemical for 2 weeks at temperatures up to 60° C, within the limits of experimental error. (Note: The above procedure for stability analysis necessarily excludes oxygen from the sample, except for any present in the small amount of headspace in the tubes. It was found that the analytical samples stored at room temperature over periods of from several weeks to several months became brown, presumably from the release of bromine. This indicates that some decomposition occurred, probably due to oxidation.)

IV. Test Chemical Stability Study Performed by the Testing Laboratory

A. Lot No. F122277

1. Storage Conditions:

Bulk chemical: 0° ± 5° C under nitrogen
Reference sample: −18° ± 7° C

2. Analytical Methods

a. Gas Chromatography:

Instrument: Varian 1400, 1440, or 3700
Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 6 ft × 2 mm ID, glass
Detector: Flame ionization
Detector temperature: 190°-260° C
Inlet temperature: 175°-190° C
Temperature program: 50° C for 5 min, then 50°-170° C at 6° C/min

b. Infrared:

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

c. Titration of Acidic Components: 5 ml of the chemical was added to 25 ml of 95% ethanol and titrated potentiometrically with 0.1N NaOH.

3. Results

a. Gas Chromatography and Titration

Date of Analysis	Percent of Major Peak		Acid Titration (ppm)	
	Reference	Bulk	Reference	Bulk
11/13/78	--	98.5	--	1,300
12/19/78	98.1	98.4	900	2,200
4/4/79	98.5	98.6	1,642	146
11/19/79	97.9	97.4	1,640	1,460
1/18/80	97.4	97.2	1,610	1,270
4/3/80	95.6	98.3	6,020	1,350
7/14/80	98.5	98.4	770	2,460
11/11/80	97.1	98.4	5,840	1,100
3/17/81	98.0	98.4	2,190	913
7/28/81	98.1	98.6	1,643	730

b. Infrared: No notable differences were observed between any of the bulk or reference sample spectra, and all were essentially identical with the original spectrum produced by the analytical chemistry laboratory.

4. Conclusion: No notable degradation occurred in the bulk sample over the course of the studies.

B. Lot No. F810626

1. Storage Conditions:

Bulk chemical: 0° ± 5° C
Reference sample: −20° C

2. Analytical Methods

a. Gas Chromatography:

Instrument: Varian 1400
Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 6 ft × 2 mm ID, glass
Detector: Flame ionization
Detector temperature: 200° C
Inlet temperature: 175° C
Temperature program: 50° C for 5 min, then 50°-170° C at 6° C/min

b. Infrared:

Instrument: Perkin-Elmer Infracord #137
Phase: Liquid film

3. Results

a. Gas Chromatography:

Date of Analysis	Percent of Major Peak		Acid Titration (ppm)	
	Reference	Bulk	Reference	Bulk
8/10/81	98.9	--	1,460	--
12/11/81	98.8	99.2	2,190	548

b. Infrared: All spectra were essentially identical with that produced by the analytical chemistry laboratory.

4. Conclusion: No notable degradation occurred in the bulk sample over the course of the studies.

APPENDIX H

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX H. PREPARATION AND CHARACTERIZATION

I. Studies Conducted at the Analytical Chemistry Laboratory

A. Sample Preparation and Storage: Chlorodibromomethane (10.191 ± 0.001 grams) was placed in a 50-ml volumetric flask and diluted to the volume mark with corn oil (42.355 ± 0.001 g) with periodic manual shaking. The chemical dissolved readily to give a concentration of 193.94 ± 0.02 mg/g of solution (19.394% ± 0.002%, w/w).

As soon as the solution had been prepared, eight accurately weighed 1.84-g aliquots were removed and sealed in separate 60-ml septum vials (Microsep F-138 gas chromatography septa with Teflon® film facing, from Canton Biomedical Products, Inc.; aluminum crimp seals from Wheaton Scientific Company, Inc.). Duplicate aliquots were used as initial, or zero-time, samples and for storage at 1, 5, and 7 days, respectively.

B. Sample Extraction and Analysis: Extracting solvent containing an internal reference standard was prepared by weighing 0.5485 ± 0.0001 g of *n*-amyl alcohol, transferring to a 1-liter volumetric flask, and diluting to the mark with absolute methanol. Concentration of reference standard: 0.5485 ± 0.0002 mg/ml.

