

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<sub>1</sub> 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**  
**TOXICOLOGY AND CARCINOGENESIS**  
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**NATIONAL TOXICOLOGY PROGRAM**  
**P.O. Box 12233**  
**Research Triangle Park, NC 27709**

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**Public Health Service**  
**National Institutes of Health**

## 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).

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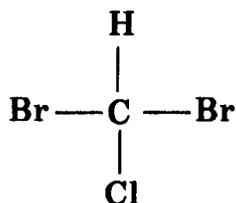
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## CHLORODIBROMOMETHANE

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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> mice, since chlorodibromomethane caused an increased incidence of hepatocellular adenomas and an increased combined incidence of hepatocellular adenomas or carcinomas.

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\*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.

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## 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

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## **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<sub>1</sub> 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**

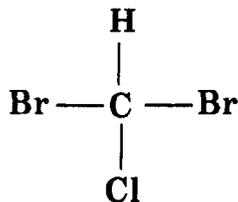
**Formation and Regulation**

**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<sub>50</sub> 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

# I. INTRODUCTION

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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<sub>1</sub> 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  
PREPARATION AND CHARACTERIZATION OF DOSE  
MIXTURES  
SINGLE-ADMINISTRATION STUDIES  
FOURTEEN-DAY REPEATED-ADMINISTRATION STUDIES  
THIRTEEN-WEEK STUDIES  
TWO-YEAR STUDIES**

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

## 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  $147 \pm 18$  ppm in lot no. F122277 and  $118 \pm 13$  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  $118.5^\circ\text{C}$  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 (Sadler 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  $0^\circ \pm 5^\circ\text{C}$ . 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  $0^\circ \pm 5^\circ\text{C}$  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  $\pm 10\%$  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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>EXPERIMENTAL DESIGN</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Testing Laboratory</b><br>EG&G Mason Research Institute                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Same as single-administration studies                                                                                                             | Same as single-administration studies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Same as single-administration studies                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Size of Test Groups</b><br>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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Doses</b><br>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                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Date of First Dose</b><br>9/26/78                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 11/26/78                                                                                                                                          | 2/26/79                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Rats--1/3/80; mice--1/9/80                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Date of Last Dose</b><br>N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 12/10/78                                                                                                                                          | 5/25/79                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Rats--12/28/81; mice--1/12/82                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Duration of Dosing</b><br>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)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Type and Frequency of Observation</b><br>Observed 1 x h for first 3 h, 2 x d thereafter for mortality and signs of moribundity; initial and final body weights taken                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Observed 2 x d for mortality and signs of moribundity; weighed 1 x wk                                                                             | Observed 2 x d for mortality and signs of moribundity; weighed on d 0, 1 x wk thereafter                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Observed 2 x d for mortality or signs of moribundity; weighed 1 x wk for 12 wk, 1 x mo thereafter                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Necropsy and Histologic Examination</b><br>Necropsy performed on 1 or 2 animals of each sex and dose level; tissues examined: gross lesions; skin; mandibular lymph node; mammary gland; salivary gland; thigh muscle; sciatic nerve; sternbrae, 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; sternbrae; 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)**

| <b>Single-Administration Studies</b>                                                                        | <b>Fourteen-Day Repeated Administration Studies</b> | <b>Thirteen-Week Studies</b>                      | <b>Two-Year Studies</b>                                  |
|-------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|---------------------------------------------------|----------------------------------------------------------|
| <b>ANIMALS AND ANIMAL MAINTENANCE</b>                                                                       |                                                     |                                                   |                                                          |
| <b>Species</b><br>F344/N rats; B6C3F <sub>1</sub> mice                                                      | Same as single-administration studies               | Same as single-administration studies             | Same as single-administration studies                    |
| <b>Animal Source</b><br>Charles River Breeding Laboratories (Portage, MI)                                   | Same as single-administration studies               | Same as single-administration studies             | Same as single-administration studies                    |
| <b>Time Held Before Start of Test</b><br>2 wk                                                               | 17 d                                                | 12 d                                              | Rats--22 d; mice--21 d                                   |
| <b>Age When Placed on Study</b><br>Rats--6 wk;<br>mice--not reported                                        | Rats--7 wk; mice--8 wk                              | Rats--6-7 wk; mice--7 wk                          | 8 wk                                                     |
| <b>Age When Killed</b><br>Rats--8 wk;<br>mice--not reported                                                 | Rats--9 wk; mice--10 wk                             | Rats--19-20 wk; mice--20 wk                       | Rats--113-114 wk;<br>mice--115-116 wk                    |
| <b>Necropsy Dates</b><br>10/11/78                                                                           | Rats--12/12-12/14/78;<br>mice--12/14-12/15/78       | Rats--5/30-6/5/79;<br>mice--5/29-5/30/79          | Rats--1/4-1/12/82;<br>mice--1/20-1/29/82                 |
| <b>Method of Distribution</b><br>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 |
| <b>Feed</b><br>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                    |
| <b>Bedding</b><br>Aspen Bed® (American Excelsior, Baltimore, MD)                                            | Same as single-administration studies               | Aspen Bed® or Betta Chips® (Agway, Northboro, MA) | Same as single-administration studies                    |
| <b>Water</b><br>Automatic watering system (Edstom Industries, Waterford, WI); freely available              | Same as single-administration studies               | Same as single-administration studies             | Same as single-administration studies                    |
| <b>Cages</b><br>Polycarbonate (Lab Products, Inc., Garfield, NJ)                                            | Polycarbonate (Lab Products, Inc., Rochelle Pk, NJ) | Same as 14-d studies                              | Same as 14-d studies                                     |
| <b>Cage Filters</b><br>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                    |
| <b>Animals per Cage</b><br>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                                                                                     |
|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| <b>ANIMALS AND ANIMAL MAINTENANCE (Continued)</b>                                                                               |                                                                                               |                                                                                                  |                                                                                                      |
| <b>Animal Room Environment</b><br>10 room air changes/h;<br>temp--23° ± 3° C;<br>fluorescent light 12 h/d;<br>humidity--32%-60% | 10 room air changes/h;<br>temp--21° ± 6° C;<br>fluorescent light 12 h/d;<br>humidity--10%-45% | 10 room air changes/h;<br>temp--19.4°-30.6° C;<br>fluorescent light 12 h/d;<br>humidity--14%-56% | 12 room air changes/h;<br>temp--17.8°-26.7° C (a);<br>fluorescent light 12 h/d;<br>humidity--15%-78% |
| <b>Other Chemicals on Test in Same Room</b><br>None                                                                             | None                                                                                          | None                                                                                             | None                                                                                                 |
| <b>CHEMISTRY</b>                                                                                                                |                                                                                               |                                                                                                  |                                                                                                      |
| <b>Lot Numbers Used</b><br>F122277                                                                                              | F122277                                                                                       | F122277                                                                                          | F122277;<br>F810626 from 8/10/81 to<br>end of study                                                  |
| <b>Supplier</b><br>Freeman Industries, Inc.<br>(Tuckahoe, NY)                                                                   | Same as single-<br>administration studies                                                     | Same as single-<br>administration studies                                                        | Same as single-<br>administration studies                                                            |
| <b>CHEMICAL/VEHICLE</b>                                                                                                         |                                                                                               |                                                                                                  |                                                                                                      |
| <b>Preparation</b><br>Compound and corn oil<br>were mixed by inversion<br>in ground-glass-stoppered<br>graduated cylinders      | Same as single-<br>administration studies                                                     | Same as single-<br>administration studies                                                        | Same as single-<br>administration studies                                                            |
| <b>Maximum Storage Time</b><br>1 d                                                                                              | 10 d                                                                                          | 10 d                                                                                             | 10 d                                                                                                 |
| <b>Storage Conditions</b><br>4° C in the dark                                                                                   | Same as single-administra-<br>tion studies                                                    | 4° C                                                                                             | 0° ± 5° C                                                                                            |

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

## II. MATERIALS AND METHODS

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### SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> (C57BL/6N × C3H/HeN MTV<sup>-</sup>) 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.

## II. MATERIALS AND METHODS

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<sub>1</sub> 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<sub>1</sub> 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.

## II. MATERIALS AND METHODS

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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

## II. MATERIALS AND METHODS

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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**

### III. RESULTS: RATS

#### 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<br>(mg/kg) | Survival (a) | Mean Body Weights (grams) |             |              |
|-----------------|--------------|---------------------------|-------------|--------------|
|                 |              | Initial (b)               | Final       | Change (c)   |
| <b>MALE</b>     |              |                           |             |              |
| 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)          |
| <b>FEMALE</b>   |              |                           |             |              |
| 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

### III. RESULTS: RATS

#### 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)   |
| <b>MALE</b>   |              |                           |              |              |
| 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)          |
| <b>FEMALE</b> |              |                           |              |              |
| 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 |
|---------------------------|-----------------|----------|-----------|-----------|-----------|-------------|
| <b>MALE</b>               |                 |          |           |           |           |             |
| 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         |
| <b>FEMALE</b>             |                 |          |           |           |           |             |
| 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         |

### III. RESULTS: RATS

#### 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<br>(mg/kg) | Survival (a) | Mean Body Weights (grams) |             |               | Final Weight Relative<br>to Vehicle Controls<br>(percent) |
|-----------------|--------------|---------------------------|-------------|---------------|-----------------------------------------------------------|
|                 |              | Initial (b)               | Final (c)   | Change (d)    |                                                           |
| <b>MALE</b>     |              |                           |             |               |                                                           |
| 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                                                      |
| <b>FEMALE</b>   |              |                           |             |               |                                                           |
| 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, 10

(f) Week of death: 5, 6, 8, 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   |
| <b>MALE</b>            |                 |          |      |       |       |       |
| <b>Liver</b>           |                 |          |      |       |       |       |
| 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  |
| <b>Kidney</b>          |                 |          |      |       |       |       |
| Toxic nephropathy      | 0/10            | (c) NE   | NE   | NE    | 0/10  | 8/10  |
| <b>Salivary Gland</b>  |                 |          |      |       |       |       |
| Inflammation           | 0/10            | NE       | NE   | NE    | 0/10  | 5/10  |
| Squamous metaplasia    | 0/10            | NE       | NE   | NE    | 0/10  | 9/10  |
| <b>FEMALE</b>          |                 |          |      |       |       |       |
| <b>Liver</b>           |                 |          |      |       |       |       |
| 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   |
| <b>Kidney</b>          |                 |          |      |       |       |       |
| Toxic nephropathy      | 0/10            | NE       | NE   | NE    | 0/10  | 9/9   |
| <b>Salivary Gland</b>  |                 |          |      |       |       |       |
| 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

### III. RESULTS: RATS

#### 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 |
| <b>MALE</b>    |                 |                  |                 |                                |                  |                 |                                |                  |
| 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              | 287             | 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               |
| <b>FEMALE</b>  |                 |                  |                 |                                |                  |                 |                                |                  |
| 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               |

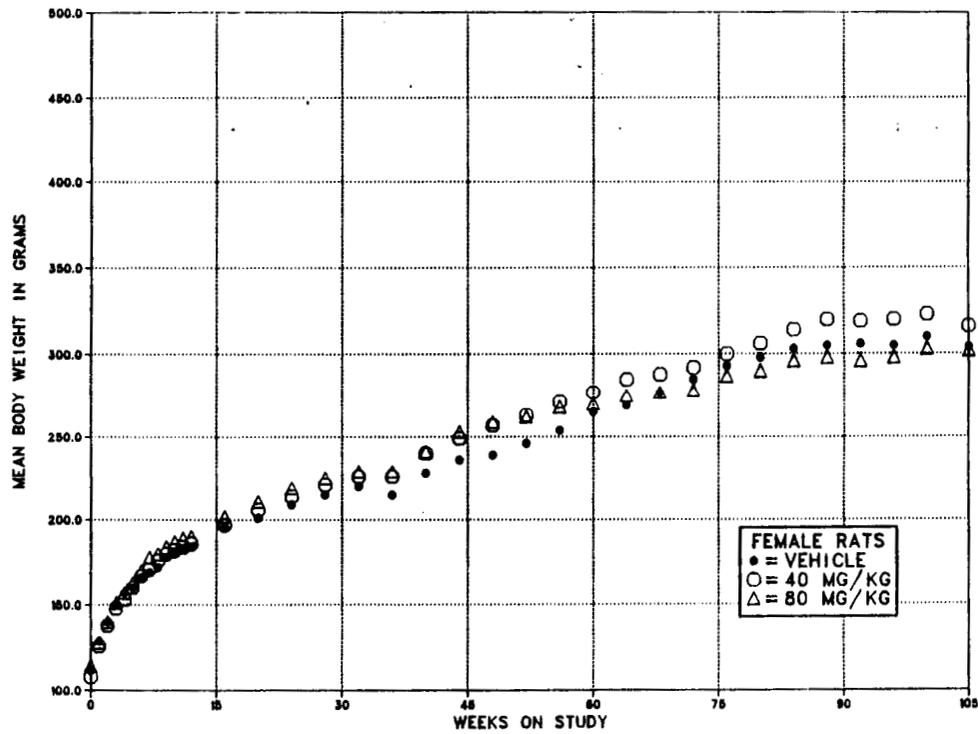
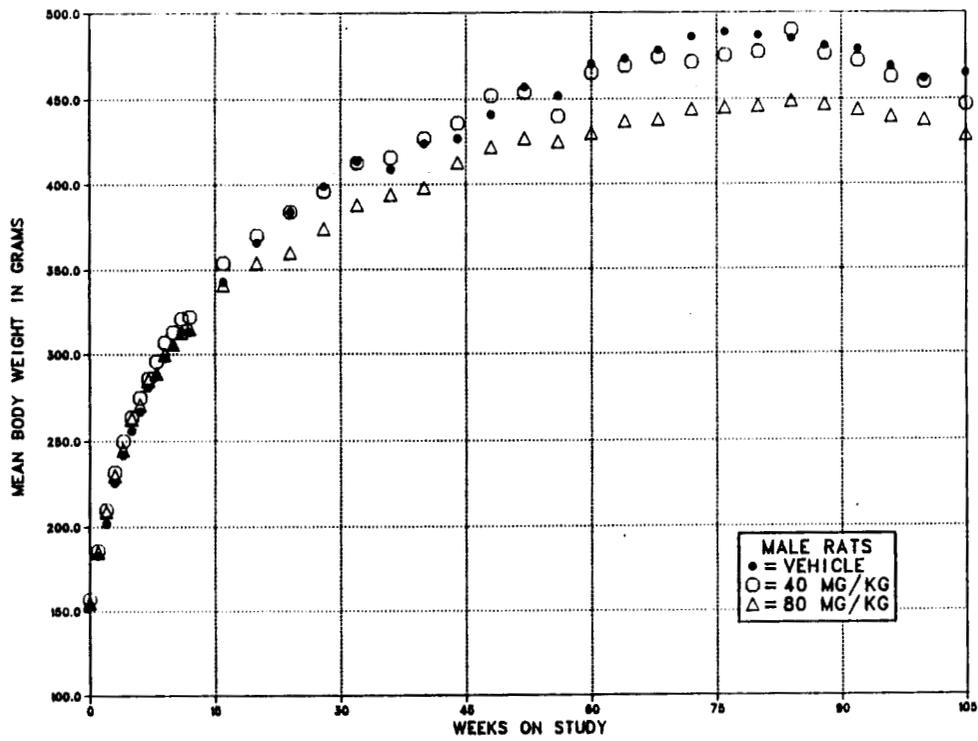


