NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 239

# CARCINOGENESIS BIOASSAY OF BIS(2-CHLORO-1-METHYLETHYL) ETHER (~70%)

(CAS NO. 108-60-1)

# CONTAINING 2-CHLORO-1-METHYLETHYL-(2-CHLOROPROPYL) ETHER (~30%)

(CAS NO. 83270-31-9)

# IN B6C3F1 MICE (GAVAGE STUDY)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Services
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 chemically induced 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 comprised of four charter DHHS agencies: the National Cancer Institute, National Institutes of Health; the National Institute of Environmental Health Sciences, National Institutes of Health; the National Center for Toxicological Research, Food and Drug Administration; and the National Institute for Occupational Safety and Health, Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

NTP TECHNICAL REPORT
ON THE

# CARCINOGENESIS BIOASSAY OF BIS(2-CHLORO-1-METHYLETHYL) ETHER (~70%) (CAS NO. 108-60-1) CONTAINING 2-CHLORO-1-METHYLETHYL(2-CHLOROPROPYL) ETHER (~30%) (CAS NO. 83270-31-9) IN B6C3F$_1$ MICE (GAVAGE STUDY)


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**December 1982**

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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## NOTE TO THE READER

This is one in a series of experiments designed to determine whether selected chemicals produce cancer in animals. Chemicals selected for testing in the NTP carcinogenesis bioassay 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 is a potential 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.

This study was initiated by the National Cancer Institute's Carcinogenesis Testing Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program.

Comments and questions about the National Toxicology Program Technical Reports on Carcinogenesis Bioassays should be directed to the National Toxicology Program, located at Room 3A-06, Landow Building, Bethesda, MD 20205 (301-496-1152) or at Research Triangle Park, NC 27709 (919-541-3991).

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to communicate any mistakes to the Deputy Director, NTP (P.O. Box 12233, Research Triangle Park, NC 27709), 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.

These NTP Technical Reports are available for sale from the National Technical Information Services, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650).

Single copies of this carcinogenesis bioassay technical report are available without charge (and while supplies last) from the NTP Public Information Office, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709.

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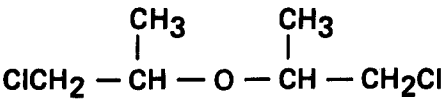
# CARCINOGENESIS BIOASSAY OF BIS(2-CHLORO-1-METHYLETHYL) ETHER

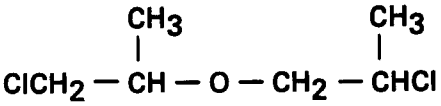


BIS(2-CHLORO-1-METHYLETHYL) ETHER

CAS NO. 108-60-1

$C_6H_{12}Cl_2O$ Mol. Wt. 171.07

(70%)



2-CHLORO-1-METHYLETHYL (2-CHLOROPROPYL) ETHER

CAS NO. 83270-31-9

$C_6H_{12}Cl_2O$ Mol. Wt. 171.07

(30%)

## ABSTRACT


A carcinogenesis bioassay of bis(2-chloro-1-methylethyl)ether (~70%), containing ~30% 2-chloro-1-methylethyl(2-chloropropyl) ether, was conducted by administering 100 or 200 mg/kg bis(2-chloro-1-methylethyl) ether in corn oil by gavage 5 times per week for 103 weeks to groups of 50 $B6C3F_1$ mice of each sex. Fifty mice of each sex received corn oil alone and served as vehicle controls. Survival and mean body weights of dosed and control mice of each sex were comparable.

The incidence of alveolar/bronchiolar adenomas occurred in a positive dose-related trend for male mice ($P<0.05$: control 5/50, 10%; low-dose 13/50, 26%; high-dose 11/50, 22%) and for female mice ($P<0.02$: 1/50, 2%; 4/50, 8%; 8/50, 16%). The number of female mice in the high-dose group with adenomas was significantly ($P<0.03$) greater than that in controls. The combined incidence of alveolar/bronchiolar adenomas or carcinomas was statistically significant in the life table and incidental tumor trend tests ($P<0.05$ for males and $P<0.01$ for females). The combined incidences in dosed males and in high-dose females were significantly higher ($P\leq0.04$ for males and $P\leq0.01$ for females) than those in the controls (males: 6/50, 12%; 15/50, 30%; 13/50, 26%; females: 1/50, 2%; 4/50, 8%; 10/50, 20%).

The incidence of hepatocellular carcinomas (5/50, 10%; 13/50, 26%; 17/50, 34%) and the combined incidence of hepatocellular adenomas and carcinomas (13/50, 26%, 23/50, 46%, 27/50, 54%) in male mice were statistically significant by the trend tests ($P<0.01$) and the incidences in the high-dose group were significantly higher than those in the controls ($P<0.01$). Metastases to the lung occurred in 1/50 control, 4/50 low-dose, 3/50 high-dose male mice. Fatty metamorphosis was found in increased incidence in the livers of dosed male mice (control 2/50; 16/50 low-dose; 15/50 high-dose).

Squamous cell papillomas were found in the stomach or forestomach in two high-dose females, one low-dose male, and one high-dose male. A squamous cell carcinoma was found in the forestomach of a third high-dose female. These tumors were probably related to administration of the test compound, since they are rarely observed in vehicle control and untreated control $B6C3F_1$ mice.

Under the conditions of this bioassay, bis(2-chloro-1-methylethyl)ether—containing 2-chloro-1-methylethyl(2-chloropropyl) ether—was carcinogenic for $B6C3F_1$ mice, causing increased incidences of alveolar/bronchiolar adenomas in males and females and hepatocellular carcinomas in males. In addition, the occurrence of a low incidence of squamous cell papillomas or carcinomas in the stomach or forestomach of females (a rare tumor in $B6C3F_1$ mice) was probably associated with the administration of bis(2-chloro-1-methylethyl) ether.

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The prechronic studies were conducted at Hazleton Laboratories (Dr. Marcelina B. Powers, Principal Investigator), 9200 Leesburg Turnpike, Vienna, Virginia 22180, under a subcontract from Tracor Jitco. The chronic bioassay of bis(2-chloro-1-methylethyl) ether was conducted at EG&G Mason Research Institute, under a subcontract to Tracor Jitco, Inc., the prime contractor for the Carcinogenesis Testing Program. The chronic study was begun in July 1978 and completed in July 1980.


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The chemicals used in this bioassay of bis(2-chloro-1-methylethyl) ether were analyzed by the Midwest Research Institute, 425 Volker Blvd., Kansas City, Missouri 64110; reanalysis of the bulk chemical and analysis of chemical/vehicle mixtures were performed at EG&G Mason Research Institute.

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# SUMMARY OF PEER REVIEW COMMENTS ON THE BIOASSAY OF BIS(2-CHLORO-1-METHYLETHYL) ETHER

On December 16, 1981 this report underwent 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 Conference Room A, Landow Building, 7910 Woodmont Avenue, Bethesda, Maryland.

Dr. Highland, a principal reviewer for the report on the bioassay of bis(2-chloro-1-methylethyl) ether (BCMEE), agreed that BCMEE was carcinogenic for B6C3F$_1$ mice, causing increased incidences of alveolar/bronchiolar adenomas in males and females and of hepatocellular carcinomas in males. The remainder of the conclusions stated that "In addition, the occurrence of a low incidence of squamous cell papillomas or carcinomas in the stomach or forestomach of males and females (a rare tumor in B6C3F$_1$ mice) may have been related to the administration of bis(2-chloro-1-methylethyl) ether." Dr. Highland proposed that, because the observed stomach tumors are rare, they should be considered as being induced by BCMEE. Dr. Haseman, NTP, said that if historical control rates were used as a basis for comparison, the incidence observed in high-dose female mice would likely be statistically significant because of the low historic background rate (1/362, 0.3%, versus 3/49, 6%, $P<0.006$).

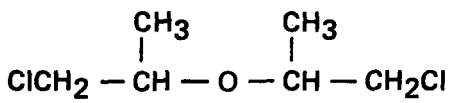
As a second principal reviewer, Dr. Scala found the conclusion in the report consistent with the data and the analysis presented. He expressed concern about the observed temperature fluctuation of 15.6° to 30.6° C and wondered about the possible impact this may have on the overall conclusions. (Table 1 in the report presents the details relating to temperature.)

Dr. Mirer suggested that, since the test chemical is a mixture containing BCMEE with 26%-29% 2-chloro-1-methylethyl (2-chloropropyl) ether, this should be indicated in the report title, and discussion of the metabolism of the impurity should be considered. (No literature was found on the impurity.)

Dr. Highland moved that the bioassay report on bis(2-chloro-1-methylethyl) ether be accepted after the incorporation of the changes agreed upon and other minor corrections. The motion was seconded and the report was approved unanimously by the Peer Review Panel.

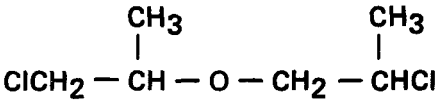
# I. INTRODUCTION

# I. INTRODUCTION



**BIS(2-CHLORO-1-METHYLETHYL) ETHER**

**CAS NO. 108-60-1**
**$C_6H_{12}Cl_2O$ Mol. Wt. 171.07**
**(70%)**



**2-CHLORO-1-METHYLETHYL (2-CHLOROPROPYL) ETHER**

**CAS NO. 83270-31-9**
**$C_6H_{12}Cl_2O$ Mol. Wt. 171.07**
**(30%)**

Bis(2-chloro-1-methylethyl) ether (BCMEE), also known as bis(2-chloroisopropyl) ether (BCPE), is a beta-haloether that has been used extensively in paint and varnish removers, spotting agents, and cleaning solutions (Hake and Rowe, 1963). BCMEE has also been used as an intermediate in the manufacture of dyes, resins, and pharmaceuticals and has been added to soap solutions to aid in textile cleaning (Hake and Rowe, 1963). Bis(2-chloro-1-methylethyl) ether has been a by-product in the manufacture of propylene oxide (Lapkin, 1965) and propylene glycol (Cook, 1971). It is the active ingredient of a nematocide developed and used on field crops in Japan (Mitsumori et al., 1979).

Bis(2-chloro-1-methylethyl) ether has been found in effluent from industrial plants, in raw intake water downstream from these plants, and in tap water from the Ohio River in Evansville, Indiana (Kleopfer and Fairless, 1972). In 1971, concentrations of bis(2-chloro-1-methylethyl) ether ranging from 0.5 to 5 $\mu$g/liter were detected in the Ohio River at Evansville and 0.8 $\mu$g/liter was found in the Evansville tap water. Bis(2-chloro-1-methylethyl) ether has been found in the Kanawha River at Nitro, West Virginia (Rosen et al., 1963), in the Mississippi River at New Orleans (Mayes, 1971), and in the Rhine and Scheldt Rivers in The Netherlands (Piet et al., 1973). The chemical is stable in aqueous media (Fishbein, 1979) and nonbiodegradable in river water (Kleopfer and Fairless, 1972).

Production of bis(2-chloro-1-methylethyl) ether in the United States was estimated at over 30 million pounds in 1975, approximately one million pounds being lost in waste water during the production process (Fishbein, 1979). Production of the chemical subsequently declined; five former manufacturers or distributors contacted in 1978 stated that they no longer carried the chemical for commercial use.* One manufacturer stated that the process for manufacturing propylene oxide had been changed to eliminate bis(2-chloro-1-methylethyl) ether as a by-product.** Current production figures are not available, but at least 5,000 pounds of bis(2-chloro-1-methylethyl) ether were produced in 1979 (USITC, 1980).

An acute oral $LD_{50}$ value of 240 mg/kg has been reported for rats of unspecified strain and sex administered bis(2-chloro-1-methylethyl) ether (Smyth et al., 1951). Single doses administered by gavage produced no deaths in F344/N rats receiving 316 mg/kg and deaths of 2/2 male and 1/2 female rats receiving 1,000 mg/kg (NCI, 1979); gavage doses of 250 mg/kg produced no deaths when administered to male and female F344/N rats 5 times per week for 13 weeks (NCI, 1979)***.

Following gavage administration of $^{14}$C-bis (2-choloro-1-methylethyl) ether, the half-life of radioactivity in the blood of female CD rats was approximately two days (Smith et al., 1977).

*Jameson, C.W., Personal communications from Dow, I.C.N. Industries, Pfaltz and Bauer, Mathison, Coleman and Bell, and Biddle Corp., 1978.

**Dow Chemical Co., Personal communication, 1978.

***Hazleton Laboratories Final Report: Range-Finding Test of Bis(2-chloroisopropyl) Ether in F344 rats. February 3, 1975.

Seven days after intraperitoneal injection of 30 mg/kg to the same strain, 63% was excreted in the urine, 6.0% in the feces, and 16% in expired air, and the rest was distributed among various organs and tissues, including the adrenals, pancreas, ovaries, fat, liver, lungs, kidneys, bladder, spleen, heart, stomach, intestines, thymus, skin, brain, and muscle. Rats of this strain administered bis(2-chloro-1-methylethyl) ether excrete the chemical in the bile and reabsorb it via the intestines (Smith et al., 1977). 1-Chloro-2-propanol (0.1 - 1.0% of the administered dose), propylene oxide (not quantitated), and 2(1-methyl-2-chloroethoxy) propionic acid (not quantitated) were identified as metabolites in the urine of animals in these studies.

Bis(2-chloro-1-methylethyl) ether was not carcinogenic for male or female F344/N rats administered 100 or 200 mg/kg by gavage 5 days per week for 103 weeks (NCI, 1979) or for ICR mice of either sex fed diets containing 0, 80, 400, 2,000,* or 10,000 ppm for 104 weeks (Mitsumori et al., 1979). Esophageal hyperkeratosis and acanthosis were observed at an increased incidence in male and female F344/N rats administered 200 mg/kg bis(2-chloro-1-methylethyl) ether by gavage for 103 weeks (NCI, 1979).

The beta-haloether, bis(2-chloroethyl) ether, a structural analog of bis(2-chloro-1-methylethyl) ether, caused increased incidences of hepatomas in 7-day-old male and female B6C3F$_1$ mice and male B6AKF$_1$ mice that received 100 mg/kg per day by gavage for 21 days and were then fed diets containing 300 ppm for 76 weeks (Innes et al., 1969; NTIS, 1968).

The alpha-haloether, bis(chloromethyl) ether, produced sarcomas at the injection site in female ICR/Ha Swiss mice (Van Duuren et al., 1972), lung adenomas in subcutaneously injected newborn ICR Swiss mice (Gargus et al., 1969), lung squamous-cell carcinomas and olfactory esthesioneuroepitheliomas in Sprague-Dawley rats inhaling the vapors (Laskin et al., 1971), and fibrosarcomas in subcutaneously injected female Sprague-Dawley rats (Van Duuren et al., 1968).

The incidence of lung cancer in workers exposed to chloromethyl methyl ether and its associated impurity, bis(chloromethyl) ether, in a chemical manufacturing plant was eight times higher than that expected (Figueroa et al., 1973; IARC, 1974a and b). Of 14 men (33 to 55 years old) in whom lung cancer developed, 13 were confirmed histologically and 12 of these had oat cell carcinoma. The duration of exposure ranged from 3 to 14 years. A total of 34 incidences of lung cancer have been associated with occupational exposure to these two chemicals in the United States (Nelson, 1976; IARC, 1974a and b).

Bis(2-chloro-1-methylethyl) ether was mutagenic for *Salmonella typhimurium* TA100 without metabolic activation. Incubation with rat or human liver microsomes enhanced its mutagenicity (Simmon et al., 1977). Results of the *Salmonella* assay conducted by the National Toxicology Program on the chemical were inconclusive.

BCMEE caused chromosome aberrations and sister chromatid exchanges in the *in vitro* cytogenetics test using Chinese hamster ovary (CHO) cells (NTP unpublished results).

The Bioassay Program tested bis(2-chloro-1-methylethyl) ether because of occupational exposure and because its chemical structure is closely related to the structures of carcinogenic haloethers, which have been associated with lung cancer in humans.

*The 2,000 ppm dose level is roughly equivalent to a dose of 190 mg/kg body weight.

# II. MATERIALS AND METHODS

## CHEMICAL ANALYSIS

## PRECHRONIC STUDIES

### Single-Dose Study

### Fourteen-Day Study

### Thirteen-Week Study

## CHRONIC STUDY

### Study Design

### Dosage Preparation

### Clinical Examinations and Pathology

### Data Recording and Statistical Methods

## CHEMICAL ANALYSIS

Bis(2-chloro-1-methylethyl) ether, also known as bis(2-chloroisopropyl) ether, was obtained in three batches from three different sources. The first batch (Lot No. 7), obtained from MC&B Manufacturing Chemists (Cincinnati, OH), was used during the prechronic studies and part of the chronic rat study at Hazleton Laboratories. The second batch (Lot No. I62976) was obtained from I.C.N. Pharmaceuticals, Inc. (Irvine, CA) and was used for the earlier rat study and first 94 weeks of this chronic mouse study. The third batch (Lot No. A2279) was obtained from Aldrich Chemical Co. (Milwaukee, WI) and was used for the final 9 weeks of the chronic study.

Analysis of each batch at Midwest Research Institute included elemental analysis, vapor-phase chromatography, and infrared and nuclear magnetic resonance spectroscopy (Appendix C). The results indicated that each batch was a mixture of isopropyl and n-propyl ethers. Additional analysis by vapor-phase chromatography/mass spectrometry at Midwest Research Institute on Lot No. I62976 indicated that the material contained 69.4% bis(2-chloro-1-methylethyl) ether, 2.1% bis(2-chloropropyl) ether, and 28.5% of the mixed iosmer 2-chloro-1-methylethyl (2-chloropropyl) ether. Lot No. A2279 contained 71.5% bis(2-chloro-1-methylethyl) ether, 2.6% bis(2-chloro-n-propyl) ether, and 26% of the mixed isomer. The isomer distribution was not checked in Lot No. 7. These results were consistent with the amounts of the isomers estimated in each batch by nuclear magnetic resonance spectroscopy. The mixture of bis(2-chloro-1-methylethyl) ether and its isomers administered to the animals in this study will be referred to in this report as bis(2-chloro-1-methylethyl) ether.

Each lot of the bulk chemical was stored under refrigeration (0° ± 5°C) at EG&G Mason Research Institute throughout the study. Analyses of the bulk material and of a reference stored at -18° ± 7°C were conducted periodically by Mason using infrared and gas-liquid chromatography (System 3 for Lots I62976 and A2279). Results of the analyses indicated no change in composition of the chemical while on test.

When formulated in corn oil at a concentration of 20 mg/ml, bis(2-chloro-1-methylethyl) ether was found to be stable for at least 14 days at 5°C (Appendix D). The dose mixtures were prepared at Mason as indicated in Table 1. Periodic analysis of these formulations indicated that only 1 of the 23 formulations analyzed was ± 10% out of agreement with specifications. The results of the analyses are listed in Appendix E. Four of the formulations analyzed by Mason were sent to Midwest Research Institute for referee analyses. The results of these referee analyses confirmed that dose mixtures were at proper concentrations.

## PRECHRONIC STUDIES

### Single-Dose Study

Groups of two B6C3F$_1$ mice of each sex were administered single doses (10, 31.6, 100, 316, or 1,000 mg/kg) of bis(2-chloro-1-methylethyl) ether in corn oil by gavage, observed for 14 days, and then killed. No controls were used. Necropsies were performed on all animals. Animals were approximately 5 weeks old when the study began (Table 1).

### Fourteen-Day Study

Groups of five male and five female mice were administered bis(2-chloro-1-methylethyl) ether (17.8, 31.6, 56.2, 100, 178, 316, or 562 mg/kg) in corn oil by gavage for 14 consecutive days. No controls were used. The mice were observed daily for mortality and were weighed on days 0, 7, and 14. Necropsies were performed on all animals. The animals were approximately 8 weeks old when the study began (Table 1).

## Thirteen-Week Study

Thirteen-week studies were conducted to evaluate the cumulative toxicity of bis(2-chloro-1-methylethyl) ether and to determine the doses to be used in the chronic studies.

Three- to four-week-old male and female mice were observed for 2-3 weeks 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. Groups of 10 mice of each sex received 0, 10, 25, 50, 100, or 250 mg/kg bis(2-chloro-1-methylethyl) ether in corn oil by gavage 7 days per week for 13 weeks.

Each animal was checked daily for mortality and signs of morbidity and observed weekly for clinical signs, including palpation for tissue masses or swelling. Body weight data were collected weekly (Table 1).

At the end of the 13-week study (within 3 days after the last dose), survivors were killed by exsanguination after anesthetization with sodium pentobarbital and necropsies were performed on all animals. The following tissues were examined for control and high-dose groups: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, bone marrow, sternebrae, femur, or vertebrae, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, liver, pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/ prostate/testes or ovaries/ uterus, brain, and pituitary. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin.

# CHRONIC STUDY

## Study Design

Five-week-old male and female B6C3F$_1$ mice were obtained from Harlan Industries (Indianapolis, IN), observed for 20 days, and assigned to cages according to a table of random numbers. The cages were then assigned to control and dosed groups according to another table of random numbers.

Groups of 50 mice of each sex were administered 100 or 200 mg/kg bis(2-chloro-1-methylethyl) ether in corn oil by gavage 5 days per week for 103 weeks. Fifty mice of each sex received corn oil alone and served as vehicle controls. All mice were housed in the same room, and no other chemicals were on test in that room (Table 1).

## Dosage Preparation

Dosage mixtures of bis(2-chloro-1-methylethyl) ether were prepared once per week. The chemical was first dissolved completely in a small amount of corn oil, and this stock solution was then diluted with additional corn oil to the desired final volume. The concentrations prepared were based on the ratio of the weight of the chemical to the volume of corn oil. Mice were administered 5 ml of solution per kilogram of body weight.

## Clinical Examinations and Pathology

All animals were observed twice daily for morbidity or mortality. Clinical signs were recorded monthly. Body weights were recorded weekly for the first 13 weeks and monthly thereafter. The mean body weight of each group was calculated by dividing the total weight of all animals in the group by the number of surviving animals in the group. Moribund animals and animals that survived to the end of the bioassay were killed with carbon dioxide and necropsied.

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. The following tissues were examined microscopically: tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, bone marrow, costochondral junction (rib), thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder, pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/ prostate/testes or ovaries/uterus, brain, and

pituitary. In addition, sections of the nasal turbinates were examined in all high-dose male mice.

Necropsies were also performed on all animals found dead unless precluded by autolysis or cannibalization. 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.

The individual animal data record (IADR) individual animal tumor pathology, pathology summary tables, and microscopic slides were sent to a quality assurance laboratory, where tabular data were checked against the IADR, tissues and slides were counted, and slides were evaluated for histotechnic quality.

The pathology summary tables were used to determine target tissues, and all target tissues and all tumor diagnoses were reviewed by pathologists at the quality assurance laboratory.

A slide set was generated consisting of all target tissues and all discrepancies between the original and the reviewing pathologists' tumor diagnoses. The quality assurance report and this slide set were reviewed by a Pathology Working Group (PWG) as described by Ward et al. (1978). Specifically, the PWG consisted of pathologists who reviewed and reached a consensus on diagnostic discrepancies. Where a difference of opinion existed between the original pathologist and the PWG pathologists, the slides and PWG comments were returned to the original pathologist for review. IADRs were updated as appropriate. The diagnoses in this report represent a consensus of the contracting pathologists and the NTP Pathology Working Group.