To extract each sample aliquot, the septum vial was opened, 50 ml of the extracting solvent was added by volumetric pipette, and the vial immediately resealed. The corn oil/methanol mixture was manually shaken for 1 minute, and 10 ml of the resulting suspension was decanted into a 12-ml centrifuge tube and centrifuged for 5 min. A portion of the clear, methanolic supernatant solution (5 ml) was then transferred to an 8.5-ml septum vial for subsequent analysis by the gas chromatographic system outlined below:

1. **Instrument:** Bendix 2500 with Hewlett-Packard 3380A Automatic Integrator
2. **Column:** 10% Carbowax 20M on 80/100 mesh Chromosorb W(AW), 1.8 m × 2 mm ID, silanized glass
3. **Detector:** Flame ionization
4. **Temperatures:**
   a. Inlet, 175° C
   b. Oven, 85° C, isothermal
   c. Detector, 225° C
5. **Carrier gas:** Nitrogen
6. **Flow rate:** 60 cc/min
7. **Volume of solution injected:** 4 µl
8. **Retention times:**
   a. Test chemical, 6.6 min
   b. Reference standard, 5.1 min

C. Results:

Storage Time (days)	Average Percent Chemical Found in Chemical/Vehicle Mixture (a) (b)
1	(c) 20.1 ± 0.3
5	19.9 ± 0.3
7	19.3 ± 0.3

(a) Zero-time recovery yield, 90% ± 1%
(b) Theoretical concentration of chemical in corn oil, 19.394% ± 0.002% (w/w)
(c) Mean ± standard deviation

D. Conclusion: Chlorodibromomethane is stable when dissolved in corn oil at a concentration of 20% and stored at room temperature for 7 days.

II. Studies Conducted at the Testing Laboratory

Compound and corn oil were mixed to visual homogeneity by inversion in ground-glass-stoppered graduated cylinders.

APPENDIX I

ANALYSIS OF DOSE MIXTURES: METHODS

APPENDIX I. ANALYSIS: METHODS

I. Testing Laboratory

Procedure: Duplicate 1-ml aliquots were extracted with 10 ml of methanol containing 0.1 mg/ml of *n*-amyl alcohol as the internal standard. The methanolic solutions were analyzed by gas chromatography with a flame ionization detector at 110° on a 6 ft × 2 mm ID glass column packed with 20% SP2100/0.1% Carbowax 1500 on 100/200 Supelcoport. Spiked standards at three concentrations were prepared and worked up in the same manner to provide calibration data.

II. Analytical Chemistry Laboratory

A. Preparation of Standard Spiked Corn Oil: Two working standard solutions of chlorodibromomethane in methanol were prepared independently and then further diluted with methanol. Aliquots (20 ml) of the five standard solutions were pipetted into individual 30-ml amber septum vials containing 2 g of undosed corn oil to make spiked corn oil standards bracketing the specified dose range of the referee sample. One 30-ml amber septum vial containing 2 g of undosed corn oil was treated with 20 ml of methanol for use as a blank. The spiked corn oil samples and the corn oil blank were extracted immediately and analyzed using the procedure below.

B. Preparation of the Referee Sample: Three separate portions (approximately 2 g each) of the dosed referee corn oil sample were transferred to individually tared 30-ml amber septum vials and were weighed to the nearest 0.001 g. Methanol (20 ml) was pipetted into each vial; then the samples were extracted immediately and analyzed by the procedure below.

C. Analysis: The vials were sealed, vigorously agitated for 1 min on a vortex mixer, then shaken for 15 min at maximum stroke on a Burrell, Model 75, Wrist-Action® shaker. After the extraction mixtures were centrifuged for 3 min, a 5-ml aliquot of the upper methanol layer from each vial was combined with 5 ml of internal standard solution (*n*-amyl alcohol in methanol, 0.17 mg/ml). The solutions were thoroughly mixed; then the chlorodibromomethane content of each solution was determined by the gas chromatography system described below:

1. **Instrument:** Varian 3700 with CDS 111-C integrator
2. **Column:** 10% Carbowax 20M on 80/100 mesh Chromosorb W(AW), 1.8 m × 4 mm ID, silanized glass
3. **Detector:** Flame ionization
4. **Detector temperature:** 250° C
5. **Injector temperature:** 200° C
6. **Temperature program:** 80° C, isothermal
7. **Carrier gas:** Nitrogen
8. **Flow rate:** 30 cc/min
9. **Sample size:** 3 µl
10. **Retention times:** Chlorodibromomethane, 7.0 min; internal standard, 5.2 min