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED CHLORODIBROMOMETHANE IN CORN OIL BY GAVAGE FOR TWO YEARS

### III. RESULTS: RATS

#### 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.

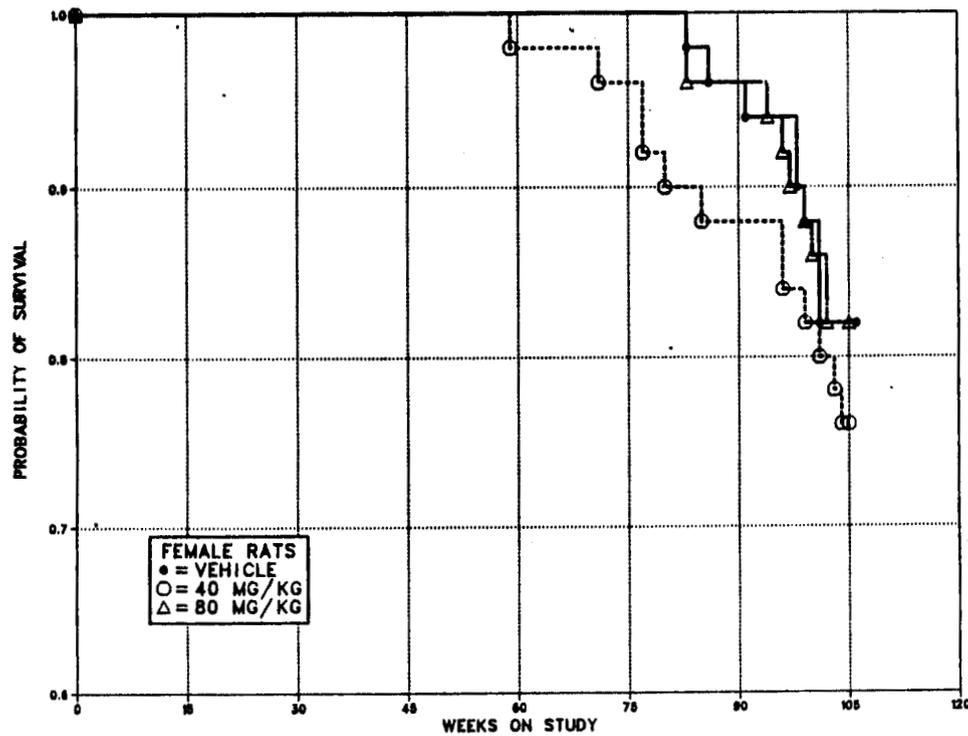
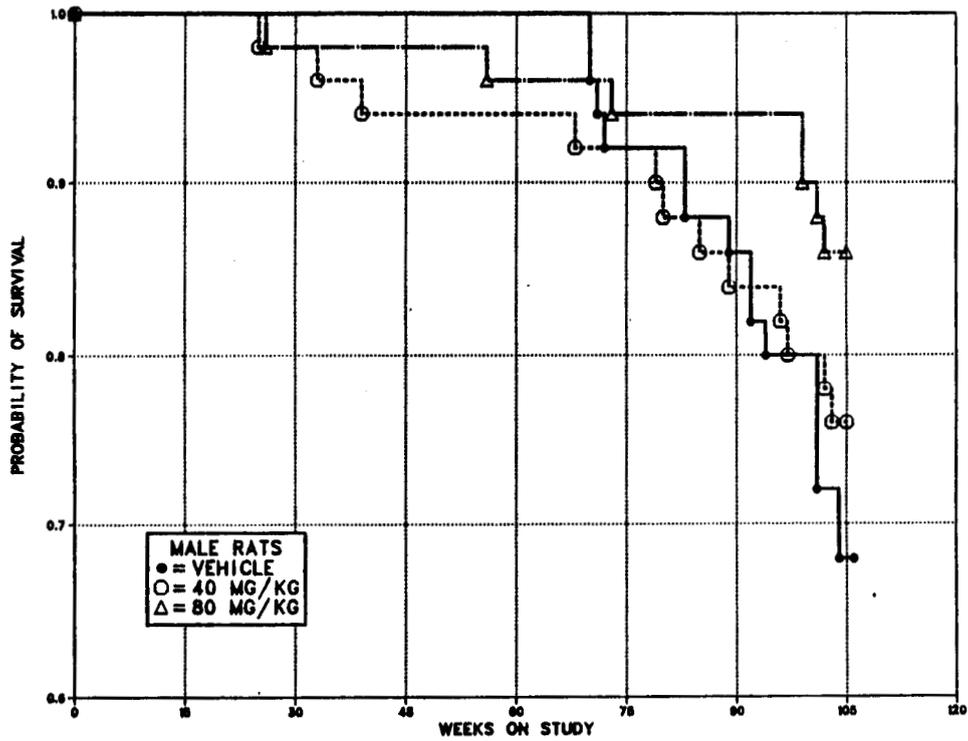
TABLE 8. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF CHLORODIBROMOMETHANE

|                                             | Vehicle Control | 40 mg/kg | 80 mg/kg |
|---------------------------------------------|-----------------|----------|----------|
| <b>MALE (a)</b>                             |                 |          |          |
| 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    |
| <b>FEMALE (a)</b>                           |                 |          |          |
| 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**

### III. RESULTS: RATS

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*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   |
|---------------------------|-----------------|-------------|------------|
| <b>Cystic Hyperplasia</b> |                 |             |            |
| Overall Rates             | 13/50 (26%)     | 3/50 (6%)   | 5/50 (10%) |
| <b>Fibroadenoma (b)</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   |
|--------------------------------------|-----------------|------------|------------|
| <b>Endometrial Stromal Polyp (a)</b> |                 |            |            |
| 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   |
| <b>Endometrial Stromal Sarcoma</b>   |                 |            |            |
| 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.

### III. RESULTS: MICE

#### 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<br>(mg/kg) | Survival (a) | Mean Body Weights (grams) |            |             |
|-----------------|--------------|---------------------------|------------|-------------|
|                 |              | Initial (b)               | Final      | Change (c)  |
| <b>MALE</b>     |              |                           |            |             |
| 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)         |
| <b>FEMALE</b>   |              |                           |            |             |
| 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

### III. RESULTS: MICE

#### 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) |
| <b>MALE</b>   |              |                           |            |            |
| 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       |
| <b>FEMALE</b> |              |                           |            |            |
| 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 |
|--------------------------------------|-----------------|----------|----------|----------|-----------|-----------|
| <b>MALE</b>                          |                 |          |          |          |           |           |
| 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       |
| <b>FEMALE</b>                        |                 |          |          |          |           |           |
| 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       |

### III. RESULTS: MICE

#### 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<br>(mg/kg) | Survival (a) | Mean Body Weights (grams) |            |              | Final Weight Relative<br>to Vehicle Controls<br>(percent) |
|-----------------|--------------|---------------------------|------------|--------------|-----------------------------------------------------------|
|                 |              | Initial (b)               | Final (c)  | Change (d)   |                                                           |
| <b>MALE</b>     |              |                           |            |              |                                                           |
| 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                                                      |
| <b>FEMALE</b>   |              |                           |            |              |                                                           |
| 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**

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

(a) Not examined

# III. RESULTS: MICE

## TWO-YEAR STUDIES

### Body Weights and Clinical Signs

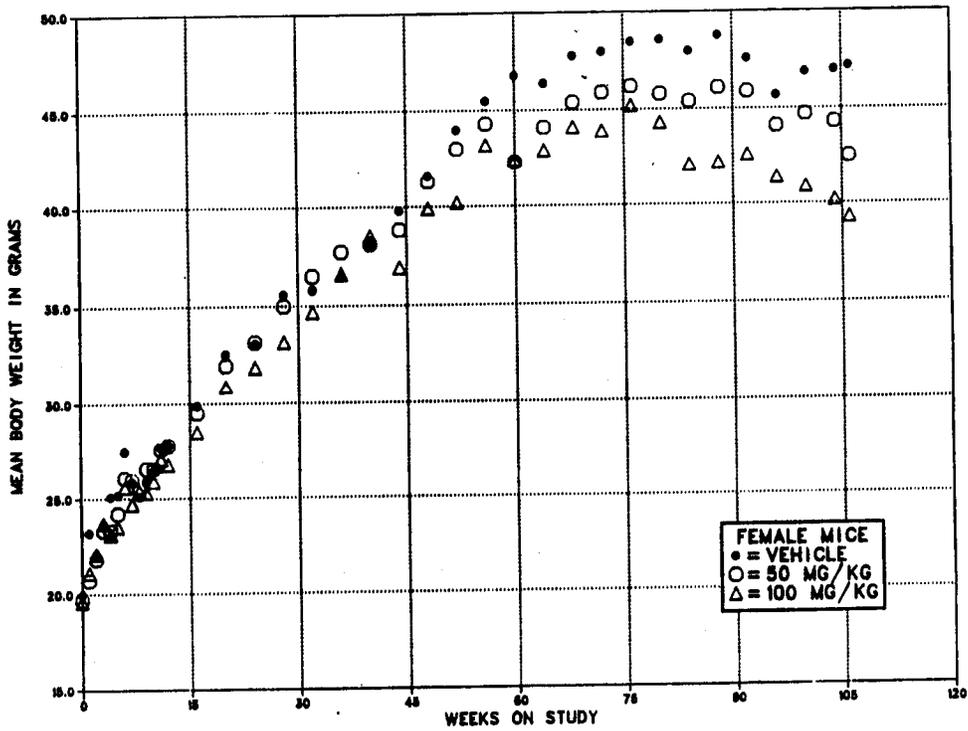
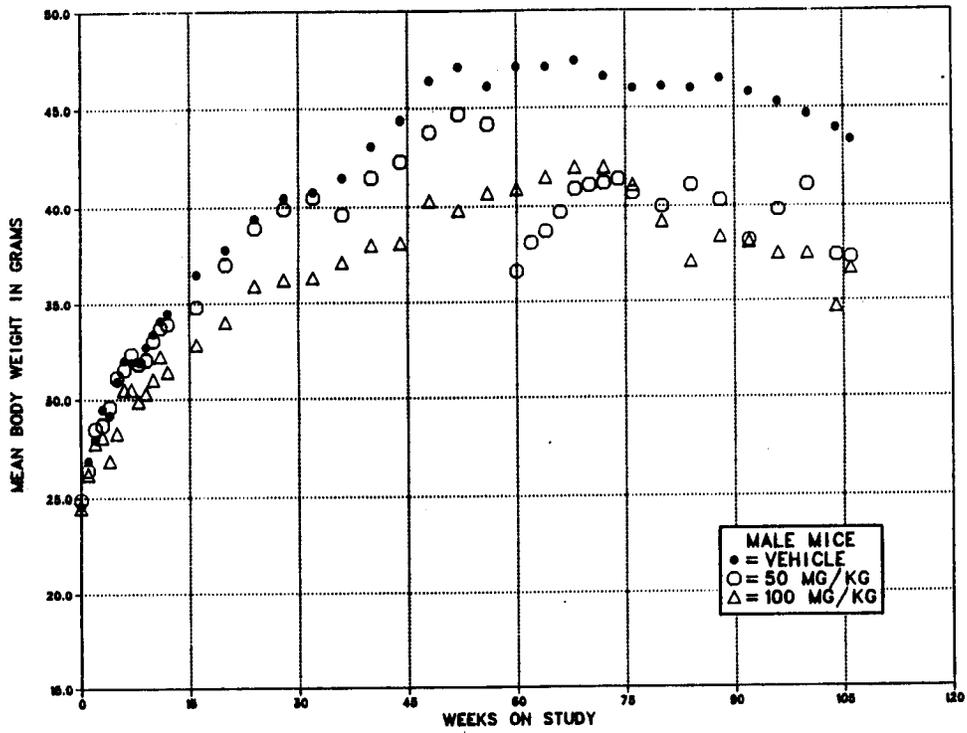
Mean body weights of high dose mice of each sex were lower than those of the vehicle controls throughout most of the study (Table 16 and Figure 3). Mean body weights of low dose mice were notably lower than those of the vehicle

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 |
| <b>MALE</b>    |                 |                  |                 |                                |                  |                 |                                |                  |
| 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              | 91.7                           | 50               | 41              | 85.1                           | 49               |
| 60             | 47              | 50               | 37              | 77.7                           | (a) 15           | 41              | 87.2                           | 48               |
| 64             | 47              | 50               | 39              | 83.0                           | (a) 15           | 42              | 89.4                           | 48               |
| 68             | 47              | 50               | 41              | 87.2                           | (a) 15           | 42              | 89.4                           | 47               |
| 72             | 47              | 50               | 41              | 87.2                           | (a) 15           | 42              | 89.4                           | 47               |
| 76             | 46              | 50               | 41              | 89.1                           | (a) 14           | 41              | 89.1                           | 46               |
| 80             | 46              | 50               | 40              | 87.0                           | (a) 14           | 39              | 84.8                           | 45               |
| 84             | 46              | 50               | 41              | 89.1                           | (a) 13           | 37              | 80.4                           | 35               |
| 88             | 46              | 48               | 40              | 87.0                           | (a) 12           | 38              | 82.6                           | 34               |
| 92             | 46              | 47               | 38              | 82.6                           | (a) 12           | 38              | 82.6                           | 34               |
| 96             | 45              | 47               | 40              | 88.9                           | (a) 10           | 37              | 82.2                           | 33               |
| 100            | 45              | 48               | 41              | 91.1                           | (a) 8            | 38              | 84.4                           | 31               |
| 104            | 44              | 45               | 37              |                                | (a) 7            | 35              | 79.5                           | 31               |
| 106            | 43              | 44               | 37              |                                | (a) 7            | 37              | 86.0                           | 29               |
| <b>FEMALE</b>  |                 |                  |                 |                                |                  |                 |                                |                  |
| 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               | 22              | 91.0                           | 50               |
| 4              | 25              | 50               | 23              | 92.0                           | 50               | 22              | 88.0                           | 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                           | (a) 50           | 43              | 93.5                           | 48               |
| 68             | 46              | 46               | 45              | 93.8                           | (a) 50           | 44              | 91.7                           | 47               |
| 72             | 48              | 44               | 46              | 95.8                           | (a) 50           | 44              | 91.7                           | 47               |
| 76             | 49              | 43               | 46              | 93.9                           | (a) 50           | 45              | 91.8                           | 47               |
| 80             | 49              | 43               | 46              | 93.9                           | (a) 50           | 44              | 89.8                           | 47               |
| 84             | 48              | 43               | 45              | 93.8                           | (a) 48           | 42              | 87.5                           | 44               |
| 88             | 49              | 42               | 46              | 93.8                           | (a) 44           | 42              | 85.7                           | 44               |
| 92             | 48              | 41               | 48              | 95.8                           | (a) 43           | 43              | 89.6                           | 42               |
| 96             | 46              | 41               | 44              | 95.7                           | (a) 40           | 41              | 89.1                           | 41               |
| 100            | 47              | 38               | 45              | 95.7                           | (a) 38           | 41              | 87.2                           | 39               |
| 104            | 47              | 33               | 44              | 93.6                           | (a) 30           | 40              | 85.1                           | 39               |
| 106            | 47              | 32               | 43              | 91.5                           | (a) 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**