## Data Recording and Statistical Methods

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, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically 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) extensions of Cox's methods for testing for a dose-related trend.

The incidence of neoplastic or nonneoplastic lesions has been 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 that 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 numbers of animals necropsied.

For the statistical analysis of tumor incidence data, two different methods of adjusting for intercurrent mortality were employed. Each used the classical methods for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of the high- and low-dose groups with controls, as well as tests for overall dose-response trends.

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

The second method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "incidental"; i.e., they were merely observed at autopsy in animals dying of an unrelated cause. According to this approach, the proportions of animals found to have tumors in dosed and control groups were compared in each of five time intervals: 0-52 weeks, 53-78 weeks, 79-92 weeks, week

93 to the week before the terminal kill, and the terminal kill period. The denominators of these proportions were the number of animals actually autopsied during the time interval. The individual time interval comparisons were then combined by the previously described methods to obtain a single overall result (see Peto et al., 1980, for the computational details of both methods).

In addition to these tests, one other set of statistical analyses was carried out and reported in the tables analyzing primary tumors: the Fisher's exact test for pairwise comparisons and the Cochran-Armitage linear trend test for dose-response trends (Armitage, 1971; Gart et al., 1979). These tests were based on the overall proportion of tumor-bearing animals. All reported P values are one-sided.

For studies in which compound administration had 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.

**TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS**

| | Single-Dose | 14-Day Study | 13-Week Study | Chronic Study |
|---|---|---|---|---|
| **Experimental Design** | | | | |
| Size of Test Groups | 2 males and 2 females | 5 males and 5 females | 10 males and 10 females | 50 males and 50 females |
| Doses | 10, 31.6, 100, 316, or 1,000 mg/kg body weight bis(2-chloro-1-methylethyl) ether in corn oil | 17.8, 31.6, 56.2, 100, 178, 316, or 562 mg/kg body weight bis(2-chloro-1-methyl-ethyl) ether in corn oil | 0, 10, 25, 50, 100, or 250 mg/kg body weight in bis(2-chloro-1-methylethyl) ether in corn oil (Duke's®); each animal received 10 ml/kg body weight | 0, 100, or 200 mg/kg body weight bis(2-chloro-1-methylethyl) ether in corn oil (Mazola®); each animal received 5 ml/kg body weight |
| Duration of Dosing | Single dose | 14 successive days | 7 days per week for 13 weeks | 5 days per week for 103 weeks; killed weeks 104-110 |
| Type and Frequency of Observation | Daily for mortality | Daily for mortality; weighed on days 0, 7, and 14 | Daily for mortality or morbidity; body weight data collected weekly | Twice daily for mortality or morbidity; clinical signs recorded monthly; body weight recorded weekly for the first 13 weeks and monthly thereafter |
| Necropsy and Histologic Examination | Necropsies were performed on all animals | Necropsies were performed on all animals | Necropsies were performed on all animals; histologic examinations were performed on all control and high-dose groups | Necropsies and histologic examinations were performed on all animals |
| **Animals and Animal Maintenance** | | | | |
| Species | $B6C3F_1$ mice | $B6C3F_1$ mice | $B6C3F_1$ mice | $B6C3F_1$ mice |
| Animal Source | Frederick Cancer Research Center (Frederick, MD) | Same as single-dose study | Same as single-dose study | Harlan Industries (Indianapolis, IN) |
| Time Held Before Start of Test | 2 weeks | 2 weeks | 2-3 weeks | 20 days |
| Age When Placed on Study | 5 weeks | 8 weeks | 5-7 weeks | 8 weeks |

**TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)**

| | Single-Dose | 14-Day Study | 13-Week Study | Chronic Study |
|---|---|---|---|---|
| Age when Killed | 7 weeks | 11 weeks | 18-20 weeks | 112-118 weeks |
| Method of Animal Distribution | Randomized by weight | Randomized by weight | Randomized by weight | Assigned to cages according to a table of random numbers; the cages were then assigned to control and dosed groups according to a second table of random numbers |
| Feed | Wayne Lab Blox® Allied Mills Inc. (Chicago, IL) | Same as single-dose study | Same as single-dose study | Same as single-dose study |
| Bedding | Sani-Chips® | Same as single-dose study | Same as single-dose study | Aspen bed®, American Excelsior Co. (Baltimore, MD) when available; otherwise, Betta Chips® Agway Corp. (Syracuse, NY) |
| Water | Water bottles | Same as single-dose study | Same as single-dose study | Automatic system Edstrom Industries (Waterford, WI); water available *ad libitum* |
| Cages | Hanging wire mesh | Hanging wire mesh | Polycarbonate, Maryland Plastics; cages replaced twice weekly | Polycarbonate Lab Products (Rochelle, NJ); cages, bedding, and food hoppers replaced twice weekly, cage racks and filters replaced once every 2 weeks |
| Cage Filters | Not applicable (N.A.) | N.A. | Spun-bonded Filtek filter bonnet | Non-woven Polyester filter sheets, Lab Products (Rochelle, NJ) or Snow Filtration (Cincinnati, OH) |

**TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS (Continued)**

| | Single-Dose | 14-Day Study | 13-Week Study | Chronic Study |
|---|---|---|---|---|
| Animals per Cage | Two | One | Five | Five |
| Animal Room Environment | 20°-24°C; 40%-45% humidity; room air was changed 12 times per hour; 12 hours of fluorescent light per day | Same as single-dose study | Same as single-dose study | 20°-26°C 92% of the time*; uncontrolled humidity; room air changed 10 -12 times per hour; 12 hours fluorescent light per day |
| Other Chemicals on Test in the same room | Dimethylterephthalate (DMP) | DMP | Sulfisoxazole, DMP, benzoin | None |
| **Chemical-Vehicle Mixture** | | | | |
| Preparation | Bis(2-chloro-1-methylethyl) ether was first dissolved completely in a small amount of Duke's® corn oil; more corn oil was then added to the desired final volume | Prepared fresh daily; bis(2-chloro-1-methylethyl) ether was first dissolved completely in a small amount of Duke's® corn oil; more corn oil was added to the desired final volume | Same as 14-day study | Bis(2-chloro-1-methyl-ethyl) ether was first dissolved completely in a small amount of Mazola® corn oil; the stock solution was then diluted with additional corn oil to the desired final volume. |
| Maximum Storage Time | N.A. | N.A. | N.A. | 7 days |
| Storage Conditions | N.A. | N.A. | N.A. | 4°C in the dark |

* Examination of the daily temperature log for this bioassay showed that temperatures were within the acceptable range of 20° - 26°C for 92% of the time (703/766 daily recordings). On 63 occasions, temperatures were out of range sporadically in one direction or the other, with the lowest reading at 15.6°C (one day during the first month of the study) and the highest reading at 32.2°C (one day during the twelfth month of the study).

# III. RESULTS

## PRECHRONIC STUDIES

### Single-Dose Study

### Fourteen-Day Study

### Thirteen-Week Study

## CHRONIC STUDY

### Body Weights and Clinical Signs

### Survival

### Pathology and Statistical Analyses of Results

## PRECHRONIC STUDIES

### Single-Dose Study

Two of two male mice and 2/2 female mice receiving 1,000 mg/kg and 1/2 male mice receiving 316 mg/kg died. No other signs of toxicity were observed.

### Fourteen-Day Study

Apparent compound-related deaths were noted at the two highest doses (316 and 562 mg/kg). One female mouse receiving 316 mg/kg and all mice receiving 562 mg/kg died (Table 2). Animals receiving the highest dose (562 mg/kg) had a hunched appearance. No other signs of toxicity were observed at the other levels, although two other mice died (one male at 56.2 mg/kg and one female at 100 mg/kg). At necropsy, no compound-related gross lesions were noted at any dose.

### Thirteen-Week Study

No deaths occurred and no compound-related changes in mean body weights were observed (Table 3). Histopathologic changes were limited to respiratory lesions at the three highest doses; focal pneumonitis occurred in 8/10 males and 4/10 females receiving 250 mg/kg, in 2/10 males and 3/10 females receiving 100 mg/kg, and in 3/10 males 1/10 females receiving 50 mg/kg.

**TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED BIS(2-CHLORO-1-METHYLETHYL) ETHER IN CORN OIL BY GAVAGE FOR FOURTEEN DAYS**

| Dose (mg/kg) | Survival *(a)* | Mean Body Weights (grams) | | |
|---|---|---|---|---|
| | | Initial | Final | Change |
| **Males** | | | | |
| 17.8 | 5/5 | 28 | 27 | -1 |
| 31.6 | 5/5 | 30 | 28 | -2 |
| 56.2 | 4/5 *(b)* | 28 | 26 | -2 |
| 100 | 5/5 | 28 | 27 | -1 |
| 178 | 5/5 | 27 | 27 | 0 |
| 316 | 5/5 | 21 | *(c)* | — |
| 562 | 0/5 *(d)* | 22 | — | — |
| **Females** | | | | |
| 17.8 | 5/5 | 22 | 23 | +1 |
| 31.6 | 5/5 | 23 | 23 | 0 |
| 56.2 | 5/5 | 23 | 23 | 0 |
| 100 | 4/5 *(e)* | 22 | 22 | 0 |
| 178 | 5/5 | 22 | 23 | +1 |
| 316 | 4/5 *(f)* | 18 | *(c)* | — |
| 562 | 0/5 *(d)* | 19 | — | — |

*(a)* Number surviving/number per group.
*(b)* Death occurred on day 7.
*(c)* Not recorded.
*(d)* Deaths occurred on day 1.
*(e)* Death occurred on day 8.
*(f)* Death occurred on day 6.

**TABLE 3. SURVIVAL AND MEAN BODY WEIGHTS OF MICE ADMINISTERED BIS(2-CHLORO-1-METHYLETHYL) ETHER IN CORN OIL BY GAVAGE FOR THIRTEEN WEEKS**

| Dose (mg/kg) | Survival *(a)* | Mean Body Weights (grams) | | |
|---|---|---|---|---|
| | | Initial | Final | Change |
| **Males** | | | | |
| 0 *(b)* | 10/10 | 24 | 30 | +6 |
| 10 | 10/10 | 24 | 30 | +6 |
| 25 | 10/10 | 24 | 32 | +8 |
| 50 | 10/10 | 24 | 30 | +6 |
| 100 | 10/10 | 24 | 30 | +6 |
| 250 | 10/10 | 24 | 30 | +6 |
| **Females** | | | | |
| 0 *(b)* | 10/10 | 19 | 23 | +4 |
| 10 | 10/10 | 19 | 24 | +5 |
| 25 | 10/10 | 19 | 24 | +5 |
| 50 | 10/10 | 19 | 23 | +4 |
| 100 | 10/10 | 20 | 24 | +4 |
| 250 | 10/10 | 20 | 24 | +4 |

*(a)* Number surviving/number per group.
*(b)* Vehicle controls received corn oil only.

## CHRONIC STUDY

### Preliminary Studies

Based on the pathologic findings in the 13-week test, a chronic mouse study at dose levels of 10 and 25 mg/kg was initiated at the same laboratory. After 71 weeks, a dosing error occurred wherein doses for a concurrent test in rats were inadvertently administered to the mice. Since the rat dosing solutions were double the concentration per milliliter compared with the mouse dosing solutions, the mice received effective doses of 200 and 400 mg/kg. A large number of deaths in the dosed mouse group resulted, and the study was terminated. Prior to the incident, survival had ranged from 80%-88%. Gross and histologic examinations, performed on all the animals, showed a low incidence of neoplasms in all groups. The results of this aborted study indicated that the chronic doses of 10 and 25 mg/kg were below the maximum tolerated dose for the chemical. Doses for this second chronic study in mice of 100 and 200 mg/kg were based on the results of the first chronic test.

### Body Weights and Clinical Signs

Mean body weights of high-dose and control male mice were comparable throughout most of the study (Figure 1 and Table 4). Mean body weight gains of low-dose mice of each sex were generally higher (5% to 17%) than those of the controls. Mean body weight gains of high-dose female mice were generally lower (5% to 16%) than those of the controls. No compound-related clinical signs were observed. At the end of the study, mean body weights and weight gains were comparable among all groups.

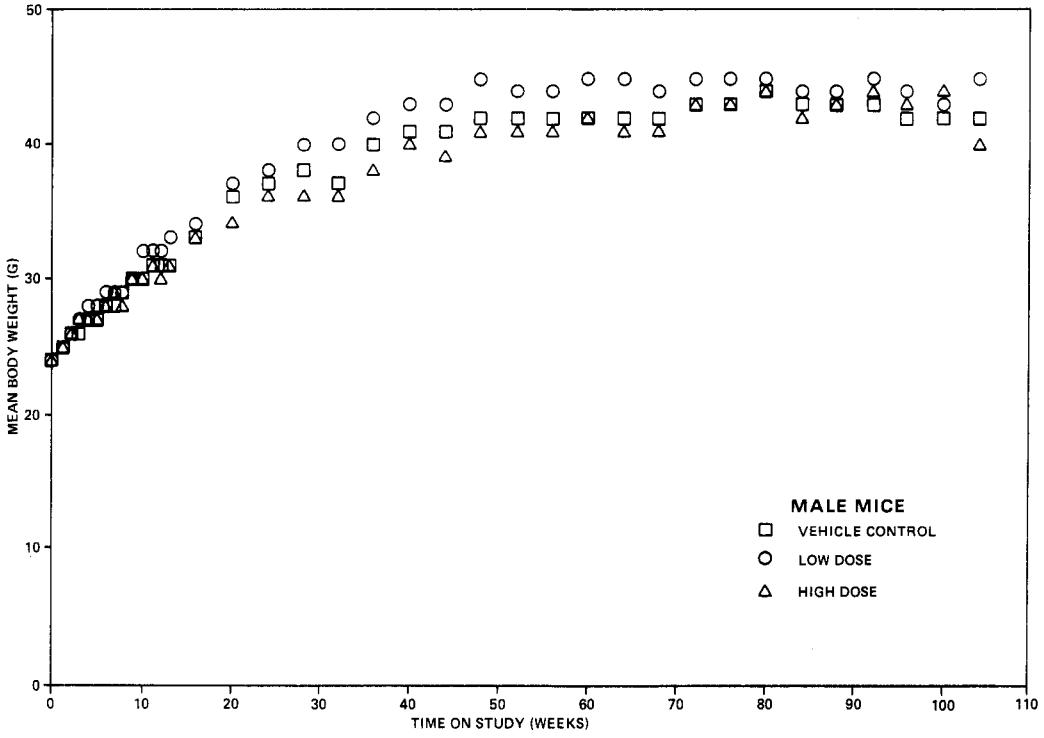
**TABLE 4. CUMULATIVE MEAN BODY WEIGHT CHANGE (RELATIVE TO CONTROLS) OF MICE ADMINISTERED BIS(2-CHLORO-1-METHYETHYL) ETHER BY GAVAGE IN THE CHRONIC STUDY**

| | Cumulative Mean Body Weight Change (grams) | | | Weight Change Relative to Controls (Percent) *(a)* | |
|---|---|---|---|---|---|
| Week No. | Control | Low Dose | High Dose | Low Dose | High Dose |
| **Males** | | | | | |
| 0 | 24 *(b)* | 24 *(b)* | 24 *(b)* | | |
| 1 | 1 | 1 | 1 | 0 | 0 |
| 20 | 12 | 13 | 10 | + 8 | -17 |
| 40 | 17 | 19 | 16 | +12 | - 6 |
| 60 | 18 | 21 | 18 | +17 | 0 |
| 80 | 20 | 21 | 20 | + 5 | 0 |
| 100 | 18 | 19 | 20 | + 6 | +11 |
| Final Body Weights | 42 | 45 | 40 | + 7 *(c)* | - 5 *(c)* |
| **Females** | | | | | |
| 0 | 20 *(b)* | 20 *(b)* | 20 *(b)* | | |
| 1 | 0 | 0 | 1 | | |
| 20 | 7 | 8 | 7 | +14 | 0 |
| 40 | 15 | 15 | 13 | 0 | -13 |
| 60 | 19 | 20 | 16 | + 5 | -16 |
| 80 | 22 | 22 | 19 | 0 | -14 |
| 100 | 21 | 22 | 20 | + 5 | - 5 |
| Final Body Weights | 41 | 42 | 38 | + 2 *(c)* | - 7 *(c)* |

*(a)* Weight change of the dosed group relative to that of the controls = $\frac{\text{Weight Change (Dosed Group)} - \text{Weight Change (Control Group)}}{\text{Weight Change (Control Group)}} \times 100$

*(b)* Initial weight

*(c)* Final body weight relative to controls (percent)



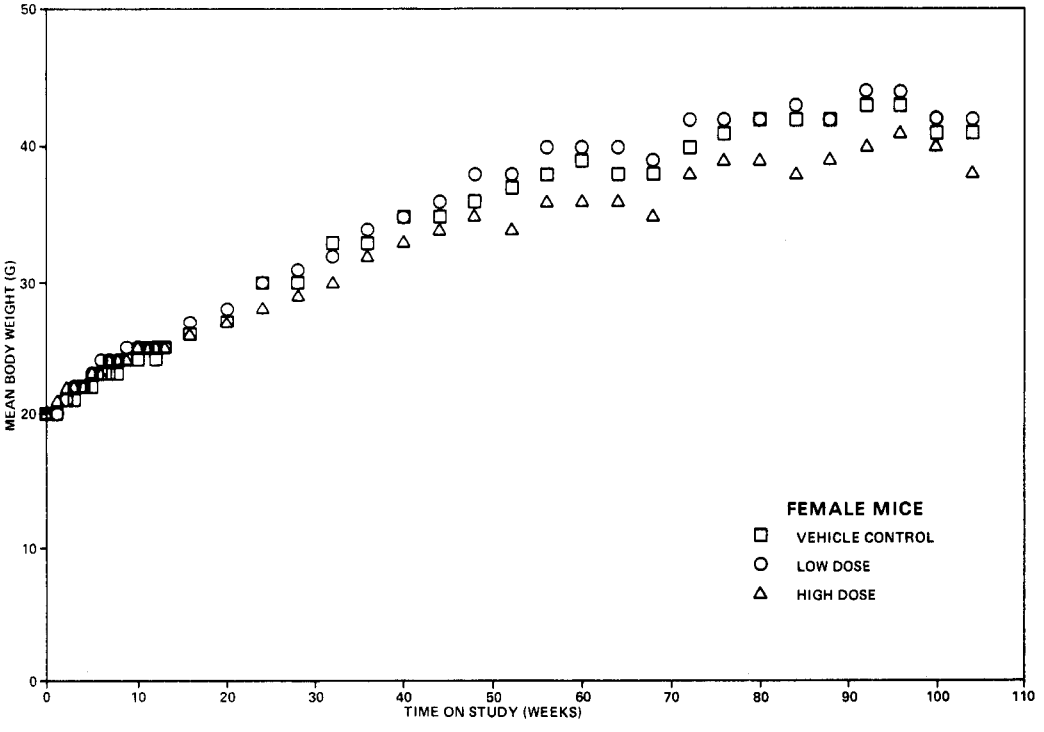




**Figure 1. Growth Curves for Mice Administered Bis(2-chloro-1-methylethyl) Ether by Gavage**

## Survival

Estimates of the probabilities of survival of male and female mice administered bis(2-chloro-1-methylethyl) ether by gavage and estimates for the control groups are shown by the Kaplan and Meier curves in Figure 2. Comparisons of survival in control and dosed groups of males or females did not reveal any significant differences.

In male mice, 41/50 (82%) of the controls, 44/50 (88%) of the low-dose group, and 37/50 (74%) of the high-dose group lived to the termination period of the study at 104-110 weeks. In female mice, 31/50 (62%) of the controls, 34/50 (68%) of the low-dose group, and 28/50 (56%) of the high-dose group lived to the termination period of the study at 105-110 weeks. One control male, one low-dose male, one high-dose male, two control females, two low-dose females, and one high-dose female died during the termination period of the study (weeks 105-110). These animals are included in the terminal incidence data analyzed in Tables 5 and 6. Five control and five low-dose female mice drowned (apparently due to faulty drinking water valves) during week 43 of the study, and one high-dose male mouse was accidentally killed at week 54. Tissues from these animals were examined histopathologically and results were included in the analysis of tumor incidences.

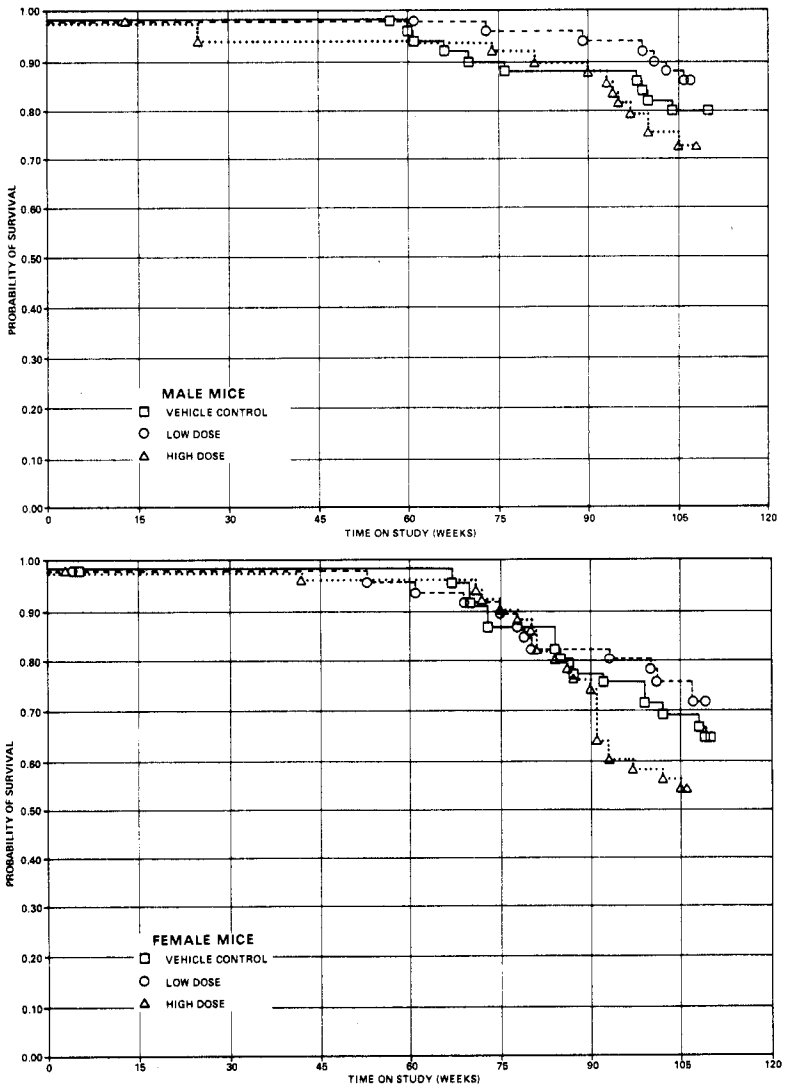



**Figure 2. Survival Curves for Mice Administered Bis(2-chloro-1-methylethyl) Ether by Gavage**

## Pathology and Statistical Analyses of Results

Histopathologic findings on neoplasms occurring in mice are summarized in Appendix A, Tables A1 and A2; Tables A3 and A4 give the survival and tumor status for each individual animal in the male and female mouse studies, respectively. Findings on nonneoplastic lesions are summarized in Appendix B, Tables B1 and B2. Tables 5 and 6 contain the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups.