APPENDIX J

ANALYSES OF DOSE MIXTURES: DATA

I. Short-Term Studies

A. Fourteen-Day: Analyses not performed

B. Thirteen-Week

Results:

TABLE J1. ANALYSIS OF DOSE MIXTURES FOR CHLORODIBROMOMETHANE IN THE THIRTEEN-WEEK GAVAGE STUDIES

Date Mixed	Concentration (a) of Chlorodibromomethane in Corn Oil for Target Concentration (mg/ml)				
	3	6	12	25	50
2/26/79	2.8	6.5	11.3	25.0	48.9

(a) The data presented are the average of the results of duplicate analyses.

II. Two-Year Studies

A. Sampling Design: Random 1 × 8 weeks; blind to formulation

B. Results:

1. Formulation Sample Data:

TABLE J2. ANALYSIS OF DOSE MIXTURES FOR CHLORODIBROMOMETHANE IN THE TWO-YEAR GAVAGE STUDIES

Date Mixed	Concentration (a) of Chlorodibromomethane in Corn Oil for Target Concentration (mg/ml)			
	8	10	16	20
2/7/80	7.2	9.2	15.4	19.1
3/6/80	7.7	10.0	16.2	21.6
5/8/80	7.6	9.5	15.4	19.6
7/17/80	7.6	10.0	15.8	21.1
8/21/80	7.7	10.1	15.2	20.1
11/20/80	7.6	9.0	15.9	20.8
1/22/81	7.4	9.9	16.0	20.2
2/12/81	(b) 7.9	(b) 70.1	(b) 16.1	(b) 21.3
2/19/81	7.9	10.2	15.5	20.8
3/26/81	7.8	10.0	16.4	20.3
6/22/81	7.7	9.9	15.1	19.3
7/20/81	7.3	9.1	15.2	19.0
7/27/81				(b) 1.4
8/3/81	(b) 8.1	(b) 9.7	(b) 15.7	(b) 19.9
9/21/81	8.1	9.9	15.8	19.5
12/14/81	8.0	9.4	15.5	19.5
Mean (mg/ml)	7.7	9.7	15.6	20.1
Standard deviation	0.26	0.41	0.41	0.82
Coefficient of variation (percent)	3.4	4.2	2.6	4.1
Range (mg/ml)	7.2-8.1	9.0-10.2	15.1-16.4	19.0-21.6
Number of samples	13	13	13	13

(a) The data presented are the results of duplicate analyses.
(b) These were special analyses and are not included in the mean.

2. Referee Sample Data:

TABLE J3. REFEREE SAMPLE DATA FOR CHLORODIBROMOMETHANE IN THE TWO-YEAR GAVAGE STUDIES

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (a)	
		Testing Lab	Referee Lab
5/08/80	16	15.4	15.9
11/20/80	10	9.0	9.0
2/12/81	10	70.1	67.4
6/22/81	20	19.3	19.4
12/14/81	20	19.4	19.2

(a) The data presented are the results of duplicate analyses.

APPENDIX K

SENTINEL ANIMAL PROGRAM

APPENDIX K. SENTINEL ANIMAL PROGRAM

I. METHODS

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect test results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the test rooms. These animals are untreated, and these animals and the test animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

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

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	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 KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai	RCV (rat coronavirus)	

II. RESULTS

Results are presented in Table K1.

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

Interval	No. of Animals	Positive Serologic Reaction for
RATS		
6 months	5/10	PVM
	10/10	Sendai
	1/10	KRV
12 months	9/10	PVM
	6/10	Sendai
	7/10	KRV
	1/10	RCV
18 months	10/10	PVM
	8/10	Sendai
24 months	9/10	PVM
	9/10	Sendai
	4/10	KRV
MICE		
6 months	3/10	MHV
12 months	9/10	PVM
18 months	(b)	None
24 months	3/10	PVM
	1/10	Sendai
	9/10	MHV

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.
(b) No positive viral antibody titers were observed for any of the nine mice tested.