### III. RESULTS: MICE

#### 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.

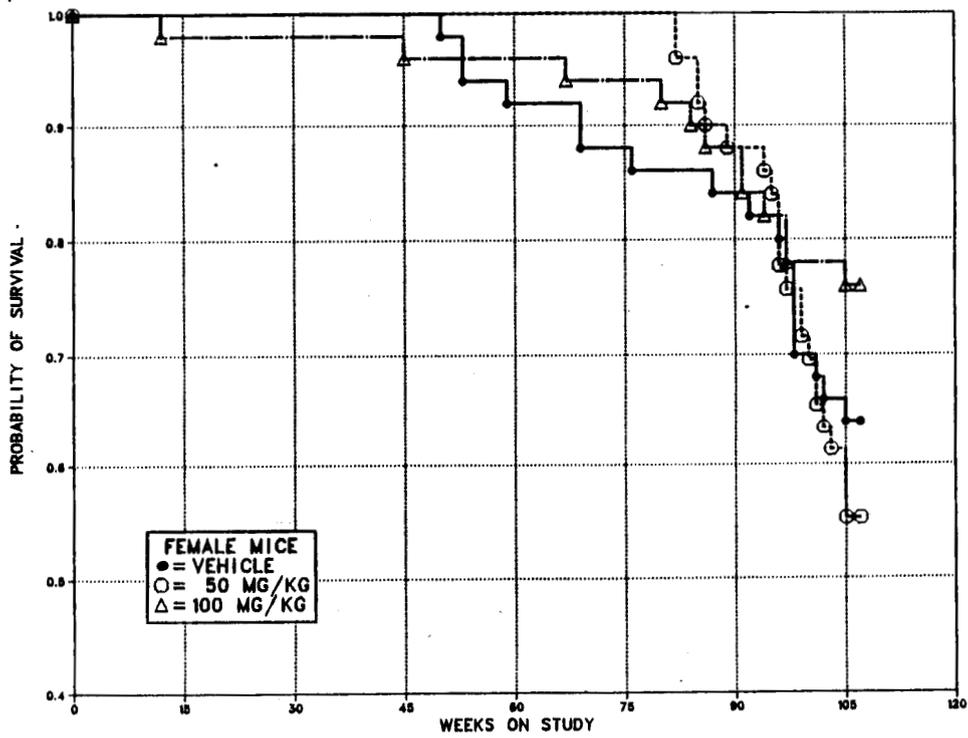
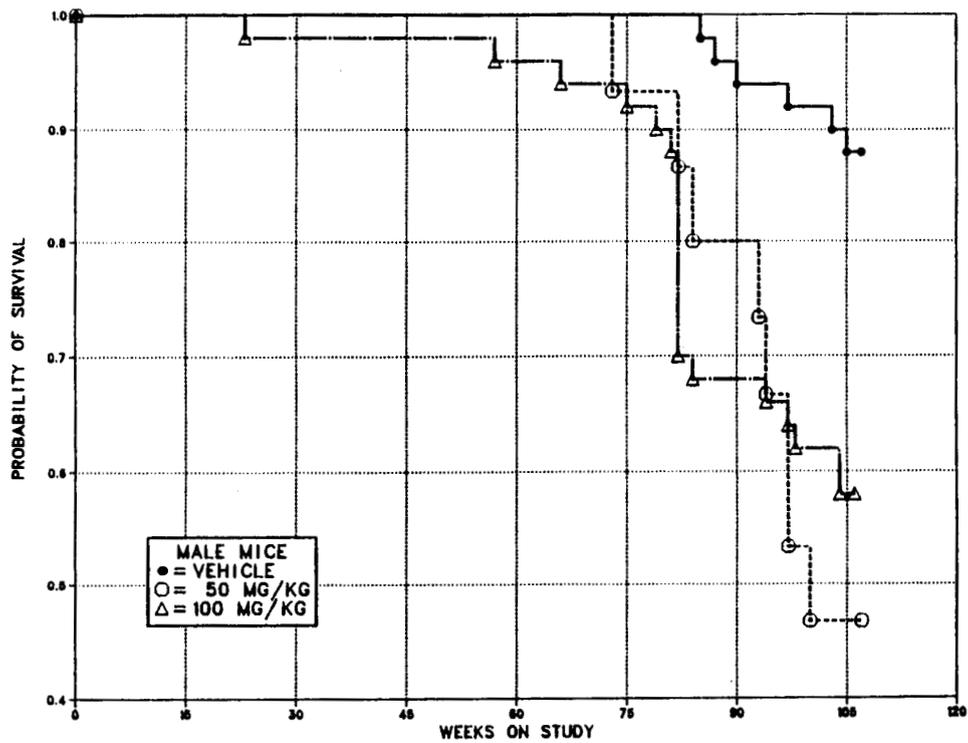
TABLE 17. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF CHLORODIBROMOMETHANE

|                                             | Vehicle Control | 50 mg/kg | 100 mg/kg |
|---------------------------------------------|-----------------|----------|-----------|
| <b>MALE (a)</b>                             |                 |          |           |
| 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     |
| <b>FEMALE (a)</b>                           |                 |          |           |
| 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**

### III. RESULTS: MICE

*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        |
| <b>Liver</b>            |                 |                              |                                                     |           |
| 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        |
| <b>Kidney</b>           |                 |                              |                                                     |           |
| 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   |
|--------------------------------------------|-----------------|-------------|
| <b>MALE</b>                                |                 |             |
| <b>Adenoma (b)</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     |
| <b>Carcinoma (c)</b>                       |                 |             |
| 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     |
| <b>Adenoma or Carcinoma (Combined) (d)</b> |                 |             |
| 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   |
|--------------------------------------------|-----------------|-------------|-------------|
| <b>FEMALE</b>                              |                 |             |             |
| <b>Adenoma (a)</b>                         |                 |             |             |
| 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     |
| <b>Carcinoma (b)</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     |
| <b>Adenoma or Carcinoma (Combined) (c)</b> |                 |             |             |
| 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%

### III. RESULTS: MICE

**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 |
|------------------------------------|-----------------|-----------|
| <b>Lymphoma, All Malignant (a)</b> |                 |           |
| 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<sub>1</sub> 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        |
|----------------------------------|-----------------|-----------------|------------------|
| <b>RATS</b>                      |                 | <b>40 mg/kg</b> | <b>80 mg/kg</b>  |
| <b>MALE</b>                      |                 |                 |                  |
| Fatty metamorphosis              | 27/50 (54%)     | 47/50 (94%)     | 49/50 (98%)      |
| Ground-glass cytoplasmic changes | 8/50 (16%)      | 22/50 (44%)     | 34/50 (68%)      |
| <b>FEMALE</b>                    |                 |                 |                  |
| Fatty metamorphosis              | 12/50 (24%)     | 23/50 (46%)     | 50/50 (100%)     |
| Ground-glass cytoplasmic changes | 0/50 (0%)       | 1/50 (2%)       | 12/50 (24%)      |
| <b>MICE</b>                      |                 | <b>50 mg/kg</b> | <b>100 mg/kg</b> |
| <b>MALE</b>                      |                 |                 |                  |
| 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%)      |
| <b>FEMALE</b>                    |                 |                 |                  |
| 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%)      |

## IV. DISCUSSION AND CONCLUSIONS

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<sub>1</sub> 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

## IV. DISCUSSION AND CONCLUSIONS

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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<sub>1</sub> 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<sub>1</sub> mice, since chlorodibromomethane caused an increased incidence of hepatocellular adenomas and an increased combined incidence of hepatocellular adenomas or carcinomas.

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

## **V. REFERENCES**

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## **APPENDIX A**

# **SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR 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        |
| <b>INTEGUMENTARY SYSTEM</b>          |               |          |           |
| *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%)    |
| <b>RESPIRATORY SYSTEM</b>            |               |          |           |
| *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%)        |          |           |
| <b>HEMATOPOIETIC SYSTEM</b>          |               |          |           |
| *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%)    |
| <b>CIRCULATORY SYSTEM</b>            |               |          |           |
| *SUBCUT TISSUE                       | (50)          | (50)     | (50)      |
| HEMANGIOPERICYTOMA, BENIGN           |               | 1 (2%)   |           |
| <b>DIGESTIVE SYSTEM</b>              |               |          |           |
| #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%)    |
| <b>URINARY SYSTEM</b>                |               |          |           |
| #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 |
|-------------------------------|---------------|----------|-----------|
| <b>ENDOCRINE SYSTEM</b>       |               |          |           |
| #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%)   |           |
| <b>REPRODUCTIVE SYSTEM</b>    |               |          |           |
| *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%)   |           |
| <b>NERVOUS SYSTEM</b>         |               |          |           |
| #CEREBRUM                     | (50)          | (50)     | (50)      |
| ASTROCYTOMA                   | 1 (2%)        |          |           |
| <b>SPECIAL SENSE ORGANS</b>   |               |          |           |
| *EAR CANAL                    | (50)          | (50)     | (50)      |
| SEBACEOUS ADENOCARCINOMA      | 1 (2%)        |          |           |
| <b>MUSCULOSKELETAL SYSTEM</b> |               |          |           |
| NONE                          |               |          |           |
| <b>BODY CAVITIES</b>          |               |          |           |
| NONE                          |               |          |           |
| <b>ALL OTHER SYSTEMS</b>      |               |          |           |
| *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 |
|----------------------------------------------------------------------------------|---------------|----------|-----------|
| <b>ANIMAL DISPOSITION SUMMARY</b>                                                |               |          |           |
| 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                                                                      |               |          |           |
| <b>TUMOR SUMMARY</b>                                                             |               |          |           |
| 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-<br>BENIGN OR MALIGNANT                      | 5             | 7        | 4         |
| TOTAL UNCERTAIN TUMORS                                                           | 5             | 8        | 4         |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>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        |
| <b>INTEGUMENTARY SYSTEM</b>          |               |          |           |
| *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%)    |
| <b>RESPIRATORY SYSTEM</b>            |               |          |           |
| #LUNG                                | (50)          | (50)     | (50)      |
| CARCINOMA, NOS, METASTATIC           |               | 1 (2%)   |           |
| ALVEOLAR/BRONCHIOLAR ADENOMA         |               |          | 2 (4%)    |
| <b>HEMATOPOIETIC SYSTEM</b>          |               |          |           |
| *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%)        |          |           |
| <b>CIRCULATORY SYSTEM</b>            |               |          |           |
| NONE                                 |               |          |           |
| <b>DIGESTIVE SYSTEM</b>              |               |          |           |
| #LIVER                               | (50)          | (50)     | (50)      |
| NEOPLASTIC NODULE                    |               | 2 (4%)   | 2 (4%)    |
| #COLON                               | (46)          | (49)     | (48)      |
| ADENOMATOUS POLYP, NOS               |               |          | 1 (2%)    |
| <b>URINARY SYSTEM</b>                |               |          |           |
| #KIDNEY                              | (50)          | (50)     | (50)      |
| TUBULAR-CELL ADENOCARCINOMA          |               | 1 (2%)   |           |
| #URINARY BLADDER                     | (50)          | (50)     | (50)      |
| LEIOMYOSARCOMA                       |               | 1 (2%)   |           |
| <b>ENDOCRINE SYSTEM</b>              |               |          |           |
| #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 |
|---------------------------------|---------------|----------|-----------|
| <b>REPRODUCTIVE SYSTEM</b>      |               |          |           |
| *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%)   |           |
| <b>NERVOUS SYSTEM</b>           |               |          |           |
| #BRAIN                          | (50)          | (50)     | (50)      |
| ASTROCYTOMA                     |               | 1 (2%)   | 1 (2%)    |
| <b>SPECIAL SENSE ORGANS</b>     |               |          |           |
| *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%)    |
| <b>MUSCULOSKELETAL SYSTEM</b>   |               |          |           |
| NONE                            |               |          |           |
| <b>BODY CAVITIES</b>            |               |          |           |
| NONE                            |               |          |           |
| <b>ALL OTHER SYSTEMS</b>        |               |          |           |
| *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 |
|----------------------------------------------------------------------------------|---------------|----------|-----------|
| <b>ANIMAL DISPOSITION SUMMARY</b>                                                |               |          |           |
| 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                                                                      |               |          |           |
| <b>TUMOR SUMMARY</b>                                                             |               |          |           |
| 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-<br>BENIGN OR MALIGNANT                      |               | 2        | 3         |
| TOTAL UNCERTAIN TUMORS                                                           |               | 2        | 3         |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>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: LOW DOSE

| ANIMAL NUMBER                  | 1 | 2 | 3 | 4  | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |
|--------------------------------|---|---|---|----|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| WEEKS ON STUDY                 | 0 | 9 | 8 | 21 | 0 | 0 | 0 | 0 | 0 | 7  | 0  | 0  | 0  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |
| <b>INTEGUMENTARY SYSTEM</b>    |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| SKIN                           | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| SQUAMOUS CELL PAPILLOMA        |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| SQUAMOUS CELL CARCINOMA        |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| BASAL-CELL TUMOR               |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| KERATOACANTHOMA                |   |   |   |    |   |   |   |   |   |    |    |    | X  |    |    |    |    |    |    |    |    |    |    |    |    |
| SUBCUTANEOUS TISSUE            | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| SARCOMA, NOS                   |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| FIBROMA                        |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| LIPOMA                         |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | X  |
| HEMANGIOPERICYTOMA, BENIGN     | X |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| <b>RESPIRATORY SYSTEM</b>      |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| LUNGS AND BRONCHI              | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| ALVEOLAR/BRONCHIOLAR ADENOMA   |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| ALVEOLAR/BRONCHIOLAR CARCINOMA |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| SARCOMA, NOS, METASTATIC       |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| TRACHEA                        | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>HEMATOPOIETIC SYSTEM</b>    |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| BONE MARROW                    | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| SPLEEN                         | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| LYMPH NODES                    | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| THYMUS                         | - | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>CIRCULATORY SYSTEM</b>      |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| HEART                          | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>DIGESTIVE SYSTEM</b>        |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| SALIVARY GLAND                 | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| LIVER                          | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| NEOPLASTIC NODULE              |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 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              |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| ESOPHAGUS                      | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| STOMACH                        | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| SMALL INTESTINE                | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| LARGE INTESTINE                | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>URINARY SYSTEM</b>          |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| KIDNEY                         | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| URINARY BLADDER                | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>ENDOCRINE SYSTEM</b>        |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| PITUITARY                      | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| ADENOMA, NOS                   |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| ADRENAL                        | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| CORTICAL ADENOMA               |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| PHEOCHROMOCYTOMA               | X |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| THYROID                        | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| FOLLICULAR-CELL ADENOMA        |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| FOLLICULAR-CELL CARCINOMA      |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| C-CELL ADENOMA                 |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| C-CELL CARCINOMA               |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| PARATHYROID                    | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| PANCREATIC ISLETS              | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| ISLET-CELL ADENOMA             |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| ISLET-CELL CARCINOMA           |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| <b>REPRODUCTIVE SYSTEM</b>     |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| MAMMARY GLAND                  | N | N | N | N  | N | N | N | N | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  |
| TESTIS                         | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| INTERSTITIAL-CELL TUMOR        |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| MESOTHELIOMA, NOS              | 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  |
| CARCINOMA, NOS                 |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| <b>NERVOUS SYSTEM</b>          |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| BRAIN                          | + | + | + | +  | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>ALL OTHER SYSTEMS</b>       |   |   |   |    |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 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                  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | TOTAL TISSUES TUMORS |   |    |    |    |
|--------------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----------------------|---|----|----|----|
| WEEKS ON STUDY                 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1                    | 1 |    |    |    |
| <b>INTEGUMENTARY SYSTEM</b>    |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    |    |    |
| SKIN                           | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | 50 |    |    |
| SQUAMOUS CELL PAPILLOMA        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   | 1  |    |    |
| SQUAMOUS CELL CARCINOMA        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   | 1  |    |    |
| BASAL-CELL TUMOR               |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   | 1  |    |    |
| KERATOACANTHOMA                |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   | 1  |    |    |
| SUBCUTANEOUS TISSUE            | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | 50 |    |    |
| SARCOMA, NOS                   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| FIBROMA                        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| LIPOMA                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| HEMANGIOPERICYTOMA, BENIGN     |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| <b>RESPIRATORY SYSTEM</b>      |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    |    |    |
| LUNGS AND BRONCHI              | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | 50 |    |    |
| ALVEOLAR/BRONCHIOLAR ADENOMA   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 3  |    |
| ALVEOLAR/BRONCHIOLAR CARCINOMA |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| SARCOMA, NOS, METASTATIC       |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| TRACHEA                        | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | 47 |    |    |
| <b>HEMATOPOIETIC SYSTEM</b>    |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    |    |    |
| BONE MARROW                    | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | 49 |    |    |
| SPLEEN                         | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 50 |    |
| LYMPH NODES                    | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 49 |    |
| THYMUS                         | - | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 38 |    |
| <b>CIRCULATORY SYSTEM</b>      |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    |    |    |
| HEART                          | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 50 |    |
| <b>DIGESTIVE SYSTEM</b>        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    |    |    |
| SALIVARY GLAND                 | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 48 |    |
| LIVER                          | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 50 |    |
| NEOPLASTIC NODULE              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 5  |    |
| HEPATOCELLULAR CARCINOMA       |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 5  |    |
| BILE DUCT                      | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 50 |    |
| GALLBLADDER & COMMON BILE DUCT | N | N | N | N | N | N | N | N | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N                    | N | 50 |    |    |
| PANCREAS                       | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 49 |    |
| MESOTHELIOMA, NOS              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| ESOPHAGUS                      | - | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 38 |    |
| STOMACH                        | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | +  | 50 |
| SMALL INTESTINE                | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 49 |    |
| LARGE INTESTINE                | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 47 |    |
| <b>URINARY SYSTEM</b>          |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    |    |    |
| KIDNEY                         | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 50 |    |
| URINARY BLADDER                | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 48 |    |
| <b>ENDOCRINE SYSTEM</b>        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    |    |    |
| PITUITARY                      | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 48 |    |
| ADENOMA, NOS                   | 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  | X  | X  | X  | X  | X                    | X | 13 |    |    |
| ADRENAL                        | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 50 |    |
| CORTICAL ADENOMA               |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 2  |    |
| PHOCHROMOCYTOMA                |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 8  |    |
| THYROID                        | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 47 |    |
| FOLLICULAR-CELL ADENOMA        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| FOLLICULAR-CELL CARCINOMA      |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| C-CELL ADENOMA                 |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 4  |    |
| C-CELL CARCINOMA               |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 4  |    |
| PARATHYROID                    | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 29 |    |
| PANCREATIC ISLETS              | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 49 |    |
| ISLET-CELL ADENOMA             |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| ISLET-CELL CARCINOMA           |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| <b>REPRODUCTIVE SYSTEM</b>     |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    |    |    |
| 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  | N  | N  | N  | N                    | N | 50 |    |    |
| TESTIS                         | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 50 |    |
| INTERSTITIAL-CELL TUMOR        | X | X | X | X | X | X | X | X | X | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | X  | 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  | N  | N  | N  | N  | N  | N  | N                    | N | N  | 50 |    |
| CARCINOMA, NOS                 |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| <b>NERVOUS SYSTEM</b>          |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    |    |    |
| BRAIN                          | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | + | +  | 50 |    |
| <b>ALL OTHER SYSTEMS</b>       |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    |    |    |
| 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  | N  | N  | N  | N                    | N | N  | 50 |    |
| MESOTHELIOMA, NOS              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| LEUKEMIA, MONONUCLEAR CELL     |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 3  |    |
| SCROTUM NOS                    |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |
| SQUAMOUS CELL PAPILLOMA        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |   |    | 1  |    |