*Lung:* Alveolar/bronchiolar adenomas occurred with statistically significant ($P<0.05$, incidental tumor test) positive trends in male and female mice (males: control, 5/50, 10%; low-dose, 13/50, 26%; high-dose, 11/50, 22%; females: control, 1/50, 2%; low-dose, 4/50, 8%; high-dose, 8/50, 16%). The incidence in the high-dose females was significantly higher than that in the controls ($P<0.030$). The combined incidence of alveolar/bronchiolar adenomas and carcinomas exhibited a significant positive trend (males, $P\leq0.033$; females, $P\leq0.004$; incidence rates: control males, 6/50, 12%; low-dose, 15/50, 30%; high-dose, 13/50, 26%; control females, 1/50, 2%; low-dose, 4/50, 8%; high-dose, 10/50, 20%). The incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in dosed male and high-dose female mice were significantly higher than those in the controls (males, $P<0.04$; females, $P<0.01$). Microscopically, the tumors were characterized as solid cells filling adjacent alveoli or, in some cases, cells having a columnar to papillary nature. The cells were uniform with moderate cytoplasm and round to oval nuclei. The tumors are not unlike the morphology of bronchiolar/alveolar tumors in control mice.

*Liver:* Hepatocellular carcinomas occurred with a statistically significant ($P\leq0.004$) positive trend in male mice, and the incidence in the high-dose group was significantly ($P\leq0.007$) higher than that in the controls (5/50, 13/50, 17/50). The combined incidence of hepatocellular adenomas and carcinomas in males was significant in the trend tests ($P\leq0.003$) and the incidence in the high-dose group was significantly higher than that in the controls ($P\leq0.005$ in all tests). Metastases to the lung occurred in 1/50, 4/50, 3/50. Incidences of liver tumors in female mice were not statistically significant.

Fatty metamorphosis was found at increased incidence in dosed male mice (control, 2/50, 4%; low-dose, 16/50, 32%; high-dose, 15/50, 30%).

*Hematopoietic System:* Histiocytic lymphomas occurred in 3/50 (6%) of the high-dose male mice (none occurred in the other groups), producing a statistically significant ($P\leq0.037$) trend. However, incidences of male mice with other types of lymphoma or female mice with any type of malignant lymphoma were not statistically significant.

*Stomach or Forestomach:* Squamous-cell papillomas were found in 2/49 high-dose female mice, 1/50 low-dose and 1/50 high-dose male mice; squamous cell carcinoma was found in one high-dose female mouse that did not have squamous cell papillomas.

TABLE 5. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)*

| | Vehicle Control | Low Dose | High Dose |
|---|---|---|---|
| **Subcutaneous Tissue: Fibrosarcoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 1/50 (2%) | 3/50 (6%) | 0/50 (0%) |
| Adjusted *(c)* | 2.4% | 6.5% | 0.0% |
| Terminal *(d)* | 1/41 (2%) | 2/44 (5%) | 0/37 (0%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.404N | P=0.329 | P=0.520N |
| Incidental Tumor Test | P=0.500N | P=0.234 | P=0.520N |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.378N | P=0.309 | P=0.500N |
| **Lung: Alveolar/Bronchiolar Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 5/50 (10%) | 13/50 (26%) | 11/50 (22%) |
| Adjusted *(c)* | 12.2% | 28.8% | 28.9% |
| Terminal *(d)* | 5/41 (12%) | 12/44 (27%) | 10/37 (27%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.048 | P=0.049 | P=0.055 |
| Incidental Tumor Test | P=0.045 | P=0.035 | P=0.067 |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.083 | P=0.033 | P=0.086 |
| **Lung: Alveolar/Bronchiolar Adenoma or Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 6/50 (12%) | 15/50 (30%) | 13/50 (26%) |
| Adjusted *(c)* | 14.1% | 33.2% | 34.2% |
| Terminal *(d)* | 5/41 (12%) | 14/44 (32%) | 12/37 (32%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.033 | P=0.038 | P=0.039 |
| Incidental Tumor Test | P=0.024 | P=0.019 | P=0.035 |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.061 | P=0.024 | P=0.062 |
| **Hematopoietic System: Malignant Lymphoma, Histiocytic Type** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 0/50 (0%) | 0/50 (0%) | 3/50 (6%) |
| Adjusted *(c)* | 0.0% | 0.0% | 7.2% |
| Terminal *(d)* | 0/41 (0%) | 0/44 (0%) | 1/37 (3%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.033 | (f) | P=0.114 |
| Incidental Tumor Test | P=0.028 | (f) | P=0.086 |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.037 | (f) | P=0.121 |
| **Hematopoietic System: All Malignant Lymphoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 6/50 (12%) | 3/50 (6%) | 7/50 (14%) |
| Adjusted *(c)* | 14.2% | 6.6% | 17.5% |
| Terminal *(d)* | 5/41 (12%) | 2/44 (5%) | 5/37 (14%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.375 | P=0.213N | P=0.430 |
| Incidental Tumor Test | P=0.429 | P=0.215N | P=0.459 |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.436 | P=0.243N | P=0.500 |

**TABLE 5. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)**

| | Vehicle Control | Low Dose | High Dose |
|---|---|---|---|
| **Circulatory System: Hemangiosarcoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 1/50 (2%) | 4/50 (8%) | 0/50 (0%) |
| Adjusted *(c)* | 2.4% | 9.1% | 0.0% |
| Terminal *(d)* | 1/41 (2%) | 4/44 (9%) | 0/37 (0%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.424N | P=0.202 | P=0.520N |
| Incidental Tumor Test | P=0.424N | P=0.202 | P=0.520N |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.391N | P=0.181 | P=0.500N |
| **Liver: Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 8/50 (16%) | 10/50 (20%) | 13/50 (26%) |
| Adjusted *(c)* | 19.0% | 22.7% | 35.1% |
| Terminal *(d)* | 7/41 (17%) | 10/44 (23%) | 13/37 (35%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.079 | P=0.463 | P=0.102 |
| Incidental Tumor Test | P=0.090 | P=0.459 | P=0.120 |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.133 | P=0.398 | P=0.163 |
| **Liver: Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 5/50 (10%) | 13/50 (26%) | 17/50 (34%) |
| Adjusted *(c)* | 11.5% | 27.6% | 40.1% |
| Terminal *(d)* | 3/41 (7%) | 10/44 (23%) | 12/37 (32%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.002 | P=0.058 | P=0.004 |
| Incidental Tumor Test | P=0.004 | P=0.023 | P=0.007 |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.004 | P=0.033 | P=0.004 |
| **Liver: Adenoma or Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 13/50 (26%) | 23/50 (46%) | 27/50 (54%) |
| Adjusted *(c)* | 29.5% | 48.9% | 64.0% |
| Terminal *(d)* | 10/41 (24%) | 20/44 (45%) | 22/37 (59%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.002 | P=0.065 | P=0.002 |
| Incidental Tumor Test | P=0.003 | P=0.030 | P=0.005 |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.003 | P=0.030 | P=0.004 |
| **Harderian Gland: Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 3/50 (6%) | 4/50 (8%) | 2/50 (4%) |
| Adjusted *(c)* | 7.3% | 9.1% | 5.4% |
| Terminal *(d)* | 3/41 (7%) | 4/44 (9%) | 2/37 (5%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.465N | P=0.538 | P=0.547N |
| Incidental Tumor Test | P=0.465N | P=0.538 | P=0.547N |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.417N | P=0.500 | P=0.500N |

**TABLE 5. ANALYSIS OF PRIMARY TUMORS IN MALE MICE *(a)* (Continued)**

*(a)* Dosed groups received doses of 100 or 200 mg/kg of bis(2-chloro-1-methylethyl) ether by gavage.
*(b)* Number of tumor bearing animals/number of animals examined at the site.
*(c)* Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
*(d)* Observed tumor incidence at terminal kill.
*(e)* Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).
*(f)* The absence of tumor incidence both in this group and in the controls precludes the use of these statistics.

**TABLE 6. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)***

| | Vehicle Control | Low Dose | High Dose |
|---|---|---|---|
| **Lung: Alveolar/Bronchiolar Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 1/50 (2%) | 4/50 (8%) | 8/50 (16%) |
| Adjusted *(c)* | 2.8% | 11.8% | 24.2% |
| Terminal *(d)* | 0/31 (0%) | 4/34 (12%) | 5/28 (18%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.008 | P=0.206 | P=0.018 |
| Incidental Tumor Test | P=0.016 | P=0.148 | P=0.029 |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.011 | P=0.181 | P=0.015 |
| **Lung: Alveolar/Bronchiolar Adenoma or Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 1/50 (2%) | 4/50 (8%) | 10/50 (20%) |
| Adjusted *(c)* | 2.8% | 11.8% | 30.8% |
| Terminal *(d)* | 0/31 (0%) | 4/34 (12%) | 7/28 (25%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.002 | P=0.206 | P=0.005 |
| Incidental Tumor Test | P=0.004 | P=0.148 | P=0.008 |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.003 | P=0.181 | P=0.004 |
| **Hematopoietic System: All Malignant Lymphoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 15/50 (30%) | 15/50 (30%) | 11/50 (22%) |
| Adjusted *(c)* | 45.2% | 42.8% | 31.0% |
| Terminal *(d)* | 13/31 (42%) | 14/34 (41%) | 5/28 (18%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.289N | P=0.473N | P=0.324N |
| Incidental Tumor Test | P=0.173N | P=0.517N | P=0.185N |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.217N | P=0.586 | P=0.247N |
| **Liver: Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 5/50 (10%) | 4/50 (8%) | 3/50 (6%) |
| Adjusted *(c)* | 16.1% | 11.8% | 10.7% |
| Terminal *(d)* | 5/31 (16%) | 4/34 (12%) | 3/28 (11%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.333N | P=0.441N | P=0.411N |
| Incidental Tumor Test | P=0.333N | P=0.441N | P=0.411N |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.291N | P=0.500N | P=0.357N |
| **Liver: Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 2/50 (4%) | 3/50 (6%) | 2/50 (4%) |
| Adjusted *(c)* | 6.5% | 8.3% | 6.2% |
| Terminal *(d)* | 2/31 (6%) | 1/34 (3%) | 1/28 (4%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.562 | P=0.543 | P=0.672 |
| Incidental Tumor Test | P=0.511N | P=0.526 | P=0.650 |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.593 | P=0.500 | P=0.691 |

**TABLE 6. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE *(a)* (Continued)**

| | Vehicle Control | Low Dose | High Dose |
|---|---|---|---|
| **Liver: Adenoma or Carcinoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 7/50 (14%) | 7/50 (14%) | 5/50 (10%) |
| Adjusted *(c)* | 22.6% | 19.4% | 16.6% |
| Terminal *(d)* | 7/31 (23%) | 5/34 (15%) | 4/28 (14%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.385N | P=0.539N | P=0.442N |
| Incidental Tumor Test | P=0.315N | P=0.552N | P=0.393N |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.326N | P=0.613 | P=0.380N |
| **Pituitary: Adenoma** | | | |
| Tumor Rates | | | |
| Overall *(b)* | 4/40 (10%) | 5/40 (13%) | 3/40 (8%) |
| Adjusted *(c)* | 16.0% | 15.7% | 12.0% |
| Terminal *(d)* | 4/25 (16%) | 3/29 (10%) | 3/25 (12%) |
| Statistical Tests *(e)* | | | |
| Life Table | P=0.442N | P=0.582 | P=0.500N |
| Incidental Tumor Test | P=0.475N | P=0.516 | P=0.500N |
| Cochran-Armitage Trend, Fisher Exact Tests | P=0.427N | P=0.500 | P=0.500N |

*(a)* Dosed groups received doses of 100 or 200 mg/kg of bis(2-chloro-1-methylethyl) ether by gavage.
*(b)* Number of tumor bearing animals/number of animals examined at the site.
*(c)* Kaplan-Meier estimated lifetime tumor incidence after adjusting for intercurrent mortality.
*(d)* Observed tumor incidence at terminal kill.
*(d)* Beneath the control incidence are the P-values associated with the trend test. Beneath the dosed group incidence are the P-values corresponding to pairwise comparisons between that dosed group and the controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as non-fatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend is indicated by (N).

# IV. DISCUSSION AND CONCLUSIONS

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A 2-year carcinogenesis bioassay of bis(2-chloro-1-methylethyl) ether was conducted in B6C3F$_1$ mice. Based on results from a 90-day subchronic test and an aborted chronic test, doses of 100 and 200 mg/kg were administered by gavage 5 times per week for 103 weeks. These doses are the same as those administered to F344/N rats in a study conducted earlier at another laboratory in the Bioassay Program (NCI, 1979).

Survival of dosed and control mice was comparable in the chronic study. Mean body weights of high-dose male mice were similar to those of the corresponding controls, but the mean body weights of high-dose females were slightly lower than those of the controls. Mean body weights and weight gains were similar among all groups at the end of the study.

To date, previous studies in animals have not established a clear association between lung tumors and administration of beta-haloethers (Mitsumori et al., 1979; NTIS, 1968). In this 2-year study in mice, the incidences of alveolar/bronchiolar adenomas and the combined incidences of alveolar/bronchiolar adenomas or carcinomas were statistically significant in the life table and incidental tumor trend tests ($P \leq 0.048$ for males and $P \leq 0.016$ for females). In pairwise comparisons, incidences of either alveolar/bronchiolar adenomas or carcinomas in the dosed males and high-dose females were significantly elevated ($P \leq 0.04$ for males and $P \leq 0.01$ for females) compared with those of the controls. Historically, the combined incidences of these tumors in control B6C3F$_1$ mice receiving corn oil by gavage for 103 weeks at all Bioassay laboratories is 34/358 (9.5%) for male mice (highest incidence, 6/45, 13.3%) and 12/360 (3.3%) for female mice (highest incidence, 4/46, 8.7%) (Appendix F, Tables F1 and F2) compared with the combined incidence of 13/50 (26%) in the high-dose males, 15/50 (30%) in low-dose males, and 10/50 (20%) in the high-dose females in the present study. No other gavage studies of 104 weeks duration have been conducted in B6C3F$_1$ mice at this laboratory.

Lung tumors have been associated with administration of alpha-haloethers. Adenomas of the lung were found at increased incidences in ICR Swiss mice given a single subcutaneous injection of bis(chloromethyl) ether (12.5 $\mu$l/kg) when 24 to 72 hours old and observed for 6 months (Gargus et al., 1969). Lung adenomas were found in these animals at the following incidences: control males, 2/30 (7%); dosed males, 25/50 (50%); control females, 5/20 (25%); dosed females, 20/50 (40%).

A structurally related beta-haloether, bis(2-chloroethyl) ether, caused an increased incidence of hepatomas when administered 100 mg/kg by gavage for 21 days followed by 300 ppm in feed to male and female B6C3F$_1$ mice and male B6AKF$_1$ mice for 76 weeks. The incidence in B6C3F$_1$ mice was: control males, 3/18 (17%); dosed males, 14/18 (78%); control females, 0/18 (0%); dosed females, 4/18 (22%). Hepatomas were observed in 1/18 (6%) control male B6AKF$_1$ mice and in 9/18 (50%) dosed males of the same strain (Innes et al., 1969; NTIS, 1968).

In this study, the administration of bis(2-chloro-1-methylethyl) ether was associated with an increased incidence of liver tumors. The incidences of hepatocellular carcinomas in male mice (control, 5/50, 10%; low-dose, 13/50, 26%; high-dose, 17/50, 34%) and combined hepatocellular carcinomas and adenomas (control, 13/50, 26%; low-dose, 23/50, 46%; high-dose, 27/50, 54%) were statistically significant by the trend tests ($P \leq 0.004$), and the incidences in the high-dose groups were significantly higher than those in the controls ($P \leq 0.007$). The incidences of combined liver tumors in dosed male mice in this study are higher than the overall incidences for these tumors in vehicle control B6C3F$_1$ mice in studies of 104 weeks duration throughout the bioassay program (Appendix F, Table F3: 98/361, 27.1%; highest incidence: 21/49, 42.9%).

Two rare tumors were observed in dosed mice. Squamous cell papillomas were seen in the stomach or forestomach of 2/49 (4.1%) high-dose females, and a squamous cell carcinoma was found in the forestomach of another high-dose female (2%). One low-dose (2%) and one high-dose (2%) male mouse were found to have squamous cell papillomas. Stomach tumors have been found in 1/362 (0.3%) female and 0/365 male vehicle controls administered corn oil in other studies in the overall Bioassay Program. The combined incidence of untreated control B6C3F$_1$ mice with all types of stomach tumors is 13/3454 (0.4%) for males and 13/3557 (0.4%) for females in the Bioassay Program. Because of the rarity of stomach tumors in this strain of mouse and the combined incidence of three squamous cell papillomas or carcinomas in high-dose female mice, the presence of these tumors in high-dose female mice was probably related to administration of bis(2-chloro-1-methylethyl) ether.

# IV. DISCUSSION AND CONCLUSIONS

Bis(2-chloro-1-methylethyl) ether was not carcinogenic when administered by gavage to F344/N rats of each sex at doses of 100 or 200 mg/kg for 103 weeks under the protocols of the Bioassay Program (NCI, 1979). There was no evidence of carcinogenicity in male and female ICR mice fed diets containing 0, 80, 400, 2,000, or 10,000 ppm for 104 weeks (Mitsumori et al., 1979). (The 2,000-ppm concentration in feed is roughly equivalent to a dose of 190 mg/kg body weight.) The stability of bis(2-chloro-1-methylethyl) ether in feed, however, was not reported; thus if the chemical was unstable in feed, the amount of chemical available to the mice would be considerably less than that stated. Mice fed the 10,000 ppm diets consumed 60%-80% of the amount of feed consumed by the controls. Weight gain was depressed by more than 50% in mice fed the 10,000 ppm diets and by more than 10% in females fed 2,000 ppm diets.

Propylene oxide, a metabolite of bis(2-chloro-1-methylethyl) ether, produced sarcomas at the injection site in 15/81 female NMRI mice following weekly subcutaneous injection of 2.5 mg doses for 39 weeks or longer; no such tumors were found in the controls (Dunkelberg, 1979). This chemical has been tested in the Bioassay Program by the inhalation route of exposure. The histopathologic examination is now in progress.

Bis(2-chloro-1-methylethyl)ether and its metabolites propylene oxide and 1-chloro-2-propanol are mutagenic for various *Salmonella typhimurium* strains: bis(2-chloro-1-methylethyl) ether in strain TA 100 (Simmon et al., 1977); propylene oxide in TA 1535, TA100, and WP2 (McMahon et al., 1979); and 1-chloro-2-propanol for TA 1530 (Rosenkranz et al., 1975). The *Salmonella* assay performed by the National Toxicology Program on bis(2-chloro-1-methylethyl) ether produced weak yet nonreproducible positive responses in TA 100 and TA 1535 strains; BCMEE did not induce any mutagenic response in strains TA 98 and TA 1537.

Bis(2-chloro-1-methylethyl) ether caused mammalian cell chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary (CHO) cells (NTP unpublished results).

*Conclusions: Under the conditions of this bioassay, bis(2-chloro-1-methylethyl) ether—containing 2-chloro-1-methylethyl(2-chloropropyl) ether—was carcinogenic for B6C3F$_1$ mice, causing increased incidences of alveolar/bronchiolar adenomas in males and females and hepatocellular carcinomas in males. In addition, the occurrence of a low incidence of squamous cell papillomas or carcinomas in the stomach or forestomach of females (a rare tumor in B6C3F$_1$ mice) was probably associated with the administration of bis(2-chloro-1-methylethyl) ether.*

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# APPENDIX A

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE ADMINISTERED BIS(2-CHLORO-1-METHYLETHYL) ETHER IN CORN OIL BY GAVAGE

## TABLE A1.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED BIS(2-CHLORO-1-METHYLETHYL) ETHER IN CORN OIL BY GAVAGE

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *SUBCUT TISSUE | (50) | (50) | (50) |
| FIBROSARCOMA | 1 (2%) | 3 (6%) | |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (50) | (50) | (50) |
| HEPATOCELLULAR CARCINOMA, METAST | 1 (2%) | 4 (8%) | 3 (6%) |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 5 (10%) | 13 (26%) | 11 (22%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | 1 (2%) | 2 (4%) | 2 (4%) |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (50) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | 5 (10%) | 2 (4%) | 3 (6%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | 2 (4%) |
| #MESENTERIC L. NODE | (48) | (43) | (43) |
| MALIGNANT LYMPHOMA, NOS | | 1 (2%) | 1 (2%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | 1 (2%) |
| MALIGNANT LYMPHOMA, MIXED TYPE | 1 (2%) | | |
| CIRCULATORY SYSTEM | | | |
| *SUBCUT TISSUE | (50) | (50) | (50) |
| ANGIOSARCOMA | | 1 (2%) | |
| #SPLEEN | (50) | (50) | (48) |
| HEMANGIOSARCOMA | 1 (2%) | 3 (6%) | |
| #LIVER | (50) | (50) | (50) |
| HEMANGIOSARCOMA | | 1 (2%) | |

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

## TABLE A1. MALE MICE: NEOPLASMS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #URINARY BLADDER | (50) | (49) | (50) |
| HEMANGIOMA | 1 (2%) | | |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (50) | (50) | (50) |
| HEPATOCELLULAR ADENOMA | 8 (16%) | 10 (20%) | 13 (26%) |
| HEPATOCELLULAR CARCINOMA | 5 (10%) | 13 (26%) | 17 (34%) |
| #STOMACH | (49) | (50) | (50) |
| SQUAMOUS CELL PAPILLOMA | | | 1 (2%) |
| SARCOMA, NOS | | | 1 (2%) |
| #FORESTOMACH | (49) | (50) | (50) |
| SQUAMOUS CELL PAPILLOMA | | 1 (2%) | |
| #JEJUNUM | (49) | (49) | (49) |
| ADENOCARCINOMA, NOS | | 1 (2%) | |
| URINARY SYSTEM | | | |
| #KIDNEY | (50) | (50) | (50) |
| TUBULAR-CELL ADENOCARCINOMA | | | 1 (2%) |
| ENDOCRINE SYSTEM | | | |
| #ADRENAL | (47) | (49) | (50) |
| CORTICAL ADENOMA | | 1 (2%) | |
| PHEOCHROMOCYTOMA | 1 (2%) | | |
| #THYROID | (45) | (47) | (47) |
| FOLLICULAR-CELL ADENOMA | 1 (2%) | | |
| FOLLICULAR-CELL CARCINOMA | 1 (2%) | 1 (2%) | 1 (2%) |
| #PANCREATIC ISLETS | (48) | (50) | (50) |
| ISLET-CELL ADENOMA | | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | |
| NONE | | | |
| NERVOUS SYSTEM | | | |
| NONE | | | |

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

## TABLE A1. MALE MICE: NEOPLASMS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| SPECIAL SENSE ORGANS | | | |
| *HARDERIAN GLAND | (50) | (50) | (50) |
| ADENOMA, NOS | 3 (6%) | 4 (8%) | 2 (4%) |
| ADENOCARCINOMA, NOS | | | 1 (2%) |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| CONNECTIVE TISSUE | | | |
| HEPATOCELLULAR CARCINOMA, INVASI | | | 1 |
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| NATURAL DEATH@ | 10 | 7 | 11 |
| MORIBUND SACRIFICE | | | 2 |
| ACCIDENTALLY KILLED | | | 1 |
| TERMINAL SACRIFICE | 40 | 43 | 36 |