APPENDIX L

MUTAGENICITY OF CHLORODIBROMOMETHANE IN SALMONELLA

TABLE L1. MUTAGENICITY OF CHLORODIBROMOMETHANE IN SALMONELLA

Strain	Dose (µg/plate)	Revertants/plate (a) −S9	+S9 (rat)	+S9 (hamster)
TA 100	0	126 ± 8.0	218 ± 18.0	199 ± 21.1
	100	142 ± 3.1	192 ± 9.4	175 ± 5.0
	333	139 ± 3.2	219 ± 5.8	176 ± 6.4
	1,000	125 ± 12.4	138 ± 19.5	0 ± 0.0
	3,333	0 ± 0.0	0 ± 0.0	0 ± 0.0
	10,000	0 ± 0.0	0 ± 0.0	0 ± 0.0
TA 1535	0	5 ± 1.2	9 ± 2.7	9 ± 1.5
	100	4 ± 1.8	6 ± 1.2	4 ± 0.3
	333	3 ± 0.3	2 ± 0.7	6 ± 0.9
	1,000	5 ± 0.9	4 ± 0.6	7 ± 1.0
	3,333	5 ± 1.5	1 ± 0.3	0 ± 0.0
	10,000	3 ± 0.3	0 ± 0.3	0 ± 0.0
TA 1537	0	5 ± 0.7	17 ± 5.2	11 ± 0.9
	100	4 ± 0.3	14 ± 1.2	11 ± 3.2
	333	7 ± 0.9	9 ± 2.3	9 ± 0.3
	1,000	10 ± 0.3	5 ± 0.7	3 ± 0.6
	3,333	8 ± 0.3	0 ± 0.0	0 ± 0.0
	10,000	0 ± 0.0	0 ± 0.0	0 ± 0.0
TA 98	0	19 ± 2.0	22 ± 1.2	20 ± 1.2
	100	16 ± 1.2	17 ± 1.2	25 ± 4.1
	333	20 ± 1.3	21 ± 2.3	11 ± 2.3
	1,000	17 ± 2.4	11 ± 0.3	14 ± 2.0
	3,333	14 ± 0.5	1 ± 0.3	0 ± 0.0
	10,000	0 ± 0.0	0 ± 0.0	0 ± 0.0

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced animals (male Sprague-Dawley rats and male Syrian hamsters). Cells and test compound or solvent (DMSO) were incubated for 20 min at 37° C in the presence of either S9 or buffer (Yahagi et al., 1975). After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 h (Ames et al., 1975). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.

APPENDIX M

DATA AUDIT SUMMARY

APPENDIX M. AUDIT

The experimental data and laboratory report of these toxicology and carcinogenesis studies of chlorodibromomethane were audited and examined for compliance with Good Laboratory Practice (GLP) Regulations (Fed. Reg., 1978) and scientific procedures by the following persons during September 12-16, 1983: National Toxicology Program--Ms. C. Davies, Dr. J. Dunnick, Ms. A. Grant, Dr. C. Lingeman, Dr. B. Schwetz, Dr. C. Whitmire, and Dr. M. Wolfe; Experimental Pathology Laboratory--Dr. D. Banas, Dr. W. Busey, and Ms. H. Cooke.

The full report of the audit of these studies is on file at the National Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. The audit included, but was not limited to, a review of all Individual Animal Data Records for correspondence between necropsy observations and histology findings, slide/block matchup for all vehicle control and high dose animals of both species, examination of all wet tissue bags for verification of animal identification number, and examination of all chemistry data and the laboratory records for animal room environment. The main findings were as follows: Temperature and relative humidity in the animal rooms were often not as well controlled as requested in the protocol. Most relative humidity measurements were in the range of 20%-70% with a few readings outside of this range. Most temperature readings were in the range of 70°-78° F. Although isolated readings ranged from 65° to 86° F, none was for prolonged periods of time. No adverse effects in the animals were directly relatable to fluctuations in temperature or humidity.

Correlations between clinical observations and necropsy observations, as well as between gross and microscopic pathologic observations, were less than desirable. Any significant gross observations not accounted for by microscopic examination were resolved, and the Technical Report reflects the revised diagnoses. During the audit, special attention was given to reviewing the diagnosed target organ (liver). Two animals were found in which liver neoplasms were not initially identified: a hepatocellular adenoma in high dose male mouse no. 13 (in addition to a hepatocellular carcinoma already identified) and a hepatocellular adenoma in vehicle control male mouse no. 6. The data recorded in this Technical Report include these two lesions.

These findings were not considered to influence significantly the final interpretation of these studies. Other minor problems not mentioned here were likewise considered not to affect the outcome of the study. In conclusion, no data discrepancies were found that influenced the final interpretation of these experiments.

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