• ANIMALS NECROPSIED

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

| ANIMAL NUMBER                     | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |  |
|-----------------------------------|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|--|
| WEEKS ON STUDY                    | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |  |
| <b>INTEGUMENTARY SYSTEM</b>       |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| SKIN                              | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| SEBACEOUS ADENOCARCINOMA          |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| SUBCUTANEOUS TISSUE               | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| FIBROMA                           |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| LIPOMA                            |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| FIBROADENOMA                      | X |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| <b>RESPIRATORY SYSTEM</b>         |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| LUNGS AND BRONCHI                 | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| TRACHEA                           | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| <b>HEMATOPOIETIC SYSTEM</b>       |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| BONE MARROW                       | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| SPLEEN                            | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| LYMPH NODES                       | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| THYMUS                            | + | - | - | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| <b>CIRCULATORY SYSTEM</b>         |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| HEART                             | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| <b>DIGESTIVE SYSTEM</b>           |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| SALIVARY GLAND                    | + | + | - | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| LIVER                             | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| NEOPLASTIC NODULE                 |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE | 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  | N  |  |
| PANCREAS                          | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| ACINAR-CELL ADENOMA               |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| ESOPHAGUS                         | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| STOMACH                           | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| SMALL INTESTINE                   | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| LARGE INTESTINE                   | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| ADENOMATOUS POLYP, NOS            |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| <b>URINARY SYSTEM</b>             |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| KIDNEY                            | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| URINARY BLADDER                   | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| <b>ENDOCRINE SYSTEM</b>           |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| PITUITARY                         | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| CARCINOMA, NOS                    |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| ADENOMA, NOS                      | X |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| ADRENAL                           | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| PHEOCHROMOCYTOMA                  |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| THYROID                           | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| C-CELL ADENOMA                    |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| C-CELL CARCINOMA                  |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| PARATHYROID                       | - | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |  |
| PANCREATIC ISLETS                 | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| ISLET-CELL ADENOMA                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| <b>REPRODUCTIVE SYSTEM</b>        |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| MAMMARY GLAND                     | N | N | N | + | N | N | N | + | + | + | +  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  |  |
| FIBROADENOMA                      |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| TESTIS                            | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| INTERSTITIAL-CELL TUMOR           |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| MESOTHELIOMA, NOS                 | 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                          | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| <b>NERVOUS SYSTEM</b>             |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| BRAIN                             | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |  |
| <b>ALL OTHER SYSTEMS</b>          |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| 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  |  |
| MALIG. LYMPHOMA, LYMPHOCTIC TYPE  |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |
| LEUKEMIA, MONONUCLEAR CELL        |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |  |



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

| ANIMAL NUMBER                           | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 |   |
|-----------------------------------------|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---|
| WEEKS ON STUDY                          | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  |   |
| <b>INTEGUMENTARY SYSTEM</b>             |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
| SKIN KERATOCANTHOMA                     | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| SUBCUTANEOUS TISSUE BASAL-CELL TUMOR    | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| <b>RESPIRATORY SYSTEM</b>               |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
| LUNGS AND BRONCHI                       | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| TRACHEA                                 | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| <b>HEMATOPOIETIC SYSTEM</b>             |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
| BONE MARROW                             | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| SPLEEN                                  | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| LYMPH NODES                             | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| THYMUS                                  | - | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | - |
| <b>CIRCULATORY SYSTEM</b>               |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
| HEART                                   | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| <b>DIGESTIVE SYSTEM</b>                 |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
| SALIVARY GLAND                          | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| LIVER LEUKEMIA, MONONUCLEAR CELL        | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| 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  | N  | N |
| PANCREAS                                | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| ESOPHAGUS                               | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| STOMACH                                 | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| SMALL INTESTINE                         | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| LARGE INTESTINE                         | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| <b>URINARY SYSTEM</b>                   |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
| KIDNEY                                  | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| URINARY BLADDER                         | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| <b>ENDOCRINE SYSTEM</b>                 |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
| PITUITARY CARCINOMA, NOS                | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| ADENOMA, NOS                            | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| ADRENAL PHEOCHROMOCYTOMA                | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| THYROID FOLLICULAR-CELL CARCINOMA       | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| C-CELL ADENOMA                          | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| C-CELL CARCINOMA                        | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| PARATHYROID                             | - | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | - |
| <b>REPRODUCTIVE SYSTEM</b>              |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
| MAMMARY GLAND ADENOCARCINOMA, NOS       | + | N | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| FIBROADENOMA                            | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| PREPUTIAL/CLITORAL GLAND CARCINOMA, 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 |
| VAGINA ENDOMETRIAL STROMAL SARCOMA      | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| UTERUS ADENOMA, NOS                     | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| ADENOCARCINOMA, NOS                     | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| ENDOMETRIAL STROMAL POLYP               | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| ENDOMETRIAL STROMAL SARCOMA             | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| OVARY SERTOLI-CELL TUMOR                | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| TUBULAR ADENOMA                         | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| <b>NERVOUS SYSTEM</b>                   |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
| BRAIN                                   | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| <b>ALL OTHER SYSTEMS</b>                |   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |   |
| 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 |
| ADENOCARCINOMA, NOS, METASTATIC         | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |
| LEUKEMIA, MONONUCLEAR CELL              | + | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | + |

+: 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                           | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | TOTAL TISSUES TUMORS |    |    |
|-----------------------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----------------------|----|----|
| WEEKS ON STUDY                          | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0  | 0                    | 0  |    |
| <b>INTEGUMENTARY SYSTEM</b>             |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    |    |
| SKIN KERATOCANTHOMA                     | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| SUBCUTANEOUS TISSUE BASAL-CELL TUMOR    | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| <b>RESPIRATORY SYSTEM</b>               |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    |    |
| LUNGS AND BRONCHI                       | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| TRACHEA                                 | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| <b>HEMATOPOIETIC SYSTEM</b>             |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    |    |
| BONE MARROW                             | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| SPLEEN                                  | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| LYMPH NODES                             | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 69 |    |
| THYMUS                                  | - | - | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 24 |    |
| <b>CIRCULATORY SYSTEM</b>               |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    |    |
| HEART                                   | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| <b>DIGESTIVE SYSTEM</b>                 |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    |    |
| SALIVARY GLAND                          | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| LIVER LEUKEMIA, MONONUCLEAR CELL        | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| BILE DUCT                               | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| GALLBLADDER & COMMON BILE DUCT          | N | N | N | N | N | N | N | N | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | 50                   |    |    |
| PANCREAS                                | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| ESOPHAGUS                               | - | - | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 32 |    |
| STOMACH                                 | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| SMALL INTESTINE                         | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| LARGE INTESTINE                         | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 46 |    |
| <b>URINARY SYSTEM</b>                   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    |    |
| KIDNEY                                  | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| URINARY BLADDER                         | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| <b>ENDOCRINE SYSTEM</b>                 |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    |    |
| PITUITARY CARCINOMA, NOS                | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 47 |    |
| ADENOMA, NOS                            |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 5  |    |
|                                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    | 11 |
| ADRENAL PHEOCHROMOCYTOMA                | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 30 |    |
|                                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    | 1  |
| THYROID FOLLICULAR-CELL CARCINOMA       | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 49 |    |
| C-CELL ADENOMA                          |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 1  |    |
| C-CELL CARCINOMA                        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 1  |    |
| PARATHYROID                             | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | 22                   |    |    |
| <b>REPRODUCTIVE SYSTEM</b>              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    |    |
| MAMMARY GLAND ADENOCARCINOMA, NOS       | N | N | + | N | N | N | + | N | N | N  | N  | +  | N  | N  | +  | N  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                   |    |    |
| FIBROADENOMA                            |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 18 |    |
| PREPUTIAL/CLITORAL GLAND CARCINOMA, 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  | N  | N  | N  | 50                   |    |    |
|                                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 2  |    |
| VAGINA ENDOMETRIAL STROMAL SARCOMA      | N | N | N | N | N | N | N | N | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | 50                   |    |    |
|                                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 1  |    |
| UTERUS ADENOMA, NOS                     | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| ADENOCARCINOMA, NOS                     |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 1  |    |
| ENDOMETRIAL STROMAL POLYP               | X | X | X | X |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 2  |    |
| ENDOMETRIAL STROMAL SARCOMA             | X |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 10 |    |
|                                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 2  |    |
| OVARY SERTOLI-CELL TUMOR                | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                   |    |    |
| TUBULAR ADENOMA                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 1  |    |
|                                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 1  |    |
| <b>NERVOUS SYSTEM</b>                   |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    |    |
| BRAIN                                   | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +                    | 50 |    |
| <b>ALL OTHER SYSTEMS</b>                |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      |    |    |
| 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  | N  | N  | N  | 50                   |    |    |
| ADENOCARCINOMA, NOS, METASTATIC         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 1  |    |
| LEUKEMIA, MONONUCLEAR CELL              |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                      | 6  |    |

N ANIMALS NECROPSIED



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

| ANIMAL NUMBER                                    | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | TOTAL ISSUES TUMORS |   |
|--------------------------------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|---------------------|---|
| WEEKS ON STUDY                                   | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1  | 1                   | 1 |
| <b>INTEGUMENTARY SYSTEM</b>                      |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     |   |
| SUBCUTANEOUS TISSUE SARCOMA, NOS                 | + | + | + | + | + | + | N | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| <b>RESPIRATORY SYSTEM</b>                        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     |   |
| LUNGS AND BRONCHI CARCINOMA, NOS, METASTATIC     | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| TRACHEA                                          | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| <b>HEMATOPOIETIC SYSTEM</b>                      |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     |   |
| BONE MARROW                                      | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 67                  |   |
| SPLEEN                                           | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| LYMPH NODES                                      | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                  |   |
| THYMUS                                           | - | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 34                  |   |
| <b>CIRCULATORY SYSTEM</b>                        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     |   |
| HEART                                            | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| <b>DIGESTIVE SYSTEM</b>                          |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     |   |
| SALIVARY GLAND                                   | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| LIVER NEOPLASTIC NODULE                          | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| BILE DUCT                                        | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| GALLBLADDER & COMMON BILE DUCT                   | N | N | N | N | N | N | N | N | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | 50                  |   |
| PANCREAS                                         | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| ESOPHAGUS                                        | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 51                  |   |
| STOMACH                                          | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| SMALL INTESTINE                                  | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| LARGE INTESTINE                                  | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                  |   |
| <b>URINARY SYSTEM</b>                            |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     |   |
| KIDNEY TUBULAR-CELL ADENOCARCINOMA               | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| URINARY BLADDER LEIOMYOSARCOMA                   | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| <b>ENDOCRINE SYSTEM</b>                          |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     |   |
| PITUITARY CARCINOMA, NOS                         | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                  |   |
| ADENOMA, NOS                                     | 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  | X  | X  | X  | 19 |                     |   |
| ADRENAL PHEOCHROMOCYTOMA                         | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| THYROID C-CELL ADENOMA                           | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 49                  |   |
| C-CELL CARCINOMA                                 |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 1                   |   |
| PARATHYROID                                      | - | - | - | - | - | - | - | - | - | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | 23                  |   |
| <b>REPRODUCTIVE SYSTEM</b>                       |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     |   |
| MAMMARY GLAND ADENOCARCINOMA, NOS                | + | + | + | + | + | + | N | N | N | N  | N  | N  | +  | +  | +  | +  | N  | +  | +  | N  | N  | +  | +  | +  | +  | +  | +  | +  | +  | 50 |                     |   |
| FIBROADENOMA                                     | X |   |   |   |   |   | X |   |   |    |    |    |    |    |    |    | X  |    |    |    |    |    |    |    |    |    |    |    |    |    | 12                  |   |
| PREPUTIAL/CLITORAL GLAND SQUAMOUS CELL CARCINOMA | N | N | N | N | N | N | N | N | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | 50                  |   |
| VAGINA LEIOMYOSARCOMA                            | N | N | N | N | N | N | N | N | N | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | 50                  |   |
| UTERUS ADENOCARCINOMA, NOS                       | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| ENDOMETRIAL STROMAL POLYP                        |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 2                   |   |
| ENDOMETRIAL STROMAL SARCOMA                      |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | 6                   |   |
| OVARY TUBULAR ADENOMA                            | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| <b>NERVOUS SYSTEM</b>                            |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     |   |
| BRAIN ASTROCYTOMA                                | + | + | + | + | + | + | + | + | + | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | 50                  |   |
| <b>SPECIAL SENSE ORGANS</b>                      |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     |   |
| HARDERIAN GLAND CARCINOMA, 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  | N  | N  | N  | 50                  |   |
| ADENOMA, NOS                                     |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     | 1 |
| <b>ALL OTHER SYSTEMS</b>                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     |   |
| 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  | N  | N  | N  | 50                  |   |
| OSTEOSARCOMA, METASTATIC                         |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     | 1 |
| LEUKEMIA, MONONUCLEAR CELL                       |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     | 4 |
| LEG NOS OSTEOSARCOMA                             |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |                     | 1 |