@ INCLUDES AUTOLYZED ANIMALS

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

## TABLE A1. MALE MICE: NEOPLASMS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 30 | 38 | 40 |
| TOTAL PRIMARY TUMORS | 34 | 58 | 57 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 17 | 23 | 21 |
| TOTAL BENIGN TUMORS | 19 | 30 | 27 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 14 | 24 | 25 |
| TOTAL MALIGNANT TUMORS | 15 | 28 | 30 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 1 | 4 | 3 |
| TOTAL SECONDARY TUMORS | 1 | 4 | 4 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | |
| TOTAL UNCERTAIN TUMORS | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

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

## TABLE A2.

## SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED BIS(2-CHLORO-1-METHYLETHYL) ETHER IN CORN OIL BY GAVAGE

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *SUBCUT TISSUE | (50) | (50) | (50) |
| FIBROSARCOMA | 2 (4%) | 1 (2%) | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #LUNG | (50) | (50) | (50) |
| HEPATOCELLULAR CARCINOMA, METAST | | 1 (2%) | |
| ALVEOLAR/BRONCHIOLAR ADENOMA | 1 (2%) | 4 (8%) | 8 (16%) |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | 2 (4%) |
| ADENOSQUAMOUS CARCINOMA, METASTA | 1 (2%) | | |
| HEMATOPOIETIC SYSTEM | | | |
| *MULTIPLE ORGANS | (50) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | 12 (24%) | 13 (26%) | 7 (14%) |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | | | 2 (4%) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | 1 (2%) | |
| MALIGNANT LYMPHOMA, MIXED TYPE | | | 1 (2%) |
| #SPLEEN | (50) | (50) | (50) |
| MALIGNANT LYMPHOMA, NOS | 1 (2%) | 1 (2%) | 1 (2%) |
| #MEDIASTINAL L.NODE | (45) | (43) | (42) |
| NEURILEMOMA, METASTATIC | 1 (2%) | | |
| #MESENTERIC L. NODE | (45) | (43) | (42) |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | 1 (2%) | | |
| #HEPATIC CAPSULE | (50) | (50) | (50) |
| MALIGNANT LYMPHOMA, MIXED TYPE | 1 (2%) | | |

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

## TABLE A2. FEMALE MICE: NEOPLASMS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| CIRCULATORY SYSTEM | | | |
| #SPLEEN | (50) | (50) | (50) |
| HEMANGIOSARCOMA | | | 1 (2%) |
| #LIVER | (50) | (50) | (50) |
| HEMANGIOMA | | | 1 (2%) |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (50) | (50) | (50) |
| HEPATOCELLULAR ADENOMA | 5 (10%) | 4 (8%) | 3 (6%) |
| HEPATOCELLULAR CARCINOMA | 2 (4%) | 3 (6%) | 2 (4%) |
| #PANCREAS | (48) | (49) | (48) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | 1 (2%) |
| #STOMACH | (50) | (49) | (49) |
| SQUAMOUS CELL PAPILLOMA | | | 1 (2%) |
| #FORESTOMACH | (50) | (49) | (49) |
| SQUAMOUS CELL PAPILLOMA | | | 1 (2%) |
| SQUAMOUS CELL CARCINOMA | | | 1 (2%) |
| #CECUM | (47) | (49) | (47) |
| LEIOMYOMA | 1 (2%) | | |
| URINARY SYSTEM | | | |
| NONE | | | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (40) | (40) | (40) |
| ADENOMA, NOS | 4 (10%) | 5 (13%) | 3 (8%) |
| #ADRENAL | (48) | (50) | (49) |
| PHEOCHROMOCYTOMA | | 2 (4%) | |

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

## TABLE A2. FEMALE MICE: NEOPLASMS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| REPRODUCTIVE SYSTEM | | | |
| *MAMMARY GLAND | (50) | (50) | (50) |
| ADENOCARCINOMA, NOS | | 1 (2%) | |
| CYSTADENOCARCINOMA, NOS | | 1 (2%) | |
| ADENOSQUAMOUS CARCINOMA | 1 (2%) | | |
| *VAGINA | (50) | (50) | (50) |
| SQUAMOUS CELL CARCINOMA | | 1 (2%) | |
| #UTERUS | (49) | (49) | (48) |
| ENDOMETRIAL STROMAL POLYP | 1 (2%) | | |
| NEUROFIBROMA | | | 1 (2%) |
| NEURILEMOMA, MALIGNANT | 1 (2%) | | |
| #OVARY/PAROVARIAN | (47) | (49) | (47) |
| SQUAMOUS CELL CARCINOMA, METASTA | | | 1 (2%) |
| NERVOUS SYSTEM | | | |
| NONE | | | |
| SPECIAL SENSE ORGANS | | | |
| *HARDERIAN GLAND | (50) | (50) | (50) |
| ADENOMA, NOS | | | 1 (2%) |
| MUSCULOSKELETAL SYSTEM | | | |
| NONE | | | |
| BODY CAVITIES | | | |
| NONE | | | |
| ALL OTHER SYSTEMS | | | |
| NONE | | | |

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

## TABLE A2. FEMALE MICE: NEOPLASMS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMAL DISPOSITION SUMMARY | | | |
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| NATURAL DEATH@ | 16 | 10 | 20 |
| MORIBUND SACRIFICE | | 3 | 3 |
| ACCIDENTALLY KILLED | 5 | 5 | |
| TERMINAL SACRIFICE | 29 | 32 | 27 |
| @ INCLUDES AUTOLYZED ANIMALS | | | |
| TUMOR SUMMARY | | | |
| TOTAL ANIMALS WITH PRIMARY TUMORS* | 26 | 29 | 29 |
| TOTAL PRIMARY TUMORS | 33 | 37 | 37 |
| TOTAL ANIMALS WITH BENIGN TUMORS | 10 | 14 | 14 |
| TOTAL BENIGN TUMORS | 12 | 15 | 19 |
| TOTAL ANIMALS WITH MALIGNANT TUMORS | 19 | 20 | 16 |
| TOTAL MALIGNANT TUMORS | 21 | 22 | 18 |
| TOTAL ANIMALS WITH SECONDARY TUMORS# | 2 | 1 | 1 |
| TOTAL SECONDARY TUMORS | 2 | 1 | 2 |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT | | | |
| TOTAL UNCERTAIN TUMORS | | | |
| TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC | | | |
| TOTAL UNCERTAIN TUMORS | | | |

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

## TABLE A3.

## INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF BIS(2-CHLORO-1-METHYLETHYL) ETHER

### VEHICLE CONTROL

| ANIMAL NUMBER | 001 | 002 | 003 | 004 | 005 | 006 | 007 | 008 | 009 | 010 | 011 | 012 | 013 | 014 | 015 | 016 | 017 | 018 | 019 | 020 | 021 | 022 | 023 | 024 | 025 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 109 | 110 | 104 | 109 | 109 | 109 | 109 | 091 | 091 | 091 | 109 | 109 | 109 | 109 | 109 | 060 | 057 | 109 | 109 | 109 | 100 | 110 | 109 | 110 | 061 |
| INTEGUMENTARY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + | + | + | + | + | + | + | + |
| FIBROSARCOMA | | | | | | | | | | | X | | | | | | | | | | | | | | |
| RESPIRATORY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR CARCINOMA, METASTA | | | | | | | | | | | | | | | | | | | | | | | | | |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | X | | | X | | | | | X | | | | | | | | | | | | | |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEMATOPOIETIC SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEMANGIOSARCOMA | | | | | | | | X | | | | | | | | | | | | | | | | | |
| LYMPH NODES | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| MALIGNANT LYMPHOMA, MIXED TYPE | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYMUS | + | - | - | - | - | - | + | - | - | - | - | + | + | - | - | - | + | - | + | - | - | - | + | - | + |
| CIRCULATORY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| DIGESTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR ADENOMA | | | | | | | | | | | X | | | | X | | | | | | | | | | |
| HEPATOCELLULAR CARCINOMA | | | | | | | | | | | | | | | | | | X | | | X | | | X | |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | N | + | N | + | + | + | N | N | + |
| PANCREAS | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + |
| URINARY SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEMANGIOMA | | | | | | | | X | | | | | | | | | | | | | | | | | |
| ENDOCRINE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | - | - | + | + | + | + | + | + | + | - |
| ADRENAL | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PHEOCHROMOCYTOMA | | | | | | | | | | | | | | | | | | | | | | | X | | |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | - | + |
| FOLLICULAR-CELL ADENOMA | | | | | X | | | | | | | | | | | | | | | | | | | | |
| FOLLICULAR-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| PARATHYROID | - | + | + | - | - | + | + | + | - | + | + | + | - | + | - | - | + | + | - | - | - | - | - | - | + |
| REPRODUCTIVE SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| TESTIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PROSTATE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| NERVOUS SYSTEM | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPECIAL SENSE ORGANS | | | | | | | | | | | | | | | | | | | | | | | | | |
| HARDERIAN GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| ADENOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| ALL OTHER SYSTEMS | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| MALIGNANT LYMPHOMA, NOS | | | X | | | | | | | | | | | X | | | | X | | | | | | | |

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

## TABLE A3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

| ANIMAL NUMBER | 026 | 027 | 028 | 029 | 030 | 031 | 032 | 033 | 034 | 035 | 036 | 037 | 038 | 039 | 040 | 041 | 042 | 043 | 044 | 045 | 046 | 047 | 048 | 049 | 050 | TOTAL TISSUES TUMORS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 110 | 110 | 110 | 110 | 066 | 110 | 110 | 110 | 110 | 110 | 110 | 110 | 098 | 076 | 110 | 110 | 110 | 110 | 070 | 099 | 110 | 110 | 110 | 110 | 110 | |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE<br>FIBROSARCOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | 50*<br>1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI<br>HEPATOCELLULAR CARCINOMA, METASTA<br>ALVEOLAR/BRONCHIOLAR ADENOMA<br>ALVEOLAR/BRONCHIOLAR CARCINOMA | + | + | + | + | + | + | + | + | + | + | +<br>X | + | + | + | + | + | + | +<br>X | + | + | + | + | + | + | + | 50<br>1<br>5<br>1 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 49 |
| SPLEEN<br>HEMANGIOSARCOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50<br>1 |
| LYMPH NODES<br>MALIGNANT LYMPHOMA, MIXED TYPE | + | + | + | + | + | + | + | + | +<br>X | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | 48<br>1 |
| THYMUS | - | - | - | - | + | - | - | - | - | - | + | - | - | - | + | + | - | - | - | + | - | - | - | - | - | 13 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| LIVER<br>HEPATOCELLULAR ADENOMA<br>HEPATOCELLULAR CARCINOMA | + | +<br>X | + | + | + | +<br>X | + | + | + | +<br>X | +<br>X | + | + | + | + | + | + | +<br>X | + | +<br>X | +<br>X | + | + | +<br>X | + | 50<br>8<br>5 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | N | + | + | + | + | N | + | + | N | + | + | + | + | N | N | N | + | + | + | + | + | 50* |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 49 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| LARGE INTESTINE | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | 47 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| URINARY BLADDER<br>HEMANGIOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50<br>1 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | - | + | 44 |
| ADRENAL<br>PHEOCHROMOCYTOMA | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | - | + | + | + | + | + | 47<br>1 |
| THYROID<br>FOLLICULAR-CELL ADENOMA<br>FOLLICULAR-CELL CARCINOMA | + | +<br>X | + | + | + | + | + | + | + | - | + | - | + | + | + | + | + | + | + | - | + | + | + | + | + | 45<br>1<br>1 |
| PARATHYROID | + | - | - | + | - | - | + | - | + | - | + | - | + | - | + | - | - | - | + | - | - | - | - | + | + | 22 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50* |
| TESTIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| PROSTATE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HARDERIAN GLAND<br>ADENOMA, NOS | N | N | N | N<br>X | N | N | N | N<br>X | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N<br>X | N | N | N | 50*<br>3 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS<br>MALIGNANT LYMPHOMA, NOS | N | N | N | N | N | N | N | N | N | N | N | N<br>X | N<br>X | N | N | N | N | N | N | N | N | N | N | N | N | 50*<br>5 |

* ANIMALS NECROPSIED

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

## TABLE A3.

## INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF BIS(2-CHLORO-1-METHYLETHYL) ETHER

### LOW DOSE

| ANIMAL NUMBER | 001 | 002 | 003 | 004 | 005 | 006 | 007 | 008 | 009 | 010 | 011 | 012 | 013 | 014 | 015 | 016 | 017 | 018 | 019 | 020 | 021 | 022 | 023 | 024 | 025 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 106 | 073 | 106 | 106 | 106 | 106 | 106 | 101 | 099 | 106 | 106 | 106 | 106 | 103 | 106 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | X | | | | | | | | |
| ANGIOSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR CARCINOMA, METASTA | | X | | | | | | | | | | | | | | | | X | | | | | | | |
| ALVEOLAR/BRONCHIOLAR ADENOMA | X | | | X | | X | | | | | X | X | | | | X | X | | | | X | | | | |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | | | | | | | | | X | X | | | | | | | | | | | |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEMANGIOSARCOMA | | | | | | | | | X | | | | | | | | | | | | | | | | |
| LYMPH NODES | - | + | + | - | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| MALIGNANT LYMPHOMA, NOS | | | | | X | | | | | | | | | | | | | | | | | | | | |
| THYMUS | - | - | + | - | - | - | - | - | + | + | - | - | - | - | - | - | + | - | - | - | - | - | - | - | - |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR ADENOMA | X | | | | | | | | | | | | | X | X | | | | | | X | | | | |
| HEPATOCELLULAR CARCINOMA | | X | | X | | | | | | | | X | | | | X | | X | | X | | | | X | |
| HEMANGIOSARCOMA | | | X | | | | | | | | | | | | | | | | | | | | | | |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | N | N | + | N | N | + | + | + | + | + | + | N | N | + | + | + | + | + | + | + | + | + | N | N | + |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | | | | | | | | X | | | | | |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | - |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| CORTICAL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | X |
| THYROID | + | + | + | + | + | + | - | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + |
| FOLLICULAR-CELL CARCINOMA | | | | | | | | | | | | | X | | | | | | | | | | | | |
| PARATHYROID | - | + | - | - | + | - | - | + | - | + | - | - | - | - | + | + | - | + | + | + | + | + | - | - | + |
| PANCREATIC ISLETS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ISLET-CELL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| TESTIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PROSTATE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HARDERIAN GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| ADENOMA, NOS | | | | | | | | | | X | | | | | | X | | | | | | | | | |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | X | | | X | | | |

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

## TABLE A3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

| ANIMAL NUMBER | 026 | 027 | 028 | 029 | 030 | 031 | 032 | 033 | 034 | 035 | 036 | 037 | 038 | 039 | 040 | 041 | 042 | 043 | 044 | 045 | 046 | 047 | 048 | 049 | 050 | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 106 | 106 | 089 | 106 | 106 | 106 | 061 | 106 | 106 | 106 | 106 | 107 | 106 | 107 | 106 | 106 | 107 | 107 | 107 | 107 | 107 | 107 | 107 | 107 | 107 | TISSUES TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50M |
| FIBROSARCOMA | | | | | | | X | | | X | | | | | | | | | | | | | | | | 3 |
| ANGIOSARCOMA | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR CARCINOMA, METASTA | | | | | | | | | | | | | | | | | | | | X | | | | | | 4 |
| ALVEOLAR/BRONCHIOLAR ADENOMA | X | | | | | X | | | X | | | | | | | | | X | | | | X | | | | 13 |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEMANGIOSARCOMA | | | | | X | | | | | | | | | | X | | | | | | | | | | | 3 |
| LYMPH NODES | + | + | - | + | + | + | - | + | + | - | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | 43 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| THYMUS | - | + | - | + | + | + | - | - | - | - | + | - | + | + | - | - | - | - | - | - | - | - | - | - | - | 11 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR ADENOMA | X | | | X | | | | | | X | | | | | | | X | | X | | | | X | | | 10 |
| HEPATOCELLULAR CARCINOMA | | | | | X | | | | X | | | | | | X | | | | | X | X | | | X | | 13 |
| HEMANGIOSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| GALLBLADDER & COMMON BILE DUCT | + | N | + | + | + | N | N | + | + | + | N | N | + | + | + | N | N | + | + | N | + | + | N | + | + | 50M |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | X | | | | | | | | | | | | | | | | | 1 |
| SMALL INTESTINE | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | 48 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | 49 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | - | + | + | - | + | - | - | + | + | + | - | + | + | + | + | + | + | + | + | 42 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | | - | + | + | + | + | + | + | + | 49 |
| CORTICAL ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| THYROID | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| FOLLICULAR-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| PARATHYROID | - | - | + | - | + | - | - | - | + | - | - | + | + | + | - | + | - | - | - | - | - | - | + | - | + | 21 |
| PANCREATIC ISLETS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ISLET-CELL ADENOMA | | | | | | | | | | | | | | | | | | | | | X | | | | | 1 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50M |
| TESTIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| PROSTATE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HARDERIAN GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50M |
| ADENOMA, NOS | | | | | | | | | | | | | | | X | | | | | | | | X | | | 4 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50M |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 2 |

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

## TABLE A3.

## INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE 2-YEAR STUDY OF BIS(2-CHLORO-1-METHYLETHYL) ETHER

### HIGH DOSE

| ANIMAL NUMBER | 001 | 002 | 003 | 004 | 005 | 006 | 007 | 008 | 009 | 010 | 011 | 012 | 013 | 014 | 015 | 016 | 017 | 018 | 019 | 020 | 021 | 022 | 023 | 024 | 025 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 104 | 104 | 104 | 104 | 095 | 090 | 104 | 104 | 094 | 104 | 104 | 013 | 104 | 097 | 104 | 104 | 105 | 104 | 105 | 105 | 105 | 105 | 093 | 105 | 054 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR CARCINOMA, METASTA | | | | X | | | | | | | | | | | | | | | | | | | | | |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | X | | | | | | | | | X | | | | X | | | X | | | X | | | | |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| TRACHEA | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPH NODES | + | + | - | + | - | + | + | + | - | + | + | + | + | - | + | + | + | + | + | + | + | + | - | + | |
| MALIGNANT LYMPHOMA, NOS | X | | | | | | | | | | | | | | | | | | | | | | | | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | |
| THYMUS | + | - | + | - | - | - | + | + | - | - | - | - | - | - | + | + | + | - | + | + | - | - | - | - | - |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR ADENOMA | | X | | X | | | | X | | X | | | X | | | | | | X | | | | | | |
| HEPATOCELLULAR CARCINOMA | | | | X | | X | | X | | | | | | | | X | X | | X | | X | X | | | |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | N | + | N | + | N | + | + | N | + | + | N | + | + | N | + | + | + | N | + | + | + | + |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS | - | + | - | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| SARCOMA, NOS | | | | | X | | | | | | | | | | | | | | | | | | | | |
| SMALL INTESTINE | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TUBULAR-CELL ADENOCARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | X | |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | - | - | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| THYROID | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + |
| FOLLICULAR-CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| PARATHYROID | + | - | - | - | + | - | + | + | - | - | + | - | - | + | + | + | - | + | - | + | - | - | - | - | - |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| TESTIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PROSTATE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HARDERIAN GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| ADENOMA, NOS | | | X | | | | | | | | | | | | | | | | | | | | | | |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | X | | | | | | | | X | | | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | |
| CONNECTIVE TISSUE NOS | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEPATOCELLULAR CARCINOMA, INVASIV | | | | X | | | | | | | | | | | | | | | | | | | | | |

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

## TABLE A3. MALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

| ANIMAL NUMBER | 026 | 027 | 028 | 029 | 030 | 031 | 032 | 033 | 034 | 035 | 036 | 037 | 038 | 039 | 040 | 041 | 042 | 043 | 044 | 045 | 046 | 047 | 048 | 049 | 050 | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 105 | 105 | 105 | 025 | 108 | 081 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 105 | 025 | 100 | 105 | 105 | 105 | 105 | 100 | 105 | 105 | 105 | 074 | TISSUES TUMORS |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR CARCINOMA, METASTA | | | | | | | | X | | | | | | | | X | | | | | | | | | | 3 |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | X | X | | | | | | X | | | | | X | | | X | | | | | X | | | | 11 |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | X | | | | | | X | | | | | | | | | | | | | | | 2 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | 48 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *BONE MARROW* | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | 49 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | - | + | + | + | + | + | + | + | + | 48 |
| LYMPH NODES | + | + | + | - | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 43 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| THYMUS | - | - | - | - | - | - | + | - | - | - | + | + | + | - | + | - | + | + | - | + | - | + | - | + | - | 19 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR ADENOMA | | X | | | | | | | X | X | | | | X | | | X | | | X | | | | X | 13 |
| HEPATOCELLULAR CARCINOMA | | | | | | X | | X | | | X | X | X | | | X | | X | | | X | | | | X | 17 |
| *BILE DUCT* | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | + | N | + | + | + | + | + | + | N | + | + | N | + | N | + | + | + | + | + | + | + | 50* |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | X | | | | | | | | | | | | 1 |
| SARCOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| LARGE INTESTINE | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| TUBULAR-CELL ADENOCARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | + | + | + | - | - | + | + | - | + | + | + | + | + | + | + | + | + | + | 42 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| THYROID | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | 47 |
| FOLLICULAR-CELL CARCINOMA | | | | | X | | | | | | | | | | | | | | | | | | | | | 1 |
| PARATHYROID | - | + | - | - | + | - | - | + | - | + | - | + | - | - | - | - | - | - | - | - | + | + | - | + | + | 19 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50* |
| TESTIS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| PROSTATE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| *BRAIN* | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HARDERIAN GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50* |
| ADENOMA, NOS | | | | | | | X | | | | | | | | | | | | | | | | | | | 2 |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | X | | | 1 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50* |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | X | | | | | | | | | X | | | 3 |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | X | 2 |
| CONNECTIVE TISSUE NOS | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEPATOCELLULAR CARCINOMA, INVASIV | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: 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 MICE IN THE 2-YEAR STUDY OF BIS(2-CHLORO-1-METHYLETHYL) ETHER

### VEHICLE CONTROL

| ANIMAL NUMBER | 001 | 002 | 003 | 004 | 005 | 006 | 007 | 008 | 009 | 010 | 011 | 012 | 013 | 014 | 015 | 016 | 017 | 018 | 019 | 020 | 021 | 022 | 023 | 024 | 025 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 084 | 110 | 099 | 110 | 110 | 092 | 005 | 070 | 110 | 110 | 110 | 110 | 110 | 073 | 110 | 110 | 110 | 102 | 099 | 110 | 110 | 110 | 110 | 108 | 110 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| FIBROSARCOMA | | | | | | | | | | X | | | | | | | | | | | | | | | |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| ADENOSQUAMOUS CARCINOMA, METASTAT | | | | | | | | | | | | | | X | | | | | | | | | | | |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | X | | | |
| LYMPH NODES | + | + | + | + | + | + | - | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + |
| NEURILEMOMA, METASTATIC | | | | | | | | | | | | | | | | | | | | | | | | | |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | X | | | | | | | |
| THYMUS | - | + | + | + | + | - | - | - | - | - | - | + | - | - | - | - | - | - | - | - | + | + | + | - | - |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| HEPATOCELLULAR ADENOMA | | X | | X | | | | | | X | X | | | | | | | | | | | | | | |
| HEPATOCELLULAR CARCINOMA | | | | | X | | | | | | | | | | | | | | | | | | | | |
| MALIGNANT LYMPHOMA, MIXED TYPE | | | | | | | | | | | | | | | | | | | | | | | | | |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | + | N | + | + | + | N | + | + | + | + | + | + | + | + | + | + | + | N | N | + | + |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LEIOMYOMA | | | | | | | | | | | | | | | | | | | | | | | | | |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | + | + | + | + | + | + | - | - | + | - | + | + | + | + | + | - | + | |
| ADENOMA, NOS | | | | | | | | | | X | | | | | | | | | | | X | | | | |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + |
| THYROID | - | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PARATHYROID | - | + | + | + | + | - | - | - | - | + | - | - | + | - | - | + | - | - | + | + | + | - | - | - | - |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | + | + | N | N | N | N | N | N | N | N | + | N | + | + | + | N | N | N | N | + | N | N | N |
| ADENOSQUAMOUS CARCINOMA | | | | | | | | | | | | | | X | | | | | | | | | | | |
| UTERUS | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ENDOMETRIAL STROMAL POLYP | | | | | | | | | | | | | | | | | | | | | | | | | |
| NEURILEMOMA, MALIGNANT | | | | | | | | | | | | | | | | | | | | | | | | | |
| OVARY | + | + | + | + | + | + | - | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| MALIGNANT LYMPHOMA, NOS | X | | | | X | | | | | X | X | | | | X | X | X | | | X | | | | X | |

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

## TABLE A4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) VEHICLE CONTROL

| ANIMAL NUMBER | 026 | 027 | 028 | 029 | 030 | 031 | 032 | 033 | 034 | 035 | 036 | 037 | 038 | 039 | 040 | 041 | 042 | 043 | 044 | 045 | 046 | 047 | 048 | 049 | 050 | TOTAL TISSUES TUMORS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 110 | 110 | 087 | 110 | 110 | 110 | 070 | 110 | 067 | 073 | 085 | 110 | 110 | 110 | 091 | 110 | 110 | 110 | 110 | 084 | 043 | 043 | 043 | 043 | 043 | |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | + | 50* |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | X | | | | | | 2 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | X | | | | | | | | | | | | | | | | | | | | | | | 1 |
| ADENOSQUAMOUS CARCINOMA, METASTAT | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| LYMPH NODES | + | + | - | + | + | + | + | + | + | + | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | 45 |
| NEURILEMOMA, METASTATIC | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| THYMUS | + | + | - | - | - | - | - | - | - | - | - | + | - | + | - | - | - | + | + | - | - | - | - | + | + | 16 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR ADENOMA | | X | | | | | | | | | | | | | | | | | | | | | | | | 5 |
| HEPATOCELLULAR CARCINOMA | | | | | | | | | | | | | | | X | | | | | | | | | | | 2 |
| MALIGNANT LYMPHOMA, MIXED TYPE | X | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | N | + | + | 50* |
| PANCREAS | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | 48 |
| ESOPHAGUS | + | + | + | - | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | 46 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | - | + | + | 47 |
| LEIOMYOMA | | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | - | + | - | + | + | - | + | + | - | + | + | + | + | + | + | + | + | - | - | + | + | + | 40 |
| ADENOMA, NOS | | X | | | | | | | | | | | | X | | | | | | | | | | | | 4 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | 48 |
| THYROID | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | 46 |
| PARATHYROID | + | + | - | - | + | - | - | + | - | - | + | + | + | + | + | + | + | + | + | + | - | - | + | + | + | 27 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | + | N | N | N | N | + | + | N | N | + | N | N | + | N | N | N | N | N | N | N | + | + | N | N | N | 50* |
| ADENOSQUAMOUS CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| ENDOMETRIAL STROMAL POLYP | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| NEURILEMOMA, MALIGNANT | | | | | | | | | | | | | | | | | X | | | | | | | | | 1 |
| OVARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | 47 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50* |
| MALIGNANT LYMPHOMA, NOS | | | | | | X | | | | | | | | X | | X | | | | | | | | | | 12 |

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: 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 MICE IN THE 2-YEAR STUDY OF BIS(2-CHLORO-1-METHYLETHYL) ETHER

### LOW DOSE

| ANIMAL NUMBER | 001 | 002 | 003 | 004 | 005 | 006 | 007 | 008 | 009 | 010 | 011 | 012 | 013 | 014 | 015 | 016 | 017 | 018 | 019 | 021 | 022 | 023 | 024 | 025 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 107 | 107 | 107 | 107 | 107 | 075 | 004 | 107 | 107 | 107 | 107 | 107 | 107 | 107 | 107 | 108 | 107 | 093 | 107 | 107 | 043 | 043 | 043 | 043 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE<br>FIBROSARCOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI<br>HEPATOCELLULAR CARCINOMA, METASTA<br>ALVEOLAR/BRONCHIOLAR ADENOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN<br>MALIGNANT LYMPHOMA, NOS | + | + | + | + | + | + | + | + | + | + | + | + X | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPH NODES | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| THYMUS | - | - | - | - | - | - | + | - | - | - | - | - | - | + | - | + | - | - | - | + | + | + | + | + |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LIVER<br>HEPATOCELLULAR ADENOMA<br>HEPATOCELLULAR CARCINOMA | + | + | + | + | + | + | + X | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | N |
| PANCREAS | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY<br>ADENOMA, NOS | - | + | + | + | + | - | - | + | + | + | + | + | + | + X | + | + | + | - | + | + X | + | + | + | + |
| ADRENAL<br>PHEOCHROMOCYTOMA | + | + | + | + | + | + | + | + | + | + | + | + | + X | + | + | + | + | + | + | + | + | + | + | + |
| THYROID | + | + | + | + | + | + | - | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + |
| PARATHYROID | - | - | + | + | - | + | - | - | + | - | - | + | + | + | + | + | + | - | + | + | + | + | + | + |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND<br>ADENOCARCINOMA, NOS<br>CYSTADENOCARCINOMA, NOS | + | N | N | + | N | + | N | + | + | N | + | N | + | + | + | N | + | N | N | + X | + | N | N | N |
| VAGINA<br>SQUAMOUS CELL CARCINOMA | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N X | N | N | N | N | N | N | N | N |
| UTERUS | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| OVARY | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS<br>MALIGNANT LYMPHOMA, NOS<br>MALIG.LYMPHOMA, HISTIOCYTIC TYPE | N<br>X | N | N<br>X | N | N<br>X | N | N | N | N | N<br>X | N | N | N | N | N<br>X | N<br>X | N<br>X | N<br>X | N | N | N | N | N | N |

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION

: NO TISSUE INFORMATION SUBMITTED
C: NECROPSY, NO HISTOLOGY DUE TO PROTOCOL
A: AUTOLYSIS
M: ANIMAL MISSING
B: NO NECROPSY PERFORMED

## TABLE A4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) LOW DOSE

| ANIMAL NUMBER | 026 | 027 | 028 | 029 | 030 | 031 | 032 | 033 | 034 | 035 | 036 | 037 | 038 | 039 | 040 | 041 | 042 | 043 | 044 | 045 | 046 | 047 | 048 | 049 | 050 | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 108 | 108 | 053 | 108 | 108 | 109 | 109 | 109 | 107 | 109 | 061 | 069 | 109 | 109 | 109 | 109 | 109 | 109 | 109 | 100 | 080 | 079 | 109 | 109 | 078 | TISSUES TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50* |
| FIBROSARCOMA | | | | | | | | | | | X | | | | | | | | | | | | | | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR CARCINOMA, METASTA | | | | | | | | | | | | | | | | | | X | | | | | | | | 1 |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | | | | X | | | | | | | X | X | X | | | | | | | | | | 4 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | • | + | + | + | + | + | + | + | + | + | 49 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| MALIGNANT LYMPHOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| LYMPH NODES | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | - | + | - | - | + | - | + | + | + | - | 43 |
| THYMUS | - | + | - | - | - | - | + | - | - | - | - | + | + | - | + | - | - | - | - | - | - | - | - | - | - | 14 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR ADENOMA | | X | | | | | | | | | | | | | | | | | X | | | | | | | 4 |
| HEPATOCELLULAR CARCINOMA | | | | | | | X | | | | | | | | | | | X | | X | | | | | | 3 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| GALLBLADDER & COMMON BILE DUCT | + | N | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | + | 50* |
| PANCREAS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| ESOPHAGUS | + | - | + | - | - | - | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 44 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LARGE INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | + | + | + | + | + | + | - | + | + | - | - | + | + | + | + | - | + | - | + | + | + | + | - | + | 40 |
| ADENOMA, NOS | | | X | | | | | | | | | | | X | | | | | | X | | | | | | 5 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| PHEOCHROMOCYTOMA | | | | X | | | | | | | | | | | | | | | | | | | | | | 2 |
| THYROID | + | + | + | + | + | + | + | + | + | - | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 46 |
| PARATHYROID | + | - | - | + | - | - | - | - | - | - | + | + | - | - | - | - | + | - | - | + | - | - | - | - | + | 24 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | + | N | N | N | N | N | + | + | N | N | + | N | N | N | N | + | 50* |
| ADENOCARCINOMA, NOS | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| CYSTADENOCARCINOMA, NOS | | | | | | | | | | | | | | | | | | | | X | | | | | | 1 |
| VAGINA | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50* |
| SQUAMOUS CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| UTERUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| OVARY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50* |
| MALIGNANT LYMPHOMA, NOS | X | | | X | | | | | X | | | | | | | | | | X | | | | | | X | 13 |
| MALIG.LYMPHOMA, HISTIOCYTIC TYPE | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |

* ANIMALS NECROPSIED

+: TISSUE EXAMINED MICROSCOPICALLY
-: REQUIRED TISSUE NOT EXAMINED MICROSCOPICALLY
X: TUMOR INCIDENCE
N: NECROPSY, NO AUTOLYSIS, NO MICROSCOPIC EXAMINATION
: 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 MICE IN THE 2-YEAR STUDY OF BIS(2-CHLORO-1-METHYLETHYL) ETHER

### HIGH DOSE

| ANIMAL NUMBER | 0 0 1 | 0 0 2 | 0 0 3 | 0 0 4 | 0 0 5 | 0 0 6 | 0 0 7 | 0 0 8 | 0 0 9 | 0 1 0 | 0 1 1 | 0 1 2 | 0 1 3 | 0 1 4 | 0 1 5 | 0 1 6 | 0 1 7 | 0 1 8 | 0 1 9 | 0 2 0 | 0 2 1 | 0 2 2 | 0 2 3 | 0 2 4 | 0 2 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 0 9 1 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 9 1 | 1 0 6 | 1 0 4 2 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 5 | 1 0 6 8 | 1 0 6 | 1 0 6 | 1 0 9 0 | 1 0 1 2 | 1 0 8 1 | 1 0 7 2 | 1 0 6 | 1 0 6 | 1 0 8 0 | 1 0 8 6 | 1 0 7 3 | 1 0 8 4 | 0 7 1 |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE FIBROSARCOMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI ALVEOLAR/BRONCHIOLAR ADENOMA ALVEOLAR/BRONCHIOLAR CARCINOMA | + | + X | + | + | + | + | + | + | + | + X | + | + | + | + | + X | + | + | + | + | + | + | + | + | + | + |
| TRACHEA | + | + | + | + | + | + | + | - | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SPLEEN HEMANGIOSARCOMA MALIGNANT LYMPHOMA, NOS | + | + | + | + | + | + | + | + | + | + | + | + X | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LYMPH NODES | + | + | + | + | - | + | - | + | + | + | + | + | + | + | - | + | - | + | + | + | + | + | + | + | + |
| THYMUS | - | + | - | + | - | - | - | - | - | - | - | - | - | - | - | - | - | - | - | + | - | - | - | - | - |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + |
| LIVER HEPATOCELLULAR ADENOMA HEPATOCELLULAR CARCINOMA HEMANGIOMA | + X | + X | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| GALLBLADDER & COMMON BILE DUCT | N | + | + | + | + | + | + | + | + | + | N | + | + | + | + | + | N | + | + | N | N | + | N | + | + |
| PANCREAS SQUAMOUS CELL CARCINOMA, METASTAT | + | + | + | + | + X | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + |
| STOMACH SQUAMOUS CELL PAPILLOMA SQUAMOUS CELL CARCINOMA | - | + | + | + | + X | + | + | + | + | + | + X | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| LARGE INTESTINE | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| URINARY BLADDER | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY ADENOMA, NOS | - | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | - | + | + X | + | - | - | + | - |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| THYROID | + | + | + | + | + | + | + | - | + | - | + | + | - | + | + | + | + | + | - | + | + | + | + | + | + |
| PARATHYROID | - | + | - | + | - | + | - | - | - | - | + | + | - | - | - | - | - | + | - | - | + | + | + | + | - |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | N | + | N | N | + | N | N | N | N | + | N | + | N | N | N | N | + | N | N | N | + | + | N |
| UTERUS NEUROFIBROMA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| OVARY SQUAMOUS CELL CARCINOMA, METASTAT | + | | | + | + X | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| HARDERIAN GLAND ADENOMA, 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 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS MALIGNANT LYMPHOMA, NOS MALIG.LYMPHOMA, LYMPHOCYTIC TYPE MALIGNANT LYMPHOMA, MIXED TYPE | N | N X | N | N | N | N | N | N | N X | N | N | N | N | N | N | N X | N | N X | N | N | N | N X | N | N | N |

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

# TABLE A4. FEMALE MICE: TUMOR PATHOLOGY (CONTINUED) HIGH DOSE

| ANIMAL NUMBER | 026 | 027 | 028 | 029 | 030 | 031 | 032 | 033 | 034 | 035 | 036 | 037 | 038 | 039 | 040 | 041 | 042 | 043 | 044 | 045 | 046 | 047 | 048 | 049 | 050 | TOTAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WEEKS ON STUDY | 093 | 106 | 106 | 106 | 003 | 106 | 097 | 106 | 106 | 093 | 091 | 106 | 106 | 106 | 091 | 078 | 106 | 106 | 106 | 091 | 106 | 106 | 106 | 081 | 106 | TISSUES TUMORS |
| **INTEGUMENTARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SUBCUTANEOUS TISSUE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50M |
| FIBROSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | X | | 1 |
| **RESPIRATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| LUNGS AND BRONCHI | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| ALVEOLAR/BRONCHIOLAR ADENOMA | | | | | | | | | X | X | | | | | | X | | X | | | X | X | | | | 8 |
| ALVEOLAR/BRONCHIOLAR CARCINOMA | | | | | | | | | | | | | | | | | X | | | | | | | | | 2 |
| TRACHEA | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| **HEMATOPOIETIC SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BONE MARROW | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| SPLEEN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEMANGIOSARCOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| MALIGNANT LYMPHOMA, NOS | | | | X | | | | | | | | | | | | | | | | | | | | | | 1 |
| LYMPH NODES | + | + | + | + | - | + | + | + | - | + | - | + | + | + | + | + | + | + | + | + | + | - | + | + | + | 42 |
| THYMUS | + | - | - | - | - | + | - | + | + | - | - | - | - | + | + | - | - | - | + | - | + | - | - | - | - | 11 |
| **CIRCULATORY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HEART | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **DIGESTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| SALIVARY GLAND | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | - | + | + | + | 47 |
| LIVER | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| HEPATOCELLULAR ADENOMA | | | | | | | | | | | | | | | | | | X | X | | X | | | | | 3 |
| HEPATOCELLULAR CARCINOMA | | | | | | | | | | | | | | | | | | | | X | | | | | | 2 |
| HEMANGIOMA | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| BILE DUCT | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| GALLBLADDER & COMMON BILE DUCT | N | N | + | + | + | + | N | + | + | N | N | + | + | + | N | + | + | + | + | + | + | + | + | + | + | 50M |
| PANCREAS | + | + | + | + | - | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| SQUAMOUS CELL CARCINOMA, METASTAT | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| ESOPHAGUS | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | 48 |
| STOMACH | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49 |
| SQUAMOUS CELL PAPILLOMA | | | | | | | | | | | | | | | X | | | | | | | | | | | 2 |
| SQUAMOUS CELL CARCINOMA | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| SMALL INTESTINE | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| LARGE INTESTINE | + | + | + | + | + | + | + | • | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| **URINARY SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| KIDNEY | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| URINARY BLADDER | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 48 |
| **ENDOCRINE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PITUITARY | + | - | + | + | + | + | + | + | + | - | - | + | - | + | + | + | + | + | + | + | + | + | + | + | + | 40 |
| ADENOMA, NOS | | | | | | | | X | | | | | | | | | | | | | | X | | | | 3 |
| ADRENAL | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | - | + | + | + | + | + | + | + | + | + | 49 |
| THYROID | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 45 |
| PARATHYROID | + | - | - | - | - | - | - | + | + | - | - | + | - | + | + | - | + | + | + | + | + | + | - | + | | 24 |
| **REPRODUCTIVE SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MAMMARY GLAND | N | N | N | N | N | N | N | N | N | N | N | + | + | N | N | + | + | N | N | N | + | N | N | N | N | 50M |
| UTERUS | + | + | + | + | - | + | + | + | + | + | + | + | + | + | + | + | • | + | + | - | + | + | + | + | + | 48 |
| NEUROFIBROMA | | | | | | | | | | | | | | | | | | | X | | | | | | | 1 |
| OVARY | + | + | + | + | - | + | - | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 47 |
| SQUAMOUS CELL CARCINOMA, METASTAT | | | | | | | | | | | | | | | | | | | | | | | | | | 1 |
| **NERVOUS SYSTEM** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| BRAIN | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50 |
| **SPECIAL SENSE ORGANS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| HARDERIAN GLAND | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50M |
| ADENOMA, NOS | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |
| **ALL OTHER SYSTEMS** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| MULTIPLE ORGANS NOS | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | 50M |
| MALIGNANT LYMPHOMA, NOS | | | | | | X | | | | | | | X | | | | | | | | | | | | | 7 |
| MALIG.LYMPHOMA, LYMPHOCYTIC TYPE | X | | | | | | | | | | | | | | | | | | | X | | | | | | 2 |
| MALIGNANT LYMPHOMA, MIXED TYPE | | | | | | | X | | | | | | | | | | | | | | | | | | | 1 |

M ANIMALS NECROPSIED

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

# APPENDIX B

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE ADMINISTERED BIS(2-CHLORO-1-METHYLETHYL) ETHER IN CORN OIL BY GAVAGE

## TABLE B1.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED BIS(2-CHLORO-1-METHYLETHYL) ETHER IN CORN OIL BY GAVAGE

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *SKIN | (50) | (50) | (50) |
| ULCER, ACUTE | 1 (2%) | | |
| *SUBCUT TISSUE | (50) | (50) | (50) |
| STEATITIS | | | 1 (2%) |
| ABSCESS, NOS | 1 (2%) | | |
| RESPIRATORY SYSTEM | | | |
| *NASAL CAVITY | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| INFLAMMATION, CHRONIC | | | 30 (60%) |
| #LUNG/BRONCHIOLE | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| #LUNG | (50) | (50) | (50) |
| HEMORRHAGE | | | 3 (6%) |
| BRONCHOPNEUMONIA, CHRONIC | 1 (2%) | | |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | | 1 (2%) | 1 (2%) |
| #LUNG/ALVEOLI | (50) | (50) | (50) |
| HYPERPLASIA, ATYPICAL | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| #SPLEEN | (50) | (50) | (48) |
| LYMPHOID DEPLETION | | 1 (2%) | |
| HEMATOPOIESIS | 2 (4%) | 1 (2%) | 2 (4%) |
| #LYMPH NODE | (48) | (43) | (43) |
| CONGESTION, NOS | 1 (2%) | | |

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

## TABLE B1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HYPERPLASIA, LYMPHOID | | 1 (2%) | |
| #MESENTERIC L. NODE | (48) | (43) | (43) |
| CONGESTION, NOS | 15 (31%) | 13 (30%) | 6 (14%) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| HYPERPLASIA, LYMPHOID | 2 (4%) | 2 (5%) | |
| #LUNG | (50) | (50) | (50) |
| LEUKOCYTOSIS, NOS | 1 (2%) | | |
| #KIDNEY/TUBULE | (50) | (50) | (50) |
| BASOPHILIC STIPPLING | 1 (2%) | 1 (2%) | 4 (8%) |
| **CIRCULATORY SYSTEM** | | | |
| #LUNG | (50) | (50) | (50) |
| PERIVASCULITIS | | | 1 (2%) |
| #MYOCARDIUM | (50) | (50) | (50) |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| #CARDIAC VALVE | (50) | (50) | (50) |
| ENDOCARDITIS, BACTERIAL | 4 (8%) | | |
| *MEDIASTINAL ARTERY | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| **DIGESTIVE SYSTEM** | | | |
| #LIVER | (50) | (50) | (50) |
| CYST, NOS | 1 (2%) | | |
| INFLAMMATION, CHRONIC FOCAL | 1 (2%) | | |
| NECROSIS, FOCAL | | 1 (2%) | 2 (4%) |
| NECROSIS, COAGULATIVE | | 1 (2%) | |
| METAMORPHOSIS FATTY | 1 (2%) | 6 (12%) | 14 (28%) |
| CYTOPLASMIC CHANGE, NOS | | 1 (2%) | |
| CLEAR-CELL CHANGE | 1 (2%) | | |
| ANGIECTASIS | | | 1 (2%) |
| #HEPATIC CAPSULE | (50) | (50) | (50) |
| INFLAMMATION, ACUTE FIBRINOUS | | | 1 (2%) |
| #LIVER/CENTRILOBULAR | (50) | (50) | (50) |
| NECROSIS, NOS | | | 1 (2%) |

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

## TABLE B1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| METAMORPHOSIS FATTY | 1 (2%) | 10 (20%) | |
| HEPATOCYTOMEGALY | 1 (2%) | | |
| #LIVER/PERIPORTAL | (50) | (50) | (50) |
| METAMORPHOSIS FATTY | | | 1 (2%) |
| #BILE DUCT | (50) | (50) | (50) |
| DISTENTION | | | 1 (2%) |
| RETENTION OF CONTENT | | | 1 (2%) |
| CYST, NOS | | 1 (2%) | 1 (2%) |
| #PANCREAS | (48) | (50) | (50) |
| DILATATION/DUCTS | 1 (2%) | | 1 (2%) |
| INFLAMMATION, ACUTE FOCAL | 1 (2%) | | |
| INFLAMMATION, CHRONIC | | | 2 (4%) |
| ATROPHY, NOS | 1 (2%) | | |
| #PANCREATIC ACINUS | (48) | (50) | (50) |
| ATROPHY, FOCAL | | 1 (2%) | |
| #DUODENUM | (49) | (49) | (49) |
| HYPERPLASIA, ADENOMATOUS | | 1 (2%) | |
| URINARY SYSTEM | | | |
| #KIDNEY | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC | | 1 (2%) | |
| INFLAMMATION, CHRONIC FOCAL | | | 3 (6%) |
| GLOMERULOSCLEROSIS, NOS | | 1 (2%) | 1 (2%) |
| #KIDNEY/CORTEX | (50) | (50) | (50) |
| INFLAMMATION, INTERSTITIAL | 1 (2%) | | |
| INFLAMMATION, CHRONIC FOCAL | 1 (2%) | | |
| METAPLASIA, OSSEOUS | | | 1 (2%) |
| #RENAL PAPILLA | (50) | (50) | (50) |
| FIBROSIS, FOCAL | | | 1 (2%) |
| #PERIRENAL TISSUE | (50) | (50) | (50) |
| NECROSIS, FAT | | 1 (2%) | |
| #KIDNEY/TUBULE | (50) | (50) | (50) |
| CYST, NOS | | 3 (6%) | 1 (2%) |
| METAMORPHOSIS FATTY | | | 1 (2%) |