\* 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        |
| <b>INTEGUMENTARY SYSTEM</b>          |               |           |           |
| *SUBCUT TISSUE                       | (50)          | (50)      | (50)      |
| SARCOMA, NOS                         |               |           | 1 (2%)    |
| FIBROSARCOMA                         | 2 (4%)        |           | 2 (4%)    |
| <b>RESPIRATORY SYSTEM</b>            |               |           |           |
| #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%)        |           |           |
| <b>HEMATOPOIETIC SYSTEM</b>          |               |           |           |
| *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%)        |           |           |
| <b>CIRCULATORY SYSTEM</b>            |               |           |           |
| #SPLEEN                              | (50)          | (49)      | (49)      |
| HEMANGIOSARCOMA                      |               |           | 1 (2%)    |
| <b>DIGESTIVE SYSTEM</b>              |               |           |           |
| #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%)    |           |
| <b>URINARY SYSTEM</b>                |               |           |           |
| #KIDNEY                              | (50)          | (50)      | (50)      |
| TUBULAR-CELL ADENOMA                 |               | 1 (2%)    |           |
| #URINARY BLADDER                     | (49)          | (50)      | (50)      |
| TRANSITIONAL-CELL CARCINOMA          |               | 1 (2%)    |           |
| <b>ENDOCRINE SYSTEM</b>              |               |           |           |
| #ADRENAL                             | (49)          | (47)      | (50)      |
| PHEOCHROMOCYTOMA                     | 1 (2%)        |           |           |
| #PANCREATIC ISLETS                   | (50)          | (48)      | (50)      |
| ISLET-CELL ADENOMA                   | 1 (2%)        |           |           |
| <b>REPRODUCTIVE SYSTEM</b>           |               |           |           |
| #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 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|----------|-----------|
| <b>NERVOUS SYSTEM</b>                                                                                                                                                                                                          |               |          |           |
| NONE                                                                                                                                                                                                                           |               |          |           |
| <b>SPECIAL SENSE ORGANS</b>                                                                                                                                                                                                    |               |          |           |
| *HARDERIAN GLAND                                                                                                                                                                                                               | (50)          | (50)     | (50)      |
| CARCINOMA, NOS                                                                                                                                                                                                                 | 1 (2%)        |          |           |
| ADENOMA, NOS                                                                                                                                                                                                                   | 4 (8%)        | 2 (4%)   | 1 (2%)    |
| <b>MUSCULOSKELETAL SYSTEM</b>                                                                                                                                                                                                  |               |          |           |
| NONE                                                                                                                                                                                                                           |               |          |           |
| <b>BODY CAVITIES</b>                                                                                                                                                                                                           |               |          |           |
| *TUNICA VAGINALIS                                                                                                                                                                                                              | (50)          | (50)     | (50)      |
| SARCOMA, NOS                                                                                                                                                                                                                   |               |          | 1 (2%)    |
| <b>ALL OTHER SYSTEMS</b>                                                                                                                                                                                                       |               |          |           |
| *MULTIPLE ORGANS                                                                                                                                                                                                               | (50)          | (50)     | (50)      |
| TRANSITIONAL-CELL CARCINOMA, MET                                                                                                                                                                                               |               | 1 (2%)   |           |
| <p># NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY<br/>           * NUMBER OF ANIMALS NECROPSIED<br/>           † LOW DOSE MALE AND FEMALE MICE RECEIVED A SEVENFOLD OVERDOSE OF CHEMICAL IN CORN OIL AT WEEK 58.</p> |               |          |           |
| <b>ANIMAL DISPOSITION SUMMARY</b>                                                                                                                                                                                              |               |          |           |
| 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                                                                                                                                                                                                                    |               |          |           |
| <b>TUMOR SUMMARY</b>                                                                                                                                                                                                           |               |          |           |
| 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-<br>BENIGN OR MALIGNANT                                                                                                                                                                    |               |          |           |
| TOTAL UNCERTAIN TUMORS                                                                                                                                                                                                         |               |          |           |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>PRIMARY OR METASTATIC                                                                                                                                                                  |               |          |           |
| TOTAL UNCERTAIN TUMORS                                                                                                                                                                                                         |               |          |           |
| <p>** PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS<br/>           ## SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN</p>                                                                   |               |          |           |

**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        |
| <b>INTEGUMENTARY SYSTEM</b>          |               |           |           |
| *SKIN                                | (50)          | (49)      | (50)      |
| SEBACEOUS ADENOMA                    |               |           | 1 (2%)    |
| *SUBCUT TISSUE                       | (50)          | (49)      | (50)      |
| SARCOMA, NOS                         | 2 (4%)        |           |           |
| FIBROSARCOMA                         | 1 (2%)        |           |           |
| OSTEOSARCOMA                         |               | 1 (2%)    |           |
| <b>RESPIRATORY SYSTEM</b>            |               |           |           |
| #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%)    |           |
| <b>HEMATOPOIETIC SYSTEM</b>          |               |           |           |
| *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%)        |           |           |
| <b>CIRCULATORY SYSTEM</b>            |               |           |           |
| #SPLEEN                              | (50)          | (49)      | (50)      |
| HEMANGIOSARCOMA                      | 2 (4%)        |           | 2 (4%)    |
| #LIVER                               | (50)          | (49)      | (50)      |
| HEMANGIOMA                           | 1 (2%)        |           |           |
| #OVARY                               | (49)          | (48)      | (49)      |
| HEMANGIOMA                           | 1 (2%)        |           | 2 (4%)    |
| <b>DIGESTIVE SYSTEM</b>              |               |           |           |
| #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 PAPILOMA               |               |           | 2 (4%)    |
| <b>URINARY SYSTEM</b>                |               |           |           |
| #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 |
|----------------------------------|---------------|----------|-----------|
| <b>ENDOCRINE SYSTEM</b>          |               |          |           |
| #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%)    |
| <b>REPRODUCTIVE SYSTEM</b>       |               |          |           |
| *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%)        |          |           |
| <b>NERVOUS SYSTEM</b>            |               |          |           |
| NONE                             |               |          |           |
| <b>SPECIAL SENSE ORGANS</b>      |               |          |           |
| *HARDERIAN GLAND                 | (50)          | (49)     | (50)      |
| ADENOMA, NOS                     | 1 (2%)        | 1 (2%)   | 3 (6%)    |
| <b>MUSCULOSKELETAL SYSTEM</b>    |               |          |           |
| NONE                             |               |          |           |
| <b>BODY CAVITIES</b>             |               |          |           |
| *ABDOMINAL CAVITY                | (50)          | (49)     | (50)      |
| SARCOMA, NOS                     | 1 (2%)        |          |           |
| <b>ALL OTHER SYSTEMS</b>         |               |          |           |
| *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 |
|----------------------------------------------------------------------------------|---------------|----------|-----------|
| <b>ANIMAL DISPOSITION SUMMARY</b>                                                |               |          |           |
| 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                                                                      |               |          |           |
| <b>TUMOR SUMMARY</b>                                                             |               |          |           |
| 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-<br>BENIGN OR MALIGNANT                      |               |          |           |
| TOTAL UNCERTAIN TUMORS                                                           |               |          |           |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-<br>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                     | 01 | 02 | 03 | 04 | 05 | 06 | 07 | 08 | 09 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|-----------------------------------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| WEEKS ON STUDY                    | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| <b>INTEGUMENTARY SYSTEM</b>       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| SUBCUTANEOUS TISSUE FIBROSARCOMA  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>RESPIRATORY SYSTEM</b>         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| LUNGS AND BRONCHI                 | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| HEPATOCELLULAR CARCINOMA, METASTA |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| ALVEOLAR/BRONCHIOLAR ADENOMA      |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| ALVEOLAR/BRONCHIOLAR CARCINOMA    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| FIBROSARCOMA, METASTATIC          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| TRACHEA                           | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>HEMATOPOIETIC SYSTEM</b>       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| BONE MARROW                       | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| SPLEEN                            | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| MALIGNANT LYMPHOMA, NOS           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| LYMPH NODES                       | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| MALIG. LYMPHOMA, HISTIOCYTIC TYPE |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| THYMUS                            | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| <b>CIRCULATORY SYSTEM</b>         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| HEART                             | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>DIGESTIVE SYSTEM</b>           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| SALIVARY GLAND                    | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| LIVER                             | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| HEPATOCELLULAR ADENOMA            |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| HEPATOCELLULAR CARCINOMA          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| BILE DUCT                         | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| GALLBLADDER & COMMON BILE DUCT    | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  | N  |
| PANCREAS                          | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| ESOPHAGUS                         | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| STOMACH                           | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| SQUAMOUS CELL CARCINOMA           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| SMALL INTESTINE                   | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| LARGE INTESTINE                   | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>URINARY SYSTEM</b>             |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| KIDNEY                            | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| URINARY BLADDER                   | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>ENDOCRINE SYSTEM</b>           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| PITUITARY                         | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| ADRENAL PHEOCHROMOCYTOMA          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| THYROID                           | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| PARATHYROID                       | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  | -  |
| PANCREATIC ISLETS                 | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| ISLET-CELL ADENOMA                |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| <b>REPRODUCTIVE SYSTEM</b>        |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| MAMMARY GLAND                     | 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                          | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>NERVOUS SYSTEM</b>             |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| BRAIN                             | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  | +  |
| <b>SPECIAL SENSE ORGANS</b>       |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| HARDERIAN GLAND                   | 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                      |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| <b>ALL OTHER SYSTEMS</b>          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 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  |
| MALIGNANT LYMPHOMA, NOS           |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

+: 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  
 G: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL  
 A: AUTOLYSIS  
 M: ANIMAL MISSING  
 B: NO NECROPSY PERFORMED

