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

## TABLE B1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (44) | (42) | (42) |
| CYST, NOS | 1 (2%) | | |
| #ADRENAL | (47) | (49) | (50) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| #ADRENAL CORTEX | (47) | (49) | (50) |
| HYPERPLASIA, FOCAL | | | 1 (2%) |
| #ADRENAL MEDULLA | (47) | (49) | (50) |
| HYPERPLASIA, FOCAL | | 1 (2%) | 1 (2%) |
| #THYROID | (45) | (47) | (47) |
| CYSTIC FOLLICLES | 1 (2%) | | |
| #PANCREATIC ISLETS | (48) | (50) | (50) |
| HYPERPLASIA, NOS | | 2 (4%) | |
| REPRODUCTIVE SYSTEM | | | |
| *PENIS | (50) | (50) | (50) |
| INFLAMMATION, ACUTE | | 1 (2%) | |
| *PREPUCE | (50) | (50) | (50) |
| INFLAMMATION, ACUTE | | 1 (2%) | |
| *PREPUTIAL GLAND | (50) | (50) | (50) |
| CYSTIC DUCTS | 1 (2%) | 1 (2%) | 1 (2%) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| INFLAMMATION, CHRONIC | 2 (4%) | | |
| *SEMINAL VESICLE | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| #TESTIS/TUBULE | (50) | (50) | (50) |
| DEGENERATION, NOS | 1 (2%) | 1 (2%) | 1 (2%) |
| CALCIFICATION, FOCAL | | | 1 (2%) |
| *EPIDIDYMIS | (50) | (50) | (50) |
| NECROSIS, FAT | | | 1 (2%) |

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

## TABLE B1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| NERVOUS SYSTEM | | | |
| #BRAIN | (50) | (50) | (50) |
| HEMORRHAGE | | | 1 (2%) |
| #CEREBRAL CORTEX | (50) | (50) | (50) |
| HEMORRHAGE | 1 (2%) | | |
| SPECIAL SENSE ORGANS | | | |
| *NASOLACRIMAL DUCT | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| INFLAMMATION, CHRONIC | | | 28 (56%) |
| MUSCULOSKELETAL SYSTEM | | | |
| *SKELETAL MUSCLE | (50) | (50) | (50) |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| BODY CAVITIES | | | |
| *ABDOMINAL CAVITY | (50) | (50) | (50) |
| NECROSIS, FAT | | 1 (2%) | 1 (2%) |
| *PERICARDIUM | (50) | (50) | (50) |
| INFLAMMATION, ACUTE FOCAL | 1 (2%) | | |
| *MESENTERY | (50) | (50) | (50) |
| HEMORRHAGE | 1 (2%) | | |
| ALL OTHER SYSTEMS | | | |
| OMENTUM | | | |
| STEATITIS | | | 1 |
| ABSCESS, NOS | | | 1 |
| NECROSIS, FAT | | | 1 |
| SPECIAL MORPHOLOGY SUMMARY | | | |
| NO LESION REPORTED | 2 | 4 | 3 |

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

## TABLE B2.

## SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED BIS(2-CHLORO-1-METHYLETHYL) ETHER IN CORN OIL BY GAVAGE

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ANIMALS INITIALLY IN STUDY | 50 | 50 | 50 |
| ANIMALS NECROPSIED | 50 | 50 | 50 |
| ANIMALS EXAMINED HISTOPATHOLOGICALLY | 50 | 50 | 50 |
| INTEGUMENTARY SYSTEM | | | |
| *SUBCUT TISSUE | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| RESPIRATORY SYSTEM | | | |
| #TRACHEA | (50) | (49) | (48) |
| INFLAMMATION, ACUTE | | 1 (2%) | |
| #LUNG/BRONCHIOLE | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC DIFFUSE | 1 (2%) | | |
| #LUNG | (50) | (50) | (50) |
| CONGESTION, NOS | 4 (8%) | 4 (8%) | |
| HEMORRHAGE | | | 1 (2%) |
| INFLAMMATION, INTERSTITIAL | | | 2 (4%) |
| INFLAMMATION, NECROTIZING | | | 1 (2%) |
| BRONCHOPNEUMONIA, ACUTE | | 1 (2%) | |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| INFLAMMATION, ACUTE SUPPURATIVE | | | 1 (2%) |
| ABSCESS, NOS | 1 (2%) | | |
| HYPERPLASIA, ALVEOLAR EPITHELIUM | 1 (2%) | 1 (2%) | 1 (2%) |
| #LUNG/ALVEOLI | (50) | (50) | (50) |
| HISTIOCYTOSIS | | | 1 (2%) |
| HEMATOPOIETIC SYSTEM | | | |
| #BONE MARROW | (49) | (50) | (49) |
| MYELOPOIESIS | | | 1 (2%) |
| #SPLEEN | (50) | (50) | (50) |
| ANGIECTASIS | 1 (2%) | | |

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

## TABLE B2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| HYPERPLASIA, LYMPHOID | 1 (2%) | | 4 (8%) |
| HEMATOPOIESIS | 7 (14%) | 4 (8%) | 8 (16%) |
| #SPLENIC CAPSULE | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| #LUMBAR LYMPH NODE | (45) | (43) | (42) |
| CYST, NOS | | 1 (2%) | |
| #MESENTERIC L. NODE | (45) | (43) | (42) |
| HEMORRHAGE | 1 (2%) | | |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| HEMATOPOIESIS | 1 (2%) | | |
| #LUNG | (50) | (50) | (50) |
| LEUKOCYTOSIS, NOS | | | 1 (2%) |
| #LIVER | (50) | (50) | (50) |
| HEMATOPOIESIS | 1 (2%) | 1 (2%) | 1 (2%) |
| #PEYER'S PATCH | (50) | (50) | (50) |
| HYPERPLASIA, LYMPHOID | 3 (6%) | | |
| CIRCULATORY SYSTEM | | | |
| #MESENTERIC L. NODE | (45) | (43) | (42) |
| THROMBOSIS, NOS | 1 (2%) | | |
| #HEART | (50) | (50) | (50) |
| FIBROSIS, DIFFUSE | | 1 (2%) | |
| #MYOCARDIUM | (50) | (50) | (50) |
| INFLAMMATION, ACUTE | | 1 (2%) | |
| #CARDIAC VALVE | (50) | (50) | (50) |
| ENDOCARDITIS, BACTERIAL | | | 1 (2%) |
| *CORONARY ARTERY | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| PERIARTERITIS | | 1 (2%) | |
| HYPERTROPHY, NOS | | 1 (2%) | |
| #PANCREAS | (48) | (49) | (48) |
| PERIVASCULITIS | 1 (2%) | | |

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

## TABLE B2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #KIDNEY | (50) | (49) | (50) |
| EMBOLUS, SEPTIC | | 1 (2%) | |
| #URINARY BLADDER | (50) | (50) | (48) |
| PERIVASCULITIS | 1 (2%) | | |
| DIGESTIVE SYSTEM | | | |
| #LIVER | (50) | (50) | (50) |
| HEMORRHAGE | | 1 (2%) | |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| ABSCESS, NOS | | | 1 (2%) |
| INFLAMMATION, CHRONIC FOCAL | | 1 (2%) | 1 (2%) |
| METAMORPHOSIS FATTY | 3 (6%) | 3 (6%) | 4 (8%) |
| HEPATOCYTOMEGALY | | 1 (2%) | |
| ANGIECTASIS | | | 1 (2%) |
| #HEPATIC CAPSULE | (50) | (50) | (50) |
| INFLAMMATION, ACUTE FIBRINOUS | 1 (2%) | | 1 (2%) |
| #LIVER/CENTRILOBULAR | (50) | (50) | (50) |
| NECROSIS, NOS | 1 (2%) | | |
| #LIVER/KUPFFER CELL | (50) | (50) | (50) |
| HYPERPLASIA, FOCAL | | 1 (2%) | |
| *GALLBLADDER/SEROSA | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| INFLAMMATION, ACUTE | 2 (4%) | | 2 (4%) |
| INFLAMMATION, ACUTE FIBRINOUS | 1 (2%) | | |
| #BILE DUCT | (50) | (50) | (50) |
| INFLAMMATION, CHRONIC DIFFUSE | 1 (2%) | | |
| #PANCREAS | (48) | (49) | (48) |
| DILATATION/DUCTS | | 2 (4%) | 1 (2%) |
| CYSTIC DUCTS | 1 (2%) | 1 (2%) | |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| INFLAMMATION, ACUTE FIBRINOUS | | | 1 (2%) |
| INFLAMMATION, CHRONIC | 1 (2%) | 1 (2%) | |
| ATROPHY, NOS | 1 (2%) | 3 (6%) | 1 (2%) |
| #PANCREATIC ACINUS | (48) | (49) | (48) |
| ATROPHY, FOCAL | 1 (2%) | | |

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

## TABLE B2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #ESOPHAGUS | (46) | (44) | (48) |
| INFLAMMATION, ACUTE | | 1 (2%) | |
| #STOMACH | (50) | (49) | (49) |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| #GASTRIC SEROSA | (50) | (49) | (49) |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| #FORESTOMACH | (50) | (49) | (49) |
| INFLAMMATION, CHRONIC | 1 (2%) | | |
| #SMALL INTEST./SEROSA | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| URINARY SYSTEM | | | |
| #KIDNEY | (50) | (49) | (50) |
| PYELONEPHRITIS, ACUTE | | 1 (2%) | 2 (4%) |
| INFLAMMATION, CHRONIC | | | 1 (2%) |
| GLOMERULONEPHRITIS, CHRONIC | 1 (2%) | | 1 (2%) |
| GLOMERULOSCLEROSIS, NOS | 1 (2%) | 1 (2%) | |
| #KIDNEY/CAPSULE | (50) | (49) | (50) |
| INFLAMMATION, ACUTE FIBRINOUS | | | 1 (2%) |
| #KIDNEY/CORTEX | (50) | (49) | (50) |
| CYST, NOS | 1 (2%) | | |
| INFLAMMATION, INTERSTITIAL | 1 (2%) | | |
| INFARCT, HEALED | | 1 (2%) | |
| #PERIRENAL TISSUE | (50) | (49) | (50) |
| HEMORRHAGIC CYST | 1 (2%) | | |
| #U.BLADDER/SEROSA | (50) | (50) | (48) |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| INFLAMMATION, ACUTE FIBRINOUS | 1 (2%) | | |
| ENDOCRINE SYSTEM | | | |
| #PITUITARY | (40) | (40) | (40) |
| ANGIECTASIS | | | 1 (3%) |

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

## TABLE B2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| #ADRENAL | (48) | (50) | (49) |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| #ADRENAL/CAPSULE | (48) | (50) | (49) |
| INFLAMMATION, ACUTE | | 1 (2%) | 1 (2%) |
| #ADRENAL CORTEX | (48) | (50) | (49) |
| HEMORRHAGE | | | 1 (2%) |
| #THYROID | (46) | (46) | (45) |
| HYPERPLASIA, C-CELL | 1 (2%) | | |
| HYPERPLASIA, FOLLICULAR-CELL | 1 (2%) | | |
| #PARATHYROID | (27) | (24) | (24) |
| CYST, NOS | | 1 (4%) | |
| #PANCREATIC ISLETS | (48) | (49) | (48) |
| HYPERPLASIA, NOS | | 1 (2%) | |
| REPRODUCTIVE SYSTEM | | | |
| #UTERUS | (49) | (49) | (48) |
| HYDROMETRA | | | 2 (4%) |
| INFLAMMATION, SUPPURATIVE | 2 (4%) | | 1 (2%) |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| NECROSIS, NOS | 1 (2%) | | |
| #UTERINE SEROSA | (49) | (49) | (48) |
| INFLAMMATION, ACUTE | 1 (2%) | | |
| #UTERUS/ENDOMETRIUM | (49) | (49) | (48) |
| INFLAMMATION, SUPPURATIVE | 2 (4%) | 1 (2%) | 3 (6%) |
| HYPERPLASIA, CYSTIC | 30 (61%) | 35 (71%) | 34 (71%) |
| #FALLOPIAN TUBE | (49) | (49) | (48) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| #OVARY | (47) | (49) | (47) |
| CYST, NOS | 9 (19%) | 5 (10%) | 9 (19%) |
| FOLLICULAR CYST, NOS | | 2 (4%) | |
| HEMORRHAGIC CYST | 1 (2%) | 1 (2%) | 2 (4%) |
| INFLAMMATION, SUPPURATIVE | 3 (6%) | 2 (4%) | 3 (6%) |
| INFLAMMATION, ACUTE | 1 (2%) | | |

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

## TABLE B2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| ABSCESS, NOS | 4 (9%) | 1 (2%) | 3 (6%) |
| INFLAMMATION, CHRONIC | 2 (4%) | | 1 (2%) |
| #RIGHT OVARY | (47) | (49) | (47) |
| INFLAMMATION, SUPPURATIVE | | | 1 (2%) |
| INFLAMMATION, ACUTE | | | 1 (2%) |
| #LEFT OVARY | (47) | (49) | (47) |
| FOLLICULAR CYST, NOS | | | 1 (2%) |
| ABSCESS, NOS | | | 1 (2%) |
| **NERVOUS SYSTEM** | | | |
| #CEREBRAL CORTEX | (50) | (50) | (50) |
| HEMORRHAGE | | 1 (2%) | |
| INFLAMMATION, ACUTE FOCAL | | 1 (2%) | |
| **SPECIAL SENSE ORGANS** | | | |
| NONE | | | |
| **MUSCULOSKELETAL SYSTEM** | | | |
| NONE | | | |
| **BODY CAVITIES** | | | |
| *ABDOMINAL CAVITY | (50) | (50) | (50) |
| ABSCESS, NOS | | | 1 (2%) |
| NECROSIS, FAT | 1 (2%) | | |
| *PERITONEUM | (50) | (50) | (50) |
| INFLAMMATION, SUPPURATIVE | 1 (2%) | | |
| INFLAMMATION, ACUTE FIBRINOUS | 2 (4%) | 1 (2%) | |
| *PLEURA | (50) | (50) | (50) |
| INFLAMMATION, ACUTE FIBRINOUS | | 1 (2%) | 1 (2%) |
| **ALL OTHER SYSTEMS** | | | |
| OMENTUM | | | |
| INFLAMMATION, ACUTE | 1 | | |

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

## TABLE B2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

| | VEHICLE CONTROL | LOW DOSE | HIGH DOSE |
|---|---|---|---|
| INFLAMMATION, CHRONIC | | | 1 |
| NECROSIS, FAT | | 1 | |

SPECIAL MORPHOLOGY SUMMARY

NONE

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

# APPENDIX C

## ANALYSIS OF BIS(2-CHLORO-1-METHYLETHYL) ETHER MIDWEST RESEARCH INSTITUTE

# APPENDIX C

## A. ELEMENTAL ANALYSIS

| Element: | C | H | Cl | 0 |
|---|---|---|---|---|
| Theory: | 42.12 | 7.07 | 41.45 | 9.35 |
| Found: Lot No. 7 | 41.92 | 6.93 | 41.78 | |
| | 41.85 | 7.05 | 41.74 | |
| Lot No. I62976 | 42.14 | 7.05 | 41.37 | |
| | 42.28 | 7.12 | 41.43 | |
| Lot No. A2279 | 41.34 | 6.60 | 42.98 | 9.02 |
| | 41.78 | 6.46 | 42.77 | 8.85 |

## B. WATER ANALYSIS (Karl Fisher)

| | |
|---|---|
| Lot No. 7 | 0.34± 0.01 (δ)% |
| Lot No. I62976 | 0.16± 0.01 (δ)% |
| Lot No. A2279 | 0.072± 0.004 (δ)% |

## C. BOILING POINT

| Determined | Literature |
|---|---|
| Lot No. 7 | |
| 181.5° to 184°C at 767 mm Hg (Dupont 900 DTA) | 187° to 188°C at 761 mm Hg (Dewael, 1930) |
| Lot No. I62976 | |
| 181.8° to 186.6°C at 765 mm Hg (Dupont 900 DTA) | |

## D. VAPOR-PHASE CHROMATOGRAPHY

1. Lot No. 7

a. System 1:

Instrument: Varian Aerograph 1400
Detector: Thermal conductivity
Column: Chromosorb 102, 2 mm x 1.8 m
Program: 100° to 250°C at 10°C/min
Results: Major peak and seven impurities

| Peak | Retention Time Relative to Bis(2-chloro-1-methylethyl) Ether | Area (Percent of Major Peak) |
|---|---|---|
| 1 | 0.01 | 0.1 |
| 2 | 0.11 | 0.3 |
| 3 | 0.21 | 0.1 |
| 4 | 0.40 | 0.1 |
| 5 | 0.42 | 0.1 |
| 6 | 0.75 | 0.4 |
| 7 | 0.96 | 6.5 |
| 8 (major) | 1.00 (13.0 min) | 100 |

b. System 2:

Instrument: Tracor MT 220
Detector: Flame ionization
Column: 3% Dexsil 400, 2 mm x 1.8 m
Program: 50°C, 14 min: 50°-200°C at 10°C/min
Results: Major peak and four impurities

| Peak | Retention Time Relative to Bis(2-chloro-1-methylethyl) Ether | Area (Percent of Major Peak) |
|---|---|---|
| 1 | 0.32 | 1.1 |
| 2 | 0.40 | 0.8 |
| 3 | 0.76 | 0.2 |
| 4 (major) | 1.00 (5.0 min) | 100 |
| 5 | 2.76 | 0.04 |

2. Lot No. I62976

a. System 1:

Instrument: Tracor MT 220
Detector: Flame ionization
Inlet temperature: 225°C
Detector temperature: 310°C
Column: 10% Carbowax 20 M-TPA on 80/100 Chromosorb W, AW, 1.8 m x 4 mm I.D., glass
Oven temperature program: 5 min at 75°C, then 75° to 200°C at 10°C/min
Results: Major peak and 32 impurities. One of these has an area of 0.89% of the major peak, one 0.20%, one 0.19%, and one 0.18% of the major peak. The others individually constitute<0.1% of the major peak and total 0.4% of the major peak.

## APPENDIX C

| Peak | Retention Time (min) | Retention Time Relative to Bis(2-chloro-1-methylethyl) Ether | Area (Percent of Major Peak) |
|---|---|---|---|
| 1 | 0.51 | 0.046 | 0.0001 |
| 2 | 0.56 | 0.052 | 0.0005 |
| 3 | 0.86 | 0.078 | 0.003 |
| 4 | 1.0 | 0.096 | 0.003 |
| 5 | 1.2 | 0.11 | 0.0006 |
| 6 | 1.8 | 0.16 | 0.0007 |
| 7 | 2.1 | 0.19 | 0.009 |
| 8 | 2.3 | 0.21 | 0.005 |
| 9 | 4.8 | 0.44 | 0.19 |
| 10 | 6.6 | 0.60 | 0.0005 |
| 11 | 7.2 | 0.66 | 0.008 |
| 12 | 7.5 | 0.68 | shoulder, 0.006-0.02 |
| 13 | 7.7 | 0.70 | 0.18 |
| 14 | 8.0 | 0.74 | shoulder, 0.0006-0.004 |
| 15 | 8.2 | 0.76 | 0.0005 |
| 16 | 8.6 | 0.78 | 0.0005 |
| 17 | 8.8 | 0.81 | 0.05 |
| 18 | 9.0 | 0.82 | shoulder, 0.0002-0.006 |
| 19 | 9.5 | 0.88 | 0.001 |
| 20 | 9.8 | 0.90 | 0.0008 |
| 21 | 10.9 | 1.00 | 100 |
| 22 | 11.5 | 1.06 | 0.89 |
| 23 | 12.3 | 1.12 | 0.02 |
| 24 | 12.4 | 1.14 | 0.03 |
| 25 | 12.6 | 1.16 | 0.002 |
| 26 | 13.0 | 1.20 | 0.05 |
| 27 | 13.5 | 1.24 | 0.01 |
| 28 | 13.9 | 1.28 | 0.005 |
| 29 | 14.3 | 1.32 | 0.20 |
| 30 | 14.6 | 1.34 | shoulder, 0.002-0.009 |
| 31 | 14.8 | 1.36 | 0.03 |
| 32 | 15.2 | 1.39 | 0.02 |
| 33 | 15.6 | 1.44 | 0.06 |

b. System 2:

Instrument: Tracor MT 220

Detector: Flame ionization

Inlet temperature: 225°C

Detector temperature: 310°C

Column: 20% SP 2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m x 4 mm I.D., glass

Oven temperature program: 5 min at 75°C, then 75° to 200°C at 10°C/min

Results: Major peak and 32 impurities. One of these has an area 0.94% of the major peak, one 0.18%, one 0.16%, and one 0.15% of the major peak. The others individually constitute<0.1% of the major peak and total<0.5% of the major peak.

## APPENDIX C

| Peak | Retention Time (min) | Retention Time Relative to Bis(2-chloro-1-methylethyl) Ether | Area (Percent of Major Peak) |
|---|---|---|---|
| 1 | 0.66 | 0.05 | <0.0002 |
| 2 | 0.91 | 0.06 | 0.0004 |
| 3 | 1.6 | 0.12 | 0.002 |
| 4 | 2.2 | 0.16 | 0.003 |
| 5 | 2.7 | 0.20 | 0.001 |
| 6 | 3.4 | 0.25 | 0.004 |
| 7 | 4.1 | 0.30 | 0.18 |
| 8 | 4.8 | 0.36 | 0.15 |
| 9 | 5.8 | 0.42 | 0.03 |
| 10 | 7.6 | 0.55 | 0.001 |
| 11 | 8.0 | 0.58 | 0.001 |
| 12 | 8.6 | 0.62 | 0.02 |
| 13 | 9.2 | 0.68 | 0.0002 |
| 14 | 9.4 | 0.70 | 0.004 |
| 15 | 10.2 | 0.75 | 0.08 |
| 16 | 10.6 | 0.78 | 0.16 |
| 17 | 11.0 | 0.80 | 0.30 |
| 18 | 11.2 | 0.82 | shoulder, 0.002-0.001 |
| 19 | 11.4 | 0.83 | 0.009 |
| 20 | 11.8 | 0.86 | 0.008 |
| 21 | 12.1 | 0.88 | 0.94 |
| 22 | 12.4 | 0.90 | 0.02 |
| 23 | 12.8 | 0.94 | 0.04 |
| 24 | 13.7 | 1.00 | 100 |
| 25 | 14.2 | 1.04 | 0.03 |
| 26 | 14.6 | 1.06 | 0.04 |
| 27 | 14.8 | 1.08 | shoulder, 0.002-0.004 |
| 28 | 15.0 | 1.10 | 0.008 |
| 29 | 15.2 | 1.11 | 0.02 |
| 30 | 15.4 | 1.12 | 0.008 |
| 31 | 15.8 | 1.16 | 0.01 |
| 32 | 16.1 | 1.18 | 0.001 |
| 33 | 16.5 | 1.20 | 0.05 |

c. System 3:

Instrument: Varian 3700

Detector: Flame ionization

Inlet temperature: 210°C

Detector temperature: 270°C

Carrier gas: Nitrogen

Column: 0.1% SP1000 on 80/100 Carbopack C, glass, 1.8 m x 4 mm I.D.