## **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        |
| <b>INTEGUMENTARY SYSTEM</b>          |               |          |           |
| *SKIN                                | (50)          | (50)     | (50)      |
| ABCESS, 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%)    |
| ABCESS, NOS                          |               | 3 (6%)   |           |
| <b>RESPIRATORY SYSTEM</b>            |               |          |           |
| #LUNG                                | (50)          | (50)     | (50)      |
| CONGESTION, NOS                      |               | 1 (2%)   |           |
| INFLAMMATION, INTERSTITIAL           |               |          | 1 (2%)    |
| INFLAMMATION, ACUTE                  | 1 (2%)        |          |           |
| ABCESS, 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%)    |
| <b>HEMATOPOIETIC SYSTEM</b>          |               |          |           |
| #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 |
|-----------------------------------------------|---------------|--------------------|-----------|
| <b>CIRCULATORY SYSTEM</b>                     |               |                    |           |
| #MYOCARDIUM                                   | (50)          | (50)               | (50)      |
| INFLAMMATION, CHRONIC FOCAL DEGENERATION, NOS | 38 (76%)      | 1 (2%)<br>24 (48%) | 22 (44%)  |
| *PANCREATIC ARTERY HYPERTROPHY, NOS           | (50)          | (50)               | (50)      |
| 1 (2%)                                        |               |                    |           |
| #PANCREAS                                     | (50)          | (49)               | (49)      |
| THROMBOSIS, NOS                               |               | 1 (2%)             |           |
| PERIVASCULITIS                                |               | 1 (2%)             |           |
| <b>DIGESTIVE SYSTEM</b>                       |               |                    |           |
| #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 FIBROSIS          | 1 (2%)        | 1 (2%)             |           |
| METAPLASIA, SQUAMOUS                          |               | 1 (2%)<br>4 (8%)   | 1 (2%)    |
| #LIVER                                        | (50)          | (50)               | (50)      |
| INFLAMMATION, ACUTE FOCAL CHOLANGIOFIBROSIS   | 1 (2%)        |                    | 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 NECROSIS, NOS            | (50)          | (50)               | (50)      |
| 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%)    |
| <b>URINARY SYSTEM</b>                         |               |                    |           |
| #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 |
|-----------------------------------|---------------|----------|-----------|
| <b>URINARY SYSTEM (Continued)</b> |               |          |           |
| #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%)        |          |           |
| <b>ENDOCRINE SYSTEM</b>           |               |          |           |
| #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%)   |           |
| <b>REPRODUCTIVE SYSTEM</b>        |               |          |           |
| *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%)   |           |
| <b>NERVOUS SYSTEM</b>             |               |          |           |
| #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 |
|----------------------------------------------------------|---------------|----------|-----------|
| <b>SPECIAL SENSE ORGANS</b>                              |               |          |           |
| *EYE                                                     | (50)          | (50)     | (50)      |
| ABCESS, NOS                                              |               |          | 2 (4%)    |
| *EAR                                                     | (50)          | (50)     | (50)      |
| ACANTHOSIS                                               |               | 1 (2%)   |           |
| <b>MUSCULOSKELETAL SYSTEM</b>                            |               |          |           |
| *MANDIBLE                                                | (50)          | (50)     | (50)      |
| INFLAMMATION, CHRONIC                                    |               |          | 2 (4%)    |
| <b>BODY CAVITIES</b>                                     |               |          |           |
| *ABDOMINAL CAVITY                                        | (50)          | (50)     | (50)      |
| NECROSIS, FAT                                            |               | 1 (2%)   |           |
| *MESENTERY                                               | (50)          | (50)     | (50)      |
| NECROSIS, FAT                                            |               |          | 2 (4%)    |
| <b>ALL OTHER SYSTEMS</b>                                 |               |          |           |
| <b>ORBITAL REGION</b>                                    |               |          |           |
| INFLAMMATION, SUPPURATIVE                                |               | 1        |           |
| <b>ADIPOSE TISSUE</b>                                    |               |          |           |
| INFLAMMATION, GRANULOMATOUS                              | 1             |          |           |
| NECROSIS, NOS                                            | 1             |          |           |
| <b>SPECIAL MORPHOLOGY SUMMARY</b>                        |               |          |           |
| 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        |
| <b>INTEGUMENTARY SYSTEM</b>          |               |          |           |
| *SKIN                                | (50)          | (50)     | (50)      |
| ACANTHOSIS                           |               | 1 (2%)   |           |
| *SUBCUT TISSUE                       | (50)          | (50)     | (50)      |
| ABCESS, NOS                          |               |          | 1 (2%)    |
| <b>RESPIRATORY SYSTEM</b>            |               |          |           |
| *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%)    |
| <b>HEMATOPOIETIC SYSTEM</b>          |               |          |           |
| #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%)        |          |           |
| <b>CIRCULATORY SYSTEM</b>            |               |          |           |
| #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%)   |           |
| <b>DIGESTIVE SYSTEM</b>              |               |          |           |
| *MOUTH                               | (50)          | (50)     | (50)      |
| ABCESS, 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 |
|-------------------------------------|---------------|----------|-----------|
| <b>DIGESTIVE SYSTEM (Continued)</b> |               |          |           |
| #LIVER                              | (50)          | (50)     | (50)      |
| ABCESS, 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%)   |
| <b>URINARY SYSTEM</b>               |               |          |           |
| #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%)   |           |
| <b>ENDOCRINE SYSTEM</b>             |               |          |           |
| #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 |
|-------------------------------------|---------------|----------|-----------|
| <b>ENDOCRINE SYSTEM (Continued)</b> |               |          |           |
| #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%)    |
| <b>REPRODUCTIVE SYSTEM</b>          |               |          |           |
| *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%)   |           |
| <b>NERVOUS SYSTEM</b>               |               |          |           |
| NONE                                |               |          |           |
| <b>SPECIAL SENSE ORGANS</b>         |               |          |           |
| *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%)    |
| <b>MUSCULOSKELETAL SYSTEM</b>       |               |          |           |
| 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 |
|-----------------------------------|---------------|----------|-----------|
| <b>BODY CAVITIES</b>              |               |          |           |
| *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%)    |
| <b>ALL OTHER SYSTEMS</b>          |               |          |           |
| SITE UNKNOWN                      |               |          |           |
| NECROSIS, NOS                     | 1             |          |           |
| OMENTUM                           |               |          |           |
| INFLAMMATION, ACUTE               |               | 1        |           |
| INFLAMMATION, CHRONIC             |               | 1        |           |
| NECROSIS, FAT                     | 2             | 3        | 3         |
| <b>SPECIAL MORPHOLOGY SUMMARY</b> |               |          |           |
| 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        |
| <b>INTEGUMENTARY SYSTEM</b>          |               |           |           |
| *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%)    |           |
| ABSCCESS, NOS                        |               | 1 (2%)    | 1 (2%)    |
| FIBROSIS                             | 1 (2%)        |           |           |
| <b>RESPIRATORY SYSTEM</b>            |               |           |           |
| #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%)    |
| <b>HEMATOPOIETIC SYSTEM</b>          |               |           |           |
| #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%)    |           |
| <b>CIRCULATORY SYSTEM</b>            |               |           |           |
| #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%)    |
| <b>DIGESTIVE SYSTEM</b>              |               |           |           |
| #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 |
|-------------------------------------|---------------|----------|-----------|
| <b>DIGESTIVE SYSTEM (Continued)</b> |               |          |           |
| #LIVER                              | (50)          | (50)     | (50)      |
| CYST, NOS                           | 2 (4%)        |          |           |
| MULTILOCLULAR 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%)        |          |           |
| HEPATOCTOMEALY                      |               |          | 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%)    |
| <b>URINARY SYSTEM</b>               |               |          |           |
| #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 |
|-------------------------------|---------------|----------|-----------|
| <b>ENDOCRINE SYSTEM</b>       |               |          |           |
| #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%)        |          |           |
| <b>REPRODUCTIVE SYSTEM</b>    |               |          |           |
| *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%)        |          |           |
| <b>NERVOUS SYSTEM</b>         |               |          |           |
| *SPINAL CORD                  | (50)          | (50)     | (50)      |
| COMPRESSION                   |               |          | 1 (2%)    |
| <b>SPECIAL SENSE ORGANS</b>   |               |          |           |
| *HARDERIAN GLAND              | (50)          | (50)     | (50)      |
| CYST, NOS                     | 1 (2%)        |          |           |
| <b>MUSCULOSKELETAL SYSTEM</b> |               |          |           |
| NONE                          |               |          |           |
| <b>BODY CAVITIES</b>          |               |          |           |
| *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        |
| <b>INTEGUMENTARY SYSTEM</b>          |               |           |           |
| *SUBCUT TISSUE                       | (50)          | (49)      | (50)      |
| INFLAMMATION, CHRONIC                | 1 (2%)        |           |           |
| <b>RESPIRATORY SYSTEM</b>            |               |           |           |
| #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%)    |
| <b>HEMATOPOIETIC SYSTEM</b>          |               |           |           |
| #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%)    |
| <b>CIRCULATORY SYSTEM</b>            |               |           |           |
| #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 |
|---------------------------------------|----------------|----------|-----------|
| <b>CIRCULATORY SYSTEM (Continued)</b> |                |          |           |
| #GASTRIC MUCOSA PERIVASCULITIS        | (50)<br>1 (2%) | (49)     | (50)      |
| #URINARY BLADDER PERIVASCULITIS       | (49)<br>1 (2%) | (46)     | (50)      |
| <b>DIGESTIVE SYSTEM</b>               |                |          |           |
| #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%)    |
| HEPATOCTOMEALY                        |                | 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%)    |
| <b>URINARY SYSTEM</b>                 |                |          |           |
| #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 |
|------------------------------------------------|---------------|----------------|-----------|
| <b>URINARY SYSTEM (Continued)</b>              |               |                |           |
| #URINARY BLADDER/SEROSA<br>INFLAMMATION, ACUTE | (49)          | (46)<br>2 (4%) | (50)      |
| <b>ENDOCRINE SYSTEM</b>                        |               |                |           |
| #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%)         |           |
| <b>REPRODUCTIVE SYSTEM</b>                     |               |                |           |
| *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%)    |
| <b>NERVOUS SYSTEM</b>                          |               |                |           |
| NONE                                           |               |                |           |
| <b>SPECIAL SENSE ORGANS</b>                    |               |                |           |
| 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 |
|-----------------------------------|---------------|----------|-----------|
| <b>MUSCULOSKELETAL SYSTEM</b>     |               |          |           |
| *SKELETAL MUSCLE                  | (50)          | (49)     | (50)      |
| INFLAMMATION, ACUTE               | 1 (2%)        | 1 (2%)   |           |
| ABSCESS, NOS                      |               |          | 1 (2%)    |
| <b>BODY CAVITIES</b>              |               |          |           |
| *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%)    |
| <b>ALL OTHER SYSTEMS</b>          |               |          |           |
| *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         |
| <b>SPECIAL MORPHOLOGY SUMMARY</b> |               |          |           |
| 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  |
|--------------------------------------------------------|-----------------|------------|-----------|
| <b>Subcutaneous Tissue: Fibroma</b>                    |                 |            |           |
| 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  |
| <b>Lung: Alveolar/Bronchiolar Adenoma</b>              |                 |            |           |
| 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  |
| <b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b> |                 |            |           |
| 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  |
| <b>Hematopoietic System: Lymphoma</b>                  |                 |            |           |
| 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   |
| <b>Hematopoietic System: Mononuclear Cell Leukemia</b> |                 |            |           |
| 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  |
| <b>Liver: Neoplastic Nodule</b>                        |                 |            |           |
| 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   |
| <b>Liver: Carcinoma</b>                                |                 |            |           |
| 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    |
|-----------------------------------------------------------------|-----------------|-------------|-------------|
| <b>Liver: Neoplastic Nodule or Carcinoma</b>                    |                 |             |             |
| 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     |
| <b>Pituitary: Adenoma</b>                                       |                 |             |             |
| 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     |
| <b>Pituitary: Carcinoma</b>                                     |                 |             |             |
| 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    |
| <b>Pituitary Adenoma or Carcinoma</b>                           |                 |             |             |
| 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    |
| <b>Adrenal: Pheochromocytoma</b>                                |                 |             |             |
| 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    |
| <b>Adrenal: Pheochromocytoma or Pheochromocytoma, Malignant</b> |                 |             |             |
| 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    |
| <b>Thyroid: Follicular Cell Carcinoma</b>                       |                 |             |             |
| 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    |
|------------------------------------------------------|-----------------|-------------|-------------|
| <b>Thyroid: Follicular Cell Adenoma or Carcinoma</b> |                 |             |             |
| 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    |
| <b>Thyroid: C-Cell Carcinoma</b>                     |                 |             |             |
| 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     |
| <b>Thyroid: C-Cell Adenoma or Carcinoma</b>          |                 |             |             |
| 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     |
| <b>Mammary Gland: Fibroadenoma</b>                   |                 |             |             |
| 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    |
| <b>Testis: Interstitial Cell Tumor</b>               |                 |             |             |
| 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    |
|--------------------------------------------------------|-----------------|-------------|-------------|
| <b>Hematopoietic System: Mononuclear Cell Leukemia</b> |                 |             |             |
| 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     |
| <b>Pituitary: Adenoma</b>                              |                 |             |             |
| 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    |
| <b>Pituitary: Carcinoma</b>                            |                 |             |             |
| 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    |
| <b>Pituitary: Adenoma or Carcinoma</b>                 |                 |             |             |
| 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    |
| <b>Adrenal: Pheochromocytoma</b>                       |                 |             |             |
| 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    |
| <b>Thyroid: Follicular Cell Carcinoma</b>              |                 |             |             |
| 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     |
| <b>Thyroid: C-Cell Carcinoma</b>                       |                 |             |             |
| 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   |
|---------------------------------------------|-----------------|-------------|------------|
| <b>Thyroid: C-Cell Adenoma or Carcinoma</b> |                 |             |            |
| 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   |
| <b>Mammary Gland: Fibroadenoma</b>          |                 |             |            |
| 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   |
| <b>Uterus: Adenoma or Adenocarcinoma</b>    |                 |             |            |
| 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   |
| <b>Uterus: Endometrial Stromal Polyp</b>    |                 |             |            |
| 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   |
|--------------------------------------------------------|-----------------|--------------|-------------|
| <b>Subcutaneous Tissue: Sarcoma or Fibrosarcoma</b>    |                 |              |             |
| 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     |
| <b>Lung: Alveolar/Bronchiolar Adenoma</b>              |                 |              |             |
| 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    |
| <b>Lung: Alveolar/Bronchiolar Carcinoma</b>            |                 |              |             |
| 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    |
| <b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b> |                 |              |             |
| 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    |
| <b>Hematopoietic System: Lymphoma, All Malignant</b>   |                 |              |             |
| 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    |
| <b>Liver: Adenoma</b>                                  |                 |              |             |
| 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    |
| <b>Liver: Carcinoma</b>                                |                 |              |             |
| 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   |
|----------------------------------------------|-----------------|-------------|-------------|
| <b>Liver: Adenoma or Carcinoma</b>           |                 |             |             |
| 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     |
| <b>Harderian Gland: Adenoma</b>              |                 |             |             |
| 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    |
| <b>Harderian Gland: Adenoma or Carcinoma</b> |                 |             |             |
| 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   |
|----------------------------------------------------------|-----------------|--------------|-------------|
| <b>Lung: Alveolar/Bronchiolar Adenoma</b>                |                 |              |             |
| 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     |
| <b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>   |                 |              |             |
| 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     |
| <b>Hematopoietic System: Lymphoma, All Malignant</b>     |                 |              |             |
| 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     |
| <b>Hematopoietic System: Lymphoma or Leukemia</b>        |                 |              |             |
| 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     |
| <b>Circulatory System: Hemangioma or Hemangiosarcoma</b> |                 |              |             |
| 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     |
| <b>Liver: Adenoma</b>                                    |                 |              |             |
| 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     |
| <b>Liver: Carcinoma</b>                                  |                 |              |             |
| 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   |
|----------------------------------------------------------|-----------------|-------------|-------------|
| <b>Liver: Adenoma or Carcinoma</b>                       |                 |             |             |
| 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     |
| <b>Pituitary: Adenoma</b>                                |                 |             |             |
| 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     |
| <b>Pituitary: Adenoma or Carcinoma</b>                   |                 |             |             |
| 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    |
| <b>Thyroid: Follicular Cell Adenoma</b>                  |                 |             |             |
| 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     |
| <b>Thyroid: Follicular Cell Adenoma or Cystadenoma</b>   |                 |             |             |
| 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     |
| <b>Thyroid: All Follicular Cell Adenoma or Carcinoma</b> |                 |             |             |
| 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     |
| <b>Harderian Gland: Adenoma</b>                          |                 |             |             |
| 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)**

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- (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<sub>1</sub> 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 |
|------------------------------------------------------------------|-----------------|-----------------|----------------------|
| <b>Historical Incidence at EG&amp;G Mason Research Institute</b> |                 |                 |                      |
| 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                 |
| <b>Overall Historical Incidence</b>                              |                 |                 |                      |
| 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          |
|------------------------------------------------------------------|-------------------|
| <b>Historical Incidence at EG&amp;G Mason Research Institute</b> |                   |
| 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              |
| <b>Overall Historical Incidence</b>                              |                   |
| 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<br>Tumor |
|------------------------------------------------------------------|----------------------------|
| <b>Historical Incidence at EG&amp;G Mason Research Institute</b> |                            |
| Diglycidylresorcinol ether                                       | 47/50                      |
| Diglycidylresorcinol ether                                       | 47/50                      |
| 1,2-Dichloropropane                                              | 45/50                      |
| Chlorodibromomethane                                             | 48/50                      |
| <b>TOTAL</b>                                                     | <b>187/200 (93.5%)</b>     |
| <b>SD (b)</b>                                                    | <b>2.52%</b>               |
| <b>Range (c)</b>                                                 |                            |
| High                                                             | 48/50                      |
| Low                                                              | 45/50                      |
| <b>Overall Historical Incidence</b>                              |                            |
| <b>TOTAL</b>                                                     | <b>1,029/1,142 (90.1%)</b> |
| <b>SD (b)</b>                                                    | <b>5.57%</b>               |
| <b>Range (c)</b>                                                 |                            |
| 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             |
|------------------------------------------------------------------|--------------------------|
| <b>Historical Incidence at EG&amp;G Mason Research Institute</b> |                          |
| Diglycidylresorcinol ether                                       | 18/50                    |
| Diglycidylresorcinol ether                                       | 17/50                    |
| 1,2-Dichloropropane                                              | 15/50                    |
| Chlorodibromomethane                                             | 18/50                    |
| <b>TOTAL</b>                                                     | <b>68/200 (34.0%)</b>    |
| <b>SD (b)</b>                                                    | <b>2.83%</b>             |
| <b>Range (c)</b>                                                 |                          |
| High                                                             | 18/50                    |
| Low                                                              | 15/50                    |
| <b>Overall Historical Incidence</b>                              |                          |
| <b>TOTAL</b>                                                     | <b>269/1,147 (23.5%)</b> |
| <b>SD (b)</b>                                                    | <b>9.38%</b>             |
| <b>Range (c)</b>                                                 |                          |
| 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         |
|------------------------------------------------------------------|------------------------|----------------------|--------------------------|
| <b>Historical Incidence at EG&amp;G Mason Research Institute</b> |                        |                      |                          |
| 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                    |
| <b>TOTAL</b>                                                     | <b>47/200 (23.5%)</b>  | <b>7/200 (3.5%)</b>  | <b>52/200 (26.0%)</b>    |
| <b>SD (b)</b>                                                    | <b>3.42%</b>           | <b>1.91%</b>         | <b>4.9%</b>              |
| <b>Range (c)</b>                                                 |                        |                      |                          |
| High                                                             | 14/50                  | 3/50                 | 15/50                    |
| Low                                                              | 10/50                  | 1/50                 | 10/50                    |
| <b>Overall Historical Incidence</b>                              |                        |                      |                          |
| <b>TOTAL</b>                                                     | <b>248/1,125 (22%)</b> | <b>23/1,125 (2%)</b> | <b>263/1,125 (23.4%)</b> |
| <b>SD (b)</b>                                                    | <b>6.74%</b>           | <b>1.72%</b>         | <b>6.88%</b>             |
| <b>Range (c)</b>                                                 |                        |                      |                          |
| 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     |
|------------------------------------------------------------------|------------------------|------------------------|--------------------------|
| <b>Historical Incidence at EG&amp;G Mason Research Institute</b> |                        |                        |                          |
| 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                     |
| <b>TOTAL</b>                                                     | <b>8/199 (4.0%)</b>    | <b>7/199 (3.5%)</b>    | <b>15/199 (7.5%)</b>     |
| <b>SD (b)</b>                                                    | <b>4.31%</b>           | <b>4.53%</b>           | <b>4.52%</b>             |
| <b>Range (c)</b>                                                 |                        |                        |                          |
| High                                                             | 5/50                   | 5/49                   | 6/49                     |
| Low                                                              | 0/50                   | 0/50                   | 1/50                     |
| <b>Overall Historical Incidence</b>                              |                        |                        |                          |
| <b>TOTAL</b>                                                     | <b>78/1,104 (7.1%)</b> | <b>34/1,104 (3.1%)</b> | <b>110/1,104 (10.0%)</b> |
| <b>SD (b)</b>                                                    | <b>5.31%</b>           | <b>3.08%</b>           | <b>5.37%</b>             |
| <b>Range (c)</b>                                                 |                        |                        |                          |
| 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<sub>1</sub> MICE RECEIVING CORN OIL BY GAVAGE (a)**