Carrier flow rate: 70 cc/min

Oven temperature program: 100°C, 5 min; 100°-210°C at 10°C/min

Samples injected: Bis(2-chloro-isopropyl) ether in hexane (1% v/v) to quantitate the areas of the two isomers present in larger amounts. A 0.04% v/v solution was used to obtain the area of the major isomer relative to the area of the third isomer present in the 1% solution at less than 5% amount.

Results: Three peaks were obtained with close to baseline resolution (>98% of largest peak). The three peaks were present in the ratios of 69.4:28.5:2.1.

| Peak No. | Retention Time (min) | Area (Percent of Major Peak) | Area (Percent of Total Area) |
|---|---|---|---|
| 1 | 18.2 | 100 | 69.4 ± 0.7 |
| 2 | 19.0 | 41.1 ± 0.7 | 28.5 ± 0.5 |
| 3 | 19.7 | 3.0 ± 0.1 | 2.1 ± 0.1 |

3. Lot No. A2279

Instrument: Varian 3700

Detector: Flame ionization

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 x 4 mm I.D., glass

Inlet temperature: 180°C

Detector temperature: 250°C

Oven temperature program: 50°C for 5 min, then 50° to 200°C at 10°/min

Samples injected: Neat liquid (3μl) and 1% and 0.5% solutions (3μl) in chloroform to quantitate the major peak and check for detector overload.

Results: Major peaks and 17 impurities, nine before and eight after the major peak. One impurity after the major peak was quantitated from a 1% injection and had an area of 1.16% relative to the major peak area. A shoulder on the leading edge of the major peak had a relative area of 0.14. The remaining 15 impurities had a combined relative area of 0.56%.

## APPENDIX C

| Peak | | Retention Time (min) | Retention Time (Relative to Major Peak) | Area (Percent of Major Peak) |
|---|---|---|---|---|
| 1 | Multiple unresolved impurities | 0.4 - 1.0 | 0.03 - 0.07 | 0.01 |
| 2 | Unresolved impurities | 10.0 | 0.70 | 0.07 |
| 3 | | 10.3 | 0.73 | |
| 4 | Unresolved impurities | 11.4 | 0.80 | 0.10 |
| 5 | | 11.7 | 0.82 | |
| 6 | | 12.5 | 0.88 | 0.05 |
| 7 | | 12.9 | 0.91 | 0.06 |
| 8 | | 13.5 | 0.95 | 0.03 |
| 9 | Shoulder to major peak | 13.9 | 0.98 | 0.14 |
| 10 | | 14.2 | 1.00 | 100 |
| 11 | | 14.9 | 1.05 | 1.16 |
| 12 | Unresolved impurities | 15.4 | 1.08 | 0.04 |
| 13 | | 15.7 | 1.11 | |
| 14 | Multiple unresolved impurities | 16.2 - 17.1 | 1.14 - 1.20 | 0.01 |
| 15 | Unresolved impurities | 17.8 | 1.25 | 0.10 |
| 16 | | 18.0 | 1.27 | |
| 17 | | 18.4 | 1.30 | |
| 18 | | 18.8 | 1.32 | 0.09 |

b. System 2:

Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m x 4 mm I.D., glass

Inlet temperature: 220°C

Detector temperature: 300°C

Oven temperature program: 50°C for 5 min, then 50° to 170°C at 10°/min

Samples injected: Neat liquid (3 $\mu$l) and 1% and 0.5% solutions (3 $\mu$l) in chloroform to quantitate the major peak and check for detector overload.

Results: Major peak and 16 impurities, 12 before and four after the major peak. Two impurities before the major peak were quantitated from a 1% injection and had relative areas of 0.75% and 1.29%, respectively. The remaining 14 impurities had a combined area of 0.45% relative to the major peak area.

## APPENDIX C

| Peak | | Retention Time (min) | Retention Time (Relative to Major Peak) | Area (Percent of Major Peak) |
|---|---|---|---|---|
| 1 | | 4.3 | 0.30 | 0.05 |
| 2 | | 5.2 | 0.37 | 0.08 |
| 3 | | 6.1 | 0.43 | 0.02 |
| 4 } | unresolved | 8.5 | 0.60 } | 0.02 |
| 5 } | impurities | 8.7-9.0 | 0.61-0.63 } | |
| 6 } | unresolved | 10.5 | 0.74 } | 0.02 |
| 7 } | impurities | 10.7 | 0.75 } | |
| 8 | | 11.4 | 0.80 | 0.75 |
| 9 | | 12.4 | 0.87 | 0.01 |
| 10 | | 12.7 | 0.89 | 1.29 |
| 11 | | 13.2 | 0.93 | 0.01 |
| 12 | | 13.6 | 0.96 | 0.01 |
| 13 | | 14.2 | 1.00 | 100 |
| 14 | | 15.6 | 1.10 | 0.02 |
| 15 | | 16.1 | 1.13 | 0.11 |
| 16 | | 16.5 | 1.16 | 0.01 |
| 17 | | 17.5 | 1.23 | 0.09 |

c. System 3 - Quantitation of Isomers:

Column: 80/100 Carbopack C/O.1% SP1000, 1.8 m x 4 mm I.D., glass

Inlet temperature: 180°C

Detector temperature: 250°C

Oven temperature program: 100°C for 5 min, then 100° to 210°C at 10°/min

Samples injected: Solution (3 $\mu$l) of 1% (v/v) bis-(2-chloro-1-methylethyl) ether in hexane to quantitate isomers and a 0.5% (v/v) solution to check for detector overload.

Results: Three peaks were obtained with nearly baseline resolution. The three isomers were present in the ratio 71.48:25.92:2.59.

| Peak No. | Retention Time (min) | Retention Time (Relative to Peak 1) | Area (Percent of Total Area) |
|---|---|---|---|
| 1 | 16.2 | 1.00 | 71.48 ± 0.40($\delta$) |
| 2 | 16.8 | 1.04 | 25.92 ± 0.43($\delta$) |
| 3 | 17.3 | 1.07 | 2.59 ± 0.04($\delta$) |

Note: The isomers were identified by vapor phase chromatography/mass spectrometry for Lot No. I62976. Peak 1 was identified as bis(2-chloro-1-methylethyl) ether, Peak 3 as bis(2-chloropropyl) ether, and Peak 2 as the mixed isomer.

## E. VAPOR-PHASE CHROMATOGRAPHY/MASS SPECTROMETRY (Lot No. I62976)

Instrument: Varian 2700 VPC/Varian 311A MS

Detector: Ion Current Monitor

Ionization voltage: 70 eV

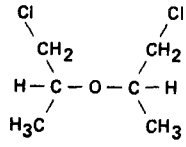
Column: 0.1% SP1000 on 80/100 Carbopack C; glass, 1.8 m x 2 mm I.D.

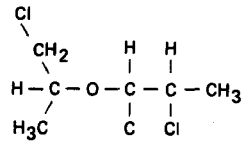
Oven temperature program: 100°C, 5 min; 100°-210°C at 10°C/min

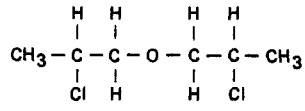
Samples injected: 1 $\mu$l of 1 $\mu$g/$\mu$l solution in hexane

Results: Three peaks, baseline resolved. Fragmentation peaks were obtained on all three isomers (Table C1). The mass peaks were consistent with all three components being isomers of bis(2-chloropropyl) ether. The mass peak of 49, found as the base peak of the first isomer and at an intensity of 48 and 5, respectively, in the other isomers is attributable to the $CH_2Cl$ fragment which can be easily formed only in the bis(2-chloro-1-methylethyl) isomer and the mixed 2-chloro-1-methylethyl, 2-chloropropyl isomer. The 107, 109 mass peaks are attributable to the fragment left after loss of $CH_3$-CHCl-. These fragments are found in highest intensity in the second and third isomer and would be predicted to be highest in the bis(2-chloropropyl) ether and in the mixed isomer. Therefore, isomer 1 can be assigned the identity of bis(2-chloroisopropyl) ether; isomer 3 is the bis(2-chloropropyl)ether and 2 is the mixed isomer (Table C1).

**TABLE C1. HIGH INTENSITY MASS FRAGMENTS OBTAINED FROM THE THREE ISOMER COMPONENTS**







| Mass | Intensity | Intensity | Intensity |
|---|---|---|---|
| 49 | 100 *(b)* | 48 | 5 |
| 51 | 51 | 15 | - |
| 58 | 82 | 94 *(a)* | 100 *(b)* |
| 59 | 99.6 *(a)* | 81 *(a)* | 13 |
| 71 | 16 | 86 *(a)* | 23 *(a)* |
| 76 | 99.8 *(a)* | 35 | 5 |
| 78 | 78 | 19 | 2 |
| 77 | 72 | 100 *(b)* | 61 *(a)* |
| 79 | 99 *(a)* | 98 *(a)* | 22 *(a)* |
| 81 | 99 *(a)* | 7 | 1 |
| 85 | 47 | 49 | 1 |
| 89 | 12 | 45 | 17 *(a)* |
| 93 | 99.9 *(a)* | 11 | - |
| 95 | 48 | 3 | - |
| 98 | 23 | 16 | 16 |
| 107 | 29 | 88 *(a)* | 52 *(a)* |
| 109 | 8 | 26 | 21 *(a)* |
| 121 | - | 98 *(a)* | - |
| 123 | 91 | 36 | - |
| 122 | 99 *(a)* | 5 | - |
| 124 | 36 | 2 | - |
| 134 | 99 *(a)* | 87 *(a)* | 27 *(a)* |
| 136 | 39 | 26 | 7 |

*(a)* Eight most intense peaks in each component.
*(b)* Base peak.

## F. SPECTRAL DATA

1. Infrared: All lots gave infrared absorption spectra (Figures 3 to 5) which were consistent with spectra given in the literature (Sadtler Standard Spectra).
   a. Lot No. 7 and Lot No. I62976
      Instrument: Beckman IR-12
      Cell: 0.015 mm liquid cell, sodium chloride windows
   b. Lot No. A2279
      Instrument: Beckman IR-12
      Cell: Thin film between silver chloride plates.
2. Ultraviolet/Visible
   Instrument: Cary 118 — No literature reference found
   a. Lot No. 7
      Solvent: Methanol
      Cell: 1 cm quartz
      Results: Shoulder at $\lambda$ = 220 nm, $\varepsilon$ max = 10.8 ± 0.4 ($\delta$)
   b. Lot No. I62976
      Solvent: Methanol
      Concentration: 2.2 mg/ml
      Results: Shoulder at $\lambda$ = 301 nm, $\varepsilon$ max = 4.4 ± 0.2 ($\delta$)
   c. Lot No. A2279
      Solvent: Methanol
      Concentration: 1% v/v
      Results: Shoulder at $\lambda$ = 222 nm, $\varepsilon$ max = 6.41 ± 0.14 ($\delta$)

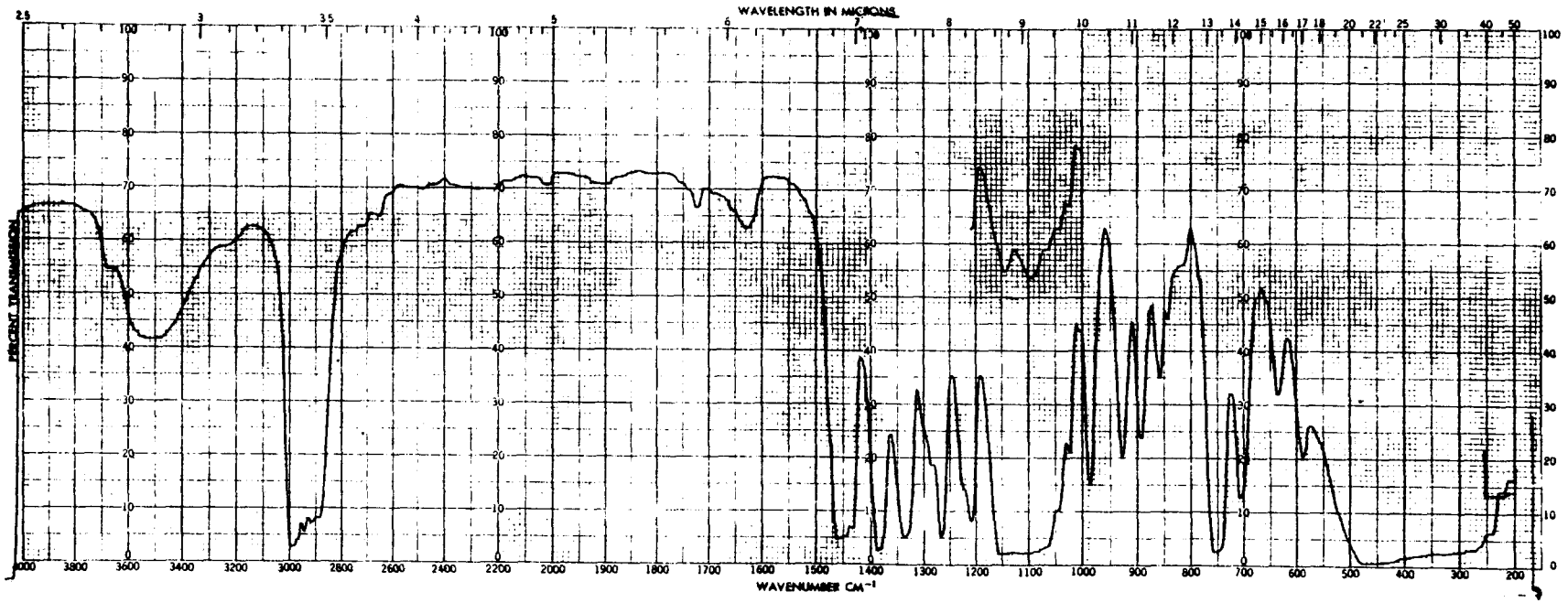



**Figure 3. Infrared Absorption Spectrum of Bis(2-chloro-1-methylethyl) Ether (Lot No. 7)**

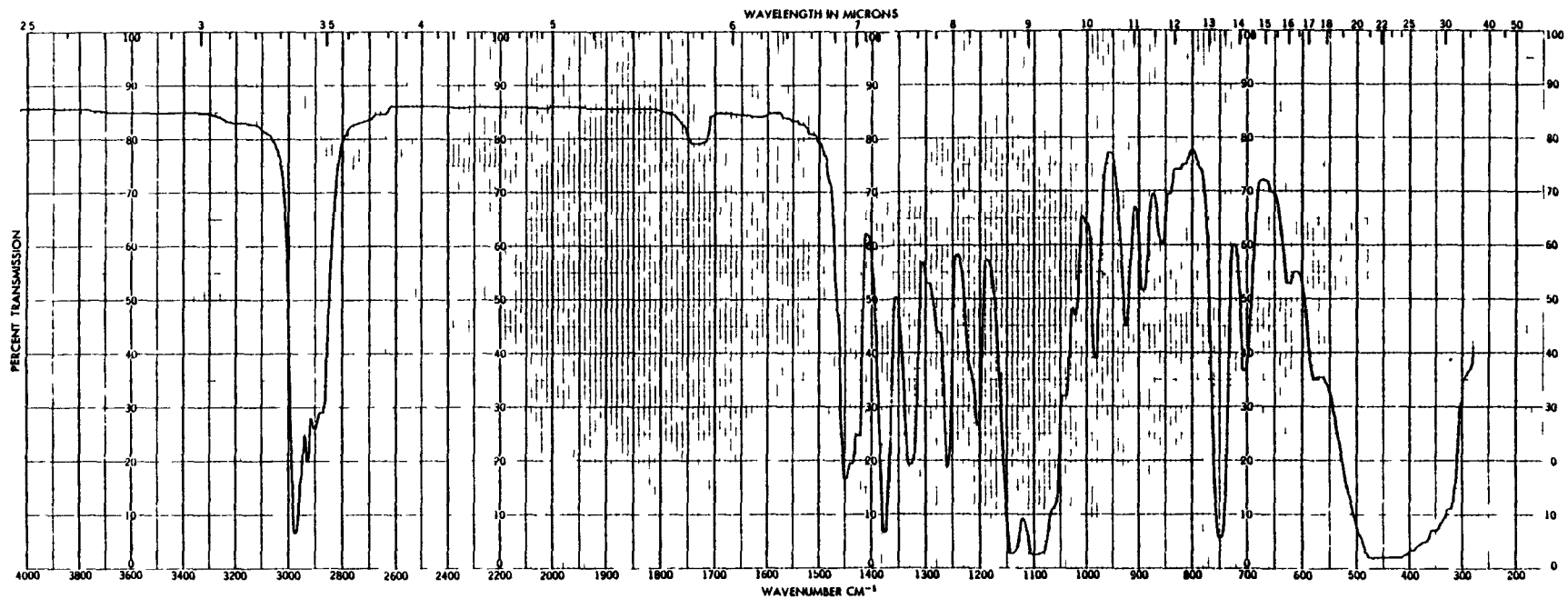



**Figure 4. Infrared Absorption Spectrum of Bis(2-chloro-1-methylethyl) Ether (Lot No. 162976)**

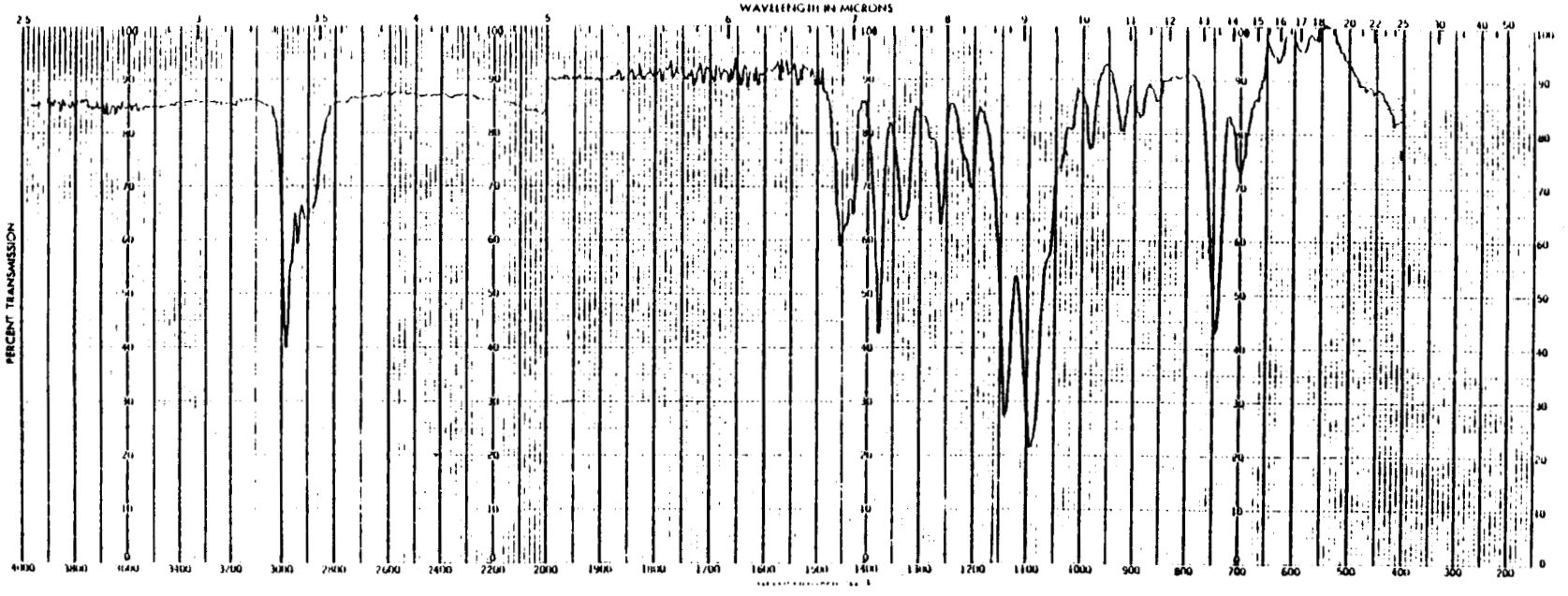



**Figure 5. Infrared Absorption Spectrum of Bis(2-chloro-1-methylethyl) Ether (Lot No. A2279)**

3. Nuclear Magnetic Resonance — No literature reference found

a. Lot No. 7

Instrument: Varian HA - 100

Solvent: Neat with tetramethylsilane

Assignments: (See Figure 6)

(a) 1.18 $\delta$ (b) 1.43 $\delta$ (impurity)
(c) 3.20 - 3.48 $\delta$ (d) 3.50 - 4.10 $\delta$
$J_{ad}$ = 6 cps
$J_{bd}$ = 6 cps

Integration Ratios

(a) 4.46
(b) 1.04
(c) and (d) 6.51

The shift for (b) agrees with that of a methyl group next to a carbon containing a hydrogen and a chlorine atom

b. Lot No. 162976

Instrument: Varian HA-100

Solvent: Neat, tetramethylsilane added

Assignments: (see Figure 7)

(a) d, $\delta$ 1.19 ppm, $J_{ad}$ = 6Hz
(b) d, $\delta$ 1.46 ppm, $J_{bc}$ = 6Hz
(c) m, $\delta$ 3.20-3.52 ppm
(d) m, $\delta$ 3.53-4.14 ppm

Integration Ratios:

(a) 4.47
(b) 1.09
(c + d) 6.44

The shift for (b) agrees with that of a methyl group next to a carbon bonded to hydrogen and chlorine

c. Lot No. A2279

Instrument: Varian EM-360A

Solvent: Neat, tetramethylsilane added

Assignments: (see Figure 8)

(a) d, $\delta$ 1.21 ppm, $J_{ad}$ = 6Hz
(b) d, $\delta$ 1.49 ppm, $J_{bc}$ = 6Hz
(c) m, $\delta$ 3.16-3.56 ppm
(d) m, $\delta$ 3.57-4.22 ppm

Integration Ratios:

(a) 4.77
(b) 1.13
(c) } 6.10
(d) }

The shift for (b) agrees with that of a methyl group next to a carbon bonded to hydrogen and chlorine