|                                                                  | Leukemia              | Lymphoma                 | Leukemia or<br>Lymphoma  |
|------------------------------------------------------------------|-----------------------|--------------------------|--------------------------|
| <b>Historical Incidence at EG&amp;G Mason Research Institute</b> |                       |                          |                          |
| 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                     |
| <b>TOTAL</b>                                                     | <b>0/200 (0.0%)</b>   | <b>29/200 (14.5%)</b>    | <b>29/200 (14.5%)</b>    |
| <b>SD (b)</b>                                                    | <b>0.00%</b>          | <b>3.00%</b>             | <b>3.00%</b>             |
| <b>Range (c)</b>                                                 |                       |                          |                          |
| High                                                             | 0/50                  | 9/50                     | 9/50                     |
| Low                                                              | 0/50                  | 6/50                     | 6/50                     |
| <b>Overall Historical Incidence</b>                              |                       |                          |                          |
| <b>TOTAL</b>                                                     | <b>6/1,090 (0.6%)</b> | <b>126/1,090 (11.6%)</b> | <b>132/1,090 (12.1%)</b> |
| <b>SD (b)</b>                                                    | <b>2.24%</b>          | <b>5.63%</b>             | <b>6.35%</b>             |
| <b>Range (c)</b>                                                 |                       |                          |                          |
| 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<sub>1</sub> MICE RECEIVING CORN OIL BY GAVAGE (a)**

|                                                                  | Adenoma                  | Carcinoma                | Adenoma or Carcinoma     |
|------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|
| <b>Historical Incidence at EG&amp;G Mason Research Institute</b> |                          |                          |                          |
| 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                    |
| <b>TOTAL</b>                                                     | <b>36/199 (18.1%)</b>    | <b>33/199 (16.6%)</b>    | <b>67/199 (33.7%)</b>    |
| <b>SD (c)</b>                                                    | <b>5.69%</b>             | <b>5.47%</b>             | <b>9.44%</b>             |
| <b>Range (d)</b>                                                 |                          |                          |                          |
| High                                                             | 14/50                    | 11/50                    | 23/50                    |
| Low                                                              | 7/50                     | 5/50                     | 13/50                    |
| <b>Overall Historical Incidence</b>                              |                          |                          |                          |
| <b>TOTAL</b>                                                     | <b>134/1,084 (12.4%)</b> | <b>222/1,084 (20.5%)</b> | <b>341/1,084 (31.5%)</b> |
| <b>SD (c)</b>                                                    | <b>6.67%</b>             | <b>7.90%</b>             | <b>10.42%</b>            |
| <b>Range (d)</b>                                                 |                          |                          |                          |
| 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<sub>1</sub> MICE RECEIVING CORN OIL BY GAVAGE (a)**

|                                                                  | Adenoma                | Carcinoma              | Adenoma or Carcinoma     |
|------------------------------------------------------------------|------------------------|------------------------|--------------------------|
| <b>Historical Incidence at EG&amp;G Mason Research Institute</b> |                        |                        |                          |
| 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                     |
| <b>TOTAL</b>                                                     | <b>25/200 (12.5%)</b>  | <b>10/200 (5.0%)</b>   | <b>34/200 (17.0%)</b>    |
| <b>SD (b)</b>                                                    | <b>3.79%</b>           | <b>5.29%</b>           | <b>5.77%</b>             |
| <b>Range (c)</b>                                                 |                        |                        |                          |
| High                                                             | 9/50                   | 6/50                   | 11/50                    |
| Low                                                              | 5/50                   | 0/50                   | 6/50                     |
| <b>Overall Historical Incidence</b>                              |                        |                        |                          |
| <b>TOTAL</b>                                                     | <b>99/1,082 (9.1%)</b> | <b>58/1,082 (5.4%)</b> | <b>155/1,082 (14.3%)</b> |
| <b>SD (b)</b>                                                    | <b>4.77%</b>           | <b>4.13%</b>           | <b>6.31%</b>             |
| <b>Range (c)</b>                                                 |                        |                        |                          |
| 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<sub>1</sub> MICE RECEIVING CORN OIL BY GAVAGE (a)**

|                                                                  | Adenoma                | Carcinoma              | Adenoma or Carcinoma   |
|------------------------------------------------------------------|------------------------|------------------------|------------------------|
| <b>Historical Incidence at EG&amp;G Mason Research Institute</b> |                        |                        |                        |
| 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                   |
| <b>TOTAL</b>                                                     | <b>10/198 (5.1%)</b>   | <b>7/198 (3.5%)</b>    | <b>17/198 (8.6%)</b>   |
| <b>SD (b)</b>                                                    | <b>4.19%</b>           | <b>3.42%</b>           | <b>5.47%</b>           |
| <b>Range (c)</b>                                                 |                        |                        |                        |
| High                                                             | 5/50                   | 4/50                   | 7/50                   |
| Low                                                              | 0/50                   | 0/48                   | 1/50                   |
| <b>Overall Historical Incidence</b>                              |                        |                        |                        |
| <b>TOTAL</b>                                                     | <b>47/1,176 (4.0%)</b> | <b>34/1,176 (2.9%)</b> | <b>80/1,176 (6.8%)</b> |
| <b>SD (b)</b>                                                    | <b>2.55%</b>           | <b>2.18%</b>           | <b>3.37%</b>           |
| <b>Range (c)</b>                                                 |                        |                        |                        |
| 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<sub>1</sub> MICE RECEIVING CORN OIL BY GAVAGE (a)**

|                                                         | Hemangioma            | Hemangiosarcoma        | Hemangioma or Hemangiosarcoma |
|---------------------------------------------------------|-----------------------|------------------------|-------------------------------|
| <b>Historical Incidence at Mason Research Institute</b> |                       |                        |                               |
| 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-methylethyl)ether                        | 0/50                  | 0/50                   | 0/50                          |
| <b>TOTAL</b>                                            | <b>3/200 (1.5%)</b>   | <b>5/200 (2.5%)</b>    | <b>8/200 (4.0%)</b>           |
| <b>SD (b)</b>                                           | <b>1.91%</b>          | <b>3.00%</b>           | <b>4.62%</b>                  |
| <b>Range (c)</b>                                        |                       |                        |                               |
| High                                                    | 2/50                  | 3/50                   | 4/50                          |
| Low                                                     | 0/50                  | 0/50                   | 0/50                          |
| <b>Overall Historical Incidence</b>                     |                       |                        |                               |
| <b>TOTAL</b>                                            | <b>9/1,187 (0.8%)</b> | <b>33/1,187 (2.8%)</b> | <b>42/1,187 (3.5%)</b>        |
| <b>SD (b)</b>                                           | <b>1.32%</b>          | <b>2.47%</b>           | <b>2.90%</b>                  |
| <b>Range (c)</b>                                        |                       |                        |                               |
| 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<sub>1</sub> MICE RECEIVING CORN OIL BY GAVAGE (a)**

|                                                                  | Adenoma                | Carcinoma              | Adenoma or Carcinoma   |
|------------------------------------------------------------------|------------------------|------------------------|------------------------|
| <b>Historical Incidence at EG&amp;G Mason Research Institute</b> |                        |                        |                        |
| 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                   |
| <b>TOTAL</b>                                                     | <b>12/199 (6.0%)</b>   | <b>3/199 (1.5%)</b>    | <b>15/199 (7.5%)</b>   |
| <b>SD (b)</b>                                                    | <b>3.27%</b>           | <b>1.91%</b>           | <b>4.42%</b>           |
| <b>Range (c)</b>                                                 |                        |                        |                        |
| High                                                             | 5/50                   | 2/50                   | 6/50                   |
| Low                                                              | 1/50                   | 0/50                   | 1/50                   |
| <b>Overall Historical Incidence</b>                              |                        |                        |                        |
| <b>TOTAL</b>                                                     | <b>36/1,103 (3.3%)</b> | <b>16/1,103 (1.5%)</b> | <b>52/1,103 (4.7%)</b> |
| <b>SD (b)</b>                                                    | <b>2.81%</b>           | <b>1.61%</b>           | <b>3.46%</b>           |
| <b>Range (c)</b>                                                 |                        |                        |                        |
| 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

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

### A. Lot No. F122277

#### 1. Physical Properties

|                   |                                                                                                      |                                   |
|-------------------|------------------------------------------------------------------------------------------------------|-----------------------------------|
| a. Boiling Point: | <u>Determined</u>                                                                                    | <u>Literature Values</u>          |
|                   | 118.5° C (visual<br>micro boiling point)<br>Endotherm 117°-120° C<br>(liquid DSC, Dupont<br>900 DTA) | 118°-122° C (Sax, 1975)           |
| b. Density:       | <u>Determined</u>                                                                                    | <u>Literature Values</u>          |
|                   | $d_{25}^{25}$ : 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 | <u>Determined</u>                           | <u>Literature Values</u>                                             |
| Instrument: | Beckman IR-12                               |                                                                      |
| Cell:       | Thin film between<br>silver chloride plates |                                                                      |
| Results:    | See Figure 5                                | Consistent with literature<br>spectrum (Sadtler Standard<br>Spectra) |

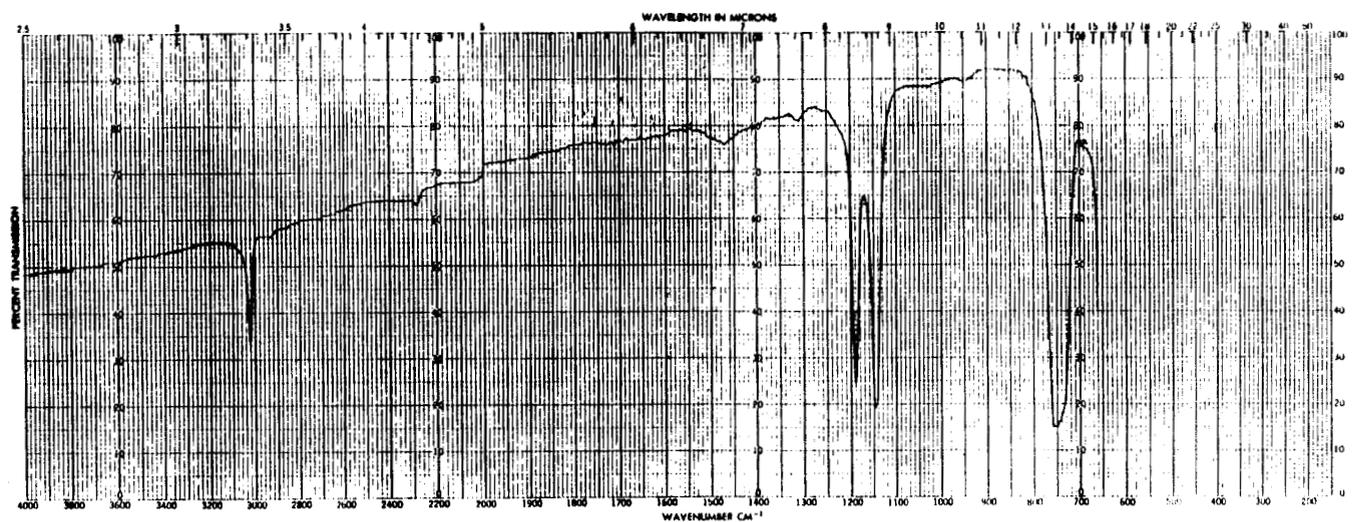


FIGURE 5. INFRARED ABSORPTION SPECTRUM OF CHLORODIBROMOMETHANE (LOT NO. F122277)

# APPENDIX G. CHEMICAL CHARACTERIZATION

| <b>b. Ultraviolet/Visible</b> | <b><u>Determined</u></b>                                                                                                                                                                                  | <b><u>Literature Values</u></b>                                    |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| <b>Instrument:</b>            | Cary 118                                                                                                                                                                                                  |                                                                    |
| <b>Solvent:</b>               | 95% Ethanol                                                                                                                                                                                               |                                                                    |
| <b>Results:</b>               | 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

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

## 3. Titration of Acidic Components with Sodium Hydroxide

a. Before cleanup:  $3,100 \pm 300$  ( $\delta$ ) ppm (as HBr)

b. After cleanup:  $147 \pm 18$  ( $\delta$ ) ppm (as HBr) (Both Br<sub>2</sub> and HBr will react with sodium hydroxide.)

## 4. Water Analysis (Karl Fischer):

$0.016\% \pm 0.006$  ( $\delta$ )%

## 5. Elemental Analysis:

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

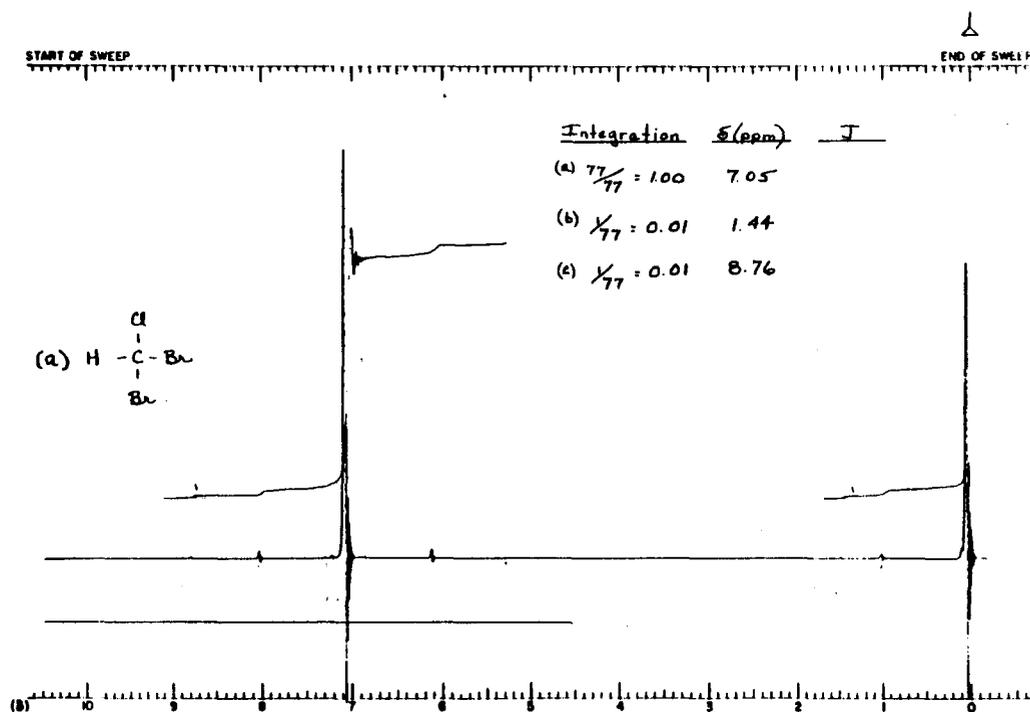


FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORODIBROMOMETHANE (LOT NO. F122277)

# APPENDIX G. CHEMICAL CHARACTERIZATION

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## 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.

| <u>Peak</u> | <u>Retention Time (min.)</u> | <u>Retention Time (relative to major peak)</u> | <u>Area (percent of major peak)</u> |
|-------------|------------------------------|------------------------------------------------|-------------------------------------|
| 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.