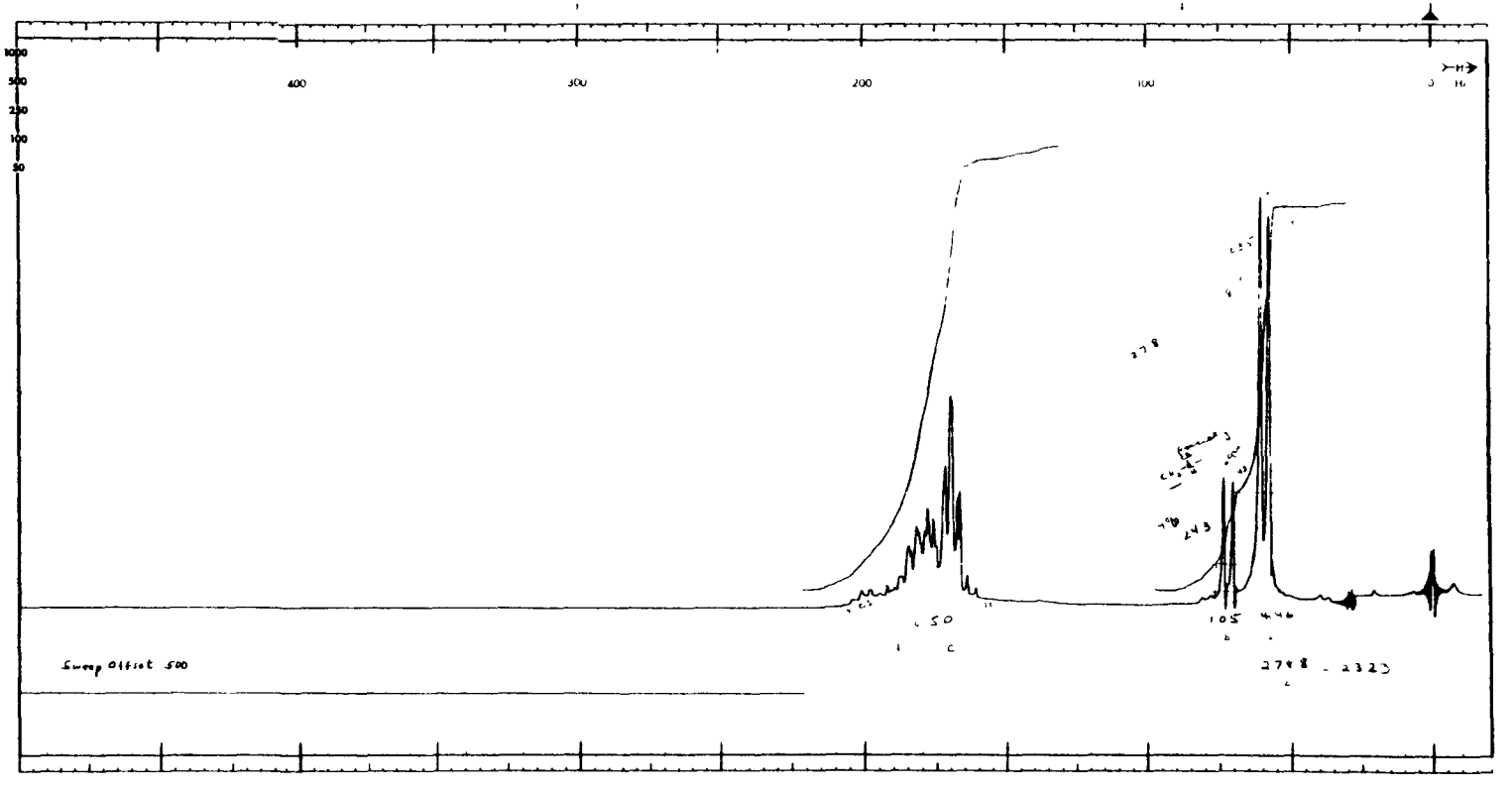



**Figure 6. Nuclear Magnetic Resonance Spectrum of Bis(2-chloro-1-methylethyl) Ether (Lot No. 7)**

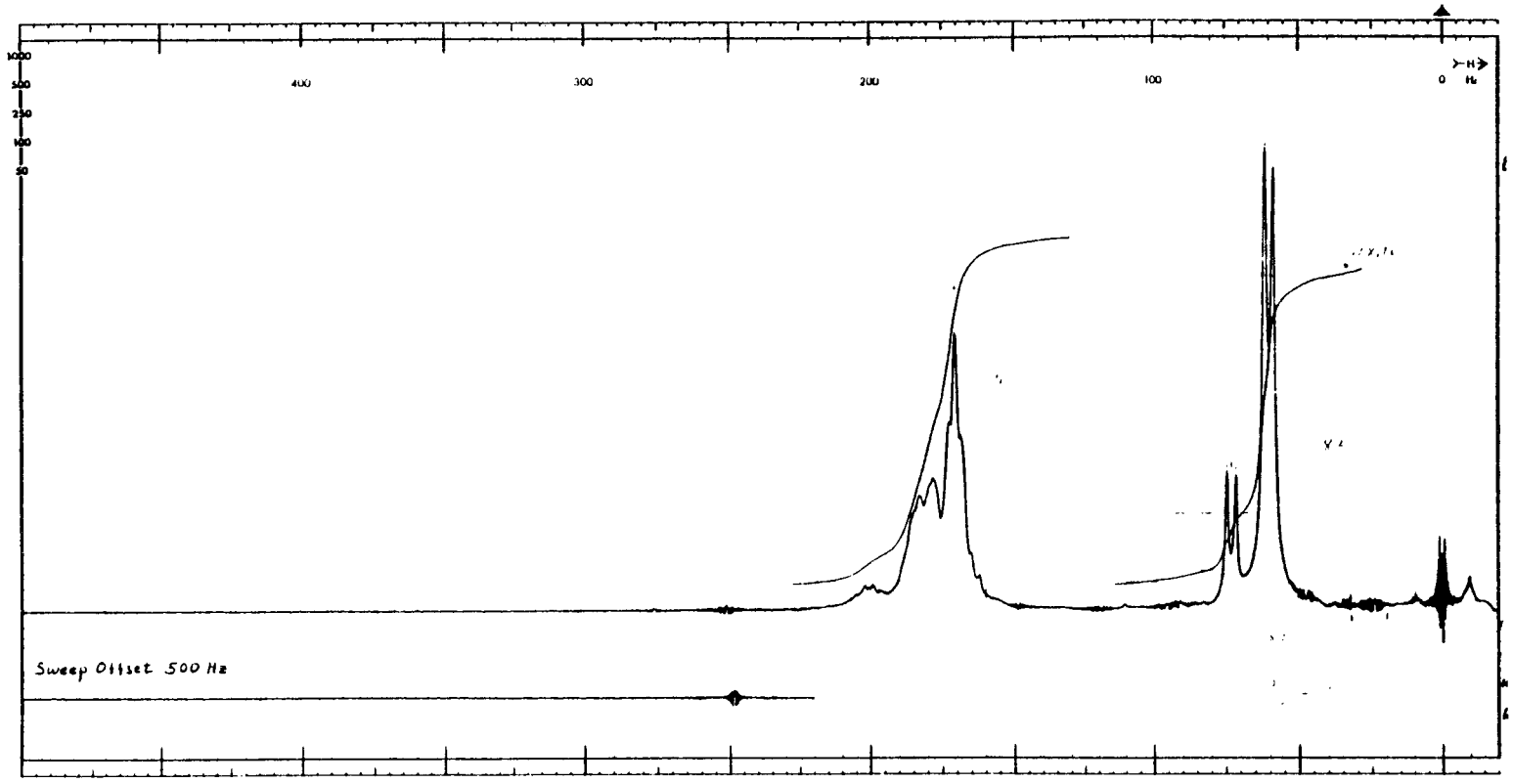



**Figure 7. Nuclear Magnetic Resonance Spectrum of Bis(2-chloro-1-methylethyl) Ether (Lot No. I62976)**

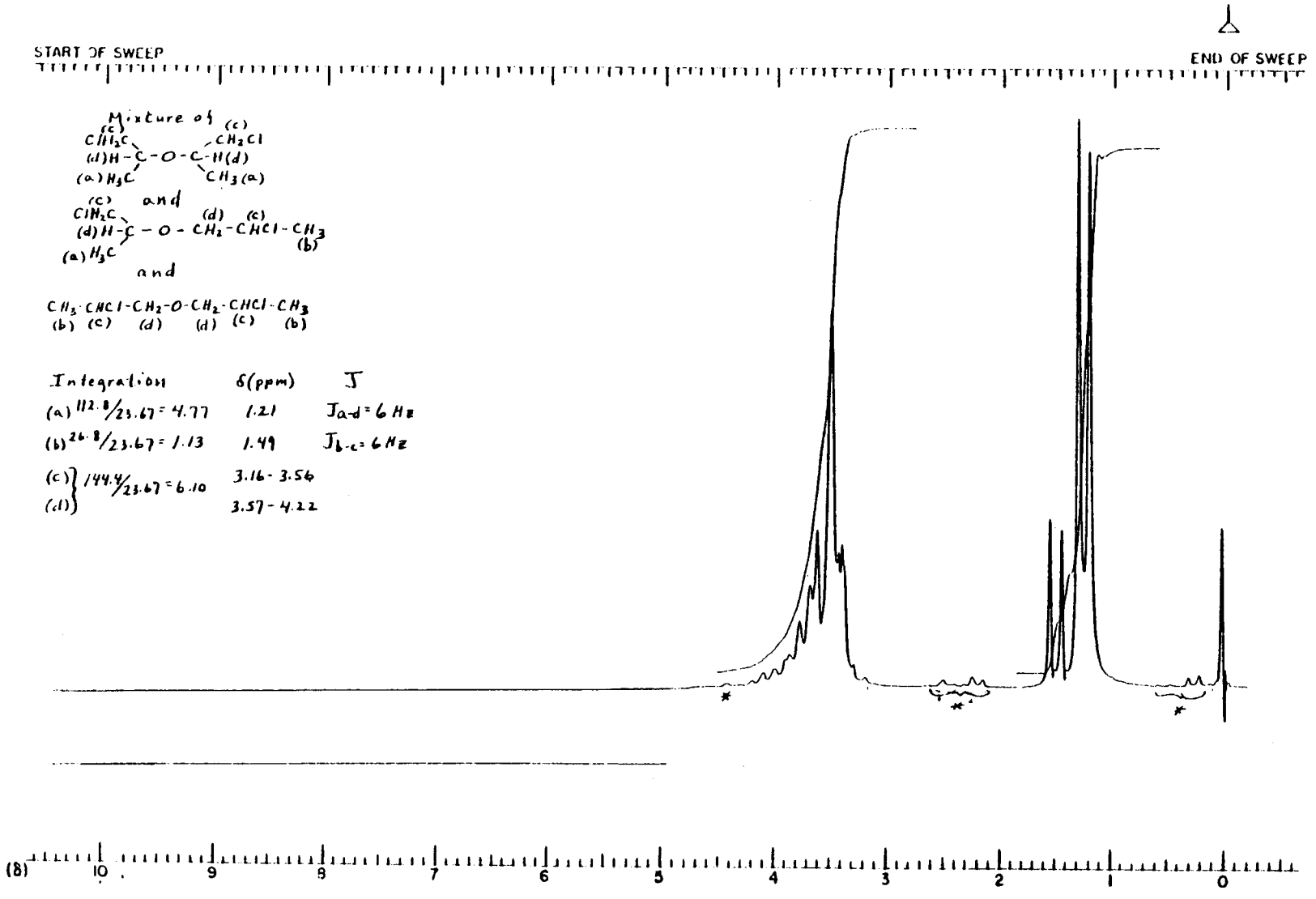



**Figure 8. Nuclear Magnetic Resonance Spectrum of Bis(2-chloro-1-methylethyl) Ether (Lot No. A2279)**

# APPENDIX D

## ANALYSIS FOR STABILITY OF BIS(2-CHLORO-1-METHYLETHYL) ETHER IN CORN OIL

# APPENDIX D

## A. TEST PARAMETERS

Concentration: 20 mg/ml

Vehicle: Corn oil

Duration: 14 days

Storage and sampling schedule: 5°C; 0, 1, 7, 11, and 14 days in the dark

Room temperature: (20°-24°C); 3 hours open to air and light

## B. SAMPLE PREPARATION AND STORAGE

Solutions of bis(2-chloro-1-methylethyl) ether in corn oil were prepared on five different days over a 14-day period. The days were chosen so that the solutions, when analyzed on the 14th day, had been stored 3 hours open to air and light, and in the dark for 1, 7, 11, and 14 days at 5°C.

The solutions were prepared in duplicate by dissolving ~200 mg (weighed to ± 0.01 mg) of bis(2-chloro-1-methylethyl) ether in ~9 g (± 1 mg) of corn oil in 10-ml septum vials. The solutions were sealed in the vials with Teflon®-lined septa and thoroughly mixed.

On day zero, triplicate solutions (50 ml each) were prepared as described above, and duplicate aliquots (~1 g) of each solution were removed for immediate analysis. The remaining portions of the solutions were transferred to tared 100-ml beakers and weighed (± 1 mg.) The solutions were stored 3 hours open to air and light in a hood, then reweighed to determine losses by evaporation, prior to sampling for analysis.

## C. ANALYSIS PROCEDURE

Aliquots of the sample (~1 g weighed to the nearest 0.01 g) were weighed into 50-ml septum vials and extracted with 20 ml of methanol by shaking the vials by hand for 1 minute and centrifuging to clear the extracts. An 8-ml aliquot of each methanol extract was combined with 2 ml of internal standard solution (n-tridecane, 4.2 µl/ml in methanol) in a 10-ml septum vial, and the bis(2-chloro-1-methylethyl) ether content of the solutions was determined by the gas chromatographic system described below.

Instrument: Varian 3700 Gas Chromatograph equipped with autosampler and CDS-111 integrator

Column: 3% OV-17 on 100/120 mesh Supelcoport, 1.8 m x 2 mm I.D. glass,

Detector: Flame ionization

Temperatures: Injection port: 120°C; oven: 85°C isothermal

Detector: 180°C

Carrier Gas: Nitrogen; flow rate, 30 ml/min

Retention Times: Bis(2-chloro-1-methylethyl) ether - 3.7 min;
n-Tridecane (internal standard) - 7.9 min

A standard solution of bis(2-chloro-1-methylethyl) ether in methanol (0.87 mg/ml) was injected after every third sample to calibrate detector response. A second, independently prepared standard was used to verify the accuracy of the calibration standard.

The concentration (mg/g) of bis(2-chloro-1-methylethyl) ether in the samples was calculated as follows:

$$\frac{\text{RRF x Sample Peak Area x mg/ml Internal Standard x DF x Vol}}{\text{Peak Area of Internal Standard x Grams of Sample x RF}}$$

where RRF is the relative response factor, calculated from the calibration standard data, as follows:

$$\text{RRF} = \frac{\text{mg/ml Test Chemical x Peak Area of Internal Standard}}{\text{Peak Area of Test Chemical x mg/ml Internal Standard}}$$

DF is the dilution factor ( $\frac{10}{8} = 1.25$)

RF is the recovery factor, determined with six zero-time samples, and Vol was the volume of original extraction solution (20 ml).

## D. RESULTS—STABILITY IN CORN OIL

**Bis(2-chloro-1-methylethyl) Ether**

| Storage Time (days) | Storage Temp. | Found *(a)* (mg/g) | Theoretical (mg/g) | Found Theoretical *(%)* |
|---|---|---|---|---|
| 0 | | 21.2 | 21.4 | 99.2 |
| | | 21.0 | 21.4 | 98.3 |
| | | 20.3 | 20.4 | 99.6 |
| | | 20.3 | 20.4 | 99.6 |
| | | 21.4 | 20.9 | 102.3 |
| | | 21.1 | 20.9 | 101.0 |
| | | | | $\bar{x}$=100.0 ± 1.4($\delta$) |
| *(b)* | Room | 21.4 *(c)* | 21.3 | 100.2 |
| | Temp. | 21.2 | 21.3 | 99.2 |
| | | 21.4 | 21.3 | 100.2 |
| | | 21.2 | 21.3 | 99.2 |
| | | | | $\bar{x}$= 99.7 ± 0.6($\delta$) |
| 4 | 5°C | | | lost |
| | | 20.8 | 20.7 | 100.4 |
| 7 | 5°C | 21.2 | 21.3 | 99.8 |
| | | 24.0 | 24.1 | 99.8 |
| | | | | $\bar{x}$= 99.5 ± 0($\delta$) |
| 11 | 5°C | 22.7 | 22.1 | 101.0 |
| | | 22.0 | 22.0 | 100.0 |
| | | | | $\bar{x}$=100.5 ± 1.9($\delta$) |
| 14 | 5°C | 20.9 | 21.0 | 99.7 |
| | | 21.7 | 21.7 | 100.0 |
| | | | | $\bar{x}$= 99.8 ± 0.2($\delta$) |

Pooled standard deviation for the method: 0.9%

*(a)* Results were corrected for 95.0% ± 1.4%($\delta$) recovery of the chemical from corn oil.
*(b)* Three hours open to air and light.
*(c)* Values corrected for 0.51% weight loss due to evaporation.

## E. CONCLUSION

Bis(2-chloro-1-methylethyl) ether dissolved in corn oil at a concentration of 20 mg/ml was stable for 2 weeks in the dark at 5°C. Solutions exposed to air and light for 3 hours were also stable. Based on the pooled standard deviation for the method, a minimum of 0.9% loss of chemical was required to conclude, at the 95% confidence level, that a sample was unstable.

# APPENDIX E

## ANALYSIS OF BIS(2-CHLORO-1-METHYLETHYL) ETHER IN CORN OIL FOR CONCENTRATIONS OF BIS(2-CHLORO-1-METHYLETHYL) ETHER

## APPENDIX E

An aliquot of 1 ml of the sample was diluted, in duplicate, to 100 ml with n-hexane and analyzed directly by VPC-FID on 3% OV-17 100/200 Supelcoport 6 ft. x 1/4 in. x 2 mm I.D. glass column at 100°, isothermal. Results of analysis are tabulated below.

| Date Mixed | Date Used | Concentration (a) of Bis-(2-chloro-1-methylethyl) Ether for Target Concentration of 20 mg/ml | 40 mg/ml |
|---|---|---|---|
| 07/19/78 | 07/19/78 | | 37.2 |
| 09/01/78 | 09/02/78 | | 38.2 |
| 11/03/78 | 11/03/78 | | 34.7 |
| 12/08/78 | 12/08/78 | 17.5 | 37.7 |
| 01/26/79 | 01/26/79 | 19.9 | 39.4 |
| 04/06/79 | 04/06/79 | 19.5 | 37.5 (41.5) *(b)* |
| 05/10/79 | 05/10/79 | 20.5 | 37.5 |
| 08/24/79 | 08/24/79 | 19.5 | 37.0 |
| 09/21/79 | 09/21/79 | 19.0 (20.6) *(b)* | 38.5 |
| 10/26/79 | 10/26/79 | 19.3 | |
| 10/30/79 | 10/30/79 | | 39.5 |
| 01/18/80 | 01/18/80 | 20.3 | 40.3 (40.0) *(b)* |
| 03/21/80 | 03/21/80 | 20.3 | 39.5 |
| 05/22/80 | 05/22/80 | 20.0 | 36.8 (39.6) *(b)* |
| Mean (mg/ml) | | 19.6 | 38.0 |
| Standard deviation | | 0.9 | 1.5 |
| Coefficient of variation (%) | | 4.6 | 3.9 |
| Range (mg/ml) | | 17.5-20.5 | 34.7-40.3 |
| Number of Samples | | 10 | 13 |

*(a)* The data presented are the average of the results of duplicate analyses
*(b)* Midwest Research Institute analysis

# APPENDIX F

## HISTORICAL INCIDENCE OF TUMORS IN B6C3F$_1$ MICE

**TABLE F1. HISTORICAL INCIDENCE OF LUNG TUMORS IN VEHICLE (CORN OIL) CONTROL MALE B6C3F$_1$ MICE *(a)***

| | Alveolar/Bronchiolar | | |
|---|---|---|---|
| | **Adenoma** | **Carcinoma** | **Adenoma or Carcinoma** |
| Frederick | 1/50 (2.0%) | 0/50 (0.0%) | 1/50 (2.0%) |
| Gulf South | 12/138 (8.7%) | 5/138 (3.6%) | 17/138 (12.3%) |
| Litton | 5/70 (7.1%) | 1/70 (1.4%) | 6/70 (8.6%) |
| Mason | 5/50 (10.0%) *(b)* | 1/50 (2.0%) *(b)* | 6/50 (12.0%) *(b)* |
| Southern | 4/50 (8.0%) | 0/50 (0.0%) | 4/50 (8.0%) |
| Total | 27/358 (7.5%) | 7/358 (2.0%) | 34/358 (9.5%) |
| High | 5/45 (11.1%) | 2/46 (4.3%) | 6/45 (13.3%) |
| Low | 1/50 (2.0%) | 0/50 (0.0%) | 1/50 (2.0%) |

*(a)* Data as of January 17, 1981. Range is presented for groups of 35 or more animals on test for at least 104 weeks.
*(b)* This study

**TABLE F2. HISTORICAL INCIDENCE OF LUNG TUMORS IN VEHICLE (CORN OIL) CONTROL FEMALE B6C3F$_1$ MICE *(a)***

| | Alveolar/Bronchiolar | | |
|---|---|---|---|
| | **Adenoma** | **Carcinoma** | **Adenoma or Carcinoma** |
| Frederick | 0/50 (0.0%) | 2/50 (4.0%) | 2/50 (4.0%) |
| Gulf South | 5/144 (3.5%) | 1/144 (0.7%) | 6/144 (4.2%) |
| Litton | 1/69 (1.4%) | 0/69 (0.0%) | 1/69 (1.4%) |
| Mason | 1/50 (2.0%) *(b)* | 0/50 (0.0%) *(b)* | 1/50 (2.0%) *(b)* |
| Southern | 2/47 (4.3%) | 0/47 (0.0%) | 2/47 (4.3%) |
| Total | 9/360 2.5%) | 3/360 (0.8%) | 12/360 (3.3%) |
| High | 3/46 (6.5%) | 2/50 (4.0%) | 4/46 (8.7%) |
| Low | 0/50 (0.0%) | 0/50 (0.0%) | 1/50 (2.0%) |

*(a)* Data as of January 17, 1981. Range is presented for groups of 35 or more animals on test for at least 104 weeks.
*(b)* This study

**TABLE F3. HISTORICAL INCIDENCE OF LIVER TUMORS IN VEHICLE (CORN OIL) CONTROL MALE B6C3F$_1$ MICE *(a)***

| | Adenoma | Carcinoma | Adenoma or Carcinoma |
|---|---|---|---|
| Frederick | 0/50 (0.0%) | 4/50 (8.0%) | 4/50 (8.0%) |
| Gulf South | 23/142 (16.2%) | 24/142 (16.9%) | 47/142 (33.1%) |
| Litton | 1/70 (1.4%) | 12/70 (17.1%) | 13/70 (18.6%) |
| Mason | 8/50 (16.0%) *(b)* | 5/50 (10.0%) *(b)* | 13/50 (26.0%) *(b)* |
| Southern | 8/49 (16.3%) | 14/49 (28.6%) | 21/49 (42.9%) |
| Total | 40/361 (11.1%) | 59/361 (16.3%) | 98/361 (27.1%) |
| High | 10/48 (20.8%) | 14/49 (28.5%) | 21/49 (42.9%) |
| Low | 0/50 (0.0%) | 4/50 (8.0%) | 4/50 ( 8.0%) |

*(a)* Data as of January 17, 1981. Range is presented for groups of 35 or more animals on test for at least 104 weeks.
*(b)* This study