## APPENDIX G. CHEMICAL CHARACTERIZATION

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| <u>Peak</u> | <u>Retention Time (min.)</u> | <u>Retention Time (relative to major peak)</u> | <u>Area (percent of major peak)</u> |
|-------------|------------------------------|------------------------------------------------|-------------------------------------|
| 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  $\mu$ l) 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.

| <u>Peak</u>   | <u>Retention Time (min.)</u> | <u>Retention Time (relative to major peak)</u> | <u>Area (percent of major peak)</u> |
|---------------|------------------------------|------------------------------------------------|-------------------------------------|
| 1             | 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                                |

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# APPENDIX G. CHEMICAL CHARACTERIZATION

**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<sub>2</sub> 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  $3,100 \pm 300$  (δ) ppm to  $147 \pm 18$  (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

| <b>a. Infrared</b>            | <b><u>Determined</u></b>                                                                                                                                                           | <b><u>Literature Values</u></b>                                   |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| <b>Instrument:</b>            | Perkin Elmer 283                                                                                                                                                                   |                                                                   |
| <b>Cell:</b>                  | Thin film between silver chloride plates                                                                                                                                           |                                                                   |
| <b>Results:</b>               | See Figure 7                                                                                                                                                                       | Consistent with literature spectrum (Sadler Standard Spectra)     |
| <b>b. Ultraviolet/Visible</b> | <b><u>Determined</u></b>                                                                                                                                                           | <b><u>Literature Values</u></b>                                   |
| <b>Instrument:</b>            | Cary 219                                                                                                                                                                           |                                                                   |
| <b>Solvent:</b>               | Ethanol                                                                                                                                                                            |                                                                   |
| <b>Results:</b>               | $\lambda_{\max}$ (nm) $\epsilon \times 10^{-2}$                                                                                                                                    |                                                                   |
|                               | 242 (shoulder) $5.03 \pm 0.04$ (δ)<br>(Observed but not reported for Lot No. F122277)<br>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 |

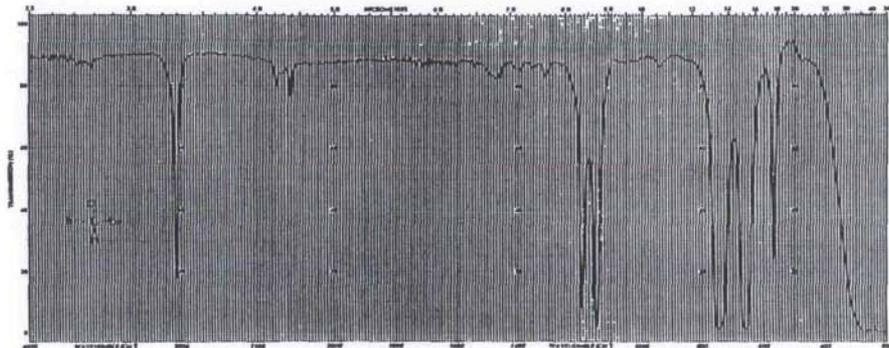


FIGURE 7. INFRARED ABSORPTION SPECTRUM OF CHLORODIBROMOMETHANE (LOT NO. F810626)

# APPENDIX G. CHEMICAL CHARACTERIZATION

## c. Nuclear Magnetic Resonance

|                     | <u>Determined</u>                                      | <u>Literature Values</u>                                      |
|---------------------|--------------------------------------------------------|---------------------------------------------------------------|
| Assignments:        | See Figure 8                                           | Consistent with literature spectrum (Sadler Standard Spectra) |
| Solvent:            | Chloroform-d <sub>1</sub> containing tetramethylsilane |                                                               |
| Chemical Shift (δ): | a s, 7.00<br>b 1.53, impurity                          |                                                               |
| Integration Ratios: | a 1.00<br>b <0.01                                      |                                                               |

## 3. Titration of Acidic Components with 0.01N Sodium Hydroxide

118 ± 13 (δ) ppm (as HBr) (Both Br<sub>2</sub> 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<br>5.65 | 0.48<br>0.51 | 73.87<br>73.67 | 16.16<br>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.

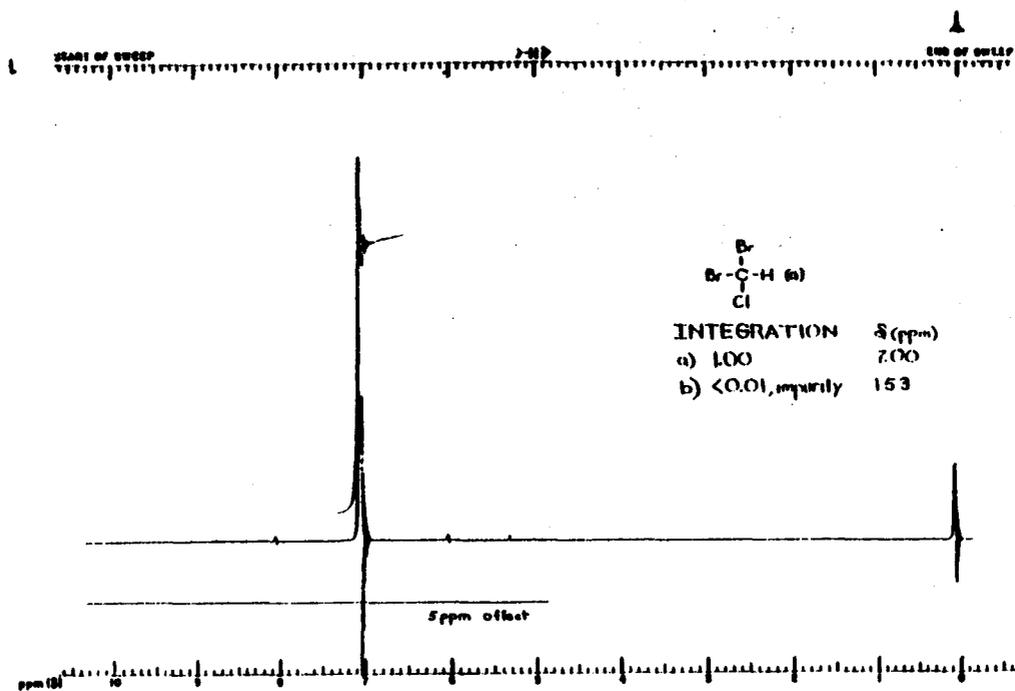


FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF CHLORODIBROMOMETHANE (LOT NO. F810626)

## APPENDIX G. CHEMICAL CHARACTERIZATION

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| <u>Peak</u> | <u>Retention Time (min.)</u> | <u>Retention Time (relative to major peak)</u> | <u>Area (percent of major peak)</u> |
|-------------|------------------------------|------------------------------------------------|-------------------------------------|
| 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                                |

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### 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.

| <u>Peak</u> | <u>Retention Time (min.)</u> | <u>Retention Time (relative to major peak)</u> | <u>Area (percent of major peak)</u> |
|-------------|------------------------------|------------------------------------------------|-------------------------------------|
| 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  $118 \pm 13$  (6) 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.

# APPENDIX G. CHEMICAL CHARACTERIZATION

## 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)

| <u>Peak</u> | <u>Retention Time (min.)</u> | <u>Retention Time (relative to major peak)</u> |
|-------------|------------------------------|------------------------------------------------|
| 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-<br>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-<br>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-<br>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                   | C Cl <sup>+</sup>                 |
| 79             | 19                   | Br <sup>+</sup>                   |
| 91             | 14                   | C Br <sup>+</sup>                 |
| 128            | 32                   | C Br Cl <sup>+</sup>              |
| 160            | 4                    | Br <sub>2</sub> <sup>+</sup>      |
| 172            | 11                   | C Br <sub>2</sub> <sup>+</sup>    |
| (a) 209        | 100                  | C Cl Br <sub>2</sub> <sup>+</sup> |
| 251            | 10                   | C Br <sub>3</sub> <sup>+</sup>    |
| (b) 288        | 0.4                  | C Cl Br <sub>3</sub> <sup>+</sup> |

(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.

# APPENDIX G. CHEMICAL CHARACTERIZATION

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## 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.

| <u>Storage Temperature</u> | <u>Percent Chlorodibromomethane</u> |
|----------------------------|-------------------------------------|
| -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.)

# APPENDIX G. CHEMICAL CHARACTERIZATION

## IV. Test Chemical Stability Study Performed by the Testing Laboratory

### A. Lot No. F122277

#### 1. Storage Conditions:

Bulk chemical:  $0^{\circ} \pm 5^{\circ} \text{C}$  under nitrogen  
Reference sample:  $-18^{\circ} \pm 7^{\circ} \text{C}$

#### 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  $\times$  2 mm ID, glass  
Detector: Flame ionization  
Detector temperature:  $190^{\circ}$ - $260^{\circ} \text{C}$   
Inlet temperature:  $175^{\circ}$ - $190^{\circ} \text{C}$   
Temperature program:  $50^{\circ} \text{C}$  for 5 min, then  $50^{\circ}$ - $170^{\circ} \text{C}$  at  $6^{\circ} \text{C}/\text{min}$

##### 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.

# APPENDIX G. CHEMICAL CHARACTERIZATION

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## B. Lot No. F810626

### 1. Storage Conditions:

Bulk chemical:  $0^{\circ} \pm 5^{\circ} \text{C}$   
Reference sample:  $-20^{\circ} \text{C}$

### 2. Analytical Methods

#### a. Gas Chromatography:

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

#### 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

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## I. Studies Conducted at the Analytical Chemistry Laboratory

**A. Sample Preparation and Storage:** Chlorodibromomethane ( $10.191 \pm 0.001$  grams) was placed in a 50-ml volumetric flask and diluted to the volume mark with corn oil ( $42.355 \pm 0.001$  g) with periodic manual shaking. The chemical dissolved readily to give a concentration of  $193.94 \pm 0.02$  mg/g of solution ( $19.394\% \pm 0.002\%$ , 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  $0.5485 \pm 0.0001$  g of *n*-amyl alcohol, transferring to a 1-liter volumetric flask, and diluting to the mark with absolute methanol. Concentration of reference standard:  $0.5485 \pm 0.0002$  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  $\mu$ l
8. **Retention times:**
  - a. Test chemical, 6.6 min
  - b. Reference standard, 5.1 min

# APPENDIX H. PREPARATION AND CHARACTERIZATION

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## C. Results:

| <u>Storage Time (days)</u> | <u>Average Percent<br/>Chemical Found in<br/>Chemical/Vehicle Mixture (a) (b)</u> |
|----------------------------|-----------------------------------------------------------------------------------|
| 1                          | (c) $20.1 \pm 0.3$                                                                |
| 5                          | $19.9 \pm 0.3$                                                                    |
| 7                          | $19.3 \pm 0.3$                                                                    |

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(a) Zero-time recovery yield,  $90\% \pm 1\%$

(b) Theoretical concentration of chemical in corn oil,  $19.394\% \pm 0.002\%$  (w/w)

(c) Mean  $\pm$  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

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## 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**

# APPENDIX J. ANALYSES: DATA

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## 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<br>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.

# APPENDIX J. ANALYSES: DATA

## 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<br>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<br>(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

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## 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<sub>1</sub> 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:

|      | <u>Hemagglutination<br/>Inhibition</u>                                                                                                                                                                    | <u>Complement<br/>Fixation</u>                                          | <u>ELISA</u>                   |
|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|--------------------------------|
| Mice | PVM (pneumonia virus of mice)<br>Reo 3 (reovirus type 3)<br>GDVII (Theiler's<br>encephalomyelitis virus)<br>Poly (polyoma virus)<br>MVM (minute virus of mice)<br>Ectro (infectious ectromelia)<br>Sendai | M.Ad. (mouse adenovirus)<br>LCM (lymphocytic<br>choriomeningitis virus) | MHV (mouse<br>hepatitis virus) |
| Rats | PVM<br>KRV (Kilham rat virus)<br>H-1 (Toolan's H-1 virus)<br>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 |
|-------------|----------------|---------------------------------|
| <b>RATS</b> |                |                                 |
| 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                             |
| <b>MICE</b> |                |                                 |
| 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<br>( $\mu\text{g}/\text{plate}$ ) | Revertants/plate (a) |                |                |
|---------|----------------------------------------|----------------------|----------------|----------------|
|         |                                        | -S9                  | +S9 (rat)      | +S9 (hamster)  |
| TA 100  | 0                                      | 126 $\pm$ 8.0        | 218 $\pm$ 18.0 | 199 $\pm$ 21.1 |
|         | 100                                    | 142 $\pm$ 3.1        | 192 $\pm$ 9.4  | 175 $\pm$ 5.0  |
|         | 333                                    | 139 $\pm$ 3.2        | 219 $\pm$ 5.8  | 176 $\pm$ 6.4  |
|         | 1,000                                  | 125 $\pm$ 12.4       | 138 $\pm$ 19.5 | 0 $\pm$ 0.0    |
|         | 3,333                                  | 0 $\pm$ 0.0          | 0 $\pm$ 0.0    | 0 $\pm$ 0.0    |
|         | 10,000                                 | 0 $\pm$ 0.0          | 0 $\pm$ 0.0    | 0 $\pm$ 0.0    |
| TA 1535 | 0                                      | 5 $\pm$ 1.2          | 9 $\pm$ 2.7    | 9 $\pm$ 1.5    |
|         | 100                                    | 4 $\pm$ 1.8          | 6 $\pm$ 1.2    | 4 $\pm$ 0.3    |
|         | 333                                    | 3 $\pm$ 0.3          | 2 $\pm$ 0.7    | 6 $\pm$ 0.9    |
|         | 1,000                                  | 5 $\pm$ 0.9          | 4 $\pm$ 0.6    | 7 $\pm$ 1.0    |
|         | 3,333                                  | 5 $\pm$ 1.5          | 1 $\pm$ 0.3    | 0 $\pm$ 0.0    |
|         | 10,000                                 | 3 $\pm$ 0.3          | 0 $\pm$ 0.3    | 0 $\pm$ 0.0    |
| TA 1537 | 0                                      | 5 $\pm$ 0.7          | 17 $\pm$ 5.2   | 11 $\pm$ 0.9   |
|         | 100                                    | 4 $\pm$ 0.3          | 14 $\pm$ 1.2   | 11 $\pm$ 3.2   |
|         | 333                                    | 7 $\pm$ 0.9          | 9 $\pm$ 2.3    | 9 $\pm$ 0.3    |
|         | 1,000                                  | 10 $\pm$ 0.3         | 5 $\pm$ 0.7    | 3 $\pm$ 0.6    |
|         | 3,333                                  | 8 $\pm$ 0.3          | 0 $\pm$ 0.0    | 0 $\pm$ 0.0    |
|         | 10,000                                 | 0 $\pm$ 0.0          | 0 $\pm$ 0.0    | 0 $\pm$ 0.0    |
| TA 98   | 0                                      | 19 $\pm$ 2.0         | 22 $\pm$ 1.2   | 20 $\pm$ 1.2   |
|         | 100                                    | 16 $\pm$ 1.2         | 17 $\pm$ 1.2   | 25 $\pm$ 4.1   |
|         | 333                                    | 20 $\pm$ 1.3         | 21 $\pm$ 2.3   | 11 $\pm$ 2.3   |
|         | 1,000                                  | 17 $\pm$ 2.4         | 11 $\pm$ 0.3   | 14 $\pm$ 2.0   |
|         | 3,333                                  | 14 $\pm$ 0.5         | 1 $\pm$ 0.3    | 0 $\pm$ 0.0    |
|         | 10,000                                 | 0 $\pm$ 0.0          | 0 $\pm$ 0.0    | 0 $\pm$ 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

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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.